Received Date: 09 June 2020
Accepted Date: 27 June 2020
Published Date: 05 July 2020

Practique Clinique et Investigation

Recent Advances in the COVID-19 Pandemic: A Review on Diagnosis, Treatment, Phenotype Analysis and Epidemiology of Major Countries

Shreya Jagtap | Sagar Trivedi* | Kamlesh Wadher | Milind Umekar

Department of Pharmaceutics, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee Nagpur, Maharashtra, India

***Correspondence:** Sagar Trivedi, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee Nagpur, Maharashtra, India 441002 E-mail: sagartrivedi2000@gmail.com

ABSTRACT

An epidemic that started in Wuhan, China after a cluster of patients was reported with pneumonia of an unknown aetiology in early December 2019 quickly unravelled into a global pandemic. An emergent novel coronavirus (COVID-19) was identified responsible for causing respiratory distress, fever, chills etc. similar to that caused by like SARS and MERS. The genotype and phenotype also indicate homological sequences to the previously identified coronavirus and confirms their link. In January, the WHO declared the newly identified COVID-19 as a public health emergency of international concerns. Currently, no vaccine or standard treatment exists however, at this time treatment is based on symptomatic relief and supportive care with repurposing existing drugs including anti-viral therapy, convalescent plasma therapy and adjunctive intervention. From Wuhan, its original epicentre the virus spread through the country and gradually the world and has infected more than 4 million people. Countries around the globe issued stringent plan of action in interest of public health like nation-wide lockdown, quarantine and isolation which are playing a major role in delaying transmission in communities. This article reviews available literature on the symptoms, diagnosis, pathogenesis, genotype and phenotype, general epidemiology of 5 countries majorly affected by the pandemic.

Keywords: *COVID-19; Phenotype and genotype; Epidemiology; Treatment; Diagnosis*

INTRODUCTION

The recently identified Coronavirus responsible for one of worst pandemic was found to belong to a family of pathogens that predominantly targets the human respiratory system. Coronavirus diseases potentially cause severe acute respiratory infection and relating complications [1]. In just a span of 5 months, it has affected more than 3 million people around the globe. The coronavirus is enveloped viruses with single positive-stranded RNA categorized under subfamily-*orthocoronavirinae*, family - *coronaviridae* [2]. These viruses have the ability to cross species barriers and in humans, can cause, illness ranging from the common cold to a more severe disease condition. Previous outbreaks of corona viruses (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 matter of public health concerns [3,4]. COVID-19 was

Citation: Shreya Jagtap, Recent Advances in the Covid-19 Pandemic: A Review on Diagnosis, Treatment, Phenotype Analysis and Epidemiology of Major Countries. Prac Clin Invest 3(S1): 9-27.

regarded as the seventh member of the human coronavirus family, belonging to subgenus sarbecovirus. Although SARS-CoV-2 is similar to the SARs and MERS-CoV, genetic analysis reveals substantial differences between them, allowing it be considered a new betacoronavirus [5]. Around first few weeks of December 2019, group of people were hospitalised with symptoms like pneumonia, but with an unknown etiology. The patients reported to have similar symptoms were connected to a common background of seafood and wet animal wholesale market in Wuhan, Hubei Province, China [3]. The patients were treated for pneumonia but no positive outcome was reported among these patients even with standard treatment and significant drugs for arising symptoms. In addition to this, the symptoms were found to show close resemblance to that of the early breakouts of SARS-CoV and MERS-CoV. The World Health Organization (WHO) was informed of 44 cases of pneumonia of unknown microbial aetiology associated with Wuhan City, Hubei Province, China on 31 December 2019. Laboratory tests ruled out severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome (MERS)-CoV, influenza, avian influenza, and other common respiratory pathogens after which the WHO announced that a novel coronavirus had been spotted in samples taken from these patients [6]. On February 11, 2020, the WHO Director-General, Dr. Tedros Adhanom Ghebreyesus, declared that the disease caused by this new CoV was called "COVID-19," which is the abbreviation of "coronavirus disease 2019". The WHO announced that the official name of the 2019 novel coronavirus is coronavirus disease (COVID-19) [6].

The first case was reported in December 2019. From December 18, 2019 through December 29, 2019, five patients were hospitalized with acute respiratory distress syndrome and one of these patients died. Initial reports predicted the onset of a possible Coronavirus outbreak and the virus identified was estimated to be significantly greater than 1 (ranges from 2.24 to 3.58) [7]. Since then, the outbreak has spiralled rapidly, WHO declaring a public health emergency of international concern on 30 January 2020. The epidemic spread briskly from a single city to an entire country in a matter of 30 days. The numbers of cases and deaths have surpassed the toll from the 2002-2003 outbreak of severe acute respiratory syndrome (SARS). Globally, approximately 4 Million cases have been reported (as of 10 May 2020) proving it is more fatal than the previous outbreaks due to corona viruses [8]. In response to this widespread, epidemiological and etiological examinations in the city of Wuhan, China was very crucial to understand its source, which was carried out by the Chinese Centre for Disease Control and Prevention (China CDC). As per the reports by investigations, WHO confirmed that the epidemic is associated with Huanan South China Seafood Marketplace, however, limited data indicated its potential origin from animals[9]. The transmission however, is suspected to be mainly Person-person. The reports have been backed up by numerous occurrences of infections within family members who weren't directly exposed to the wet seafood market. The person-to-person transmission is mostly via droplets or fomites around an infected person. It could spread either via direct contact by getting exposed to droplets released on coughing or sneezing by the infected person or by indirect exposure to surfaces in direct contact or items used by an infected person [10,11].

In view of public health concerns, the WHO has released precautionary guidelines to limit person-person transmission which includes regularly washing hands or using alcohol based hand sanitizer, social distancing (with minimum 3 feet distance between people), wearing masks and gloves and avoid touching eyes, mouth and nose. In addition to this, people who may exhibit any mentioned symptoms for COVID-19 must report to a health care professional and in mild cases must self-isolate to protect themselves and to avoid contamination and subsequent spreading of the infection [12].

PATHOPHYSIOLOGY

Both in-vitro and iv-vivo study reveals that the growth of nCoV-19 is restricted to the respiratory epithelial cells, which on getting infected become vacuolated with damaged cilia that may turn to syncytia. This damage to host cell triggers an immune response and release inflammatory cytokines responsible for nasal secretions and inflammation that lead to obstruction in the airways [13]. As per the estimation by World health organization and the US Centres for Disease Control and Prevention, the incubation period of COVID-19 lies between 1-14 days with 5 days' median incubation period during with the transmission is most likely to occur [14]. According to studies conducted outbreak by Lu, Zhao and Li, et al. [15,16] studied the genomic characterization and epidemiology of novel coronavirus with regards to the pathophysiology of the pandemic, the structural evidences suggested ACE2 i.e. angiotensin-converting enzyme-2 receptor in humans as the potential binding site (alike to the pathogenesis of other virus of corona family). Studies propose that, the unique spike like glycoprotein receptor binding domain of COVID-19 could possibly be responsible for its invasion in the host cell and further binding to the ACE2 receptor. The morphological studies suggest that furin like cleavage site has been identified in the spike protein of the virus this structures were to be found absent in predominant members of corona family, this feature makes COVID-19 unique from other SARS-like corona viruses [15,16]. The pathological data reported by Lei et al. opine that COVID-19 patients presented increased leukocyte numbers, atypical respiratory findings, and higher levels of plasma pro-inflammatory cytokines. Infected individuals by the SARS-CoV-2 case reports showed a patient at 5 days of fever contemporaneously with a cough, coarse breathing sounds of both lungs, and with a high body temperature of 39.0°C. Accompanied with leukopenia with leukocyte counts of 2.91 × 10^9 cells/L of which 70.0% were neutrophils. Further blood C-reactive protein was found to be on a higher side, a value of 16.16 mg/L of was noted which is above the normal range (0 mg/L - 10 mg/L). Presence of COVID-19 virus in the host is proportionate to alleviated erythrocyte sedimentation rate and presence of D-dimer [17]. Patients with COVID-19 infection, exhibited unusually high levels of cytokines and chemokines in blood, particularly IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Along with this, certain cases presented rising levels of pro-inflammatory cytokines such as IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα, which served as an extra severity factor to physiological conditions of patient [14]. Post initial symptoms, the nasal and throat swabs detected high viral loads, and the viral shedding pattern matched to that of patients with influenza. An asymptomatic patient was found to have a similar viral load compared with symptomatic patients. Eventually COVID-19 infection gravely attacks the hosts' respiratory system which progresses into severe pneumonia, RNAaemia, combined with the incidence of ground-glass opacities, and acute cardiac damage [18].

