



OUTBREAK OF CORONA VIRUS

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ABSTRACT

This year 2020 have started with enormous fear and pessimism, mainland whole universe is suffering from a new respiratory virus, quite infamously known as Corona virus. Corona virus (COVID-19) is an enveloped RNA virus that is many times found in humans and wildlife creatures. A total six species of the virus, have been identified that infect humans. They are known to infect the neurological, respiratory, enteric and hepatic system. Few decennary have seen endemic out breaks in the form of Middle East Respiratory Syndrome coronavirus and Severe Acute Respiratory Syndrome coronavirus. Due to few, strain called SARS -CoV-2 virus. Most recent initially outbreak abandoned as pneumonia of rummy etiology in a fascicle of patients in Wuhan, China. Highly contagious disease is known as SARS-CoV-2 and has been gotten in a swift pandemic of COVID -19. SARS-CoV was transmitted from civet cats to human and MERS-CoV from dromedary camels to human. Its droplets do help in the transmission of the disease. Aged people and cardiac patients have more chances of getting infected by this severe respiratory disease. Hand wash is the best desisting from this respiratory virus. Primary and secondary health care provides a means to flourish awareness during this current pandemic. The clinical information for the fecund, legislation, repulsion and monitor of patients universally are most up-to-date. Avoid crowds with humid atmosphere, so try your best to remain away from any public gatherings and use mask to isolate yourself from others, preventing the spread of virus through each other's sputum. Take sufficient water to keep yourself hydrated and maintain good immune, also prefer taking some immunity boosters, keep away from stress, and sleep well. . Avoid medication without prescription and have more of proteinaceous food.

KEYWORDS: COVID-19, severe acute respiratory syndrome corona virus 2, epidemiology, public health, communicable diseases, emerging.

1) INTRODUCTION

The world Health Organization (WHO) has declared that corona virus 2019 (COVID-19) is a pandemic disease.^[1,3]

The 2019 novel corona virus or the severe acute respiratory syndrome coronavirus2 as it is now called SARS -CoV-2 is rapidly spreading from its origin in Wuhan, China.

These patients appearing with a constellation of symptoms such as fever, dyspnea, dry cough and radiological findings showed bilateral lung glassy opacities.^[1]

Recent epidemics of viral respiratory diseases in the world have started from China (except for MERS that originated in Saudi Arabia), and there are several possible reasons for this. From an economic perspective,

China has emerged as one of the leading countries in the production of various commodities, especially in the past decade, and have exchanged an enormous volume of trade, tourism and military transactions with other countries, there is no doubt that the virus would spread from here to other parts of the world.^[2-4]

Number of COVID-19 cases have risen substantially in the world compared to SARS and MERS, and it would probably take a long period of time to reduce the disease cases; meaning that control measures would have to be in place for a longer duration. WHO has announced that Corona virus epidemic is progressively increasing in three countries, including Italy, South Korea, and Iran. The shared string that links these three countries is the pandemic of MERS in 2013, which was transmitted through close human contacts.^[5-8]

Corona viruses are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East Respiratory Syndrome (MERS -CoV) and Severe Acute Respiratory Syndrome (SARS -CoV). Corona virus are transmitted from animals to humans and vice versa. This disease takes one- two weeks to show symptoms like cold, fever, dry cough, diarrhea etc.^[9-10]

In severe cases, it causes pneumonia, respiratory failure, renal failure etc.^[11]

COVID-19 was predominantly more prevalent among adults of more than or equal to 15 years of age, in early stages of the outbreak and proportion of confirmed cases among children was relatively small.

The mysterious virus is unfolding day by day. We must be aware of its symptoms and features. It's a novel virus. It's far different from the other Corona viruses. Along with treatment the Medical community is trying hard to understand the disease. But unfortunately we know very less of it till now. Vaccine trials are underway. So maintain social distancing and hand washing, are only solution we have deduced to until now.^[12-16]

Types of Coronavirus

Coronaviruses belong to the subfamily *Coronavirinae* in the family *Coronaviridae*. Different types of coronavirus vary, in terms of the severity of disease that they cause and how far they spread. Doctors currently recognize seven types of coronavirus that can infect humans. Common types are-

