



## Review Article

## From epidemic to pandemic covid-19 world crisis!

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## ABSTRACT

There is a new public health crises threatening the world with the emergence and spread of 2019 novel corona virus (2019-nCoV) The virus originated in bats and was transmitted to humans through yet unknown intermediary animals in Wuhan, Hubei province, China in December 2019. It caused a total of 80,868 confirmed cases and 3101 deaths in Chinese mainland until March 8, 2020. This novel virus spread mainly through respiratory droplets and close contact. According to the current pandemic situation the worldwide report of death due to COVID-19 is 165,877,654, cases confirmed and 3,445,463 death and 146,583,420 recovered. The symptoms are usually fever, cough, sore throat, breathlessness, fatigue, malaise among others. The disease is mild in most people; in some, usually the elderly and those with comorbidities, it may progress to pneumonia, acute respiratory distress syndrome (ARDS) and multi organ dysfunction. As COVID-19 has triggered enormous human casualties and serious economic loss posing global threat, an understanding of the ongoing situation and the development of strategies to contain the virus's spread are urgently needed. Currently, various diagnostic kits to test for COVID-19 are available and several repurposing therapeutics for COVID-19 have shown to be clinically effective. In addition, global institutions and companies have begun to develop vaccines for the prevention of COVID-19. Here, we review the current status of epidemiology, diagnosis, treatment, and vaccine development for COVID-19.

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## 1. Introduction

In December, 2019, Wuhan, Hubei province, China, became the center of an outbreak of pneumonia of unknown cause, which raised intense attention not only within China but internationally. Chinese health authorities did an immediate investigation to characterize and control the disease, including isolation of people suspected to have the disease, close monitoring of contacts, epidemiological and clinical data collection from patients, and development of diagnostic and treatment procedures.<sup>1</sup>

Till 05/03/2020 around 96,000 cases of corona virus disease 2019(COVID-19) and 3300 deaths had been

reported.<sup>2</sup> India had reported more than 2.6 core active cases till date and the death toll raises up to 2.91 lakhs. Fortunately so far, children have been infrequently affected with no deaths. But the future course of this virus is unknown. This article gives a bird's eye view about this new virus. Since knowledge about this virus is rapidly evolving, readers are urged to update themselves regularly.<sup>3</sup>

## 1.1. Epidemiology

The COVID-19 epidemic expanded in early December from Wuhan, China's 7th most populous city, throughout China and was then exported to a growing number of countries. The first confirmed case of COVID-19 outside China was diagnosed on 13th January 2020 in Bangkok

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(Thailand).<sup>4</sup> On the 2nd of March 2020, 67 territories outside mainland China had reported 8565 confirmed cases of COVID-19 with 132 deaths, as well as significant community transmission occurring in several countries worldwide, including Iran and Italy and it was declared a global pandemic by the WHO on the 11th of March 2020.<sup>5</sup> The number of confirmed cases is constantly increasing worldwide and after Asian and European regions, The number of coronavirus cases worldwide has surpassed 160 million according to the recent statistics.<sup>6</sup> Globally, in the past week, the number of new cases and deaths continued to decrease, although overall counts for both remained high with just over 4.8 million new cases and nearly 86 000 new deaths reported in the past week. All regions reported a decline in new cases this week with the exception of the Western Pacific where the number of new cases was similar to the previous week.<sup>7</sup>

## 2. History

In recent times, several life threatening viruses have emerged. They have been responsible for causing significant human mortality, in addition to raising serious public health concerns worldwide. Due to modern life, extensive travel of humans and goods, their outbreak anywhere in the world could potentially be a risk everywhere. Two novel viruses were implicated to be responsible for severe acute illness in recent times, i.e. Middle East Respiratory Syndrome-Corona-Virus (MERS-CoV) and severe acute respiratory syndrome-corona-virus (SARS-CoV). These two viruses are causing acute and often fatal illness. Due to their high fatality rate (30–90%), they have had dual effect: fear among public from contracting one or more of them as well as high burden on the healthcare system, including the treating physician and other health care workers. The reservoir of the viruses is usually animal, including: bats, camels, or chimpanzees. Apart from animal to human transmission, human to human transmission has been reported, usually from an infected patient to a member of the health care team and to other patients in the hospital. These novel viruses represent significant challenges to public health in general and to public health services and infection control in specific. Intensive education awareness and multi directional care does improve disease outcome.<sup>8</sup>

