



COVID-19 and its Ramifications

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Abstract

Coronavirus Disease 2019 (COVID-19) is caused by SARS-CoV-2). The WHO has declared it as pandemic. Globally it has affected more than 2.5 million people and caused more than 0.2 million deaths as on April 27, 2020. It is spread through contact with the virus released by the infected person. Its incubation period ranges from 10 to 15 days. The primary prevention method is to avoid exposure to the virus. People affected by the virus are quarantined and given treatment. Presently steps are on to develop new drugs and vaccines to combat this virus.

Keywords

COVID-19, aetiology, transmission, prevention, treatment

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Ethical Statement: There is no violation of ethical regulations.

INTRODUCTION:

Corona virus disease 2019 (COVID-19) is a potentially severe acute respiratory infection caused by Severe Acute Respiratory Syndrome Coronavirus -2 (SARS-CoV-2). The virus was identified as the cause of an outbreak of pneumonia of unknown origin in Wuhan City Hubei Province, China in December 2019. [1] It is believed that this virus was initially transmitted from bats and pangolins to humans in China.

The World Health Organization (WHO) has as a public health emergency of international concern and rates the global risk as very high. The situation is evolving rapidly with global case counts and deaths increasing each day.

Epidemiology:

The WHO was informed of 44 cases of pneumonia of unknown microbial aetiology associated with Wuhan city on 31 December 2019. [4] A novel coronavirus had been detected in samples taken from these patients. Laboratory tests ruled out the involvement of severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory Syndrome (MERS)-CoV, influenza, avian influenza, and other common respiratory pathogens. [5] After this, WHO declared public health emergency of international concern on 30 January 2020.

Infections:

Nearly 80000 cases and approximately 2800 deaths have been reported in China (as of 1 March 2020). The majority of cases are in Hubei Province. [6][7] At least 7000 cases and 104 deaths have been reported in the following 58 countries outside China (as of 1 March 2020); Afghanistan, Algeria, Australia, Austria, Azerbaijan, Bahrain, Belarus, Belgium, Brazil, Cambodia, Canada, Croatia, Denmark, Ecuador, Estonia, Finland, France, Georgia, Germany, Greece, Egypt, India, Iran, Iraq, Ireland, Israel, Italy, Japan, Kuwait, Lebanon, Lithuania, Malaysia, Mexico, Monaco, Nepal, Netherlands, New Zealand, Nigeria, North Macedonia, Norway, Oman, Pakistan, Philippines, Qatar, Romania, Russia, San Marino, Singapore, South Korea, Spain, Sri Lanka, Sweden, Switzerland, Thailand, United Arab Emirates, the UK, the US, and Vietnam. In addition to this, 705 cases have been reported on an international conveyance (a cruise ship) in Japan. [6]

Total number of COVID-19 positive cases rose to 2088 in India (including 1764 active cases, 157 cured/ discharged / migrated people and 56 deaths), according to the latest tally published by the union Ministry of Health and Family Welfare on April 4, 2020. Among the 27 states and union territories having (C should be small) virus patients,

Maharashtra has the highest tally of positive cases at 338, followed by Kerala at 241.

India has been under a lockdown in a bid to prevent the spread of COVID-19 infection. The lockdown is now extended to May 3rd 2020. In some states, under the discretion of the CM, some allowances like barber shop functioning on Saturdays and Sundays is allowed. At least 20 countries have reported local transmission (as of 1 March 2020) : Australia, Canada, Croatia, France, Germany, Iran, Italy, Japan, Malaysia, Netherlands, Norway, San Marino, Singapore, South Korea, Spain, Thailand, United Arab Emirates, the UK, the US, and Vietnam. [6]

These case counts are correct at the time of writing; however, they are increasing daily, Logical error.[WHO: novel coronavirus (COVID-19) SITUATION DASHBOARD]; [WHO: corona virus disease (COVID-2019) situation reports]; [CDC: coronavirus disease 2019 (COVID-19) in the US]; [CDC: locations with confirmed COVID-19 cases]; [National Health Committee of the people's Republic of China: outbreak report]; The Chinese Center for disease Control and Prevention recently published data from the largest case series to date (72,314 cases from 31 December 2019 to 11 February 2020). (Inset this data in a table)

Aetiology:

Coronaviruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, SARS, MERS), and others that circulate among mammals (e.g., bats, camels and birds). (Reference) Rarely, animal coronaviruses can spread to humans and subsequently spread between people, as was the case with SARS and MERS. (Reference)