1. 229E (alpha coronavirus)
2. NL63 (alpha coronavirus)
3. OC43 (beta coronavirus)
4. HKU1 (beta coronavirus)

2) Virology

A single-stranded RNA-enveloped virus, targets cells through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor. Following receptor binding, the virus particle uses host cell receptors and endosomes to enter cells. A host type 2 transmembrane serine protease, TMPRSS2, facilitates cell entry via the S protein. Once inside the cell, viral polyproteins are synthesized that encode for the replicase-transcriptase complex. The virus then synthesizes RNA via its RNA-dependent RNA polymerase. Structural proteins are synthesized leading to completion of assembly and release of viral particles. These viral lifecycle steps provide potential targets for drug therapy. Promising drug targets include nonstructural proteins (eg, 3-chymotrypsin-like protease, papain-like protease, RNA-dependent RNA polymerase), which share homology with other novel corona viruses (nCoVs). Additional drug targets include viral entry and immune regulation pathways.^[17-19]

3) Epidemiology

The illness onset of the first laboratory-confirmed case of 2019-nCoV infection was on December 1, 2019 in Wuhan, China. Initially, an outbreak within a local market, the Huanan Seafood Market, infecting at least 41 people was reported. The local health authority issued an "epidemiologic alert" on December 31, 2019, and the market was shut down on January 1, 2020. A total of 59 suspected cases with fever and dry cough were referred to a designated hospital (the Jin Yin-tan Hospital). Of the 59 suspected cases, 41 patients were confirmed by next-generation sequencing or real-time reverse transcription-polymerase chain reaction (RT-PCR). Twenty-seven (66%, 27/41) patients had history of Huanan Seafood Market exposure. However, there is a caveat that the first case on December 1 did not show any history of Huanan Seafood Market exposure and the subsequent cases started on December 10, nine days later. In the following days, an outburst of enormous number of cases was speeding from Wuhan to the whole Hubei province. Subsequently, many cities and provinces were attacked by this virus. One of the reasons may be due to the heavy transportation of loads during the Chinese Lunar New Year (on January 25) period. The first exported case in Thailand was on January 13, 2020. However, the disease spread rapidly and globally. Not only familial clusters but also outbreaks in ocean liners were reported. As of February 6, 2020, a total of 28,276 confirmed cases with 565 deaths globally were documented by WHO, involving at least 25 countries. By the time, WHO issued Public Health Emergencies of International Concern (PHEIC) alarm on January 30, 2020. Many stringent quarantine procedures and fever surveillance were underway. The initial mortality rates for patients in the hospital were estimated to be 11%–15%, but more recent data were 2%–3%. It is very likely that person-to-person transmissions occur via droplets and contacts.^[20,21]

4) Transmission

The initial cases were presumably linked to direct exposure to infected animals (animal-to-human transmission) at a seafood market in Wuhan, China. However, clinical cases with diversity in exposure history have emerged. This helps us, further elaborate that human-to-human transmission of the virus is also possible. Therefore, human-to-human transmission is now considered the main form of transmission. Individuals who remain asymptomatic could also transmit the virus. However, the most common source of infection is symptomatic ones. Transmission occurs from the spread of respiratory droplets through coughing or sneezing. Data also suggest that close contact between individuals can also result in transmission. This also leads to the possibility of rapid transmission within closed spaces due to elevated aerosol concentrations.

SARS-CoV-2 has a basic reproduction number of 2.2. This suggests that a patient can transmit the infection to two other individuals. Current data suggests that the virus has an incubation period of three to seven days.^[22]

5) Etiology

Coronaviridae (coronaviruses) – SARS, MERS, 2019 novel coronavirus (2019-nCoV). Corona viruses (CoV) are a family of enveloped, positive-sense, single-stranded RNA (+ssRNA) viruses. They tend to cause mild upper respiratory diseases in humans. Of the 7 known species of CoV, only 3 are known to cause severe infections in humans.^[22]

Severe Acute Respiratory Syndrome Corona virus (SARS-CoV): emerged in 2003 in southern China from civet cats.^[22,23]

Middle East Respiratory Syndrome Corona virus (MERS-CoV): emerged in 2012 in Saudi Arabia from dromedary camels.^[22,23]

