



Review

Genome Organization of Covid-19 and Emerging Severe Acute Respiratory Syndrome Covid-19 Outbreak: A Pandemic

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Abstract

The World Health Organization (WHO) announced Covid-19 disease as a pandemic caused by SARS-CoV-2 which has reached 204 countries and territories. Around 15 lakh people are infected and about 1 lakh have died till April 8, 2020. A global social and economic stress have been observed. SARS-CoV-2 is a rapidly evolved zoonotic single strand, positive sense RNA virus belonging to the genus betacoronavirus which contains structural and nonstructural proteins. It transmits through airborne droplets and rapidly spreads through person-to-person contacts in the human population. It causes both upper and lower respiratory tract disease to be associated with more severe illnesses, such as bronchitis, bronchiolitis, pneumonia, organ failure and respiratory distress syndrome. The symptoms of Covid-19 are fever, tiredness, dry cough, sore throat and difficulty in breathing. 5-10% people require critical care subjected to ventilation. Medicines are being used in combinations worldwide to overcome the disease. On the basis of research findings, we hypothesize that antimalarial drugs, regular BCG vaccination and higher temperature may reduce the infectivity of Covid-19. Physical distancing is a potential way to control community transmission of the pandemic. Vaccination is required to mitigate Covid-19 virus, while vaccine development is subject to further research.

Keywords: COVID-19, physical distancing, transmission

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The World Health Organization (WHO) announced Covid-19 disease as pandemic. It is a novel infection with serious clinical manifestations, including death, and it has transmitted over 204 countries and territories (Fig. 1). About sixteen lakh people are infected (Fig. 2) and about one lakh people have died till April 08, 2020 (Table 1).^[1] Covid-19 is contagious and highly progressive infectious which can affect healthy persons after trivial contacts.^[2] It has been established that Covid-19 is caused by severe acute respiratory syndrome virus known as SARS-CoV-2. Coronaviruses are

diverse with single-strand, positive-sense RNA. It has been shown that coronaviruses can be found around the world in bats, birds, cats, dogs, pigs, mice, horses, whales, and humans.^[3] SARS-CoV-2 is the third zoonotic coronavirus which has created a frightening crisis around the world on human health.^[4,5] Initial cases of covid-19 occurred in Wuhan, Hubei Province, China, in December 2019 and mushroomed over the globe. Human-to-human transmission has been observed during covid-19 infection since the middle of December 2019. Mostly older people (mean age 45 year)

