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Review Article

Insight into the COVID-19 Outbreak: Current Intervention Strategies

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Abstract

The outbreak of the coronavirus disease (COVID-19) was first reported to the World Health Organization (WHO) on December 31, 2019 from Wuhan city of China. SARS-CoV-2, the causative agent of COVID-19 is an enveloped RNA virus, from the genus Beta-coronavirus. As of April 5th, 2020 more than 1,235,730 cases and 67,195 deaths have been reported globally. This review article discuss the latest updates and essential information about the COVID-19 outbreak including the current pharmaceutical and non-pharmaceutical interventions.

Keywords: COVID-19; World Health Organization (WHO); Betacoronavirus

Covid-19 outbreak

The outbreak of the novel coronavirus disease (COVID-19) is a major public health emergency of the 21st century. Three months ago no one knew about the existence of the COVID-19 and now the virus has spread to almost every country of the world. As of April 5th, 2020 more than 1,235,730 cases and 67,195 deaths have been reported globally, with rapid growth of the numbers in many countries. Human coronavirus were first discovered in mid-1960s and are named as coronaviruses because of the crown-like spikes on their surface. It often occurs in animals and in rare cases, it can spread to humans. There are seven coronaviruses that can infect humans, the 229E (Alphacoronavirus), NL63 (Alphacoronavirus), OC43 (Betacoronavirus), HKU1 (Beta coronavirus), MERS-CoV (the Betacoronavirus that causes Middle East Respiratory Syndrome, or MERS), SARS-CoV (the Betacoronavirus that causes severe acute respiratory syndrome, or SARS), SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19) [1]. People who are at more risk from the COVID-19 are older people and people with underlying medical conditions like diabetes, high blood pressure, heart diseases, renal failure, liver diseases, immunocompromised people such as those on cancer treatments and people with asthma (and other lung diseases). A wide spread of the COVID-19 started in December, 2019 the origin of which is linked to the live animal market in Wuhan city of China, where some individuals have infected by this virus or may have used infected animals or birds as a source of food and now it is spreading from human to human. The WHO has declared this outbreak of virus, a global pandemic on March 11, 2020 (An epidemic that has spread over several countries and is affecting large number of individuals). The US declared the outbreak as a public health emergency on February 1, 2020.

How does the coronavirus spread?

We are still learning how the COVID-19 disease spreads. The virus mainly spreads from person-to-person through the respiratory droplets produced when an infected person coughs or sneezes. These droplets are heavy and they quickly fall to the ground/surfaces. These droplets can land in the mouths or noses of people who are within 1 to 2 meters (3 to 6 feet) of someone who is ill and possibly be inhaled into the lungs. The virus may live on the surfaces that people have coughed or sneezed on. As per the New England Journal of Medicine, the virus may be live in the air for 3 hours, on copper surface for 4 hours, on cardboard for 24 hours, on stainless steel surfaces for 2 - 3 days and on polypropylene plastic for up to 3 days [2]. As per the recent study published in the Journal of Hospital Infection, an increase in the temperature by 18-degree Fahrenheit from 68 degrees to 86 degrees, decreased the life span of virus by at least half [3]. As per new research, the increase in the relative humidity reduces the spread of the virus between people [4]. It is probable that person can be infected with the COVID-19 by touching a surface that has virus on it and then touching their own mouth, nose or eyes. According to the report published on ccn.com on March 30, 2020, Japanese scientist found a third transmission route for the coronavirus spread. They found that a simple

conversation in close proximity with the infected person without cough and sneeze could spread the virus. This transmission mechanism can be called as micro droplet aerosolization infection. Micro-droplets which are produced when we talk loud or breathe heavily, carry many viruses and when the people around us inhale them they get infected. The risk of infection through the micro-droplet transmission is greater in a close place with poor ventilation [5].