SYMPTOMS

The predetermining factors age and immune system of has dominating effect on COVID-19 symptoms to death ranged from 6 days to 41 days and generally narrowing of this range is observed in patients which are already suffering from other diseases like hypertension , diabetes , cancer etc. and underlying health conditions or are above 70. Symptoms of COVID-19 generally starts in an individual during the incubation period i.e. of 14 days and median period on 5 days - 6 days [19]. Initially the indications start with a mild anorexia, confusion, dizziness, sore throat, rhinorrhoea, and sputum production. Many patients sometimes suffer from chest pain or haemoptysis. Very rarely gastrointestinal symptoms such as diarrhoea, nausea, vomiting, and abdominal are seen, although this may not be underestimated [20,21]. Therefore, it is important to test faecal and urine samples to exclude a potential alternate route of transmission, specifically via health care workers, patients

etc. Thus, development of methods to identify the potential transmission modes such as faecal and urine samples are urgently warranted in order to develop strategies to inhibit and/or minimize transmission and to develop therapeutics to control the disease [22]. After gathering substantial indications, the CDC (Centers for Disease Control in March, 2020) added four new symptoms including fever, chills, chills with repeated shaking, muscle pain, sore throat, ageusia and anosmia.The unique clinical manifestation of COVID-19 shows excessive sneezing and sore throat and respiratory depression leading to insufficiency in oxygen and causing hypoxemia. Importantly, whereas patients infected with COVID-19 developed gastrointestinal symptoms like diarrhoea, a low percentage of MERS-CoV or SARS-CoV patients experienced similar GI distress. 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 [19]. Approximately 90% of patients were presented with more than one symptom, and 15% of patients present with fever, cough, and dyspnoea. It appears that fewer patients have prominent upper respiratory tract or gastrointestinal symptoms compared with SARS, MERS, or influenza. Retrospective reports of clinical characteristics in pregnant women with COVID-19 were found to be similar to those reviewed for non-pregnant adults [23,24]. A retroactive case series from Zhejiang province that included 62 infected candidates were observed to have clinical features less severe than those of the primary infected patients from Wuhan City, signifying that second-generation infection might cause milder infection [25].These are certain cases that, even after exposure to the virus, do not develop any symptoms. These infected individuals although do not develop any clinical manifestation but are termed as “asymptomatic and silent carriers” that are responsible for transmission of the virus without being aware of it. The WHO reported (April 1, 2020) that about 25% confirmed cases continued to show no signs of infection. Studies by Zou et al. [18] have shown that an asymptomatic patient was found to have a similar viral load compared to symptomatic patients, but viral load in patients with advanced infection was higher than patients with a mild-moderate case. However, the study included only 1 asymptomatic patient out of 18 and hence needs more data as substantial evidence. Another set of cases that showed symptoms rather later than never were the “pre-symptomatic” patients. These cases, even after getting infected and incubating the virus take between 5 days to up to 2 weeks to show any symptoms. Data from around the world suggests that pre-symptomatic cases are a more common category than completely asymptomatic [26,27].

EPIDEMIOLOGY TIMELINE OF MAJOR COUNTRIES AFFECTED BY COVID-19

The spread of pandemic COVID-19 mounted its roots worldwide and caused severe effects to humanity. Initially it started spreading from China, further hotspots moved to USA, Spain, Italy and moreover exponentially increasing day-by-day in India too. The epidemiologic timeline comparison of the chief pretentious countries explicated here gives a brief appraisal of statistically COVID-19 cases reported in this countries and corresponding deaths occurring there in.

CHINA

Around the first week of December 2019, a cluster of patients with fever, dry cough that later advanced into pneumonia of an unidentified etiology was admitted to a hospital in Wuhan, in Hubei province of China. The first patient was admitted around 1 December 2019 to Jin Yin Tan hospital and subsequent cases rolled in 9 days later on 10 December 2019. On 31 December 2019, the WHO country office in China was informed of these cases by the Wuhan Center for Disease Control and Prevention, after which potential infections like influenza, avian influenza, adenovirus, SARS-CoV and MERS-CoV were eliminated [28]. Since then, until 3 January 2020, almost 44 patients had been identified with similar symptoms with

unknown causative agent [29]. During this time period, the National health commission of the people's Republic of China traced a common link of these patients to a nearby wet seafood market i.e., the Huanan Seafood Wholesale Market; of which almost 66% of the staff was affected. The market was shut on 1 January 2020, disinfected and Wuhan was put under lockdown. By 7 January 2020, the causative agent was identified as a novel coronavirus and its first genome sequence was reported by Prof. Yong-Zhen Zhang and his research team on 10 January 2020 [30]. Based on molecular analysis of the isolated virus, it was initially names as 2019-nCoV, later officially named as COVID-19 by the WHO and SARS-CoV-2 by the International committee on taxonomy of viruses (ICTV). The local outbreak transitioned into the second phase as number of cases kept rising due to nosocomial infections as well as close contact transmission [31]. Shortly, other provinces in china reported cases including Hubei (258 cases), Guangdong (14), Beijing municipality (5) Shanghai municipality (1) and the first death due to the COVID-19 infection was reported on 11 January 2020. On 15 January 2020, the first ever imported case of laboratory-confirmed novel coronavirus (2019-nCoV) from Wuhan was stated by Ministry of Public Health, Thailand. By 20 January 2020, the epidemic has spread to Republic of Korea and Japan [32].

The WHO affirmed the outbreak as a PHEIC (Public Health Emergency of International Concern) on 30 January 2020 which later recognized and was stated as a global pandemic on 11 March 2020. By the end of January globally 9826 cases in 19 countries were reported with China accounting for almost 9720 confirmed cases and 213 deaths, which was attributed as the third phase of the outbreak. A steady growth in the number of patients was observed in the country which peaked on February 5th with 3892 new cases taking the total to 24363 cases post which the graph lowered until the next major peak observed in daily new lab-confirmed cases reported in a day on February 13 with 15,152 which crossed the 50,000 mark. Around the same time a sharp increment in number of deaths was witnessed with 11 new deaths on 11 February to 157 deaths on 13 February. However, the number of deaths declined for a while in an unsteady fashion until the biggest surge on April 17, with 1290 deaths in a day. The number of positive cases as well as deaths exhibited a steady decline after sharp peaks in China. At this point, the epicenter had already shifted from the China to European regions being an additional reason for China's quick recovery apart from other precautionary measures. As per the reports by WHO, the number of deaths due to COVID-19 dropped to almost zero in early April and has been stable ever since (as of 10 May 2020). The number of positive cases have also declined significantly. In the light of these positive recovering outcomes, the lockdown was recently lifted in Wuhan, which once was the epicenter of COVID-19 disaster and emerged as powerful example for the world. Although, China was able to flatten the curve, asymptomatic patients and easing of precautionary measures still pose a threat to the public health and a second wave of infection may occur [32,33].