## 3. Origin and spread of Covid-19

The SARS-CoV-2 is a  $\beta$ -coronavirus, which is enveloped non-segmented positive-sense RNA virus (subgenus sarbecovirus, Orthocoronavirinae subfamily).<sup>9</sup> Coronaviruses (CoV) are divided into four genera, including  $\alpha$ - $\beta$ - $\gamma$ - $\delta$ -CoV.  $\alpha$ - and  $\beta$ -CoV are able to infect mammals, while  $\gamma$ - and  $\delta$ -CoV tend to infect birds. Previously, six CoVs have been identified as human-susceptible virus, among which  $\alpha$ -CoVs HCoV-229E and

HCoV-NL63, and  $\beta$ -CoVs HCoV-HKU1 and HCoV-OC43 with low pathogenicity, cause mild respiratory symptoms similar to a common cold, respectively. The other two known  $\beta$ -CoVs, SARS-CoV and MERS-CoV lead to severe and potentially fatal respiratory tract infections.<sup>10</sup>

In December 2019, adults in Wuhan, capital city of Hubei province and a major transportation hub of China started presenting to local hospitals with severe pneumonia of unknown cause. Many of the initial cases had a common exposure to the Huanan wholesale seafood market that also traded live animals. The surveillance system put into place after the SARS outbreak was activated and respiratory samples of patients were sent to reference labs for etiologic investigations. On December 31st 2019, China notified the outbreak to the World Health Organization and on 1st January the Huanan sea food market was closed. On 7th January the virus was identified as a corona virus that had >95% homology with the bat corona virus and >70% similarity with the SARS- CoV. Environmental samples from the Huanan sea food market also tested positive, signifying that the virus originated from there.<sup>11</sup> The number of cases started increasing exponentially, some of which did not have exposure to the live animal market, suggestive of the fact that human-to-human transmission was occurring.<sup>12</sup>

Cases continued to increase exponentially and modelling studies reported an epidemic; In fact on the 12th of February, China changed its definition of confirmed cases to include patients with negative and pending molecular tests but with clinical, radiologic and epidemiologic features of COVID-19 leading to an increase in cases by 15,000 in a single day.<sup>13</sup> As of 20/05/2021 90,000 cases in China and 87 other countries and 1 international conveyance<sup>14</sup> It is important to note that while the number of new cases has reduced in China lately, they have increased exponentially in other countries including South Korea, Italy and Iran.<sup>15</sup> Of those infected, 20% are in critical condition, 25% have recovered, and 3310 (3013 in China and 297 in other countries) have died.<sup>16</sup> India, reported only 3 cases till 2/3/2020, has also seen a sudden spurt in cases after that. By 5/3/2020, 29 cases had been reported; mostly in Delhi, Jaipur and Agra in Italian tourists and their contacts. One case was reported in an India who traveled back from Vienna and exposed a large number of school children in a birthday party at a city hotel. Many of the contacts of these cases had been quarantined.<sup>16</sup>

### 3.1. Clinical features

As an emerging acute respiratory infectious disease, COVID-19 primarily spreads through the respiratory tract, by droplets, respiratory secretions, and direct contact for a low infective dose.<sup>17</sup> Based on current epidemiological investigation, the incubation period is 1–14 days, mostly 3–7 days. And the COVID-19 is contagious

during the latency period.<sup>18</sup> It is highly transmissible in humans, especially in the elderly and people with underlying diseases. The median age of patients is 47–59 years, and 41.9–45.7% of patients were females.<sup>19</sup> As it is designated SARS-CoV-2, COVID-19 patients presented certainly similar symptoms, such as fever, malaise, and cough.<sup>20</sup> Most adults or children with SARS-CoV-2 infection presented with mild flu-like symptoms and a few rapidly develop acute respiratory distress syndrome, respiratory failure, multiple organ failure, even deaths.<sup>21</sup>

### 3.2. Diagnostic criteria

The viral research institution in China has conducted preliminary identification of the SARS-CoV-2 through the classical Koch's postulates and observing its morphology through electron microscopy.<sup>22</sup> So far, the golden clinical diagnosis method of COVID-19 is nucleic acid detection in the nasal and throat swab sampling or other respiratory tract sampling by real-time PCR and further confirmed by next-generation sequencing.