SARS-CoV-2: emerged in December 2019 in China possibly from bats or pangolins (still under investigation) 3.9% fatal (as of March 16, 2020, based on identified cases and may change) Clinical manifestation; Fever > 37,8°C (100,0°F), muscle pain, lethargy, cough, sore throat, malaise^[24-25], Shortness of breath/ pneumonia (direct viral or secondary bacterial) Mild infection: fever, dry cough, muscle pain, lethargy, dehydration.^[26]

Severe infection: high fever, shortness of breath, chest pain, hemoptysis.^[26]

Complications: pneumonia, ARDS, sepsis, multi-organ failure

NEC: Necrotizing enterocolitis ARDS: Acute respiratory distress syndrome.^[26-27]

The SARS-CoV-2 virion is ~125 nm in diameter, and its genome ranges from 26 to 32 kilo bases, the largest for an RNA virus. It has 4 structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N).^[27]

N protein forms a complex with RNA and aids in the viral assembly after its replication. S, E, and M proteins create the viral envelope.

S protein, is a club-shaped surface projection, giving the virus its characteristic crown-like appearance on electron microscope which is responsible for its viral entry into the human cell.^[28]

SARS-CoV-2 attaches to the host cell by binding its S protein to the receptor protein, angiotensin-converting enzyme 2 (ACE2). ACE2 is expressed by epithelial cells of the intestine, kidney, blood vessels, and present most abundantly in type II alveolar cells of the lungs. The virus induces a drop of ACE2 in human cells, possibly inducing lung damage.^[28]

The human enzyme transmembrane protease, serine 2 (TMPRSS2) is also used by the virus for S protein priming and to aid in membrane fusion.^[21]

CoV are zoonotic or transmitted to humans through animals. It is hypothesized that horseshoe bats are the natural reservoir of SARS-CoV-2 since its genome is 97% identical to that of a bat corona virus. The intermediate host is still unknown.^[23]

Once in humans, the virus is transmitted mainly via inhalation of respiratory droplets through coughing, sneezing, or talking of symptomatic individuals. In the air, larger droplets tend to drop towards the ground within 1 m (3 ft), while smaller droplets can travel as an aerosol cloud over 2 m (6 ft) and remain viable in the air for up to 3 hours under certain conditions. Other forms of transmission include.^[28]

Direct transmission through hand-to-face contact from infected surfaces Fecal-oral transmission is hypothesized (observed in SARS infection, but is still under investigation). Vertical transmission (mother-to-child) has not been reported.^[27-28]

Asymptomatic individuals are also infectious, albeit to a slightly lesser degree, posing a real challenge for contagion prevention.

Production of high viral loads Efficient and prolonged shedding of virions from the upper respiratory tract (URT) Median duration of viral RNA shedding from URT: 20 days.^[22]

Can remain infectious on surfaces outside a host from a few hours up to a few days. Viral life-span depends on the type of surface, temperature, and humidity levels.

6) Clinical Manifestations

COVID-19 has a mean incubation period of 5.2 days (95% confidence interval, 4.1–7.0). The infection is acute without any carrier status. Symptoms usually begin with nonspecific syndromes, including fever, dry cough, and fatigue. Multiple systems may be involved, including respiratory (cough, short of breath, sore throat, rhinorrhea, hemoptysis, and chest pain), gastrointestinal (diarrhea, nausea, and vomiting), musculoskeletal (muscle ache), and neurologic (headache or confusion). More common signs and symptoms are fever (83%–98%), cough (76%–82%), and short of breath (31%–55%). There were about 15% with fever, cough, and short of breath. Conjunctival injection was not reported in the early series and cases with age under 18 were few. After onset of illness, the symptoms are somehow mild and the median time to first hospital admission is 7.0 days (4.0–8.0). But the disease progresses to short of breath (~8 days), acute respiratory distress syndrome (ARDS) (~9 days), and to mechanical ventilation (~10.5 days) in about 39% patients. Patients with fatal disease develop ARDS and worsened in a short period of time and died of multiple organ failure. The mortality rate in the early series of hospitalized patients was 11%–15%, but the later statistics was 2%–3%.^[25-26]

The 2019-nCoV virus may enter the host through respiratory tract or mucosal surfaces (such as conjunctiva). Oral-fecal transmission has not been confirmed. The virus has a preferential tropism to human airway epithelial cells and the cellular receptor, like SARS, is ACE2. Theoretically lungs are the majorly involved organ.^[11-13]