Transmission dynamic of the virus is currently unknown, and the situation is evolving. Person-to-person spread has been confirmed in community and healthcare settings in China and other countries. [6] An initial assessment of the transmission dynamics in the first 425 confirmed cases found that 55% of cases before 1 January, 2020 were linked to the Huanan South China Seafood Market, whereas only 8.6% of cases after this date were linked to the market Reference. This confirms that person-to-person spread occurred among close contacts since the middle of December 2019, including infections in healthcare workers. One study of a family cluster of five patients in Shenzhen who had a history of travel to Wuhan City (with one other family member who did not travel to Wuhan city) found that person-to-person spread was possible in both hospital and family settings. [9] Nosocomial transmission in healthcare workers and patients has been reported in 41% of patients in one case series. [10]

COVID-19 SPREAD (TRANSMISSION):

The disease can spread from person to person through small droplets from the nose or mouth when an infected person coughs or exhales. These droplets land on objects and surfaces around the person. People can catch COVID-19 by touching these objects or surfaces, touching their eyes, nose or mouth. People may also get infected if they breathe in droplets from an infected person who coughs out or exhales droplets. This is why, it is important to stay more than 6-feet away from a person who is sick.

COVID-19 virus spreads easily from person to person by contact. Virus carrying droplets dry fast enough to form droplet nuclei and remain airborne eventually landing on different surfaces. SARS-CoV-2 has been detected in aerosols for up to three hours and on plastic and stainless-steel surfaces for up to three days. [11]

Researchers from national institute of health published in NEJM that the virus can survive for 24 hours on cardboard, 4 hours on copper, two days on steel, three days on plastic and a few hours in droplets from the air. Besides, the virus is known to survive longer in the presence of mucus and other bodily fluids. [12]

Droplets are small particles between 1-5 μ and they can travel up to 3m. They can adhere to surfaces like plastic crates of vegetables and other surfaces. They can remain viable for few hours until it finds the human host where it multiplies. However, there are studies that have published reports on Microdroplets which are smaller than 5 μ and can travel farther than 3m and remain viable on surfaces for longer periods. Anecdotal reports suggest that some people can act as super spreaders early in the course of their infection. These individuals can pass the infection on to large numbers of contacts, including healthcare workers Reference. This phenomenon is well documented for infection such as SARS and Ebola virus infection, and more recently with MERS. [13][14] Some of these individuals are also super shedders of virus, but the reason underlying super spreader events are often more complex than just excess virus shedding and can include a variety of Spelling error and environmental factors. [13]

It is known whether perinatal transmission via breastfeeding is possible but based on data from the SARS and MERS outbreaks, this is unlikely. [15] Retrospective review of pregnant women with COVID-19 found that there is no evidence for intrauterine infection caused by vertical transmission in women who develop the infection late in pregnancy Reference. However, there is currently a lack of data about the risk of transmission to the newborn during vaginal delivery. [16][17]

Pathophysiology:

Current estimates of the incubation period range from 1 to 14 days, according to the WHO and the US Centers for Disease Control and Prevention.[18][19]. The median incubation period has been estimated to be 5 days.[19] Transmission may be possible during the incubation period.[20] Preliminary reports suggest that the reproductive number (R_0), the number of people who acquire the infection from an infected person, is approximately 2.2.[9][21] However, as the situation is still evolving, the R_0 may actually be higher or lower. R_0 of a virus is defined as the number of people that a single person can transmit the virus.

In the case of COVID-19, it is 2.7-3.25 (Italian data) Reference. In China, the number was calculated to be 3.28. This means that every person has the potential to transfer infection to at least three people. R_0 can be altered through administrative and community intervention. This is an extremely important fact and is one of the basics of our present stand of social distancing and lockdown. By increasing the physical separation between individuals, we can reduce R_0 .

In other words, R_0 of any virus is not a fixed number. Just like the attack rate of the virus, R_0 also can be modified according to the nature and the behavior of the target population. Case Fatality Rate (CFR) is defined as the people who will die if a hundred people were to get the infection. At this time, in Europe, the case fatality rate is 5.4%. Reference

While the pathophysiology (P should be small) of this condition is currently unknown, a structural analysis suggests that the virus may be able to bind to the angiotensin-converting enzyme-2 (ACE2) receptor in humans, which suggests that it may have a similar pathogenesis to SARS.[22] However a unique structural feature of the spike glycoprotein receptor binding domain of SARS-Co-2 (which is responsible for the entry of the virus into host cells) confers potentially higher binding affinity for ACE2 on host cells compared to SARS-CoV. [23] A furin like cleavage site has been identified in the spike protein of the virus; this does not exist in other SARS- like coronaviruses.[24]

In the case of patients on hypertensive drugs and with chronic underlying health conditions on therapy might be on blood thinners that increases the ANGIOTENSIN CONVERTING ENZYME-2 receptors in humans Reference and thus allow easy binding to coronavirus 2019 when exposed to the droplets that contain the virus or the hands that are soiled with virus laden droplets Reference.

