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Question

1. Write a comprehensive review of the etiology of COVID-19, its pathogenesis, histopathological features and the current potential therapies to address it. Also, comment on the future of COVID-19 on public health.

The coronavirus disease (COVID-19) has been identified as the cause of an outbreak of respiratory illness in Wuhan, Hubei Province, China beginning in December 2019. As of 31 January 2020, this epidemic had spread to 19 countries with 11 791 confirmed cases. The coronavirus belongs to a family of viruses that may cause various symptoms such as pneumonia, fever, breathing difficulty, and lung infection. These viruses

are common in animals worldwide, but very few cases have been known to affect humans. The World Health Organization (WHO) used the term 2019 novel coronavirus to refer to a coronavirus that affected the lower respiratory tract of patients with pneumonia in Wuhan, China on 29 December 2019. The WHO announced that the official name of the 2019 novel coronavirus is coronavirus disease (COVID-19). And the current reference name for the virus is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was reported that a cluster of patients with pneumonia of unknown cause was linked to a local Huanan South China Seafood Market in Wuhan, Hubei Province, China in December 2019.

In response to the outbreak, the Chinese Center for Disease Control and Prevention (China CDC) dispatched a rapid response team to accompany health authorities of Hubei province and Wuhan city to conduct epidemiological and etiological investigations. The WHO confirmed that the outbreak of the coronavirus epidemic was associated with the Huanan South China Seafood Marketplace, but no specific animal association was identified. Scientists immediately started to research the source of the new coronavirus, and the first genome of COVID-19 was published by the research team led by Prof. Yong-Zhen Zhang, on 10 January 2020 . Within 1 month, this virus spread quickly throughout China during the

Chinese New Year a period when there is a high level of human mobility among Chinese people. Although it is still too early to predict susceptible populations, early patterns have shown a trend similar to Severe Acute Respiratory Syndrome (SARS) and Middle East respiratory syndrome (MERS) coronaviruses. Susceptibility seems to be associated with age, biological sex, and other health conditions (Fehr AR,2017).

COVID-19 has now been declared as a Public Health Emergency of International Concern by the WHO.

Aetiology

CoVs are positive-stranded RNA viruses with a crown-like appearance under an electron microscope (*coronam* is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. The subfamily *Orthocoronavirinae* of the *Coronaviridae* family (order *Nidovirales*) classifies into four genera of CoVs: Alphacoronavirus (alphaCoV), Betacoronavirus (betaCoV), Deltacoronavirus (deltaCoV), and Gammacoronavirus (gammaCoV). Furthermore, the betaCoV genus divides into five sub-genera or lineages.Genomic characterization has shown that probably bats and rodents are the gene sources of alphaCoVs and betaCoVs. On the contrary, avian species seem to represent the gene sources of deltaCoVs and gammaCoVs.

Members of this large family of viruses can cause respiratory, enteric, hepatic, and neurological diseases in different animal species, including camels, cattle, cats, and bats. To date, seven human CoVs (HCoVs) capable of infecting humans have been identified. Some of HCoVs were identified in the mid-1960s, while others were only detected in the new millennium.

In general, estimates suggest that 2% of the population are healthy carriers of a CoV and that these viruses are responsible for about 5% to 10% of acute respiratory infections.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a previously unknown betacoronavirus that was discovered in bronchoalveolar lavage samples taken from clusters of patients who presented with pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019.(Ren LL,*et al, 2020)*

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

SARS-CoV-2 belongs to the *Sarbecovirus*subgenus of the *Coronaviridae* family, and is the seventh coronavirus known to infect humans. The virus has been found to be similar to SARS-like coronaviruses from bats, but it is distinct from SARS-CoV and MERS-CoV.

A preliminary study suggests that there are two major types of the SARS-CoV-2 virus in China, designated L and S. The L type was found to be more prevalent during the early stages of the outbreak in Wuhan City and may be more aggressive (although this is speculative), but its frequency decreased after early January. The relevance of this finding is unknown at this stage and further research is required.

