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The SARS-CoV-2 Pandemic a Global Emergency: The Journey from Bats to Humans

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Abstract

Bats are considered as the reservoirs of coronaviruses (CoVs) which resulted in severe disease outbreaks in humans. Zoonotic coronaviruses responsible for Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), were originated from bats and remain highly pathogenic to humans during the last two decades. Recently, an acute respiratory disease outbreak which spread in Wuhan, China was caused by a novel coronavirus (SARS-CoV-2) also known as 2019-nCoV, received worldwide attention. The World Health Organization (WHO) officially declared the COVID-19 epidemic caused by SARS-CoV-2 as a public health emergency. The emergence of SARS-CoV-2 has been considered as the third highly pathogenic epidemic of the 21st century. The SARS-CoV-2 belongs to β-coronavirus group with highly identical genome to bat coronavirus RaTG13, assuming bat as the natural host. According to WHO as of December 21, 2020, approximately 75,479,471 persons were infected with 16,86,267 deaths in 222 countries. Whereas the in Pakistan according to WHO as of December 21, 2020, around 4 57,288 persons were infected with 9, 330 death reported in the country.

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1. Introduction

Bats are ecologically important group of mammals. More than 1300 species of bats belong to the order Chiroptera [1]. Bats have ability to fly over long ranges to migrate as compared to other mammals. The mammalian host–virus relationship analysis confirmed that bats harbor a significant proportion of zoonotic viruses than any other mammal species [2]. Therefore, bats are recognized as important reservoir of Coronaviruses [3]. Coronaviruses belong to family *Coronaviridae*, and subfamily Orthocoronavirinae. Within the subfamily Orthocoronavirinae, there are four genera of coronaviruses alpha, beta, gamma and delta coronavirus. Alpha and beta coronaviruses are present in mammals, whereas gamma and delta coronaviruses are found in birds [4]. Coronaviruses are positive-sense single stranded RNA viruses with nucleocapsid of helical symmetry. As the name indicates, when observed under an electron microscope the external spike protein displayed a typical crown shape structure [5], The CoV has round or elliptic shape with diameter of around 60–140 nm [6]. The CoV genome is 27–32 kb in size, naturally, the two thirds of the genomic RNA encode two large overlapping polyproteins, ORF1a and ORF1b, which are processed into RNA dependent RNA polymerase (RdRp) and other nonstructural proteins which are involved in RNA synthesis. The remaining genome encodes for four structural proteins such as spike (S), envelope (E), membrane (M), and nucleocapsid (N) [7]. When out of the host cell this virus is protected by lipid bilayer envelope, membrane proteins and nucleocapsid. As the coronavirus is commonly associated with acute respiratory infections in humans, its ability to infect multiple host species and a variety of diseases makes it a complex pathogen [8]. The frequent interactions of wild animals with humans make them a common source of zoonotic infections. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) are zoonotic pathogens that can cause severe respiratory diseases in humans [9]. A novel coronavirus designated as 2019-nCoV is another human pathogen. This new virus was first discovered in 2019 when viral metagenomics was carried out on three bronchoalveolar-lavage specimens from Chinese adult patients with unexplained severe pneumonia [10]. In addition, 2019-nCoV is the new member of the genus *Betacoronavirus.* Many Betacoronavirus have been discovered mainly in bats of genus Rhinolophus which have acted as the reservoir of the SARS-CoV-2 virus [11].

1.1. Virus Transmission in Host

The viral transmission from human to human resulted through respiratory droplets caused by sneezing and coughing as the virus remain in air for almost 3 hrs. The coronavirus spike protein interaction to the host cell receptor is an important criterion to determine infectivity, the tissue tropism and range of species for the virus.

The SARS coronavirus attached to the angiotensin-converting enzyme 2 (ACE2) receptor to infect human cells. Moreover, it is also important to note that in healthy persons ACE2 does not occur in large quantities. ACE2 receptors are mostly present in the cardiac and diabetic patients who take different medicines such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). The SARS-CoV-2 contains a mutated gene that is similar to the HIV virus, and besides ACE2 receptors it could bind to another target called furin which is an enzyme that works as a protein activator in the human body especially in lungs, liver and intestines so the virus has multiple sites to attack the healthy humans. Typically, many proteins when produced remain dormant and to activate their certain functions they need to be cut at specific points, so the furin do this in the human cellular pathways.