Primary prevention:

The only way to prevent infection is to avoid exposure to the virus and people should be advised to wash hands often with soap and water or an alcohol-based hand sanitizer and avoid touching the eyes, nose, and mouth with unwashed hands.[25] Also avoid close contact with people (i.e., maintain a distance of at least 1 meter [3 feet]), particularly those who have fever or cough or sneezing

Practicing respiratory hygiene (i.e., cover mouth and nose when coughing or sneezing, discard tissue immediately in a closed bin, and wash hands) is important Seeking medical care early if they have a fever, cough and breathing difficulty and sharing their previous travel and contact history with their healthcare provider are important. Avoiding direct unprotected contact with live animals and surfaces in contact with live animals when visiting live markets in affected areas is essential.

Avoiding the consumption of raw or undercooked animal products, and handling raw meat, milk, or animal organs with care as per usual good food safety practices are important.[WHO: coronavirus disease (COVID-19) advice for the public][26]

COMMUNITY CARE:

Sneezing or coughing on the inner side of our elbow and not into our hands must be kept in mind. Using a tissue and throwing it away immediately is recommended. Avoiding travel or visiting crowded places if we are sick care recommended. Wearing a mask if we are sick and also if we are taking care of someone with the symptoms is important. Practicing social distancing, which means avoiding group and social gatherings, theatre outings, retail stores, gyms, malls, mass transport systems (crowded buses, metro trains, etc.) are important.

When we are not well, we have to seek immediate medical attention. If we have fever, cough or difficulty in breathing we must stay indoors. We must call the nearest health center or call 011-23978046 and follow their advice. If we have come in contact with a confirmed case or a suspect case, we must follow the home quarantine period for 14 days. During the quarantine period, we must (strictly) follow the hand hygiene rules and avoid sharing household items like utensils, clothes, towels etc. Within the family members.

Medical masks:

The WHO does not recommend that people wear a medical mask in community settings if they do not have a respiratory symptom as there is no evidence available on its usefulness to protect people who are not ill. However, masks may be worn in some

countries according to local cultural habits. Individuals with fever respiratory symptoms are advised to wear a mask, particularly in endemic areas.[28-]It is mandatory to wear a medical mask in public in certain areas of China and local guidance should be consulted for more information.

Masks lower the chances of coronavirus entering the respiratory system through droplets still in the air from an infected person. Reducing the chances of inhaling the virus by wearing a protective mask is possible. The masks can be cleaned thoroughly using a combination of approaches that use heat, UV light, water, soap and alcohol. This is vital to stop its spread.

Homemade reusable masks only reduce the chances of inhaling droplets still in the air from infected person. They do not give full protection. Homemade reusable masks must be washed and heated each day, as instructed. Reuse without washing should be done. Disposable masks should not be washed and re-used. They must be disposed according to instructions. Provide citations to all sentences

The key differences between disposable and homemade cotton masks are related to their single or multiple use and their effectiveness.

Screening and quarantine:

People travelling from areas with a high risk of infection may be screened using questionnaires about their travel, contact with ill persons, symptoms of infection, and / or measurement of their temperature. Combined screening of airline passengers on exit from an affected area and on arrival elsewhere has been relatively ineffective when used for other infections such as Ebola virus infection, and has been modeled to miss up to 50% of cases of COVID-19, particularly those with no symptoms during an incubation period, which may exceed 10 days .[28] Symptom-based screening processes have been reported to be ineffective in detecting SARS-CoV-2 infection in a small number of patients who were later found to have evidence of SARS-CoV-2 in a throat swab.[29]

Enforced quarantine has been used in some countries to isolate easily identifiable cohorts of people at potential risk of recent exposure (e.g. groups evacuated by aero plane from affected areas, or groups on cruise ships with infected people on board). The psychosocial effects of enforced quarantine may have long-lasting repercussions [30][31].

Vaccine:

There is currently no vaccine available. Vaccines are in development, but it may take up to 12 months before a vaccine is available.[32] An mRNA vaccine (mRNA-1273) has been shipped to the National

Institute of Allergy and infectious Diseases for phase I clinical trials in the US, with a start date of 6 March 2020. [33]

Secondary prevention:

Early recognition of new cases is the cornerstone of prevention of transmission. Immediately, all suspected and confirmed cases must be isolated. We must implement recommended infection prevention and control procedures according to local protocols, including standard precautions at all times, and contact, droplet and airborne precautions while the patient is symptomatic. [34] We must report all suspected and confirmed cases to local health authorities.