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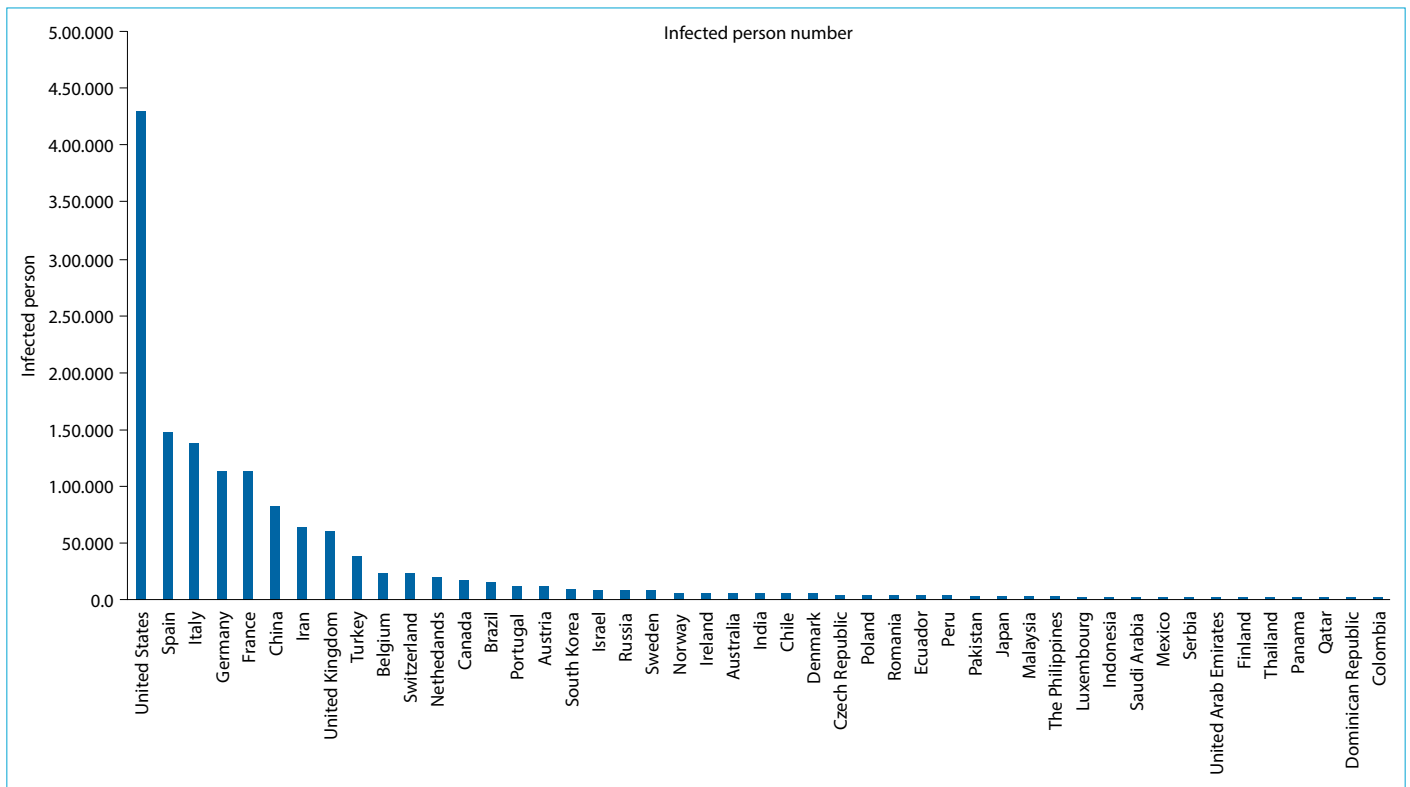


Figure 1. Data shows Corona patient numbers in different countries till 08 April, 2020.

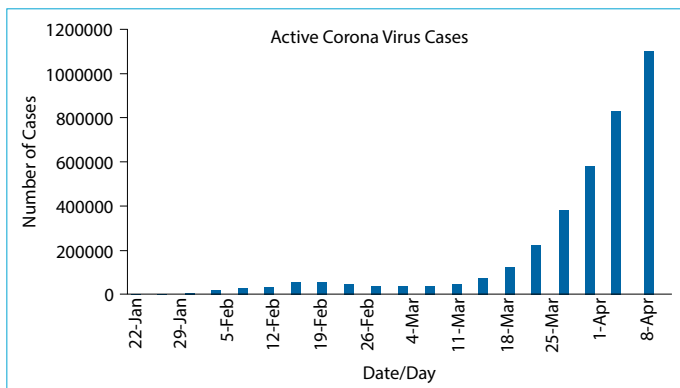


Figure 2. Date wise increasing numbers of active cases are depicted on the Y-axis till 08, April 2020.

get more infected as compared to younger one. The basic reproductive number (R_0) is estimated to be 2.0 (95% CI, 1.4 to 3.9) and Covid-19 doubles in size approximately every 7.4 days. (2020_10). The WHO has estimated mortality rate to be ~ 3.48 for Covid-19. Evidences showed that SARS-CoV-2 can survive from 3 hours in aerosol up to 72 hours on plastic, stainless steel, copper and cardboard surfaces.^[6] In March, 2003 an outbreak was observed in Hong Kong, causing a large amount of death due to respiratory disease which was named as SARS by the World Health Organization (WHO). In SARS, the neutrophil count and lactate dehydrogenase enzyme level were used as disease identification markers.^[7] A similar outbreak was caused by Middle East respiratory syndrome coronavirus (MERS-CoV) in September 2012^[8] which was not transmissible among humans like the SARS-CoV epidemic in 2003.^[9] Serologic and genomic data confirmed that camels and bats act as intermediate hosts for human MERS-CoV and SARS-CoV, respectively.^[10, 11] Recently, various kinds of studies were conducted worldwide which indicate that Malayan pangolin is the closest intermediate host (Fig. 3) for SARS-CoV-2 after Bat.^[12]