UNITED STATES OF AMERICA (USA)

Weeks after the preamble of a novel virus of the corona family to the world, a wave of panic was sent as cases were identified outside of mainland china. A public health emergency was declared soon after; which resulted in citywide quarantines, cancellation of several international events as well a travel restriction. The virus, although identified in China late last year has since spread to more than 212 countries (including UTs) [34]. Shortly after China and Italy started reporting increment in cases at an alarming rate, USA caught up and attained high number of cases in time shorter than expected. The US soon became the epicenter of the COVID-19 pandemic after reported cases surpassed those officially reported by China [35]. The first reported case in the U.S. was identified in Washington state on January 21, 2020, when a man with travel history to Wuhan, China tested positive. A few days later, second case was reported of a woman who had

just returned from the same region. A day later, the third case was confirmed in Orange county, California followed by two more cases reported on January 26, both with travel history to China. All the initially reported cases were advised to self-isolate for two weeks as a precautionary measure [36]. Despite the basic measures, the first case of person-to-person transmission in the country was reported in Chicago on January 30, between a married couple, after the wife returned from China [37]. With every passing day new cases surfaced across the country, those tracing back to either people with recent travel history to China or repatriated college students from Wuhan, China. By 20 February 2020 around 40 cases were reported and on 26 February first case of community transmission was confirmed in Solano County, California. Soon after, the First death due to COVID-19 in the Unites States was reported on 28 February in Washington. A state of debacle was set in motion as numbers kept rising and the situation kept worsening hereafter. By March the virus was no longer contained to a couple of states but had now spread to states including Massachusetts, Minnesota, New York, Illinois and many more and coronavirus cases reached to 100 on March 2.By March 6, ten more states had report their first case of coronavirus that included: Hawaii, Utah, Nebraska, Kentucky, Indiana, Minnesota, Connecticut, South Carolina, Pennsylvania, and Oklahoma along with previously recognized states with cases including Nevada, Colorado, Tennessee, and Maryland. Several cases at this point were associated with passengers from the Grand Princess Cruise ship, which was being held off the California coast close to San Francisco. By March 8 the total confirmed US deaths due to coronavirus were 22: Out of which 19 were reported in Washington, 1 in California, and 2 in Florida. Iowa , Virginia, Kansas, Missouri and Vermont made it to the list and report their first case of infection with the coronavirus by then. In matter of 9 days (by 11 March 2020) the number of positive cases increased by 10 folds to 1,205 with 37 deaths. States which previously had no positive cases such as Arkansas, Delaware, Mississippi, New Mexico, North Dakota and Wyoming reported their first cases. By March 17, 5,145 were infected with the coronavirus while 91 deaths were reported. The infection had now spread to all the states, West Virginia being the last one to report its first case. With each passing day thousands of COVID-19 cases were being reported in the country. On March 22, 20202, highest increment in the number of positive cases of 8,631 was reported which brought the total count to 32,341 then and 110 COVID-19 akin deaths, which brought the count to a cumulative of 409. Since then the count of positive cases started to grow exponential by figures of 10,000 to 20,000 new cases being reported every day. On March 26, in United States the total number of reported confirmed surpasses that of China with over 85,000 cases, making it the country with the highest number of patients affected by the coronavirus, in the world [38]. By 31 March 2020, the country had 185,791 positive COVID-19 patients and 3,737 coronavirus related deaths. The cases reached 300,000 mark by reporting a total of 307,318 cases in the USA and about 9559 reported fatalities by April 7, indicating an anticipated 10,000 cumulative deaths by the following week.

As per the gloomy prognosis of about deaths cause by the novel coronavirus, the death toll surpassed 10,000 deaths on the very next day (April 8) with 1286 reported new deaths and total of 10,845 deaths till date. The number of casualties increased by the day and the country reported a leap in the cases on April 9, reporting 1895 new deaths that day, increasing the cumulative to startling number of 12,740 which increased to 14665 (new deaths - 1925) on April 10 and 16596 (new cases - 1931) on April 11. By April 11, the number of cases in country had risen to a total of 461275 with New York reporting most cases (1,80,458) and fatalities (8,627) followed by New Jersey with 58,151 positive tested cases and 2183 deaths in the state. The number of cases rose to 32,549 as 3,838 new cases were reported on April 18 which lowered and occasionally rose to a peak on April 30, when it crossed 1,00,000 cases (reporting - 1,003,974 cases total). The number of cases reported daily is slowing down but are increasing gradually till date, making the USA as one of the worst hit countries

by the COVID-19 pandemic. As of May 14, 2020, the total number of reported cases worldwide is 4,248,389 with USA accounting for a total 1,361,522 in it. Besides, 28% of the worldwide deaths (292046) were also reported in the USA (82,119) [39-40]. In defiance of the harrowing conditions prevailing across the country, USA is determined to develop vaccine for the novel corona virus and has been examining drugs with potential action against the same.

ITALY

The novel corona virus traced back to Wuhan, Hubei Province of China has sent shockwaves throughout the globe. From what started as a 'pneumonia of unknown etiology' to unravelling into a full-fledged outbreak across major countries in the world is addressed as "the worst crisis since the world was II". One such country that is gravely affected includes Italy. The country under the WHO European region reported its first case on 1st February 2020 when two Chinese tourists in Rome were confirmed positive for the virus. The number began to rise exponentially as a multitude of cases were detected, beginning with 16 positive cases from Lombardy on February 21, to 60 new cases and first reported death in the region on February 22. The situation took an appalling turn as the virus was suspected to have spread throughout the country by the beginning of March [41]. Even after limited proximity to the hotspot regions in the initial phase and being considered as one of the countries with the best healthcare system. Italy is said to be world's worst-affected country in the COVID-19 pandemic (based on per head of population) stating that there are 521 confirmed cases for every 1 million Italians [42]. Several reasons could be presented to account for the worsening of situation such as; Italy having one of the second-oldest populations in the world and the lack of proactive measures taken to contain the spreading of the virus. Although In late January 2020, following the progress of COVID-19 epidemic in mainland China, on 3 February, Italy established precautionary screening measures, including thermal cameras and medical staff at airports as well as canceled all flights to and from China and declared a state of emergency. On the contrary, citing a comparative: India reported its first case around the same time as Italy and yet, Italy reported its 100 cases within 23 days in contrast to India's 45 days despite early precautionary measure [43].

Some facet of this catastrophe can definitely be credited to bad timing or what Italians call *sfortuna (*bad luck*)* that weren't in the hands of the policymakers. Some other factors, per contra indicate to the lack of understanding the degree of threat posed by COVID-19 and taking efficient measures in the early stage. The Italian government handled the COVID-19 pandemic by imposing a series of strategies that progressively escalates the restrictions within lockdown areas labelled "red zones", which were then broadened until they ultimately were applied to the entire country. Which did more harm than good [44]. Italy also failed to scale up testing. And within a couple of weeks the hospitals were overwhelmed with COVID-19 patients and a shortage of hospital beds, equipment and especially protective gear arose directly exposing the frontline healthcare workers to a potential risk of contracting infection [45].