Detailed guidance on infection prevention and control measures are available with the WHO and the Centers for Disease Control and Prevention. [35][36]The Indian government has been notified by IMA about 1) the urgent need to ramp up production of PPE(Personal Protective Equipment), 2) Cohosting (the process of identifying places to admit patients after existing facilities become full) and 3) to declare hospitals as special zones where armed police aid posts should be present and there will be zero tolerance of altercations of any kind. Reference

Step-by-step diagnostic approach:

Early recognition and rapid diagnosis are essential to prevent transmission and provide supportive care in a timely manner. There is a high index of clinical suspicion for COVID-19 in all patients who present with fever and/or respiratory symptoms and who report a travel history to an affected area or close contact with a suspected or confirmed case in the 14 days prior to symptom onset. Evaluation should be performed according to pneumonia severity indexes and sepsis guidelines (If sepsis is suspected) in all patients with severe illness.

Infection prevention and control:

Triaging all patients on admission and immediately isolating all suspected and confirmed cases in an area separate from other patients are important. Appropriate infection prevention and control procedures must be implemented. Screening questionnaires may be helpful. All suspected and confirmed cases must be reported to local health authorities.

The WHO recommends the following basic principles. [34] Immediately isolate all suspected cases in an area that is separate from other patients. Implement standard precautions at all times: Practice hand and respiratory hygiene, offer a medical mask to patients who can tolerate one, Wear personal protective equipment, prevent needle stick and sharps injury, practice safe waste management,

environmental cleaning, and sterilization of patient care equipment and linen.

Implement additional contact and droplet precautions until the patient is asymptomatic: Place patients in adequately ventilated single rooms; when single rooms are not available, place all suspected cases together in the same ward, wear a medical mask, gloves, an appropriate gown, and eye/ facial protection (e.g., goggles or a face shield), use single-use or disposable equipment. Consider limiting the number of healthcare workers, family members, and visitors in contact with the patient, ensuring optimal patient care and psychosocial support for the patient. Consider placing patients in negative pressure rooms, if available. Implement airborne precautions when performing aerosol-generating procedures. All specimens collected for laboratory investigations should be regarded as potentially infectious. It is important to disinfect inanimate surfaces in the surgery or hospital as patients may touch and contaminate surfaces such as door handles and desktops.[35] Isolation rooms and wards will have negative air pressure. Covid pneumonia patients must be immediately isolated.

CASE REPORT:

Taking a detailed history to ascertain the level of risk for COVID-19 and assessing the possibility of other causes are very important. Travel history is key; it is crucial for timely diagnosis and to prevent further transmission. The diagnosis should be suspected in patients with fever and / or signs / symptoms of lower respiratory illness (e.g., cough, dyspnoea) who reside in or have travelled to a country/area or territory reporting local transmission of COVID-19 or who report close contact with a confirmed or probable case of COVID-19 in the 14 days prior to symptom onset.[36][37][38]

Clinical presentation:

The clinical presentation resembles viral pneumonia, and the severity of illness ranges from mild to severe. Approximately 80% of patients present with mild illness, 14% present with severe illness, and 5% present with critical illness. Early reports suggest that illness severity is associated with older age and the presence of underlying health conditions.[39]

Some patients may be minimally symptomatic or asymptomatic. Large-scale screening in non-endemic areas may pick up more of these types of patients. A milder clinical course has been reported in cases identified outside of China, with most patients being healthy adults.[40] Based on an early analysis of case series, the most common symptoms are :Fever, Cough, Dyspnea, Myalgia, Fatigue; less common symptoms include: Anorexia, Sputum production

,Sore throat, Confusion, Dizziness, Headache, Rhinorrhoea, Chest pain, Haemoptysis, Diarrhoea, Nausea / Vomiting and Abdominal pain[41][42][10]

We need to perform a physical examination. Patients may be febrile (with or without chills/rigors) and have obvious cough and / or difficulty in breathing. Auscultation of the chest may reveal inspiratory crackles, rales, and/ or bronchial breathing in patients with pneumonia or respiratory distress. Patients with respiratory distress may have tachycardia, tachypnoea, or cyanosis accompanying hypoxia. Crackles / rales on auscultation (uncommon) may be present in patients with acute respiratory distress.

Patients may have nausea or diarrhea 1 to 2 days prior to onset of fever and breathing difficulties.[10] Most children present with mild symptoms, without fever or pneumonia. However, they may have signs of pneumonia on chest imaging despite having minimal or no symptoms.[15][43][44] Retrospective reviews of pregnant women with COVID-19 found that the clinical characteristics in pregnant women were similar to those reported for non-pregnant adults. [16][17] A retrospective case series of 62 patients in Zhejiang province found that the clinical features were less severe than those of the primary infected patients from Wuhan City, indicating that second-generation infection may result in milder infection. This phenomenon was also reported with MERS.[45] Early reports suggest that illness severity is associated with older age and the presence of underlying health conditions. [39]

Initial investigations:

Routine investigation with non-infective parameters is done. The following investigations can be done in all patients with severe illness: Pulse oximetry, ABG (as indicated to detect hypercarbia or acidosis), FBC, Comprehensive metabolic panel and Coagulation screen. Infective parameters such as inflammatory markers (serum procalcitonin and C-reactive protein), Serum troponin, Serum lactate dehydrogenase and Serum creatine kinase reveal if infection is present.