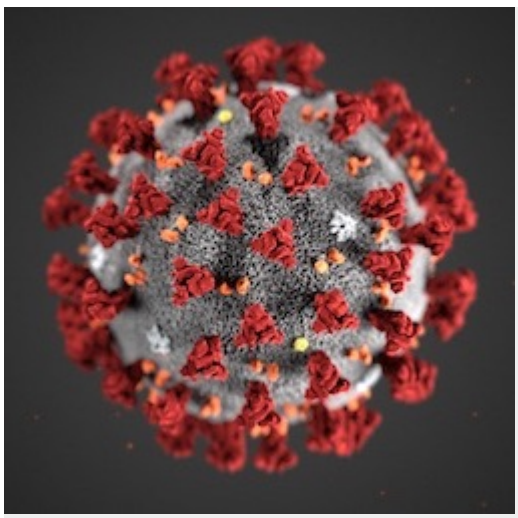
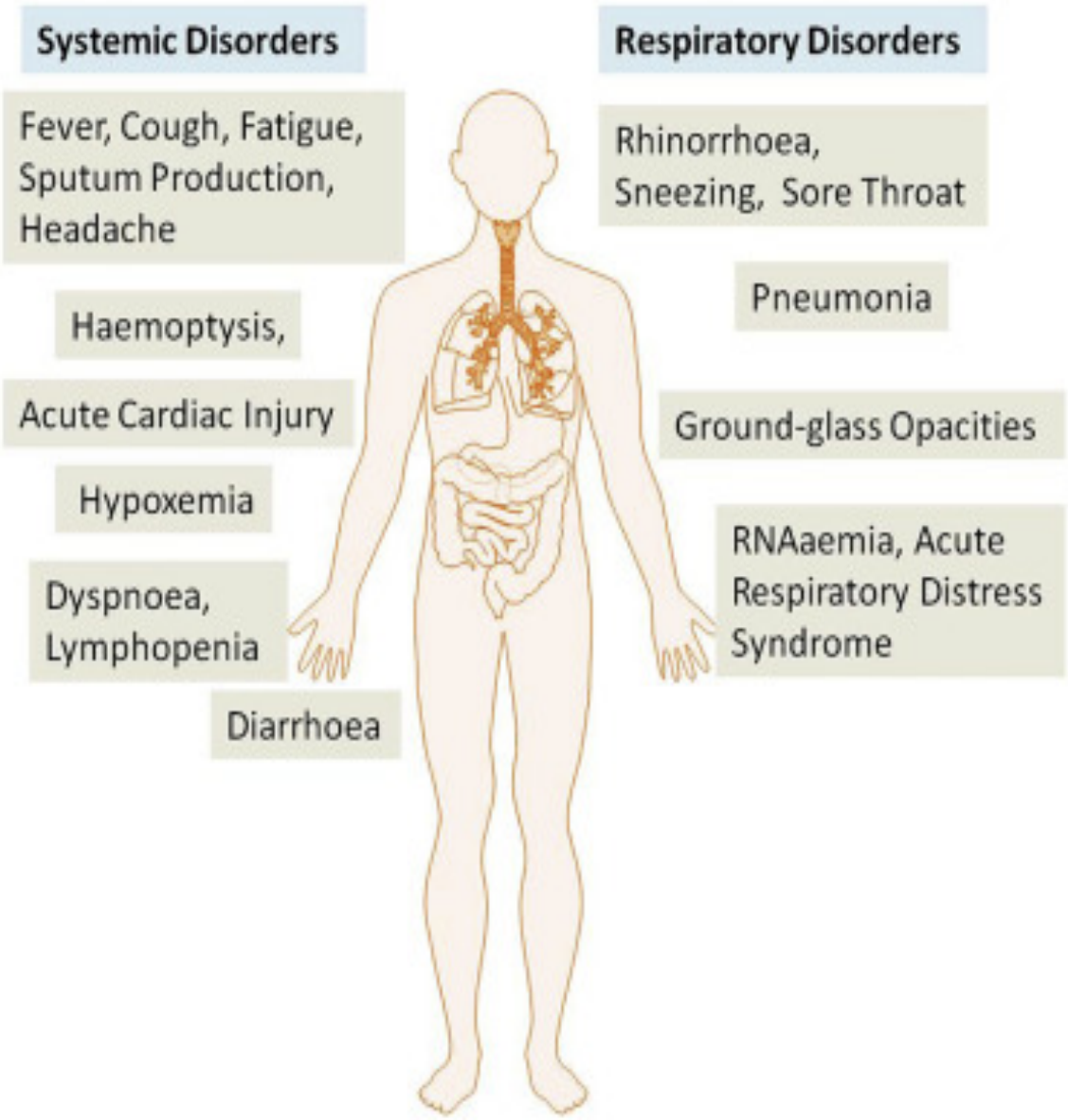


Illustration revealing ultrastructural morphology exhibited by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) when viewed with electron microscopically*Centers for Disease Control and Prevention*

SYMPTOMS

The symptoms of COVID-19 infection appear after an incubation period of 6 to 41 days with a median of 14 days . This period is dependent on the age of the patient and status of the patient's immune system. It was shorter among patients >70-years old compared with those under the age of 70. The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, headache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia . Clinical features revealed by a chest CT scan presented as pneumonia, however, there were abnormal features such as RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities that led to death .