The aftermath of their delay in making stern plan of action can be seen in the rapid growth in the number of cases that are increasing at higher rates than anticipated. On 31 March 2020, Italy crossed 100,000 cases (total reported cases 101739) and increasing with 11591 reported deaths, making it the region with most confirmed cases in the European region. However, a plunge in the number was seen for three consecutive days; reported number of new cases was 4805 which fell to 4316 on April 6 to 3039 on April 7. Similarly, new deaths per day fell from 681 (on April 5) to 527 on April 6, however, a slight increment was recorded on the next day i.e. April 7 with 604 deaths in 24 hours. On April 13, the total confirmed cases

surpassed 150000 and reported a tally of 156363 cases with 19,901 deaths. It increased to 207428 on May 2 with only 1965 newly reported cases, lowest in weeks. The number of reported cases per day started decreasing and fell as low as 802 cases as reported on May 11 and 165 deaths, lowest deaths reported in a day in a month. The number of confirmed cases as of this writing (May 16 2020) is 223,096 and the total number of deaths are 31,368. Evidentially, this small yet somewhat significant fall in numbers is a relief. An increase in the numbers could be anticipated but subsequent fall in the numbers would indicate an alleviation in number of cases and causalities and give hope and raise moral of millions [8,46].

SPAIN

After Wuhan, China the hotspot moved to various major countries like Iran to Italy and Later to Spain, which recorded some of the highest numbers of infected individuals in the world [47].

On 13 March 2020, the World Health Organization declared Europe as the new epicentre of the pandemic. By then, European regions had more cases than rest of the world combined and had even more reported cases than China at its peak of the epidemic [48,49]. Italy had initially the fastest spreading rate followed by Spain, which later surpassed it in number of confirmed cases and deaths. Spain soon became the one of the worst hit country with COVID-19 in the entire European region [50]. Spain recorded its first COVID-19 case on 31 January 2020 when a German tourist, who was in close contact with people who had recently visited china, tested positive in La Gomera, Canary Island. The second case was of a British citizen infected in the Alps who was tested positive on February 10. The transmission was still in Phase I and the increment in number of cases was exponential yet slow. However, in late-February, first 4 new cases related to an Italian cluster were identified positive for COVID-19 and soon enough community transmission broke into Spain and the number of cases began to shoot up. One major reason suspected behind this is the Champion's league football match in Milan which was attended by more than 40,000 people on 19 February. Around 2500 Valencia players along with fans and journalists had attended the event which is anticipated to have caused the explosion of cases in early March.

A total of 10,000 cases was surpasses when on March 17 the total confirmed cases rose to 11,178. The first major peak, however, was observed on March 19 with 893 cases confirmed in a day that grew to 2113 cases in one day on March 21. Within a span of 3 days, an almost 2-fold upsurge in the total confirmed cases was reported on March 20 to be almost 20,000 (19,980) to 30,000 (33,089) on 24 March and crossed 40,000 (39,673) COVID-19 cases on the next day i.e. 25 March, 2020.Data from March 30 suggests that all 50 provinces in Spain had active cases with no exceptions. By the end of March, Spain had reported more than 50,000 cases and grew to cross 100,000 cases (to 102,136) on April 20. Amidst that time, on April 3, Spain recorded 950 deaths in 24 hours - highest at that time recoded by any country in a day [51,52]. Although, the number of COVID-19 cases increased through the first two months since the first case was identified, the graph lowered in mid-April with occasional hikes in daily reported cases and deaths. For instance, on April 15 almost 3,061 new cases were identified but the graph kept lowering for a month until spiking up on May 13, with 2234 cases in 24 hours. On the same day (May 13) the Spanish government released the results of its first wave of seroprevalence study that indicated a rough number of 2 million people to be infected by SARS-CoV-2 (5%), but the number of patients was 10 times higher than anticipated statistic on the same day. Although the figures have been decreasing significantly, the occasional rise in numbers could indicate a potential wave in the country. As of May 14, the number of COVID-19 cases in Spain stands at 228,691 and 27,104 deaths over time [8].

INDIA

The devastating ramification of a global outbreak due to the SARS-CoV-2 has affected almost all countries and is responsible for millions of deaths and an economic slowdown worldwide. One such country is India that shares borders with China- the initial epicentre of COVID-19. The proximity to china, population, poverty and an already overburdened healthcare system were primary concerns that could've caused a boom in cases however, rapid response and precautionary measures like rigorous containment policies, assiduous contact tracing, self-isolation, quarantine facilities and a nationwide lockdown are major reasons responsible to curb an explosion in the number infected cases. An additional reason stated was lower R_o value i.e. the basic reproduction number that indicates average number of people that may get infected by a lab-confirmed case. In India, the R_o was found to be 1.7 in India compared to higher numbers reported from countries like china (2.14). Italy (2.4), Spain (2.74) however, the exact cause for this low R-naught value is still unidentified [53]. India reported its first lab-confirmed COVID-19 positive patient on 30 January 2020 in Kerala and reported no further cases for a month, until 2 March 2020, when 2 new cases emerged. All the 3 patients were students who had recently travelled back from Wuhan, China. A stable yet slow growth was observed until march 29, when unexpectedly 255 confirmed cases were identified in a day [54]. The country was in phase one for months after the first case was reported. However, the country transitioned into phase II in early March, when one Sikh preacher with travel history to Italy and Germany attended a public gathering and became a super spreader, infecting around 27 people and 40,000 people were ordered to be quarantined. In a similar incident in Delhi, in a Tablighi Jamaat religious congregation attended by 2000 including 281 foreigners, around 24 people tested positive and around 200 attending the event displayed symptoms [55]. The first death due to nCoV-19 infection was reported on 13 March 2020, the deceased had returned from Saudi Arabia and has exhibited symptoms ever since [53]. A sudden increase in deaths was observed on April 8, with 30 new deaths taking the tally to 35 causalities which increased to 50 by April 22 with 1383 confirmed cases nationwide. A 2.7-fold increment in deaths was observed as 72 new deaths were reported on 4 May and peaked on 5 May with 123 new deaths. A sharp upsurge has been noted in number of cases as well as deaths due to COVID-19 but the country has yet to report any incident of community transmission which indicated prolonged phase II and a delay in stage III. India's quick response and diligent counteractive measure such as the nationwide lockdown when only a handful cases were confirmed has been proven beneficial in delaying phase III transmission. As of May 12, the total confirmed cases in India stand at 70,756 and 22953 deaths [56].

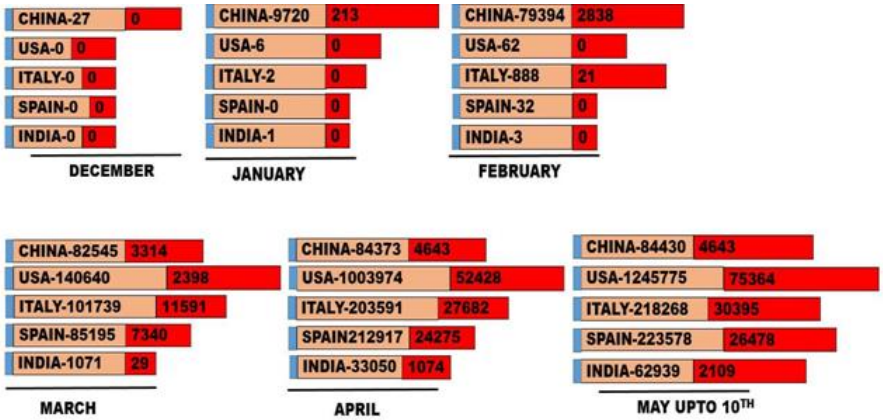

Figure 1: Outspread of Novel Corona virus in five major Countries around the world statically comparatively indicating the total cases reported in each month and deaths occurring. Deaths accounting in red section and cream part indicates the reported cases.