The most common laboratory abnormalities in patients hospitalized with pneumonia include leucopenia, lymphopenia, leukocytosis, and elevated liver transaminases Reference. Other abnormalities include neutrophilia, thrombocytopenia, decreased hemoglobin, decreased albumin, and renal impairment.[46][47][10]

Blood and sputum cultures:

Specimens should be collected prior to starting empirical antimicrobials if possible.

Molecular testing:

Molecular testing is required to confirm the diagnosis. Diagnostic tests should be performed according to guidance issued by local health authorities.

Real-time reverse-transcription polymerase chain reaction (RT-PCR) assays for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in all patients with suspected infection must be performed.[48]

Collecting lower respiratory tract specimens (sputum, endotracheal aspirate, bronchoalveolar lavage) where possible and depending upon the patient's condition is important. Upper respiratory tract specimens (nasopharyngeal aspirate or combined nasopharyngeal and oropharyngeal swabs) may be used if lower respiratory tract specimens cannot be collected. If initial testing is negative in a patient who is strongly suspected to have COVID-19, re-collection of specimens from multiple respiratory tract sites (nose, sputum, endotracheal aspirate) and retesting are essential.

Blood, urine, and stool specimens may also be used to monitor for the presence of the virus; however, sensitivity of diagnoses at these sites is uncertain. Also, to rule out infection with other respiratory pathogens (e.g., influenza, atypical pathogens) collecting nasopharyngeal swabs for testing is important. Serological testing is not available as yet, but assays are in development [49]

Imaging:

All imaging procedures should be performed according to local infection prevention and control procedures to prevent transmission.

Chest X-ray:

A chest x-ray can be taken in all patients with suspected pneumonia. Unilateral lung infiltrates are found in 25% of patients, and bilateral lung infiltrates are found in 75% of patients.[46][47][50]

Computed tomography (CT) chest:

A CT scan of the chest can also be taken. It is particularly helpful in patients with suspected pneumonia who have a normal chest x-ray in order to detect infiltrates with greater sensitivity. [50][51][52][53] Evidence of viral pneumonia on CT may precede a positive RT-PCR result for SARS CoV-2 in some patients.[54] CT is the primary imaging modality in China.[55] Nearly all patients in the initial cohort of 41 patients had bilateral multiple lobular and subsegmental areas of consolidation. The most important tests are RT-PCR and CT. [36]

Patients in the US who meet the following criteria should be evaluated as a PUI (Patients under investigation), reference

- A. Fever or signs/signs/symptoms of lower respiratory illness (e.g., cough or dyspnoea) and

any person, including healthcare workers, who (confirm grammar) close contact with a laboratory-confirmed case within 14 days of symptom onset: OR

- B. Fever and signs/symptoms of lower respiratory illness (e.g., cough or dyspnoea) requiring hospitalization and a history of travel from affected geographic areas (regions where widespread or sustained community transmission has been identified) within 14 days of symptom onset: OR
- C. Fever with severe acute lower respiratory illness (e.g. pneumonia, acute respiratory distress syndrome) requiring hospitalization and without an alternative explanatory diagnosis and no source exposure has been identified. (Why AND as capital?)

Fever may be subjective or confirmed. Close contact is defined as being within approximately 2 meters (6 feet) of a confirmed case for a prolonged period of time while not wearing personal protective equipment. Close contact is also defined as having direct contact with the infectious secretions of a case while not wearing personal protective equipment. [56]

Special patient groups:

Pregnant women:

Data on pregnant women are limited; however, they can generally be treated with the same supportive therapies detailed above, taking into account the physiological changes that occur with pregnancy.[57]

Children:

Data on children are limited; however, guidance for the treatment of children has been published [15]

INITIAL

For Suspected SARS-CoV-2 infection^{1st} infection prevention and control procedures, plus supportive care plus monitoring and Adjunct empirical antimicrobials are recommended.

ACUTE

For Confirmed SARS-CoV-2 infection with pneumonia or comorbidities ^{1st} hospital admission and infection Prevention and control procedure, plus supportive care plus monitoring and Adjunct mechanical ventilation and Adjunct experimental therapies are recommended. For cases without pneumonia or comorbidities ^{1st} consider home care and isolation. Plus, supportive care plus monitoring are recommended.