7) Asymptomatic cases

Can transmit the virus

Represent >50% of all infections (still under investigation) May not develop any noticeable symptoms Anosmia, hyposmia, and dysgeusia have been reported in many laboratory-confirmed cases of patients that were otherwise asymptomatic. It has not been clearly determined how long asymptomatic individuals remain contagious after initial infection. Mild cases: Dry cough and moderate fever Common flu-like symptoms, including fatigue, malaise, runny nose, nasal congestion, and sore throat Less frequently: diarrhea, nausea, vomiting, diffuse abdominal pain, productive cough, headache, and muscle or joint pain

Recovery time: ~2 weeks.^[19-20]

Severe cases and complications

~1 in 6 people with COVID-19 experience clinical deterioration and/or develop a complication in the 2nd week of illness.

Median time from onset of symptoms to the onset of critical care/ICU transfer: 8-9 days

Patients develop dyspnea, high fever, chest pain, hemoptysis, respiratory crackles, and progressive respiratory failure

Recovery time: ~3-6 weeks.^[23-27]

8) Diagnosis

The U.S. CDC has developed criteria for persons under investigation (PUI). If a person is deemed a PUI, immediate prevention and infection control measures are undertaken. Epidemiological factors are used to assess the requirement of testing. These include close contact with a laboratory-confirmed patient within 14 days of symptoms or travel history to an infected area within 14 days of symptom onset.^[29]

The WHO recommends collecting samples from both the upper and lower respiratory tracts. This can be achieved through expectorated sputum, bronchoalveolar lavage, or endotracheal aspirate. These samples are then assessed for viral RNA using polymerase chain reaction (PCR). If a positive test result is achieved, it is recommended to repeat the test for re-verification purposes. A negative test with a strong clinical suspicion also warrants repeat testing.^[29]

Polymerase chain reaction (PCR) is currently the only test being used to confirm cases of COVID-19 infection and should be performed as soon as possible once a

person under investigation (PUI),^[20-21] is identified. The specimens used for testing include:

Nasopharyngeal (NP) and/or oropharyngeal (OP) swab (for mild or asymptomatic suspected cases)

NP is the first choice. OP swabs are acceptable only if other swabs are not available.^[27]

Can be negative initially. If suspicion of COVID-19 remains, retest every 2-3 days.

In severe cases, NP and OP swabs may be negative, while specimens from the lower respiratory tract are positive,^[22]

Sputum (for patients with productive cough, inducing is not recommended)

Bronchial and tracheal secretions or bronchoalveolar lavage (for patients receiving invasive mechanical ventilation).^[29]

During an ongoing COVID-19 outbreak, laboratory testing should be prioritized^[12-16] as follows according to the CDC:

Hospitalized patients with compatible signs and symptoms (especially those presenting with unexplained viral pneumonia or respiratory failure)

Healthcare professionals with compatible signs and symptoms.^[29-30]

Symptomatic individuals who are at high risk of developing a severe form of the disease or a complication (e.g., patients who are elderly, immunocompromised, or have chronic conditions)

Critical infrastructure workers with compatible signs and symptoms.^[30]

Any individual, including healthcare professionals, who had close contact with a suspect or laboratory-confirmed COVID-19 patient within 2 weeks of their symptom onset, or has a history of traveling within affected geographic areas in the last 2 weeks.^[20]

Individuals without symptoms.

Patients with COVID-19 present with the following laboratory and radiological findings. These are more pronounced and common in severe cases but can be present even in mild infections.^[32]

WBC count: leukopenia, leukocytosis, and lymphopenia (most common)

Inflammatory markers: ↑ LDH and ferritin

Liver markers: ↑ AST and ALT

Chest x-ray and CT: non-specific imaging findings most commonly found in atypical or organizing pneumonia, with a bilateral, peripheral, and/or basal distribution
Multiple areas of consolidation.^[30]

Ground-glass opacities (GGOs)

Crazy paving appearance (GGOs + inter-/interlobular septal thickening)

Bronchovascular thickening

In hospitalized COVID-19 patients with severe infections, regular laboratory testing.^[20-21] and imaging are necessary for the assessment of disease progression and complications.^[30]

CBC: severe cases present with advanced lymphocytopenia and thrombocytopenia

ABG: to assess levels of hypoxia.^[6-7] and acid-base balance

ARDS presents initially as hypoxemic respiratory failure with low PaO₂ and respiratory alkalosis, later progressing into hypercapnic respiratory failure.