Some recent studies showed that the SARS-CoV-2 spike proteins could target GRP78 receptors (Glucose Regulated Protein 78) to infect human cells. It was also reported in a research finding that SARS-CoV-2 invade the host cells through another novel route CD147-spike protein. The viral spike protein attached to CD147 receptor on the host cells to facilitate the viral invasion of the human host [12]. So, these studies revealed this virus has 4 major sites for attachment in the human host which is alarming situation for the scientists working on the vaccines of SARS-CoV-2.

The infection begins when the virus enters the host organism and the spike protein attaches to its complementary host cell receptor. After attachment to the host cell, the protease from the host cell cleaves and activates the receptor-attached viral spike protein. The cleavage and activation depend on the available protease which allows cell entry through endocytosis or direct fusion of the viral envelop with the host membrane.

1.3. Coronavirus Epidemics

The strains of coronaviruses showed significant variation in risk factor. The one had killed 35% of those infected such as MERS-CoV, and others are relatively harmless, such as the common cold viruses. Coronaviruses can cause cold with fever and sore throat from the swollen adenoids, occurring primarily in the winter and early spring seasons. They may also resulted in pneumonia and bronchitis.

The seven important strains of human coronaviruses are,

1. Human coronavirus 229E (HCoV-229E)
2. Human coronavirus OC43 (HCoV-OC43)
3. Severe acute respiratory syndrome coronavirus (SARS-CoV)
4. Human coronavirus NL63 (HCoV-NL63)
5. Human coronavirus HKU1
6. Middle East respiratory syndrome-related coronavirus (MERS-CoV)
7. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as novel coronavirus 2019 (2019-nCoV)

1.4. Severe acute respiratory syndrome (SARS)

The SARS-CoV, which caused severe acute respiratory syndrome (SARS) was discovered in 2002, resulted in unique pathogenesis due to its involvement in both upper and lower respiratory tract infections. SARS-CoV human to human transmission resulted in a global SARS epidemic which remained for 8 months [13]. Initial studies investigating animal sources of the virus from wet markets in the Guangdong province of China suggested that Himalayan palm civets and raccoon dogs were the most likely hosts responsible for human transmission [14]; however, the role of bats as the original animal reservoir hosts of SARS-CoV was speculated as similar viruses were detected in them [15,16]. Later on, during an ecological surveillance of bats in the same region, a SARS-like CoV that closely matched the human SARS-CoV was isolated from the Chinese horseshoe bat [17]. More than 8,000 people were infected and about 10% of them were died in this outbreak.

1.5. Middle East respiratory syndrome (MERS)

MERS-CoV occurred in Saudi Arabia in 2012 and resulted in case fatality rate of 35% [18]. Dromedary camels were found to be the cause and reservoir of MERS-CoV. In the Arabian Peninsula and in Northern Africa, the seroprevalence rate for MERS-CoV in dromedary camels ranged from 70% to 100% [19]. While camels were believed to be the primary zoonotic host of transmission in humans, it was also evident that bats acted as reservoir for MERS-CoV [20,21].

1.6. Coronavirus disease 2019 (COVID-19)

Infection with SARS-CoV-2, the virus that caused COVID-19 appears to be highly contagious in nature and spread by droplet infection. A pneumonia outbreak was reported in Wuhan, China, on December 31, 2019, the outbreak was traced to a novel strain of coronavirus, which was given the interim name 2019-nCoV by the World Health Organization (WHO), later renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses. It was reported in earlier studies that the virus may come from the Huanan Seafood Wholesale Market that become the source of viral transmission to humans.

The Wuhan strain emerged as a new Betacoronavirus strain having 70% genetic similarity to the SARS-CoV. It is thought to have a zoonotic origin. The genetic analysis revealed that the coronavirus clustered genetically with the genus *Betacoronavirus*, in subgenus *Sarbecovirus* (lineage B) together with two bat-derived strains. It is 96% identical at the whole genome level to bat coronavirus BatCov RaTG13, isolated from a bat species *Rhinolophus affinis* (Chinese horseshoe bat) collected from China's Yunan Province, so it is widely suspected to originate from bats as well. Some studies reported that there may an intermediate host may be a snake or pangolin which transferred the virus to humans. The coronavirus isolated from the Malaysian pangolin (*Manis javanica*) showed 90% genomic similarity to SARS-Cov-2. Furthermore, based on the genomic comparisons it is anticipated that the SARS-Cov-2 virus may be the result of a recombination between two different viruses, BatCoV RaTG13 and the pangolin coronavirus [11]. The pandemic has resulted in serious travel restrictions globally affecting 201 countries and territories, more than 45 countries are under partial or complete lockdown. As of June 15, 2020, as reported by WHO there has been at least 431,541 confirmed deaths and more than 7,823,289 confirmed cases of the coronavirus pandemic globally with 5.5% mortality rate. This pandemic has affected USA severely, the infected cases are 2,182,950 with 118,283 deaths more than any other country. Pakistan is also suffering due to this outbreak with 148,921 infected cases and 2839 deaths [22].