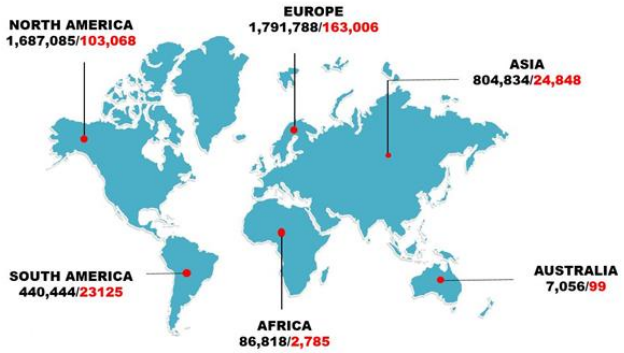

Figure 2: The spread of COVID-19 symbolizing throughout the world and demonstrating statistics Continent wise signifying the total cases stated and followed by demises in red.

DIAGNOSIS

One deceptive facet of the novel corona virus infection is its early stage generic symptoms with manifestations as simple as a runny nose, cough and mild fever that eventually progress into pneumonia, it is difficult to draw a clear distinction between a common viral infection from corona and hence, a confirmation test is important [56]. The laboratory tests to confirm infection cause by SARS-CoV-2 can be broadly classified into three categories mainly Molecular assay - to confirm an active infection, Serological tests - which detects a preceding infection by antibody (produced against the antigen) detection but may/may not serve to diagnostic purposes and Medical imaging (supplementary test). The existing diagnosis include three distinct types: Reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP). A reverse transcription polymerase chain reaction (RT-PCR) requires samples from the oropharyngeal and/or nasopharyngeal swabs or sputum specimen. Results generate within a couple of hours to up to 2 days. However, with passing time the virus moves lower from throat into the lungs to multiply and thus by the second week of infection, the sample must be collected from the deeper airways by coughed up phlegm or by a catheter [57]. Although the test is rapid and precise, factors such as the site collection of sample and the time of collection are equally important during laboratory testing for accurate diagnosis of the SARS-cov-2 and to confirm it as an underlying cause for the existing infection and pneumonia. For the detection of the HCOVs, the most suitable site for sample collection is the upper and the lower respiratory tract; particularly the throat, nasopharyngeal aspirate, phlegm, Bronchoalveolar Lavage.

This sample is intended to acquire the virus genetic material which is converted to the DNA utilizing an enzyme reverse transcriptase. Then, to identify the complimentary virus sequence specific primers are added and subsequently a short length of viral DNA copy is produced using another enzyme (mostly modified taq polymerase). This operation is continued for almost 30 cycles that amplify the viral DNA copies and avail for detection. This amplified admixture of DNA is then subjected to the RT-PCR machine and exposed to varying temperatures to set off chemical reactions that duplicate a target segment of the viral DNA. To these newly formed DNA strands, marker labels anchor and release a fluorescent dye. The presence and intensity of the dye is measured by an attached computer and presented on screen in real time. The confirmation of a virus being present is done when the measure surpasses a particular level of fluorescence [58]. Various serology diagnostic test producers have designed and made available testing devices that can be operated outside a laboratory set-up to tackle with the overwhelming number of testing samples, limited lab-based testing capabilities, reagents and to rule out results rapidly. These kits detect either proteins from the SARS-CoV-2 (apparent in throat swabs and

phlegm) or detect the presence of antibodies in blood or serum that generate against the antigen proteins expressed by the virus. In response to an antigen invasion that causes an infection, our bodies respond by releasing antibodies including IgG and IgM. As per FDA, the IgM antibodies produced against the SARS-CoV-2 are perceptible in blood days after the preliminary infection whereas, IgG antibodies are detectable only after an infection. This is the principle on which the diagnostic test is based [59].The diagnostic kit is a plastic case enclosing a paper strip anchored with specific antibodies, to which the antigen binds if present in adequate concentration. This reaction generated a signal which can be observed visually and takes no more than 30 minutes. However, there are various factors that affect the accuracy of the test including time since the initial stage of disease, density of virus in samples, test apparatus and its reagents. It is only when the virus would be actively replicating that the antigen will be expressed [60]. The presence of these antibodies in blood samples not only reveal that the individual was exposed to the causative agent (SARS-CoV-2) but can also help to identify the magnitude of people that have contracted the disease as well as the people that may be asymptomatic/silent carriers or have recovered and considered immune to it now [3]. In addition to this, the test aids in prioritized testing of vulnerable and high risk communities such as the frontline workers including doctors, nurses, sanitation workers, etc. who may have developed a certain level of immunity [61].

Another diagnostic test i.e. a CT scan can be used supplementary to other tests to confirm and asses the degree of infection. However, for patients with high clinical manifestations linked to risk factors and indications it is not reliable for a standard screening. The chest films are although not as sensitive in the early stages of the disease. But in a few days, the CT scan usually reveals bilateral multipolar ground-glass opacities with a perhipheral, asymmetric and mostly posterior dispersion. As the disease progress, subpleural bands, consolidation and crazy paving may develop. But usually in the initial stage of the disease, the GGO may be limited to the inferior lobe of the right lung and present as unifocal lesions [62]. Advanced stage disease could be characterized by a substantial increased rate of vacuolar sign, fibrotic streaks, air bronchogram, pleural effusion and bronchus distortion. Even though the chest films cannot be taken into consideration as sole evidence to confirm the disease it can be beneficial in the follow-up of the disease and it proves to be advantageous in ways including - estimation of condition worsening or improvement and may play a role in triage of patients to prioritize the patients based on severity of the disease [63].

Research and development Diagnostic companies from Taiwan have paved a new diagnostic test similar to the rapid influenza test, which would detect the binding of monoclonal antibodies to the nucleocapsid protein (N protein) of the SARS-CoV-2 which is expected to produce results within 20 minutes. WHO declared (as of April 8) that these tests are in investigation stage only.