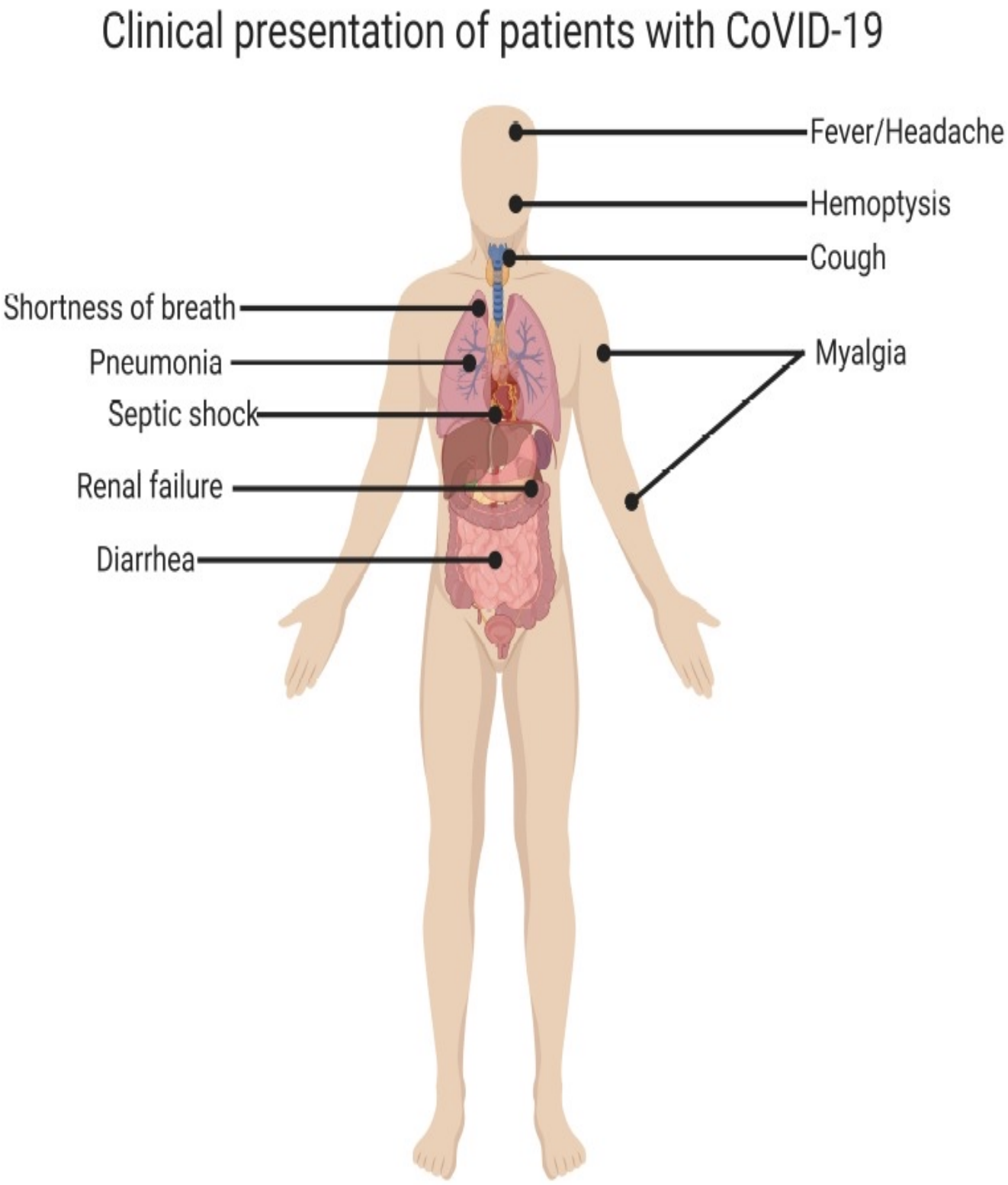

Systemic Disorders
Fever, Cough, Fatigue, Sputum Production, Headache
Haemoptysis,
Acute Cardiac Injury
Hypoxemia
Dyspnoea, Lymphopenia
Diarrhoea
Respiratory Disorders
Rhinorrhoea, Sneezing, Sore Throat
Pneumonia
Ground-glass Opacities
RNAaemia, Acute Respiratory Distress Syndrome