## 4. Treatment

The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock.<sup>23</sup> Different strategies can be used depending on the severity of the patient and local epidemiology.<sup>24</sup> Home management is appropriate for asymptomatic or paucisintomatic patients. They need a daily assessment of body temperature, blood pressure, oxygen saturation and respiratory symptoms for about 14 days. Management of such patients should focus on prevention of transmission to others and monitoring for clinical status with prompt hospitalization if needed. Outpatients with COVID-19 should stay at home and try to separate themselves from other people in the household. They should wear a face mask when in the same room or vehicle with other people and when presenting to health care settings. Disinfection of frequently touched surfaces is also important. The optimal duration of home isolation is uncertain, but in consideration of incubation time around 14 days without symptoms (fever, dyspnea, others) are considered sufficient to end home isolation. Some patients with suspected or documented COVID-19 have severe disease that warrants hospital care. Management of such patients consists of ensuring appropriate infection control, and supportive care. Patients with severe disease often need oxygenation support. High-flow oxygen and noninvasive positive pressure ventilation have been used. Some patients may develop acute respiratory distress syndrome and warrant intubation with mechanical ventilation; extracorporeal membrane

oxygenation may be indicated in patients with refractory hypoxia.

### 4.1.

#### 4.1.1. Uses of HydroxyChloroquine and Chloroquine In CovId-19 (SARS-Cov-2)

The worldwide effects of the SARS-CoV-2 pandemic have been unparalleled and it has prompted the scientific community to consider all possible solutions. Due to covid-19 similarities to SARS-CoV, several researchers have proposed the use of hydroxy-chloroquine and chloroquine on the novel virus. Wang et al tested the effect of several FDA (Food and Drug Administration) approved antiviral drugs on the virus in vitro. Remdesivir showed post entry blockage of viral infection with an effective concentration at 50% of EC50=0.77 $\mu$ M and a cytotoxic concentration of 50% of CC50>100 $\mu$ M. Chloroquine was found to have an effective concentration at 50% of EC50=1.13 $\mu$ M, a cytotoxic concentration at 50% of CC50>100 $\mu$ M and an effective concentration at 90% EC90 of 6.90 $\mu$ M.<sup>17</sup> Chloroquine showed effectiveness at an entry and post entry level, while remdesivir was only effective at a post entry level. This further suggests the possible prophylactic use of chloroquine on SARS-CoV-2.<sup>16</sup> Yao et al also tested the effect of hydroxychloroquine and chloroquine in vitro. They divided the experiment into two phases: treatment study and prophylaxis study. In the treatment study, the EC50 values for chloroquine were 23.90 and 5.47 $\mu$ M at 24 and 48hours, respectively, and the EC50 values for hydroxychloroquine were 6.14 and 0.72 $\mu$ M at 24 and 48hours, respectively. In the prophylaxis study, the EC50 values for chloroquine were >100 and 18.01 $\mu$ M at 24 and 48hours, respectively, and the EC50 values for hydroxychloroquine were 6.25 and 5.85 $\mu$ M at 24 and 48hours, respectively.<sup>22</sup>

## 5. Prevention

Prevention is, so far, the best practice in order to reduce the impact of COVID-19 considering the lack of effective treatment. At the moment, there is no vaccine available and the best prevention is to avoid exposure to the virus.<sup>24,25</sup> In order to achieve this goal, the main measures are the following: (1) to use face masks; (2) to cover coughs and sneezes with tissues; (3) to wash hands regularly with soap or disinfection with hand sanitizer containing at least 60% alcohol; (4) to avoid contact with infected people; (5) to maintain an appropriate distance from people; and (6) to refrain from touching eyes, nose, and mouth with unwashed hands.<sup>26</sup> Interestingly, the WHO issued detailed guidelines includes: (I) Regularly and thoroughly clean your hands with an alcohol-based hand rub or wash them with soap and water; (II) Avoid touching eyes, nose and mouth; (III) Practice respiratory hygiene covering your mouth and nose with your bent elbow or tissue when you cough or sneeze;

(IV) If you have fever, cough and difficulty breathing, seek medical care early; (V) Stay informed and follow advice given by your healthcare provider; (VI) Maintain at least 1 m (3 feet) distance between yourself and anyone who is coughing or sneezing.<sup>27</sup>

## 6. Specific Dental Treatment Recommendations

Patients with active febrile and respiratory illness will most likely not present to dental practices. In order to have clarity on what constitutes an emergency condition, dentists can refer to recent American Dental Association recommendations. Certain instances such as dentoalveolar trauma and progressive facial space infection warrant emergency dental intervention. In the unlikely event of providing dental care to suspected or confirmed cases of COVID-19 infection, dentists should be cognizant of the following recommendations: Dentists should follow standard, contact, and airborne precautions including the appropriate use of personal protective equipment and hand hygiene practices.<sup>27</sup>