TREATMENT

Recently identified virus of the corona family, the SARS-CoV-2 is behind one of the most disastrous pandemics ever and virus has claimed more than 250,000 deaths across the globe. The virus, even though mere nanometers in size, has proven to be a very challenging nemesis for researchers and health care professionals in terms of developing a definite cure against it and hence, patients were administered with a variety of treatments to overcome the current the situation [64]. The two major strategies till date are mainly based on two principles i.e. alleviation of the destruction caused by the virus and reinforcing the body's remedial actions, supportive care in ICU to manage pestilential disease of COVID-19 and for potential

nosocomial infections, and additionally, rigorous volume management, multi organ function monitoring, nutritional estimation and nutrition level to patients suffering from SARS-CoV-2 [65]. At present, there are no specific antiviral drugs or vaccine against COVID19 infection for potential therapy of humans. Some researchers are scrutinizing pre-existing drugs that prove effective against infection by SARS-CoV-2 while others are employing recently advances and discoveries regarding the virus and attempting to design novel treatments and vaccines [66]. The most efficient path to cease COVID 19 might be to assess the clinical significance of an already existing molecule. The rechanneled drugs, which were previously approved and marked safe would save time by surpassing the testing and will be available in the market already [67]. The only option available is using broad-spectrum antiviral drugs like Nucleoside analogues and also HIV-protease inhibitors that could attenuate virus infection until the specific antiviral becomes available. Gautret P et al. performed a study in which the drugs previously indicated in conditions like malaria, rheumatoid arthritis and lupus has been under investigation for its potential action against SARS-CoV-2. A group of patients which were confirmed cases of COVID-19 were included in a single arm protocol, they received 600mg of hydroxychloroquine daily and their viral load in nasopharyngeal swabs was tested daily. Depending on their clinical presentation, azithromycin was added to the treatment. Twenty cases were treated in this study and showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin added to hydroxychloroquine was significantly more efficient for virus elimination. Substantial evidence of these drugs defeating the corona virus by two methods: Firstly, they make anchoring of the virus to the host cell difficult and prevent their entry in cell and subsequently stop their multiplication. Secondly, even if the virus manages to enter the host cell, the drugs are capable of killing the virus before it starts replicating [68]. As per two reported uncontrolled studies it was recorded that Chloroquine is responsible for QT interval prolongation and impel arrhythmias, contraindicating it in patients with cardiac problems. In addition, concomitant administration of azithromycin may synergistically prolong QT interval [69]. This risk, though can be avoided by referring to the patient's medical history and vigilant monitoring during treatment [70].

Another course of treatment getting wide consideration for its potential action against the disease caused by the n-CoV19 is the antiviral therapy, Anti-bacterial therapy and adjuvents therapy with corticosteroids, interleukins or gamma globulins. Several drugs used in to treat HIV and SARS/MERS respiratory syncytial virus, hepatitis C virus, and some viral hemorrhagic fevers are under scrutiny [8]. Combination therapy of antiviral drugs showed promising effect in treatment of COVID-19 virus, lopinavir-ritonavir and fabiravir –ribavirin are such combination of drugs which came out with some encouraging results. This combination reportedly inhibits protease enzyme in both, in vitro and in vivo animal studies and is deemed to be efficacious in treating COVID-19 based on its good outcomes in treatment during the SARS and MERS outburst [71]. Remdesivir (GS-5734) is a new nucleoside analog and has been recognized as a potential and promising antiviral drug against a wide array of RNA viruses, including SARS/MERS-CoV. The drug shows ability to inhibit the target enzyme RNA-dependent RNA polymerase (RdRp) that the virus needs to reproduce; an enzyme nearly similar in SARS, MERS as well as the SARS-CoV-2. The drug showed promising effects in SARS and MERS cases and is most likely to be effective against the ncov-19 [65]. As a candidate drug that has not been approved, information about the side effects of remdesivir has not been reported yet. At present, two randomized, controlled, double-blind clinical trials are ongoing to evaluate the efficacy and safety of remdesivir (200 mg loading dose on Day 1, followed by 100 mg i.v. once-daily maintenance dose for 9 days) in hospitalized patients with mild/moderate or severe COVID-19 respiratory disease [72]. According to a trial called Adaptive COVID-19 treatment trial supported by the National Institute of Allergy and

Infectious Diseases (NIAID), the recovery rate of patients hospitalized with progressive nCoV-19 infection with affected lungs was 31% faster than patients receiving placebo treatment. In addition, the mortality rate of patients treated with remdesivir was 8% compared to the placebo group's mortality rate of 11.6% [73]. Another experimental theory being highly considered is the immune based options such as: convalescent plasma therapy, hyper immune serums and i.v. immunoglobulins, out of which the benefits of the convalescent plasma therapy surpass that of the rest two. The therapy is also more preferred over other immune based therapies as it is easy to administer in patients and does not require pharma companies' intervention. The convalescent plasma therapy can be given in any stage of infection including before exposure (to improve immunity), after exposure and to patient critically ill or in a non- critical condition A study published by the proceedings of National Academy of science of the United States of America, stated that an improvement in outcomes was observed on administration of plasma therapy in patients. Furthermore, India reported (as of April 26) full recovery with "promising prognosis" of the first patient to receive the plasma therapy in the country [74-80]. Another strategy considered for COVID-19 was to enforce immunomodulators. Aged patients with pre-existing conditions with advanced COVID-19 infection was found to have a lower count of lymphocytes especially CD4+ T cells which indicates a deficient immune system making these patients even more susceptible for progression of COVID-19 or nosocomial infections. Moreover, the invading virus triggers immune response causing cytokine storm that might worsen the condition. These reasons call for a treatment modulating the immune system including options such as cortecosteriods, thymosin alpha-1, tocilizumab, interferons, cyclosporine-A and antibacterial agents [74].

An investigation led by Bert Schepens and Xavier Saelens of the VIB life-sciences institute in Ghent, Belgium, and Jason McLellan of the University of Texas at Austin recognized that the antibodies isolated from llamas have the ability to bind to the spike proteins, an entryway for the SARS-CoV-2 into cells. The trial revealed that the antibodies can neutralize both, SARS and MERS-CoV and the combination of human and llama antibody generated a hybrid antibody with the ability to potentially neutralize the nCoV-19. This study could prove to be a breakthrough in the treatment of infection by novel corona virus but the data is limited to make any strong assumptions of its range of activity [75]. One of the safest and effective treatments against the malicious coronavirus could be a vaccine. A vaccine introduces attenuated virus into the body and triggers an immune response imitating an infection, this helps body to prepare its defense and retaliated faster on second exposure. A vaccine would offer a head start to the host's immunity to develop antibodies against the virus and develop certain degree of resistance to it [76]. The vaccine may consist of viral spike protein, a crucial component of the nCoV-19 that could be used to form a nontoxic and efficacious vaccine. This spike consists of a receptor binding site that identifies and anchors to a surface component of the human cell and enters into it [77]. The ability of BCG (and other live vaccine) to persuade metabolic and epigenetic alterations that could improve the immune response to viral infection called trained immunity is what makes it a candidate for testing. Through this mechanism it decreases the viral load in the blood after invasion of the virus resulting into milder infection and faster recovery from COVID-19. A random controlled trial reported BCGs possible action in preventing respiratory infection. More such trials are underway in Netherlands and Australia [78].

A new study conducted by Elfiky AA showed test of anti-HCV drugs against COVID-19 RNA dependent RNA polymerase (RdRp). The results suggest the electiveness' of Sofosbuvir, IDX-184, Ribavirin, and Remidisvir as potent drugs against the newly emerged HCoV disease. The present study presents a perfect model for COVID-19 RdRp enabling its testing in silico

against anti-polymerase drugs. Besides, the study presents some drugs that previously proved its efficiency against the newly emerged viral infection [79].

Adjuvant therapy plays as vital role in management of COVID-19 similarly, Melatonin is elective in critical care patients by reducing vessel permeability, anxiety, sedation use, and improving sleeping quality, which might also be beneficial for better clinical outcomes for COVID-19 patients. Notably, melatonin has a high safety profile. There is significant data showing that melatonin limits virus-related diseases and would also likely be beneficial in COVID19 patients a study summarized by Herrera EA et al. [80].

Multiple treatment options, both novel and pre-existing are under rigorous analysis and testing for their potential activity against the viral infection caused by the SARS-CoV-2. Hundreds of clinical trials are underway around the globe and experimental treatments as well as supportive care are provided to the patients in hope to cease the progression of the disease and its spread. No standard approved treatment for COVID-19 exists (As of May 1, 2020).