PATHOGENESIS OF COVID-19

Coronavirus is one of the major pathogens that primarily targets the human respiratory system. Previous outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which have been previously characterized as agents that are a great public health threat. The severe symptoms of COVID-19 are associated with an increasing numbers and rate of fatalities specially in the epidemic region of China. On January 22, 2020, the China National Health Commission reported the details of the first 17 deaths and on January 25, 2020 the deathFigure cases increased. The percentage of death among the reported 2684 cases of COVID-19 was approximately 2.84% as of Jan 25, 2020 and the median age of the deaths was 75 (range 48–89) years. Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines. One of the COVID-19 case reports showed a patient at 5 days of fever presented with a cough, coarse breathing sounds of both lungs, and a body temperature of 39.0 °C. The patient's sputum showed positive real time polymerase chain reaction results that confirmed COVID-19 infection. The laboratory studies showed leucopenia with leukocyte counts of 2.91 × 10^9 cells/L of which

70.0% were neutrophils. Additionally, a value of 16.16 mg/L of blood C-reactive protein was noted which is above the normal range (0–10 mg/L). High erythrocyte sedimentation rate and D-dimer were also observed . The main pathogenesis of COVID-19 infection as a respiratory system targeting virus was severe pneumonia, RNAaemia, combined with the incidence of ground-glass opacities, and acute cardiac injury. Significantly high blood levels of cytokines and chemokine were noted in patients with COVID-19 infection that included IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some of the severe cases that were admitted to the intensive care unit showed high levels of pro inflamatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα that are reasoned to promote disease severity. Based on the large number of infected people that were exposed to the wet animal market in Wuhan City where live animals are routinely sold, it is suggested that this is the likely zoonotic origin of the COVID-19. Eff orts have been made to search for a reservoir host or intermediate carriers from which the infection may have spread to humans. Initial reports identified two species of snakes that could be a possible reservoir of the COVID-19. However, to date, there has been no consistent evidence of coronavirus reservoirs other than mammals and

birds. Genomic sequence analysis of COVID-19 showed 88% identity with two bat-derived severe acute respiratory syndrome (SARS)-like coronaviruses , indicating that mammals are the most likely link between COVID-19 and humans. Several reports have suggested that person-to-person transmission is a likely route for spreading COVID-19 infection. This is supported by cases that occurred within families and among people who did not visit the wet animal market in Wuhan. Person to person transmission occurs primarily via direct contact or through droplets spread by coughing or sneezing from an infected individual. In a small study conducted on women in their third trimester who were confirmed to be infected with the coronavirus, there was no evidence that there is transmission from mother to child. However, all pregnant mothers underwent cesarean sections, so it remains unclear whether transmission can occur during vaginal birth. This is important because pregnant mothers are relatively more susceptible to infection by respiratory pathogens.


Clinical presentation of patients with CoVID-19
Fever/Headache
Hemoptysis
Cough
Shortness of breath
Pneumonia
Septic shock
Renal failure
Diarrhea
Myalgia

POTENTIAL THERAPIES TO ADRESS COVID-19

No specific antiviral treatment is recommended for COVID-19. Infected patients receive supportive care to help alleviate symptoms. Vital organ function is supported in severe cases.

No vaccine is currently available for SARS-CoV-2. Avoidance is the principal method of deterrence.

But these method are implemented

1-Traditional epidemiological approaches effectively control the transmission

Professionally speaking, three steps are necessary to taken once an infectious disease outbreaks in certain regions, including controlling infectious sources, blocking the transmission routes, and protecting the susceptive population. While, as COVID-19 spreading so fast and people's travelling so frequent during the Chinese New Year (Spring Festival) season, it cannot control effectively if only taking the normal or general countermeasures. Therefore, the Chinese government has quickly taken actions to contain its transmission inside China, including detecting the disease early, diagnosis and reporting early, isolating and treatment of cases early, tracing all possible contacts, persuading people to stay at

home, and promoting social distancing measures commensurate with the risk, etc., based on the current knowledge about epidemiological features and transmission patterns of COVID-19.