The most common symptoms of COVID-19 are fever, tiredness, and dry cough. Body temperature more than 38 degree Celsius (high fever) has been observed in covid-19 infected patients. Different case studies have shown that 20-25% people don't develop any symptoms and don't show any symptoms while they are infected, consequently they promote community transmission. Clinical investiga-

Table 1. Worldwide Covid-19 infected cases in various stages

Attributes	Cases (In Numbers)	Percentage (%)
Currently Infected	1.137.187	71.74
Case with Outcome	447.795	28.26
Mild Condition	1.088.244	96
Recovered/Discharge	353.075	79
Serious/Critical	48.953	4
Deaths	94.720	21

Total = Infected + Case Outcome, Outcome = Death + Recovered, Mild condition % = Non Critical/Currently Infected X 100, Recovered Patients % = Recovered/Case with Outcome X 100, Death % = Patients Died/Case with Outcome X100. Serious = Critical Cases/Currently Infected X100.



Figure 3. Potential intermediate host of novel coronavirus named as SARS-CoV-2.

tions have revealed that most of the people recover from the disease.^[13] Researchers showed interest in the presence of virus in feces but no evidence has been found yet.^[14] Nasal, throat swab and sputum samples are being used for diagnostic purposes by health specialists. The data so far suggest that the virus has a case fatality risk around 1%; this rate would make it many times more severe than typical seasonal influenza, putting it somewhere between the 1957 influenza pandemic (0.6%) and the 1918 influenza pandemic (2%).^[15] The Covid-19 pandemic caused worldwide shortage of hospital beds, ICU beds, and ventilators. The SARS-CoV-2 has a large economic and social impact on the human population. As still no potential therapy has been developed so lockdown has been implemented by different countries to weaken the viral spread.^[16]

Classification

2019-nCoV named as SARS-CoV-2 by considering its taxonomic and genomic relationships with the species of severe acute respiratory syndrome-related coronaviruses.^[17] Phylogenetic studies have established that SARS-CoV-2 was distinct from SARS-CoV in a phylogeny of the complete RNA-dependent RNA polymerase (RdRp) gene and virus belongs to the subgenus Sarbecovirus (Fig. 4).^[18] The genome of the SARS-CoV-2 showed similarity with bat-derived coronavirus strains, bat-SL-CoVZC45 and bat-SL-CoVZXC21, including the virus that caused the SARS outbreak of 2003.^[19]

Structure and Genome Organization

In the past two decades, covid-19 is the third rapidly evolved zoonotic RNA coronavirus, emerged in the human

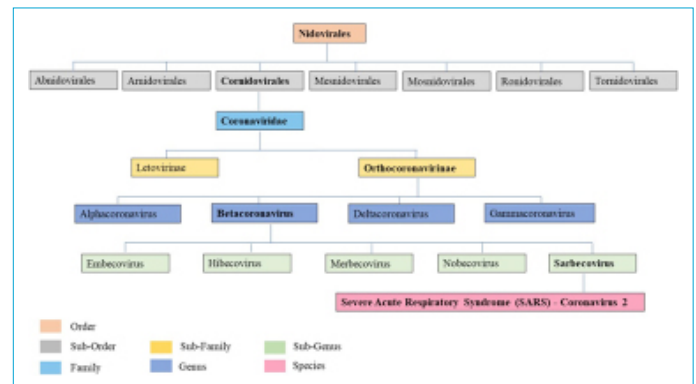


Figure 4. Taxonomic classification of Covid-19 (SARS-CoV-2). It belongs to the subgenus sarbecovirus of genus betacoronavirus.