EMERGING ANTIVIRALS:

Various antivirals are on trial in patients with COVID-19 (e.g., oseltamivir, lopinavir/ritonavir, ganciclovir, favipiravir, baloxavirmarboxil, umifenovir, interferon alfa); however, there are no data to support their

use.[41] [47] [10] [58] [59] 60] [61] [62] Remdesivir shows in vitro activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has been used to treat patients in China, as well as the first patient in the US, [63] [64]. Clinical trials with remdesivir have started in the US and China. [65] [66] [67]

Intravenous immunoglobulin:

Intravenous immunoglobulin is being tried in some patients with COVID-19; however, there are no data to support this.[47]

Chloroquine and Hydroxychloroquine:

Chloroquine and hydroxychloroquine are being tried in some patients with COVID-19; however, there (Confirm grammar) no data to support this. [68] [69] [70] Chloroquine shows in vitro activity against SARS-CoV-2. [64] Chloroquine is likely to be added to the updated version of the Chinese management guidelines.[84]

Traditional Chinese Medicine:

Traditional Chinese Medicine is being tried in some patients with COVID-19 (e.g., Xue-Bi-Jing, Shuang-huang-Lian, Xin-Guan-2); however, there are no data to support this.[71] [72] [73]

The compassionate use of Hydroxychloroquine is reported among health care workers. This is primarily to stop the cytokine storming in the lungs that causes respiratory distress. The combination of Hydroxychloroquine and Azithromycin is used when the healthcare worker becomes symptomatic. The immune balance is disrupted and Covid pneumonia sets in. As of **26th March, 2020** no medication has been approved by the FDA for prevention or treatment of Covid 19 (Incomplete sentence). Randomized controlled trials to study chloroquine are ongoing including one from Oxford University as well as from the University of Minnesota. The results of these will be helpful when available. reference There is no biological plausibility for adding azithromycin, which itself is not meant to be used with chloroquine due to danger of cardiotoxicity. Besides, *in vitro* activity of a drug, in this subject Chloroquine is not a guarantee for *in vivo* effect. If it may be appropriate to quote a dangerous outcome of the initial excitement on Chloroquine was the tragic death of a man from Arizona who consumed chloroquine off the counter on his own to prevent COVID 19. reference

The use of antivirals generated results which were negative. An important trial done on Kaletra was published in the New England Journal of Medicine as a negative result. This was a combination of Lopinavir and Ritonavir, both of which were HIV medicines. The rising epidemic curve in the case of coronavirus 2019 can be flattened when a country as large as

India with a population of 1300 million or 130 crore and with a population density of 464/sq. km takes unprecedented assertive action. Fortunately, we are not too late in implementing strict stringent measures to enforce social distancing. The Kerala Government has taken this lock down very seriously having a population of 34 million with a population density of 860/sq.km. Mumbai alone has 22 million people at a density of 30,000/ sq.km.

REFERENCES:

1. Ren LL, Wang YM, Wu ZQ, et al., Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J (Engl) (2020)
2. Gorbalenya AE., Severe acute respiratory syndrome-related coronavirus: the species and its viruses – a statement of the Coronavirus Study group. February 2020 [internet publication]. Full text
3. World Health Organization. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020 [internet publication]. Full text
4. World Health Organization. Pneumonia of unknown cause-China. January 2020 [internet publication]. Full text
5. World Health Organization. Novel coronavirus – China. January 2020 [internet publication]. Full text
6. World Health Organization. Coronavirus disease (COVID-2019) situation reports. 2020 [internet publication]. Full text
7. National Health Commission of the People's Republic of China. 2020 [internet publication] Full text
8. Apollo Hospitals-Book COVID-19 CORONA VIRUS # Break Corona April 2020
9. Li Q, Guan X, Wu P, et al., Early transmission dynamics in Wuhan, China of novel coronavirus-infected pneumonia. N Engl J Med. (2020)
10. Wang D, Hu C, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA, (2020)
11. Evidence based answers to questions that doctors commonly ask about COVID-19, Dr Rajeev Jayadevan., 26 March 2020.
12. Masks for curbing the spread of SARS-CoV-2 coronavirus. A manual in homemade masks., Office of principle Scientific Advisor to GoI, March 30, 2020.
13. Stein RA., Super-spreaders in infectious diseases. Int J Infect Dis, 15(8):510-3 2011)
14. Hui DS., Super-spreaders events of MERS-CoV infection. Lancet, 388(10048):942-3, (2016)
15. Chen ZM, Fu JF, Shu Q, et al., Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World J Pediatr, (2020)
16. Chen H, Guo J, Wang C, et al., Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. Lancet, (2020)