Inflammatory markers:

↑ IL-6 and C-reactive protein in severe cases

↑ procalcitonin in bacterial coinfection,^[20] with pneumonia and/or sepsis

↑ lactate in sepsis and septic shock

Hemostasis tests

Prolonged PT and PTT times

↑ D-dimer in cardiac injury and septic shock

Assessment of organ function,^[20-26] abnormal findings may indicate multi-organ failure

Creatinine, urea, and BUN used to assess renal function

AST, ALT, GGT, and bilirubin used to assess hepatic function

Troponin and ECG used to assess cardiac function

Chest X-ray and CT: severe infections may also present

Pleural thickening and effusion

Lymphadenopathy.^[23]

Air bronchograms and atelectasis

Solid white consolidation

Differential Diagnoses.^[26]

Drinking a lot of fluids

Getting plenty of rest

Taking over-the-counter medicines

9) Testing of Corona Virus

- Swab test– In this case, a special swab is used to take a sample from your nose or throat
- Nasal aspirate – In this case, a saline solution will be injected into your nose and, then a sample is taken with a light suction
- Tracheal aspirate – In this case, a thin tube with a torch, also known as a bronchoscope, is put into your mouth to reach your lungs from where a sample is collected.
- Sputum Test – Sputum is thick mucus that gets accumulated in the lungs and comes out with a cough. During this test, you're required to cough up

sputum in a special cup or a swab is used to take a sample from your nose.

- Blood test – In this case, a blood sample is taken from a vein in the arm.

10) Treatment

Currently, there is no validated treatment for COVID-19. The main strategies are symptomatic and supportive care, such as keeping vital signs, antiviral and retro viral medications, maintaining oxygen saturation and blood pressure, blood plasma transfusion and treating complications, such as secondary infections or organs failure.^[7]

And currently no specific antiviral treatment for COVID -19 have been found. Early reports from China and France suggested that patients with severe symptoms COVID -19 improve more quickly when given hydroxychloroquine. Some doctors were using a combination of hydroxychloroquine and Azithromycin with some positive effect.^[15-20]

11) Prevention

Preventive measures must focus on optimizing infection control protocols, self-isolation, and patient isolation during the provision of clinical care. The WHO has advised against close contact with patients, farm animals, and wild animals. Patients and the general public must cover coughs and sneezes to help prevent aerosol transmission. Frequent hand washing with soap and water is also required. As an alternative measure, hand sanitizers can also be used. (20) Immunocompromised individuals are advised to avoid public gatherings. Emergency medicine departments must apply strict hygiene measures for the control of infections. Healthcare personnel must use personal protective equipment such as N95 masks, FFP3 masks, eye protection, gloves, and gowns.

It is now a global recommendation that all individuals are advised to help prevent the spread of COVID-19 infection. General recommendations include.^[20-23]

Home isolation and/or avoidance of public/crowded areas, whenever possible, minimize.^[16-18] the chance for exposure

Cover coughs and sneezes with a tissue or the inner elbow Wash hands regularly for at least 20 seconds with soap and water or sanitize them with an alcohol-based hand sanitizer that contains at least 60% alcohol.^[20]

Maintain 1–2 m (~3–6 ft) distance from other people, “social distancing”.^[30]

Regular cleaning of all ‘high-touch’ surfaces within the home The use of face masks is now recommended for the general population.

Face masks help prevent the wearer from becoming infected and, more importantly,^[26] prevent the wearer

from transmitting the disease (also known as “source control”).^[27]

Face masks and personal protective equipment, or PPE, are of special importance for healthcare personnel due to higher exposure to infected individuals as well as aerosol-generating procedures (AGPs). AGPs include the following:

Open suctioning of airways
Sputum induction
Cardiopulmonary resuscitation (CPR)
Endotracheal intubation.^[30-31] and extubation
Non-invasive ventilation (e.g., BiPAP, CPAP)
Bronchoscopy.