There are three stages of the transmission of the COVID-19. In the first stage, the virus is imported into the country by travelers. Stage two is the local transmission of the disease when person can get infection from known sources. Stage three is the community transmission, in this stage the source of the infection is not known and the new positive cases can no longer be traced to diagnosed cases.

Symptoms

As per the Centers for Disease Control and Prevention (CDC) and the WHO, the most common symptoms reported so far by the patients are fever, dry cough, shortness of breath, tired feeling, runny nose, aches and pains, sore throat, headaches, diarrhea, nausea. However, as per CDC, it may take 2 to 14 days for symptoms to appear.

What happens to your body when virus attacks?

The lungs are usually affected first. Some people show only minor respiratory symptoms, while in some cases there is a severe lung damage. More frequently, the COVID-19 patients showed a development of the syndrome called the acute respiratory distress syndrome (ARDS). In ARDS the fluid from the small blood vessels get leaked into the lungs and accumulate into the air sacs or alveoli which makes it difficult for the lungs to transfer oxygen to the blood. Few people reported the gastrointestinal symptoms like nausea or diarrhea. COVID-19 can also affect the heart and the blood vessels. The blood supply to the tissues gets low and the patient may show irregular heart rhythms. Immune system of the body responds by attacking the virus and helps body to get rid of the infection, but sometimes it also cause collateral damage in the body. The immune system of the body produce cytokines to combat infection, but if lot of cytokines are released in the body, it can cause intense inflammatory response, sometimes called as cytokines storm [6].

Safety guidelines

CDC recommended that everyone should cough or sneeze into their elbows or use a tissue paper to cough or sneeze. As per the guidelines published by Johns Hopkins University, the virus is very fragile and its outer layer is made up of a thin fat layer. Use of soap or detergent is sufficient to cut the fat layer, the protein molecules disperses and breaks down to kill the virus. Thus, washing the hands often with soap and warm water for 20 to 30 seconds is recommended. Alcohol 65% or above helps to dissolve the external lipid layer of the virus and that is why use of an alcohol-based hand sanitizer is recommended [7].

As per research, 0.1% sodium hypochlorite or 62 to 71% ethanol significantly reduces coronavirus infectivity within 1 min exposure time [3]. It is recommended to avoid touching your eyes, nose or mouth and to stay away from people who are sick or have been in contact with someone who is sick. It is not recommended by the WHO nor by the CDC to wear mask to protect yourself from getting sick, but people who are sick or who are caregivers should wear it. The virus needs cold weather, moisture and darkness to stay stable. The dehumidified, dry, warm and bright environment will destroy it faster. UV light effectively breaks down the virus protein. The virus cannot enter into the body through the healthy skin.

Structure of the corona virus

The corona viruses are spherical in shape and have spikes on its surface [8]. The virus can alter their morphology, biological functions or reproductive modes as per environmental conditions. The diameter of the virus particles is 120 nm [9]. The viral envelop is made-up of a lipid bilayer and inside the envelop there is a nucleocapsid, which is attached to the positive-sense single-stranded RNA genome [10]. The virus is protected by the lipid bilayer envelope, membrane proteins, and nucleocapsid when it is outside the host cell [11]. The spikes on the surface of the virus are proteins which bind to receptors on the human cell surface called angiotensin-converting enzyme 2 (ACE2) and undergo a structural change which allows the viral membrane to fuse with the host cell membrane. The viral genes thus enters in to the host cells to be copied and produce more viruses in the host [12].

Figure 1: The electron microscopic image of the SARS-CoV-2 [12].

Interventions

Pharmaceutical interventions (PI)

World health organization wants to repurpose the drugs that have already been approved for other diseases and have acceptable safety profiles rather than developing a new drugs from scratch and testing them. Following candidates are under clinical trial studies for the treatment of COVID-19 disease.