1.7. Pathogenesis

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 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 [23].

1.8. Symptoms

Symptoms of COVID-19 are non-specific and those infected may either be asymptomatic or develop flu like symptoms such as fever, cough, fatigue, shortness of breath, or muscle pain. Further development can lead to severe pneumonia, acute respiratory distress syndrome, sepsis, septic shock and death. Some of those infected may be asymptomatic, returning test results that confirm infection but show no clinical symptoms, so researchers have issued advice that those with close contact to confirmed infected people should be closely monitored and examined to rule out infection. The usual incubation period (the time between infection and symptom onset) ranges from one to fourteen days; and on average to five days in majority of the cases, therefore, 14 days isolation/ quarantine from the suspected cases is necessary .

It is important to note that there are similarities in the symptoms between COVID-19 and earlier betacoronavirus such as fever, dry cough, dyspnea, and bilateral ground-glass opacities on chest CT scans [24]. However, COVID-19 showed some unique clinical features that include the targeting of the lower airway as evident by upper respiratory tract symptoms like rhinorrhoea, sneezing, and sore throat [25]. Importantly, some patients infected with COVID-19 developed gastrointestinal symptoms like diarrhoea, a low percentage of MERS-CoV or SARS-CoV patients experienced similar GI distress. Therefore, it is important to test faecal and urine samples to exclude a potential alternative route of transmission, specifically through health care workers and patients [25]. Therefore, development of methods to identify the various modes of transmission such as feacal 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. The virus is also present in spinal fluid this shows that virus may cause encephalitis in infected people. Other studies revealed that few positive cases of CoV19 caused loss of senses of smell (anosmia) in the patients without showing any other symptoms which is also critical situation [26].

2. Treatment

At present, there are no specific antiviral drugs or vaccine against COVID-19 infection for potential therapy of humans recommended by FDA or WHO. The person-to-person transmission of COVID-19 infection led to the isolation of patients. 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 [27]. Another report showed that the broad-spectrum antiviral drug remdesivir and chloroquine showed positive results invitro against SAR-CoV-2 infection [28]. The use of hydroxychloroquine in some COVID-19 patients seems to act as a zinc ionophore, thereby allowing extracellular zinc to enter inside the cell and inhibit viral RNA dependent RNA polymerase to stop the virus multiplication.

2.1 Total coronavirus and active cases in Pakistan

The number of cases has approximately increased during the month of March -July. The comparison of the number of COVID −19 cases has expanded after reducing in lockdown (Fig 1). If the condition continues to get worse as shown in the trend, flattening the curve and containing a virus may become impossible without taking serious steps. A further breakdown of cases reported every 15 days since the first case appeared is shown in Fig

2. The number of confirmed cases has significantly increased over the period of 6 months, however, it remained low in August and October 2020.