2-Response strategies coping with local conditions

In dealing with the outbreak, China has been adopting the way of tailoring interventions into local settings, from quickly finding each infected person, tracing close contacts and placing them under quarantine, to promoting basic hygiene measures to the public, such as frequent hand washing, cancelling public gathering, closing schools, extending the Spring Festival holiday, delaying return to work, and to the most severe measure of city lockdown of Wuhan. By adapting response strategies to the local context, it may avoid blockading the city when it is not needed, and also prevent from a major outbreak without taking any action.

3-Mobilizing resources quickly to support the emergency responses

Under the strong leadership of the Central Government of China, the mobilization for the emergency responses has been effectively promoted

in following ways. Firstly, a Joint Prevention and Control Mechanism of the State Council has established involving 32 Ministries, with subgroups on control of outbreak, medical rescue, scientific research, information and communication, international cooperation, logistics, and frontline coordination. This multi-sectoral cooperation mechanism at high level is to ensure the facilities and supplies have been well arranged to support the emergency responses in all provinces, with focus on the Hubei Province, for example, more than 10 mobile hospitals and two big hospitals with each one having the capacity of holding more than 1000 beds have been built within 10 days. Secondly, more than 40 000 medical professionals from other provinces or military institutions have been dispatched to Hubei Province to implement emergency responses, including medical care and treatment, epidemiological investigations, environmental sterilization for disinfection, and data and information management to support the policy making.

4-Encouraging people proactively and orderly participate in this battle against COVID-19

It is important to protect the community from exposure to the infection, all residents in the potential risk areas were encouraged to stay at home, which is an effective way to block the transmission routes. Local community health workers and volunteers, after the specific training, proactively participate in screening the suspicious infections, and help in implementing proper quarantine measures by providing support services, such as driving patients to the mobile hospitals. All those activities logistically managed at the community level.

At the same time, from medical care side, the medical doctors and nurses worked very hard in the hospitals, to screen the suspected cases, provide medical care for the confirmed cases, and taking emergency response to rescue severe patients to reduce the fatality. While epidemiologists working in centers for disease control and preventions provided the statistical results for the dissemination of epidemiological data correctly, and provide the well-prepared datasets for the decision makers for coordination of necessary resources, and many health workers investigate the suspected contactors for quick medical quarantine of the suspected cases at the community level.

6-Preventing the pandemic of COVID-19

With the conceptualization on building a community with a shared future for mankind proposed by Chinese President Xi Jinping in 2013, Chinese people have taken following actions to prevent the pandemic of the diseases by:

(i) sharing the sequences of SARS-Cov-2 virus with the World Health Organization (WHO) and other countries which are important information for other countries to prepare the tests for screening and diagnosis,

(ii) all epidemiological data with clinical treatment in China has been published in the international journals,

(iii) prevent spreading of the disease by traveling ban in Wuhan,

(iv) medical quarantine has been performed for all suspected contactors,

(v) body temperature measuring facilities were equipped in all railway stations and airports, etc. In order to take very strict contain measures for COVID-19 outbreak tailored to local settings, the travelling ban was

executed in Wuhan, and encouraging no gathering and less travelling in other cities out of Hubei Province. Those actions were implemented by strong coordinating of the Chinese government in cooperation with local residents. To date, the epidemiological data has showed more than thousands of people have been protected from the infections, and increasing pattern of the transmission has been suppressed significantly in China.

Future of covid19 on public health

With understanding more about the nature of COVID-19, it is necessary to understand clearly the current challenges against COVID-19 become increasing.

COVID-19 and better allocate enough health resources from the world, the recommendations are as follows:

-Intervention and coordination globally

The fast spreading of COVID-19 to more than 90 countries/territories, with some cluster cases occurred in a few countries, demonstrated that this new disease has higher transmissibility compared with SARS and MERS. The nature of high transmissibility for COVID-19 requires us to

(i) prepare the battle globally as soon as possible, by taking the advantage of the time window opened by Chinese battle against COVID-19,

(ii) invest more weapons or tools against the diseases by better global coordination, and

(iii) take proper quarantine measures globally . We are able to win the battle only if our actions are coordinated better at a global level.