Remdesivir: An antiviral drug that has received a lot of attention is remdesivir (1, figure 2). Scientist all over the world are testing it to see if it can be used to treat COVID-19. So far the results are convincing and suggests that remdesivir may help limit the reproduction and spread of these viruses in the body. Remdesivir is a prodrug which metabolizes into its active form GS-441524. GS-441524 interferes with the action of viral RNA polymerase causing a decrease in viral RNA production. Animal studies have shown that the drug was effective in treating the corona virus. Remdesivir is under clinical trials in China and United States [13].

Lopinavir and ritonavir: A combination of the two HIV inhibitors, lopinavir and ritonavir (2, figure 2), is also under clinical trial. Lopinavir most likely inhibits one or more of the coronavirus proteases, while the ritonavir was initially intended as protease inhibitor but was found to boost the half-life of lopinavir by inhibiting cytochrome P450 [14,15].

Chloroquine and hydroxychloroquine: Studies indicates that two related drugs chloroquine and hydroxychloroquine (3, figure 2), both kills the COVID-19 virus in the laboratory dish. Two mechanism of actions are proposed for these drugs. The COVID-19 virus enters into the host cell by binding to a cell surface enzyme called angiotensin-converting enzyme 2 (ACE2). Chloroquine and hydroxychloroquine may reduce the glycosylation of the ACE2, thereby preventing the virus from effectively attaching itself to the host cell and thus inhibit the entry of virus into the cell and stops its multiplication [16]. Secondly, even if the virus manage to enter into the host cell, these drugs kills it before it multiplies. Scientists across the world are working on these two drugs to see if these can work in humans to treat COVID-19 disease and we should have solid answer within a few months [17,18].

Favipiravir: The antiviral drug Favipiravir (4, figure 2), is also approved for use in the clinical trials for treating coronavirus disease (induce) pneumonia [19]. The mechanism of action of Favipiravir is thought to be related to the selective inhibition of viral RNA-dependent RNA polymerase [20].

Galidesivir: Galidesivir (5, figure 2), is a nucleoside RNA polymerase inhibitor designed to disrupt the viral replication process. Galidesivir is one of several antiviral drugs being tested for coronavirus disease 2019 [21].

Darunavir/cobicistat: Darunavir (6, figure 2)/Cobicistat (7, figure 2) combination is one of the several antiviral drugs being tested for coronavirus disease 2019 [21]. Darunavir is an HIV protease inhibitor and cobicistat increases the effectiveness of darunavir by blocking its metabolism by the enzyme CYP3A.

Baricitinib and *ruxolitinib*: Both baricitinib (8, figure 2) and ruxolitinib (9, figure 2) are anti-Janus kinase inhibitor (anti-JAK) which acts against JAK1 and JAK2. Both of them reduces the passage of the virus into target cells and inhibit the JAK1- and JAK2-mediated cytokine release [22].

Camostat: Camostat (10, figure 2) Mesilate is a potent serine protease inhibitor and it blocks the entry of virus into the host cells [23].

Fingolimod: The sphingosine-1-phosphate receptor regulators Fingolimod (11, figure 2) (FTY720) is an effective immunology modulator. Fingolimod is being tested as a treatment for COVID-19 associated ARDS [24].

Umifenovir: Umifenovir (12, figure 2) is a membrane fusion inhibitor targeting viral entry in to the host cells. It is being considered in a Phase IV clinical trial for pneumonia associated with COVID-19 [25].

Thalidomide: Thalidomide (13, figure 2) will be used in two different clinical trials studies against COVID-19 [26]. The anti-inflammatory action of the thalidomide is due to its ability to speed up the degradation of messenger RNA and thus reduce tumor necrosis factor-α (TNFα). Furthermore, thalidomide can also increase the secretion of interleukins and activate natural killer cells.

Studies are underway in China to determine if the high doses of vitamin C helps in the speedy recovery, however, so far there is no convincing evidence found that it works for COVID-19 infections [17].