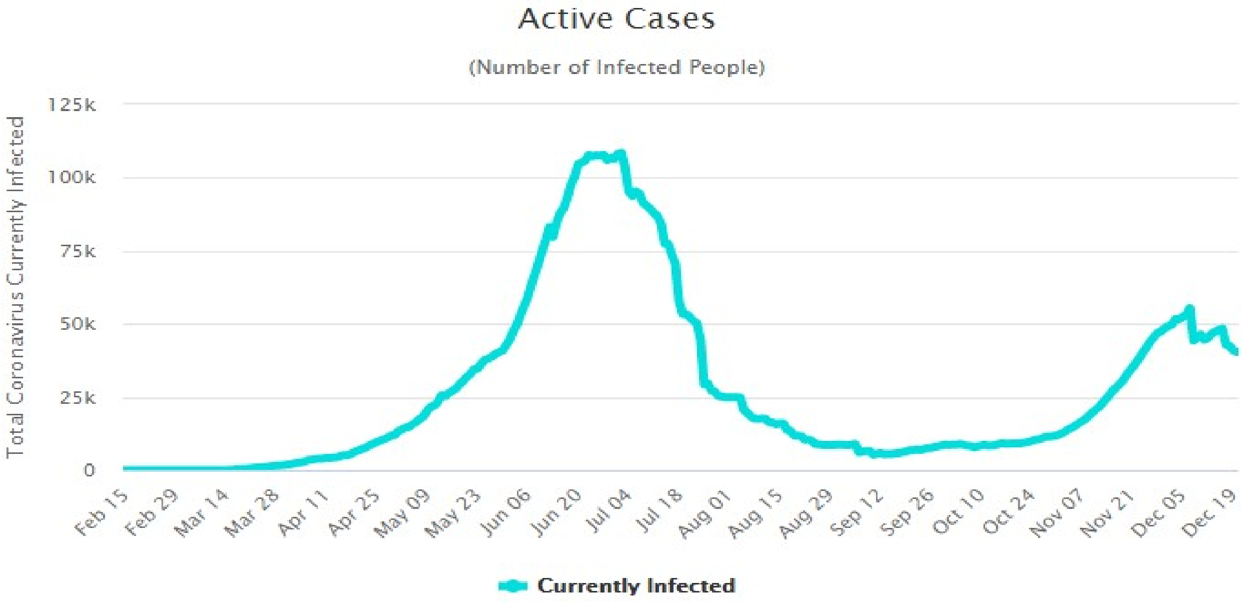

Fig. No 1 Active Cases Source: https://www.worldometers.info/coronavirus/country/pakistan/

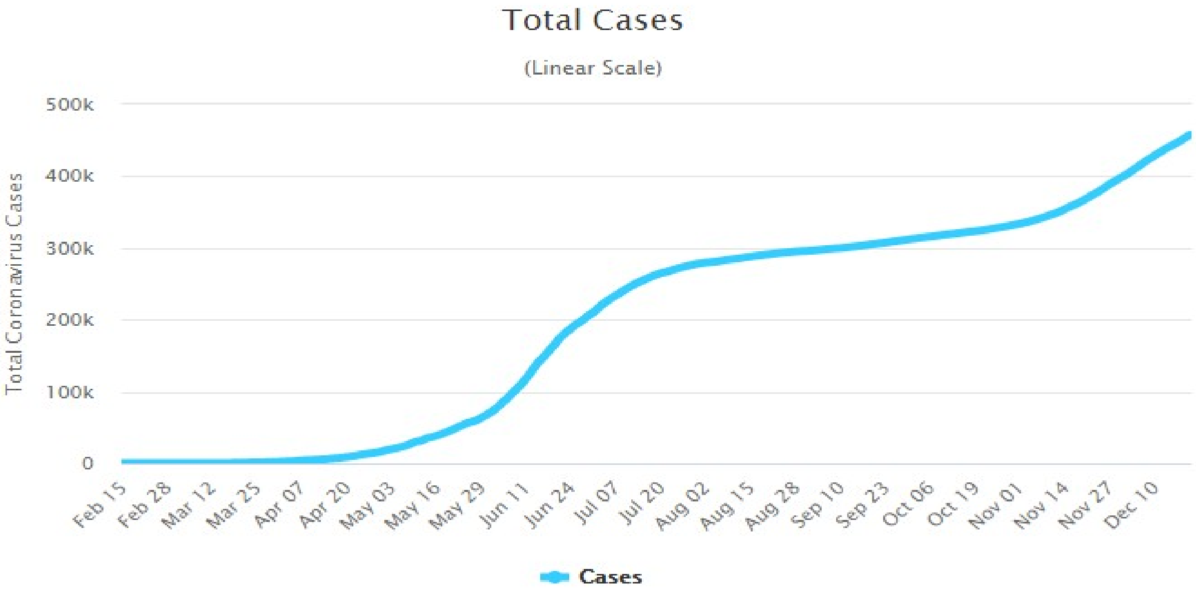

Fig. No 2 Source: Total Coronavirus Cases in Pakistan ttps://www.worldometers.info/coronavirus/country/pakistan/

3. Conclusions

It is summarized that the emerging pneumonia, COVID-19, caused by SARS-CoV-2, is a contagious disease and exhibit strong infectivity. The virus originated in Wuhan, China may be from bats as reservoir and then entered in unknown intermediate hosts, from there it is transmitted to human host and then human to human transmission started. SARS-CoV-2 emerged as super virus and spread to 201 countries. Therefore, extensive measures to reduce person-to-person transmission of COVID-19 are required to control the current outbreak. Special attention and efforts to protect or reduce transmission should be applied in susceptible populations including children, health care providers, and especially elderly people. Further, social distancing is need of the day to restrict the spread of the virus in the community.

5. Conflicts of Interests: -The authors declare that there are no conflicts of interests regarding the publication of this paper.

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