17. Zhu H, Wang L, Fang C, et al., Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *TranslPediatr*, (2020)
18. World Health Organization. Novel coronavirus (2019-nCoV) situation report – 6 January 2020 [internet publication]. Full text
19. Centers for disease Control and Prevention. Coronavirus disease 2019 (COVID-19): symptoms. February 2020 [internet publication]. Full text
20. Yu P, Zhu J, Zhang Z, et al., A familial cluster of infection associated with the 2019 novel coronavirus indicating potential person-to-person transmission during the incubation period. *J infect Dis*, (2020)
21. Riou J, Althaus CL., Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. *Euro Surveill*, 25(4), (2020)
22. Lu R, Zhao X, Li J, et al., Genomic characteristics and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*, (2020)
23. Chen Y, Guo Y, Pan Y, et al., Structure analysis of the receptor binding of 2019-nCoV. *Biochem Biophys Res Commun*, pii, S0006-291X(20):30339-9, (2020)
24. Coutard B, Valle C, de Lamballerie X, et al., The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. *Antiviral Res*, 176:104742, (2020)
25. Centers for disease Control and prevention. Criteria to guide evaluation of patients under investigation (PUI) for COVID-19. February 2020 [internet publication]. Full text
26. WHO: coronavirus disease (COVID-19) advice for the public (external link)
1. 27. BMJ: facemasks for the prevention of infection in healthcare and community settings (external link)
27. World Health Organization Advice on the use of masks in the community, during home care and in health care settings in the context of the novel coronavirus (2019-nCoV) outbreak. January 2020 [internet publication]. Full text
28. Quilty BJ, Clifford S, CMMID nCoV working group 2, et al., Effectiveness of airport screening at detecting travelers infected with novel coronavirus (2019-nCoV). *Euro surveillance*, 25(5) (2020)
29. Hoehl S, Berger A, Kortenbusch M, et al., Evidence of SARS-CoV-2 infection in returning travelers from Wuhan, China. *N Engl J Med*, (2020)
30. Mahase E., China Coronavirus: what do we know so far? *BMJ*, 368:m308. Full text Abstract, (2020)
31. Brooks SK, Webster RK, Smith LE, et al., The psychological impact of quarantine and how to reduce it: rapid review of the evidence. *Lancet*, (2020)
32. National Institutes of Health. NIH officials discuss novel coronavirus that recently emerged in China. January 2020 [internet publication]. Full text
33. Clinicaltrials.gov. safety and immunogenicity study of 2019-nCoV vaccine (mRNA-1273) to treat novel coronavirus. ClinicalTrials.gov identifier NCT04283461. February 2020 [internet publication]. Full text
34. World Health Organization. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected. January 2020 [internet publication]. Full text
35. Kampf G, Todt D, Pfaender S, et al., Persistence of coronavirus in inanimate surfaces and its inactivation with biocidal agents. *J Hospinfect*, (2020)
36. Centers for Disease Control and prevention. Criteria to guide evaluation of patients under investigation (PUI) for COVID-19. February 2020 [internet publication]. Full text
37. World Health Organization .Global surveillance for human infection with coronavirus disease (COVID-19) February 2020 [internet publication]. Full text
38. CDC: flowchart to identify and assess coronavirus disease 2019 (COVID-19) (external link)
39. ZhonghuaLiu Xing BingXueZaZhi., The epidemiological characteristics of an outbreak of 2019 novel coronavirus disease (COVID-19) in China.Novel Coronavirus Pneumonia Emergency Response Epidemiology Team,41(2):145-151 (2020)
40. Chang, Lin M, Wei L, et al., Epidemiologic and clinical characteristics of novel coronavirus infections involving 13 patients outside Wuhan, China. *JAMA*, (2020)
41. Huang C, Wang Y, Li X, et al., Clinical features infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, (2020)
42. Chen N, Zhou M, Dong X, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*, (2020)
43. Shen KJ, Yang YH., Diagnosis and treatment of 2019 novel coronavirus infection in children: a pressing issue. *World J Pediatr*, (2020)
44. Wang XF, Yuan J, Zheng YJ, et al., Clinical and epidemiological characteristics of 34 children with 2019 novel coronavirus infection in Shenzhen [in Chinese]. *Zhonghua ErKeZaZhi*, 58(0): E008, (2020)
45. XuXW,Wu XX, Jiang XG, et al., Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-CoV-2) outside of Wuhan, China: retrospective case series. *BMJ*,368:m606 (2020)
46. Huang C, Wang Y, Li X, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*, (2020)
47. Chen N, Zhou M, Dong X, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* (2020)
48. World Health Organization Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases. January 2020 [internet publication]. Full text
49. Li Z, Yi Y, Luo X, Et al., Development and clinical application of a rapid IgM-IgG combined antibody test for SARS-CoV-2 infection diagnosis. *J Med Virol* (2020)
50. Song F, Shi N, Shan F, et al., Emerging coronavirus 2019-nCoV pneumonia. *Radiology*: 200274, (February 2020)