About 35 companies and academic institutions are working on to make a vaccine for the COVID-19 disease. Few of them are at the animal research stage and will do the human trials later in the year. A part or all of the pathogen is injected into the human body at low dose to prompt the system to produce antibodies to the pathogen. The vaccine cannot cause the COVID-19 disease, but contains a harmless genetic code copied from the virus that causes the disease. Even if the scientist are able to develop a vaccine this year, these vaccines still need to be produced on large scale. Which

Figure 2: Drugs under clinical trial studies for the treatment of COVID-19.

means, more realistically it will not be ready to use for masses until at least the middle of the next year.

Non- pharmaceutical interventions (NPIs)

Two fundamental non-pharmaceutical intervention strategies proposed to stop the spread of pandemic of COVID-19 are mitigation and suppression. Mitigation is one of the most readily available interventions to help slow transmission of the virus in communities. It is a set of actions taken to help slow the spread of respiratory virus infections and is especially important before a vaccine or drug becomes widely available. Few of the important mitigation strategies published by CDC includes: 1. Know the signs and symptoms of COVID-19 and if you are sick stay at home, call your health care provider's office in advance of a visit, limit movement in the community, limit visitors. 2. Know what additional measures those at high-risk and who are vulnerable should take. 3. Implement personal protective measures (e.g. stay home when sick, hand washing, respiratory etiquette, clean frequently touched surfaces daily) etc [27]. Although, the mitigation strategy would help in slowing of the spread but would not be helpful in stopping the pandemic.

Suppression on other hand focuses on reversing pandemic, reducing number of cases and maintaining the situation for long time. Suppression would involve combinations of case isolation in the home, voluntary home quarantine, social distancing of entire population and closure of schools and universities. A recent analysis from the University of Pennsylvania estimated that social-distancing measures can reduce infection rates by 95%. As per Stephen Kissler from Harvard University, "we need to be prepared to do multiple periods of social distancing".

Absence of these non-pharmaceutical interventions (NPIs) may lead to peak in mortality rate.

Beyond non- pharmaceutical interventions (NPIs)

The war against COVID-19 has to continue for a long time. Once interventions are relaxed after the pandemic, infections may begin to rise, resulting into epidemic in certain parts of the world. As long as the virus persists in some part of the world, there is a chance that a traveler may bring back the virus to the countries who has already eradicated it. This is already happening in the counties like China and Singapore. One strategy would be, the whole world should manage to simultaneously eradicate the COVID-19 infection, chances of which are very limited.

Asymptomatic transmission is a biggest challenge. Experts have mentioned that asymptomatic carriers are driving force in the community spread and we do not know who is an asymptomatic carrier of COVID-19. Hence there is a need to design successful strategies to prevent relapses post COVID 19 pandemic. One of the strategies could be to build-up individual's immune response and this may be achieved by modification of the diet by considering the seasonal regimes and supplementing with the anti-oxidants. Goal is to achieve equilibrium in body post COVID-19 pandemic. The United Kingdom initially was trying to consider the herd immunity strategy, but backed up from the initial plan after learning about the consequences through the models.

Conclusion

The outbreak of the novel coronavirus disease (COVID-19) is a major public health emergency. It has crashed economies throughout the world, shattered health-care systems, filled hospitals with patients and emptied public spaces. Clearly, the world was not ready to handle the pandemic like this. To contain this virus efforts should be made to identify infected people with the help of tests on a massive scale, isolate the infected ones, and trace those they've had contact with. Social distancing is the key to cut off chains of transmission. Avoiding the social distancing would be catastrophic. Apart from non-pharmaceutical interventions, a quick development of antiviral drugs and vaccines is a need of time. Clinical trial studies are underway. At least 12 potential COVID-19 treatments are being tested, including drugs already in use for HIV, malaria and antibody-rich plasma from people who have just recovered from COVID-19 disease. Re-

searchers and doctors around the world are tackling the problem with urgency and that is the only way to find a solution to this biggest problem. Use of multiple strategies to combat the COVID-19 disease is the need of the hour