Results of PCR testing from at least 2 consecutive sets of paired nasopharyngeal and throat swab specimens collected \geq 24 hours apart (total of 4 specimens: 2 nasopharyngeal and 2 throat).

For at-home patients: negative results of PCR testing from at least 2 consecutive nasopharyngeal swab specimens collected $>$ 24 hours alert.^[35]

12) DISCUSSION

World Health Organization has brought pictorial posters to raise the awareness.

1. In the present date, there is no specific medicines recommended to prevent the new coronavirus.
2. Even the new coronavirus can stay few hours or several days on the surfaces. The virus will persist on a surface after being moved exposed to different conditions and temperature. If you think surface may be contaminated use a disinfectant to clean it. After that Clean your hands with alcohol based hand sanitizer.
3. There is no reason to believe that cold weather can defeat the new coronavirus.
4. Frequently cleaning your hands is the best way to protect yourself against COVID -19.
5. Don't be panicked, maintain social distance and take all precautions. (As per WHO)

13) Fact about Coronavirus Outbreak- DO's-

1. **Hand Wash-** washing hand after Coughing and sneezing, when caring for the sick, before, during and after preparing the food, before eating, after toilet use. Regular hand wash for 30 seconds will help you avoid germs or any kind of infection.
2. **Cover your mouth & Nose-** Covering your mouth and nose while sneezing or when anyone next to coughs or sneezes can do you a lot better. Coronavirus usually spreads through cough and covering your nose and mouth will save you from this epidemic.
3. **Consult a doctor if sick-** If you are suffering from a common cold, cough, nausea, vomiting, shortness of breath and fatigue make it a point to consult a doctor

at the earliest. Any of these symptoms could be a sign that you are suffering from the virus.

4. **Stay Indoors-**Avoid being in crowded places. An infected person can spread the virus instantly and crowded places is a good way to accomplish this. Make sure you wear full sleeves shirts with anti-pollution masks when you travel. Staying indoors is a rather safe option.

Don'ts

1. **Avoid close contact with anyone-** Do not get close to anyone, especially touching or laughing closely. Also, use anti-pollution masks when out with friends or family.
2. **Do Not Spit-** Spitting can increase the spread of the virus. Avoid spitting at in public and home. Also, avoid getting close to a sick person suffering from cold and cough.
3. **Avoid Using Public Transport-** Travelling by cab, flight, bus, train and tramp can get you infected. Use anti-pollution masks and carry a hand sanitizer with you everywhere. Consider travelling by your own vehicle and avoid public transport.
4. **Do Not Use over The Counter Medicines-** If you are suffering from dry cough, back pain, nausea and shortness of breath it is recommended that you consult a doctor rather than opt for self-medication that can leave you battling with a deadly illness.
5. **Don't Panic, take it Easy-** All you need to keep in mind is hygiene i.e. regular hand wash, use of anti-pollution masks and consult a doctor if you are sick.
6. **Don't Touch your Face-** Do not touch your face, nose and mouth often. This avoids the risks of developing the virus. Wash your hands with soap or hand sanitizer and this will do you good

14) CONCLUSION

According to above discussion COVID -19 is pandemic due to no specific vaccine or medicine to control spread over population. Hence maintain social distancing and hand sanitization to control spreading.^[30]

There are hundreds of corona viruses, most of which circulate in animals. Only seven of these viruses infect humans and four of them cause symptoms of the common cold. But, three times in the last 20 years, a corona virus has jumped from animals to humans to cause severe disease.^[31]

COVID-19, a new and sometimes deadly respiratory illness, is believed to have originated in a live animal market in China, has spread rapidly throughout that country and the world.^[32]

The covid -19 pandemic is spreading across the globe at an alarming rate.

It is a respiratory virus. It's transmission is done by droplets of water and mucus drops coming out by sneeze and cough of the infected ones.^[33]

Hand wash is the best prevention method from most of the respiratory virus adding to alcohol based hand sanitizer.

Protect yourself and other from getting sick, do not go to crowds, use masks.^[32]

Everyday people are making news about false claims to prevent corona, some say take arsenic, some say take basil leaves. Please don't believe in any such hearsays. Don't take medication without prescription.^[32]

Don't be panicked. But be aware and make others aware and take all precautions.^[32-35]

- STAY HEALTHY
- STAY SAFE
- STAY HOME.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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