GENOTYPE AND PHENOTYPE OF COVID-19

The recently identified COVID-19 is an enveloped virus with single stranded (positive-sense) RNA with matrix protein covered by a capsid which contains nucleoproteins.

Based on the phylogenetic relationships and genomic structures, the COVID-19 belongs to genera Betacoronavirus, and falls into the sub-family of orthocoronavirinae, family - *Coronaviridae*. Typically, a CoV comprises of six ORFs in its genome, out of which ORF 10,11 on the one-third of the genome close to the 30 -terminus is responsible for encoding for four major structural proteins. All these proteins and supplementary proteins are decoded from sgRNAs of the COV. The genetic and phenotypic arrangement of COVID-19 is crucial in regards to its pathogenicity. An initial study of the genetic sequence of nCoV-19 revealed around 80% similarity to SARS-CoV and 50% to MERS-CoV which has originated from bats. Hence, the phylogenetic analysis designates SARS-CoV-2 to genus betacoronavirus along with SARS-CoV responsible to infect bats, humans, etc. In addition to this, the ACE2 receptor from a variety of animal was found homologous therefore, linking these animal species as potential carriers of the COVID-19 infection; which is yet another indicator of its origin from bats.

Although the N-CoV-19 has several similarities with the genotype and phenotype of other human betacoronavirus (SARS-CoV and MERS-CoV), it also exhibits several special characteristics that affects its pathogenesis. The genetic sequence data and phylogenetic reports, when explored in depth, showed plenty differences from the SARS-CoV to be considered a novel betacoronavirus strain. In betacoronaviruses, the structural organization of nucleocapsid protein (N), envelope protein(E), and membrane protein (M) also differs [81]. A strong association was found between the time of sample collection and gathering of genetic diversity of the COVID-19 by Volz, et al. through their study of analysis of 53 NCoV-19 whole genome (up to February 3,2020). By means of Bayesian inference and phylogenetic methods, the introduction of COVID-19 in humans was traced back to Wuhan, China in the beginning of December, 2019 [82].

FUTURE DIRECTIONS TO CURB THE SPREAD OF COVID-19

The COVID-19, a highly contagious viral infection has made the entire world come to a standstill. The repercussion of

spreading of the viral infection are not limited to the health but has had severe impact on socio-economic and mental health of the general public as well. The estimates about the effects of COVID-19 in the near future, at this point are highly subjective as the only predictable thing about this virus has been its extensive unpredictability. Yet, the society and heath care professionals, collectively can take measure to avoid further transmission. Several stringent protocols must be followed for the next couple of months including: prevention of human to human transmission via social distancing, innovative approach to meet health care services demands utilizing new approaches like telehealth facilities [83]. The international health agencies must keep working on emergency response and short term support to better understand the threats of the outbreak. In addition to this, the WHO guidelines must be strictly followed and any recent findings related to treatment, epidemiology must be shared and made accessible to researchers around the world. Lastly, considering the world is suffering collectively, the matter must be worked upon on a humanitarian basis to fight the battle against COVID-19. The restoration of normal life activities outside the precautionary norms can't be ascertained, but hope the humankind will come out of this crisis stronger than ever.

CONCLUSION

COVID-19 has unwrapped into one of the worst pandemics in history and has affected more than 4 million people globally. It is responsible for major public health concerns but has also brought about social and economic challenges in the society. Although the researchers have been successful in characterizing the novel coronavirus (COVID-19) and are extensively working on production of a vaccine; no significant therapy or treatment has yet come forth for the infection. However, quick diagnosis, isolation and quarantining potential cases have attained notable results. The preliminary widespread of the infection is now decelerating and the curve is lowering. A second wave in many regions is feared but the prominent decrease in number of daily reported cases indicates some scope of the improvement in the situation in the near future. At this point, whether the pandemic gains further momentum or dwindles with time remains to be seen.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENT

The authors express their gratitude to the management of Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee Maharashtra, India.

REFERENCES

1. Perlman S, Netland J (2009) Coronaviruses post-SARS: Update on replication and pathogenesis. Nature Reviews, Microbiology 7(6): 439-450.
2. Woo PCY, Lau SKP, Huang Y, et al. (2009) Coronavirus diversity, phylogeny and interspecies jumping. Experimental Biology and Medicine 234(10): 1117-1127.
3. Bogoch II, Watts A, Thomas-Bachli A, et al. (2020) Pneumonia of unknown aetiology in Wuhan, China: Potential for

international spread via commercial air travel. Journal of Travel Medicine 27(2).

4. Lu H, Stratton CW, Tang YW (2020) Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. Journal of Medical Virology 92(4): 401-402.
5. Zhu N, Zhang D, Wang W, et al. (2020) A novel coronavirus from patients with pneumonia in China, 2019.The New England Journal of Medicine 382: 727-733.
6. WHO (2020) Novel Coronavirus - China.
7. Zhao S, Lin Q, Ran J, et al. (2020) Preliminary estimation of the basic reproduction number of novel coronavirus (2019-nCoV) in China, from 2019 to 2020: A data-driven analysis in the early phase of the outbreak. International Journal of Infectious Diseases 92: 214-217.
8. COVID-19 situation reports (2020).
9. WHO (2020) Novel Coronavirus - Japan (ex-China).
10. Rothan HA, Byrareddy SN (2020) The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity 109: 102433.
11. Salehi S, Abedi A, Balakrishnan S, et al. (2020) Coronavirus disease 2019 (COVID-19): A systematic review of imaging findings in 919 patients. American Journal of Roentgenology 215(1): 87-93.
12. COVID-19 Advice for public (2020).
13. Tyrrell DAJ, Myint SH (1996) Coronaviruses. In: Medical Microbiology. 4th (Edn.).
14. Riou J, Althaus CL (2020) Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV). Eurosurveillance 25(4).
15. Coutard B, Valle C, de Lamballerie X, et al. (2020) The spike glycoprotein of the new coronavirus 2019-nCoV contains a furin-like cleavage site absent in CoV of the same clade. Antiviral Research 176.
16. Lu R, Zhao X, Li J, et al. (2020) Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet 395: 565-574.
17. Abrishami A, Samavat S, Behnam B, et al. (2020) Clinical course, imaging features, and outcomes of COVID-19 in kidney transplant recipients. European Association of Urology.
18. Zou L, Ruan F, Huang M, et al. (2020) SARS-CoV-2 viral load in upper respiratory specimens of infected patients. The New England Journal of Medicine 382: 1177-1179.
19. Li Q, Guan X, Wu P, et al. (2020) Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. The New England Journal of Medicine 382: 1199-1207.
20. Chen ZM, Fu JF, Shu Q, et al. (2020) Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World Journal of Pediatrics 16: 240-246.
21. Wang XF, Yuan J, Zheng YJ, et al. (2020) Clinical and epidemiological characteristics of 34 children with 2019 novel coronavirus infection in Shenzhen, Zhonghua Er Ke Za Zhi. Chinese Journal of Pediatrics 58: E008.
22. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, et al. (2013) Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: A descriptive study. The Lancet Infectious Diseases 13(9): 752-761.
23. Chen H, J Guo, C Wang, et al. (2020) Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: A retrospective review of medical records. Lancet 395: 809-815.