51. Lei J, Li J, Li X, et al. CT imaging of the 2019 novel coronavirus (2019-nCoV) pneumonia. *Radiology*:200236, (January 2020)
52. Chen L, Liu HG, Lui W, et al., Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia [in Chinese]. *ZhonghuaJie He He Xi ZaZhi*, 43(0):E005 (2020).
53. Shi H, Han X, Zheng C., Evolution of CT manifestations in a patient recovered from 2019 novel coronavirus (2019-nCoV) pneumonia in Wuhan, China. *Radiology*: 200269 (February 2020).
54. Xie X,Zhong Z, Zhao W, et al., Chest CT for typical 2019-nCoV pneumonia: relationship to negative RT-PCR TESTING. *Radiology*, (2020)
55. Jin YH, Cai L, Cheng ZS, et al., A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Mil Med Res*, 7(1):4 (2020)
56. CDC: criteria to guide evaluation of person under investigation (PUI) for COVID-19 (external link)
57. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. January 2020 [internet publication]. Full text
58. Chinese Clinical Trial Registry. A randomized, open-label, blank-controlled trial for the efficacy and safety of lopinavir/ritonavir and interferon-alpha 2b in hospitalized patients with 2019-nCoV pneumonia (novel coronavirus pneumonia, NCP). February 2020 [internet publication]. Full text
59. Chinese Clinical Trial Registry. A randomized, open-label, multi-centre clinical trial evaluating and comparing the safety and efficiency of ASCO9/ritonavir and lopinavir/ritonavir for confirmed cases of novel coronavirus pneumonia (COVID-19). February 2020 [internet publication]. Full text
60. Chinese Clinical Trial Register. Clinical study and efficacy of favipiravir in the treatment of novel coronavirus pneumonia (COVID-19). February 2020 [internet publication]. Full text
61. Chinese Clinical Trial. Clinical of arbidol hydrochloride tablets in the treatment of novel coronavirus pneumonia (COVID-19). February 2020 [internet publication]. Full text
62. Chinese Clinical Trial Register. Randomized, open-labelled, controlled trial for evaluating of the efficacy and safety of baloxavirmarboxil, favipiravir and lopinavir-ritonavir in the treatment of novel coronavirus pneumonia (COVID-19) patients. February 2020 [internet publication]. Full text
63. Holshue ML, DeBolt C, Lindquist S, et al., First case of 2019 novel coronavirus in the United States. *NEngl J Med*, (2020)
64. Wang M, Cao R, Zhang L, et al., Remdesivir and cloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*, (2020)
65. ClinicalTrials.gov. Mild/moderate 2019-nCoV remdesivir RCT. ClinicalTrials.gov identifier: NCT0425664. February 2020 [internet publication]. Full text
66. ClinicalTrials.gov. severe 2019-nCoV remdesivir RCT. ClinicalTrials.gov identifier: NCT04257656. February 2020 [internet publication]. Full text
67. ClinicalTrials.gov. Adaptive COVID-19 treatment trial. ClinicalTrials.gov identifier: NCT04280705 February 2020 [internet publication]. Full text
68. Chinese Clinical Trial Registry. A prospective, Open-label, multiple-center study for the efficacy of chloroquine phosphate in patients with novel coronavirus pneumonia (COVID-19). February 2020 [internet publication]. Full text
69. Chinese Clinical Trial Registry. Therapeutic effect of hydroxychloroquine on novel coronavirus pneumonia (COVID-19). February 2020 [internet publication]. Full text
70. ZhonghuaJie He He Hu Xi ZaZhi., Expert consensus on Chloroquine phosphate for the treatment of novel coronavirus pneumonia [in Chinese]. Multicenter Collaboration Group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for Chloroquine in the Treatment of Novel Coronavirus Pneumonia, 43(0):E019, (2020)
71. Gao J, Tian Z, Yang X., Breakthrough: chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*, (2020)
72. Chinese Clinical Trial Registry. A prospective comparative study for Xue-Bi-Jing injection in the treatment of novel coronavirus pneumonia (COVID-19). February 2020 [internet publication].
73. Chinese Clinical Trial Registry. A Randomized, open-label, blank-controlled, multicenter trial for Shuang-Huang-Lian oral solution in the treatment of novel coronavirus pneumonia (COVID-19). February 2020 [internet publication]. Full text
74. Chinese Clinical Trial Registry. A clinical observational study for Xin-Guan-2 formula in the treatment of suspected novel coronavirus pneumonia (COVID-19). February 2020 [internet publication].