## 7. Current Economic Situation World Wide

The ongoing spread of the new corona virus has become one of the biggest threats to the global economy and financial markets. To contain the COVID-19 outbreak, Chinese authorities locked down cities, restricted movements of millions and suspended business operations — moves that will slow down the world's second-largest economy and drag down the global economy along the way. "The economic impact of the 2020 coronavirus pandemic in India has been largely disruptive. India's growth in the fourth quarter of the fiscal year 2020 went down to 3.1% according to the Ministry of Statistics. The Chief Economic Adviser to the Government of India said that this drop is mainly due to the coronavirus pandemic effect on the Indian economy. Notably India had also been witnessing a pre-pandemic slowdown, and according to the World Bank, the current pandemic has "magnified pre-existing risks to India's economic outlook".<sup>28</sup>

## 8. Covid-19 Vaccine in India

In January, 2021, India's drug regulator issued a restricted emergency approval for COVAXIN, alongside COVISHIELD (the Oxford–AstraZeneca developed vaccine that is also made in India). On Jan 16, 2021, India began the world's largest vaccination programme for COVID-19, targeting an initial group of 300 million people.<sup>29</sup> The lack of data for COVAXIN leaves those who have been given it in an uncertain position regarding their status. The vaccine may work out to be safe and efficacious, but that would be owed more to good luck than to good government policy", said Jammi Nagaraj Rao, a public health physician and epidemiologist.<sup>29</sup>

COVAXIN's approval in India came before the company had finished recruiting for the drug's phase 3 trial. Given that there is no efficacy data for COVAXIN yet, some health workers "may not have confidence in COVAXIN and that is understandable."<sup>29</sup>

The first phase of the rollout involved health workers and frontline workers including police, paramilitary forces, sanitation workers, and disaster management volunteers. By 1 March, only 14 million healthcare and frontline workers had been vaccinated, falling short of the original goal of 30 million.<sup>30</sup> The next phase of the vaccine rollout covered all residents over the age of 60, residents between the ages of 45 and 60 with one or more qualifying comorbidities, and any health care or frontline worker that did not receive a dose during phase 1. Online registration began on 1 March via the Aarogya Setu app and the Co-WIN website. From 1 April, eligibility was extended to all residents over the age of 45.<sup>31</sup> On 8 April, amid the beginnings of a major second wave of infections in the country, Prime Minister Narendra Modi called for a four-day Teeka Utsav ("Vaccine Festival") from 11 to 14 April to mark the respective birthdays of Jyotirao Phule and B. R. Ambedkar, with a goal to increase the pace of the program by vaccinating as many eligible residents as possible. By the end of the Utsav, India had reached a total of over 111 million vaccine doses to-date.<sup>32</sup> On 12 April, the DCGI approved Russia's Sputnik V vaccine for emergency use in India. A phase 3 trial had been conducted in the country in September 2020, which showed 91.6% efficacy.<sup>31</sup> The local distributor Dr. Reddy's Laboratories stated that it planned to have the vaccine available in India by late-May 2021.<sup>32</sup> On 25 April, India exceeded a total of 140 million doses administered.<sup>33</sup> On 19 April, it was announced that the next phase of the vaccine program would begin on 1 May, extending eligibility to all residents over the age of 18. Registration for the next phase began on 28 April; a single-day record of nearly 13.3 million people registered.<sup>34</sup> On 14 May 2021, the Government of India said that an estimated 200+ crore (2 billion) COVID-19 vaccines from would be made available between August and December 2021, with 7.6 crore (76 million) doses of Covishield and Covaxin.<sup>35</sup>

### 8.1. Thapsigargin: Antiviral treatment to treat covid-19

Thapsigargin is non-competitive inhibitor of the sarco/endoplasmic reticulum  $\text{Ca}^{2+}$  ATPase (SERCA). Structurally, thapsigargin is classified as a sesquiterpene lactone, and is extracted from a plant, *Thapsia garganica*. It is a tumor promoter in mammalian cells.<sup>36</sup> Thapsigargin raises cytosolic (intracellular) calcium concentration by blocking the ability of the cell to pump calcium into the sarcoplasmic and endoplasmic reticula. Store-depletion can secondarily activate plasma membrane calcium channels, allowing an influx of calcium into the cytosol. Depletion of ER calcium stores leads to ER

stress and activation of the unfolded protein response. Non-resolved ER stress can cumulatively lead to cell death.<sup>36</sup> The researchers mentioned that thapsigargin is a promising antiviral as it is effective against viral infection when used before or even during active infection. The drug is also able to prevent a virus from making new copies of itself in cells for at least 48 hours after a single 30-minute exposure, researchers stated.<sup>36</sup>

## 9. Conflicts of Interest

All contributing authors declare no conflicts of interest.

## 10. Source of Funding

None.

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