Bibliography

1. National Center for immunization and Respiratory Diseases (NCIRD), D. of V. D. Coronavirus | Human Coronavirus Types | CDC (2020).
2. Van Doremalen N., *et al*. "Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1". *The New England Journal of Medicine* (2020).
3. Kampf G., *et al.* "Persistence of Coronaviruses on Inanimate Surfaces and Their Inactivation with Biocidal Agents". *Journal of Hospital Infection* (2020).
4. Wang J., *et al.* "High Temperature and High Humidity Reduce the Transmission of COVID-19". *SSRN Electron Journal* (2020).
5. Japanese Scientists Find New Coronavirus Transmission Route in Breakthrough Study (2020).
6. Tisoncik JR., *et al.* "Into the Eye of the Cytokine Storm". *Microbiology and Molecular Biology Reviews* (2012).
7. Article: Tips for Avoiding Coronavirus | OpEdNews (2020).
8. Goldsmith CS., *et al.* "Ultrastructural Characterization of SARS Coronavirus". *Emerging Infectious Diseases* (2004).
9. Fehr AR and Perlman S. "Coronaviruses: An Overview of Their Replication and Pathogenesis. In Coronaviruses: Methods and Protocols (2015).
10. Chang CK., *et al.* "The SARS Coronavirus Nucleocapsid Protein - Forms and Functions". *Antiviral Research* (2014).
11. Neuman BW., *et al.* "A Structural Analysis of M Protein in Coronavirus Assembly and Morphology'. *Journal of Structural Biology* 174.1 (2011): 11-22.
12. Novel coronavirus structure reveals targets for vaccines and treatments | National Institutes of Health (NIH) (2020).
13. NIH clinical trial of remdesivir to treat COVID-19 begins | National Institutes of Health (NIH) (2020).
14. Sham HL., *et al.* "ABT-378, a Highly Potent Inhibitor of the Human Immunodeficiency Virus Protease". *Antimicrobial Agents and Chemotherapy* (1998).
15. Dyall J., *et al*. "Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome: Current Therapeutic Options and Potential Targets for Novel Therapies". *Drugs* (2017).
16. Rolain JM., *et al.* "Recycling of Chloroquine and Its Hydroxyl Analogue to Face Bacterial, Fungal and Viral Infections in the 21st Century". *International Journal of Antimicrobial Agents* 30.4 (2007): 297-308.
17. Coronavirus Resource Center - Harvard Health (2020).
18. Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting - Full Text View – Clinical Trials. (2020).
19. Fujifilm Announces the Start of a Phase III Clinical Trial of Influenza Antiviral Drug Avigan (favipiravir) on COVID-19 in Japan and Commits to Increasing Production - Drugs.com MedNews (2020).
20. Jin Z., *et al.* "The Ambiguous Base-Pairing and High Substrate Efficiency of T-705 (Favipiravir) Ribofuranosyl 5′-Triphosphate towards Influenza A Virus Polymerase". *PLoS One* (2013).
21. Coronavirus outbreak: Top coronavirus drugs and vaccines in development (2020).
22. Stebbing J., *et al.* "COVID-19: Combining Antiviral and Anti-Inflammatory Treatments". *Lancet Infectious Diseases* (2020).
23. Hoffmann M., *et al*. "SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor". *Cell* 181.2 (2020): 271-280.
24. Fingolimod in COVID-19 - Full Text View – Clinical Trials (2020).
25. Senanayake SL. "Drug Repurposing Strategies for COVID-19". *Future Drug Discovery* (2020): 0010.
26. The Efficacy and Safety of Thalidomide in the Adjuvant Treatment of Moderate New Coronavirus (COVID-19) Pneumonia - Full Text View – Clinical Trials (2020).
27. HHS CDC. Implementation of Mitigation Strategies for Communities with Local COVID-19 Transmission (2020).