-Resources mobilization globally

One of lessons learnt from the battle in Wuhan is the speed of resources gathering against COVID-19 outbreak could not catch up the speed of the coronavirus spreading in early stage of the outbreak, and it is in need of

support or assistances from outside of epicenter, including medical doctors, nurses, and facilities of PPE used in hospitals, and facemasks for residents. The strong support from outside of epicenter quickly to ensure all infectious sources either controlled through quarantine measures or treated in the specialized hospitals. Therefore, for those countries with weak health system, it is so urgent to get help from other parts of the world. WHO needs to mobilize its certified global emergency medical teams to get ready to be dispatched to other countries where health workers are in short supply while an outbreak occurs.

-Jointly fighting against common enemy ─ COVID-19

As said by WHO Director-General in the news press on Public Health Emergency of International Concern declaration that "this declaration is not a vote of no confidence in China, our greatest concern is the potential for the virus to spread to countries with weaker health systems." Therefore, international community needs to work together to prepare for the containment of COVID-19 transmission and spreading in other countries, under the scenario that more countries may be affected by the new coronavirus . These containment works have to quickly take readiness on active surveillance, early detection, isolation and case

management, contact tracing and prevention of onward spread of COVID-19.

Therefore, at this stage, with more countries having confirmed more and more COVID-19 cases, all countries need work together on the following global actions on:

. (i)

fighting against COVID-19 spreading, including sharing the information of the disease transmission and epidemiological knowledge, sharing the experiences on case management and treatment approaches both for severe cases or light symptoms, and sharing new technologies or strategies to contain the transmission;

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. (ii)

fighting against violating International Health Regulation, by following the WHO's authoritative advices which called on all countries to implement decisions that are evidence-based and convincing. We need to improve our quarantine measures to replace the disconnection of international traveling and trade restrictions, with an assistance of the

improved active surveillance systems and AI-based technology to trace the contactors;

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. (iii)

fighting against stigmatization, since the stigmatization is always present when the disease outbreak and people facing the sudden attack of this kind of epidemic. These phenomena on stigmatization may be at a scale of epicenter areas, or may be at a country and regional scale, and even at global scale. Thus, we need fight with the real and common enemy which is the new coronavirus, rather than the infected people. The international community needs the solidarity and sympathy to start the battle against the common enemy – the new coronavirus, as well as against stigmatization at the same time.

—Global cooperation in priority settings

By considering COVID-19 is spreading so fast which causes difficulties in containing the disease, we, as a community of shared future for mankind, need better coordination in global cooperation and further improvement in the multi-sectoral cooperation in order to quickly take response and prevent from the pandemic . In addition, we also need better

coherence of our resources with more international partners, at least, we can quickly improve our priority settings in sharing information and data, on research priority settings, on surveillance and response to outbreaks at a global level.

-Cooperation on sharing information and data

In order to quickly share the information and datasets for countermeasures, the actions on fast and open reporting of outbreak data and sharing of virus samples, genetic information, and research results are encouraged for all international communities, non-governmental organizations (NGOs), as well as governmental institutions around the world. Through regional and country office of WHO, more preventive information against COVID-19 can be disseminated to the public in the vulnerable countries.

-Coordination on surveillance and response

With understanding the importance of human health in the planet, multi-sectoral and multi-lateral cooperation against COVID-19 pandemic are recommended at global level. Particularly, the scientific communities, governments and NGOs in different fields, such as public health,

agriculture, ecology, epidemiology, governance planning, science, and many others need to collaboratively prevent future outbreaks, with better coordination. Government need take the responsibility to coordinate the actions on protecting the planetary health by systematic approaches, such as EcoHealth, One Health, Planetary Health and Urban Health, and making sure public resources are worthwhile investing in strengthening surveillance and response systems for preventing future outbreaks of emerging infectious diseases.

-Coherence on research priority settings

We urgently encourage all governments and international foundation to support short-term and emergency response-related research projects to improve our understanding of the causes, risks, infectiousness, and threats of a pandemic . Health institutions at international level should be encouraged to organize the research priority settings on preventing the pandemic or averting the emergence of the disease. International conservation organizations start to take investigations on types of wildlife-pathogens interactions affecting human health. International environmental agencies can initiate researches on unsustainable transformations of natural environments and ecosystems that provide life-supporting services for our health.

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