population.^[5, 20, 21] Zhang, Wu et al. conducted metagenomic study and established that Malayan Pangolin coronavirus (SARS-CoV2-like) show 91.02% and 90.55% similarity at genomic level to SARS-CoV-2 and BatCoV, respectively. This study has revealed the Pangolin-CoV as the most closely related CoV to SARS-CoV-2 after BatCoV. In Pangolin-CoV and SARS-CoV-2 five conserved amino acid residues interact with human ACE2, but in Bat-CoV mutations are present in four amino acid. A putative furin recognition sequence motif at the S1/S2 cleavage site was observed in the Covid-19, which was absent in both Pangolin-CoV and BatCoV.^[12] The genome of Covid-19 has been sequenced and deposited to NCBI reported from different laboratories across the world. Updated sequence information has been provided in the Table 2. It has been found that covid-19 has a single, positive, sense stranded RNA. It contains 29.811 bp longs nucleotides (cDNA) broken down as follows: 8.903 (29.86%) adenosines, 5.482 (18.39%) cytosines, 5.852 (19.63%) guanines, and 9.574 (32.12%) thymines. Five mutations have been identified including T8782C (in ORF1a, codons AGT to AGC, silent mutation), T9561C (in ORF1a, codons TTA to

Table 2. List of genomes sequenced by different countries

Accession Number	Strain/Origin
MN988668	2019-nCoV WHU01
NC_045512	Wuhan-Hu-1
MN938384.1	2019-nCoV_HKU-SZ-002a_2020
MN975262.1	2019-nCoV_HKU-SZ-005b_2020
MN988713.1	2019-nCoV/USA-IL1/2020
MN994467.1	2019-nCoV/USA-CA1/2020
MN994468.1	2019-nCoV/USA-CA2/2020
MN997409.1	2019-nCoV/USA-AZ1/2020
MN985325.1	2019-nCoV/USA-WA1/2020
MT072688	SARS0CoV-2/61-TW/human/2020/NPL
MT106054	2019/nCoV/USA-TX1/2020
MT012098.1	SARS-CoV-2/human/IND/29/2020
MT050493.1	SARS-CoV-2/human/IND/166/2020

TCA, non-silent mutation), C15607T (in ORF1b, codons CTA to TTA, silent mutation), C28144T (in ORF8b, codons TCA to TTA, non-silent mutation), and T29095C (in Nucleocapsid, codons TTT to TTC, silent mutation).^[22] Different types of protein sequences have been identified in the viral genome which code for various structural and nonstructural proteins. Structural proteins include RNA dependent RNA polymerase (RdRp), Spike protein (S), Envelope protein (E), Membrane protein (M), Nucleocapsid protein, 5' UTR and 3' UTR. Nonstructural proteins such as ORF3a, ORF7a, and ORF8 function as accessory proteins playing a role in viral pathogenesis.^[23] In a few studies, it was shown that mutation in SARS CoV-2 was present at nucleotide level in gene S, nsp1, nsp3 and nsp15 but not at amino acid level.^[24, 25]

In addition, the SARS-CoV-2 strain found in the US, the Nucleocapsid (N) protein gene has three mutations (28881G>A, 28882G>A, and 28883G>C). Studies have revealed that the N protein of SARS-CoV is responsible for the formation of the helical structure during virion assembly. The N protein has potential value in vaccine development because it may cause immune response. Also, mutations associated with spike glycoprotein have been found. The significant SNP mutation (23403A>G) occurred in the gene encoding spike glycoprotein (S protein: D614G). The mutation D614G is located in the putative S1–S2 junction region near the furin recognition site (R667) for the cleavage of S protein when the virus enters or exits cells.^[26] Spike glycoprotein structure was predicted in SARS-CoV-2 (Fig.