24. Zhu H, Wang L, Fang C, et al. (2020) Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. Translational Pediatrics 9(1): 51-60.
25. Xiao-Wei X, Xiao-Xin W, Xian-Gao J, et al. (2020) Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: Retrospective case series. BMJ 368: m606.
26. Hu Z, Song C, Xu C, et al. (2020) Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Science China Life Science 63: 706-711.
27. Lai CC, Liu YH, Wang CY, et al. (2020) Asymptomatic carrier state, acute respiratory disease, and pneumonia due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2): Facts and myths. Journal of Microbiology, Immunology, Infection 53(3): 404-412.
28. WHO (2020) COVID-19 situation reports.
29. The novel cornavirus pneumonia emergency response epidemiology team (2020) The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) - China, 2020. China CDC Weekly 2(8): 113-122.
30. Adhikari SP, Meng S, Wu YJ, et al. (2020) Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: A scoping review. Infectious Diseases of Poverty.
31. Sun YJ, He WT, Wang L, et al. (2020) COVID-19: Epidemiology, evolution, and cross-disciplinary perspectives. Trends in Molecular Medicine 26(5): 483-495.
32. https://COVID19.who.int/region/wpro/country/cn.
33. Muccari R, Chow D, Murphy J (2020) Coronavirus timeline: Tracking the critical moments of COVID-19. NBC News, USA.
34. Timeline: How the new coronavirus spread | Coronavirus pandemic News, Al Jazeera (2020).
35. Orange County Register (2020) Orange county coronavirus patient released, in good condition, health officials say. Orange County Register, Los Angeles, USA.
36. Lee J (2020) Coronavirus update: First U.S. case of person-to-person transmission confirmed, 195 U.S. citizens in isolation and WHO declares a public health emergency. MarketWatch.
37. Timeline of the COVID-19 pandemic in the United States (2020).
38. COVID-19 situation reports (2020).
39. WHO (2020) Coronavirus disease (COVID-19) dashboard.
40. Flaxman S, Mishra S, Gandy A, et al. (2020) Estimating the number of infections and the impact of non-pharmaceutical interventions on COVID-19 in 11 European countries. Imperial College London 1-35.
41. Fleming S (2020) Italian coronavirus: Epidemiology expert explains flattening the curve. World Economic Forum, Italy.
42. Brahma D, Chakraborty S, Menokee S (2020) The early days of a global pandemic: A timeline of COVID-19 spread and government interventions. Brookings, USA.
43. Pisano GP, Sadun R, Zanini M (2020) Lessons from Italy's response to coronavirus, Harvard Business Review, USA.
44. Penney J (2020) Coronavirus started in China but Europe became the hub for its global spread. The Intercept.
45. WHO (2020) Coronavirus Disease (COVID-19) situation reports. WHO, Italy.
46. How did Spain get its coronavirus response so wrong? World news, The Guardian (2020).
47. WHO (2020) Europe now world's COVID-19 epicenter | Centre for Infectious Disease Research and Policy.

48. Lau H, Khosrawipour V, Kocbach P, et al. (2020) Internationally lost COVID-19 cases. Journal of Microbiology, Immunology and Infection 53(5): 454-458.
49. Coronavirus world map: Which countries have the most cases and deaths? World news, Support the Guardian (2020).
50. Spain: WHO coronavirus disease (COVID-19) dashboard (2020).
51. Timeline of the COVID-19 pandemic - Wikipedia (2020).
52. Sahu KK, Mishra AK, Lal A, et al. (2020) India fights back: COVID-19 Pandemic. Heart & Lung.
53. Kaushik S, Kaushik S, Sharma Y, et al. (2020) The Indian perspective of COVID-19 outbreak. Virus Disease 1-8.
54. https://COVID19.who.int/region/wpro/country/in.
55. Carter LJ, Garner LV, Smoot JW, et al. (2020) Assay techniques and test development for COVID-19 diagnosis. ACS Central Science 6(5): 591-605.
56. Loeffelholz MJ, Tang YW (2020) Laboratory diagnosis of emerging human coronavirus infections - the state of the art. Emerging Microbes & Infections 9(1):747-756.
57. (2020) Institute of epidemiology, disease control and research, Bangladesh.
58. (2020) COVID-19 Diagnostics explained. Asian scientist magazine, science, technology and medical news updates from Asia.
59. Jawerth N, IAEA office of public information and communication (2020) How is the COVID-19 virus detected using real time RT-PCR? International Atomic Energy Agency.
60. Vos LM, Bruning AHL, Reitsma JB, et al. (2019) Rapid molecular tests for influenza, respiratory syncytial virus, and other respiratory viruses: A systematic review of diagnostic accuracy and clinical impact studies. Clinical Infectious Diseases 69(7): 1243-1253.
61. Roche develops new serology test to detect COVID-19 antibodies (2020).
62. Zhou S, Wang Y, Zhu T, et al (2020) CT features of coronavirus disease 2019 (COVID-19) pneumonia in 62 patients in Wuhan, China. American Journal of Roentgenology 214(6): 1287-1294.
63. Coronavirus disease 2019 (2020).
64. Jean SS, Lee PI, Hsueh PR (2020) Treatment options for COVID-19: The reality and challenges. Journal of Microbiology, Immunology and Infection 53(3): 436-443.
65. Synbiota (2020) Timeline shows 3 paths to COVID-19 treatment and prevention (INFOGRAPHIC).
66. Abd El-Aziz TM, Stockand JD (2020) Recent progress and challenges in drug development against COVID-19 coronavirus (SARS-CoV-2) - an update on the status, Infection, Genetics and Evolution 83: 104327.
67. Gautret P, Lagier JC, Parola P, et al. (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents 56(1): 105949.
68. Fihn SD, Perencevich E, Bradley SM (2020) Caution Needed on the Use of Chloroquine and Hydroxychloroquine for Coronavirus Disease 2019. JAMA Network Open 3(4): e209035.
69. US Food & Drug Administration (2020) FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems.
70. Zhai P, Ding Y, Wu X, et al. (2020) The epidemiology, diagnosis and treatment of COVID-19. International Journal of Antimicrobial Agents 55(5): 105955.
71. A trial of remdesivir in adults with mild and moderate COVID-19.

72. National Institutes of Health (NIH) (2020) NIH clinical trial shows Remdesivir accelerates recovery from advanced COVID-19.
73. India News (2020) India's first COVID-19 patient treated with plasma therapy recovers.
74. Li L, Li R, Wu Z, et al. (2020) Therapeutic strategies for critically ill patients with COVID-19. Annals of Intensive Care 10:45.
75. Nature (2020) Coronavirus papers: Viral proteins point to potential treatments.
76. Gallagher J (2020) Coronavirus vaccine: When will we have one? - BBC News.
77. Curtis N, Sparrow A, Ghebreyesus TA, et al. (2020) Considering BCG vaccination to reduce the impact of COVID 19, Lancet 395: 1545-1546.
78. Elfiky AA (2020) Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sciences 248: 117477.
79. Zhang R, Wang X, Ni L, et al. (2020) COVID-19: Melatonin as a potential adjuvant treatment. Life Sciences 250: 117583.
80. Rothan HA, Byrareddy SN (2020) The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity 109: 102433.
81. van Elsland SL, O'Hare R (2020) COVID-19: Imperial researchers model likely impact of public health measures. Imperial News, Imperial College London.
82. Fontanarosa B P, Bauchner H (2020) COVID-19 - looking beyond tomorrow for health care and society | infectious diseases. JAMA Network 323(19): 1907-1908.
83. Qian X, Ren R, Wang Y (2020) Fighting against the common enemy of COVID-19: A practice of building a community with a shared future for mankind. Infectious Diseases of Poverty 9:34.