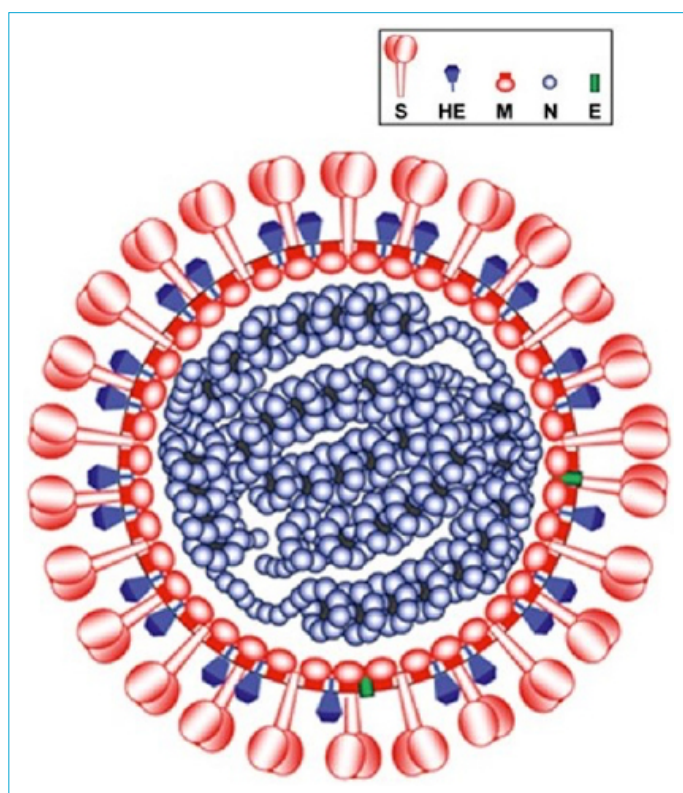


Figure 5. Schematic structural representation of Covid-19 (SARS CoV 2).

5) and two conformations, closed and open deduced via cryo-electron microscopy deposited to the protein data bank with pdb id 6VXX and 6VYB, respectively. It has been suggested that SARS-CoV polyclonal antibodies may inhibit SARS-CoV-2 spike mediated entry into cells.^[27] It has been found that the S1 domain of spike protein mediates an initial high-affinity association with their ACE2 receptor.^[28, 29] Walls et al and Zhou et al. have demonstrated experimentally that SARS-CoV-2 uses ACE2 (human angiotensin-converting enzyme 2) to enter inside the target cell and shows a similar affinity towards ACE2 as SARS-CoV.^[30] Consequently, the spike protein has been considered a viral target. The Mechanisms of viral entry may include membrane fusion upon receptor binding and induced conformational changes in spike protein followed by cathepsin L (CTSL) proteolysis which leads to activation of membrane fusion within endosomes.^[31, 32] Yadav et al. demonstrates that the SARS-CoV-2 shares approximate 96% whole genome identity with a BatCoV (RaTG13), from *Rhinolophus affinis* from Yunnan Province.^[33]

Transmission

The epidemic of 2019 novel coronavirus (now called SARS-CoV-2, causing the disease Covid-19) has expanded from Wuhan throughout China and is being exported to a growing number of countries (Fig. 6),^[13] some of which have seen onward transmission.^[34] It has been seen in the transmission of sars-cov-2 in Thailand, where taxi driver get infected from close contact of Chinese tourists who wore masks, which indicates asymptomatic transmission.^[35] Local transmission has been identified as a case of locally transmitted infection in Taiwan from a wife (who returned from Wuhan, China) to her husband.^[36] Research findings have been shown that the potential cause for spreading of covid-19 infection is human to human transmission by close contact via airborne droplets generated by coughing and sneezing (Fig. 7).^[37] Tedros Ghebreyesus, director-general of the WHO, said that 41% of the Covid-19 cases in Wuhan resulted from hospital-related transmission.^[38] Also, it has been observed that during this pandemic, the important thing is to separate clinicians providing care from those making triage decisions.^[39] Subclinical symptomatic^[40] or asymptomatic persons are being considered potential sources of Covid-19 infection may warrant a reassessment of transmission dynamics of the current outbreak.^[41] Study conducted in various countries demonstrates that Covid-19 shows sustained transmission and supports the implementation of physical distancing measures to rapidly control the outbreak. Worldwide data of infected persons established that older people (mean age 45 year) get more infected as compared to younger one (Table 3).^[42] Also, case studies have been confirmed that Covid-19 occurred in children, causing moderate-to-severe respiratory illness, in the early phase of the SARS-CoV-2.^[43, 44] It has been found that transmission of SARS-CoV-2 is affected by high tem-

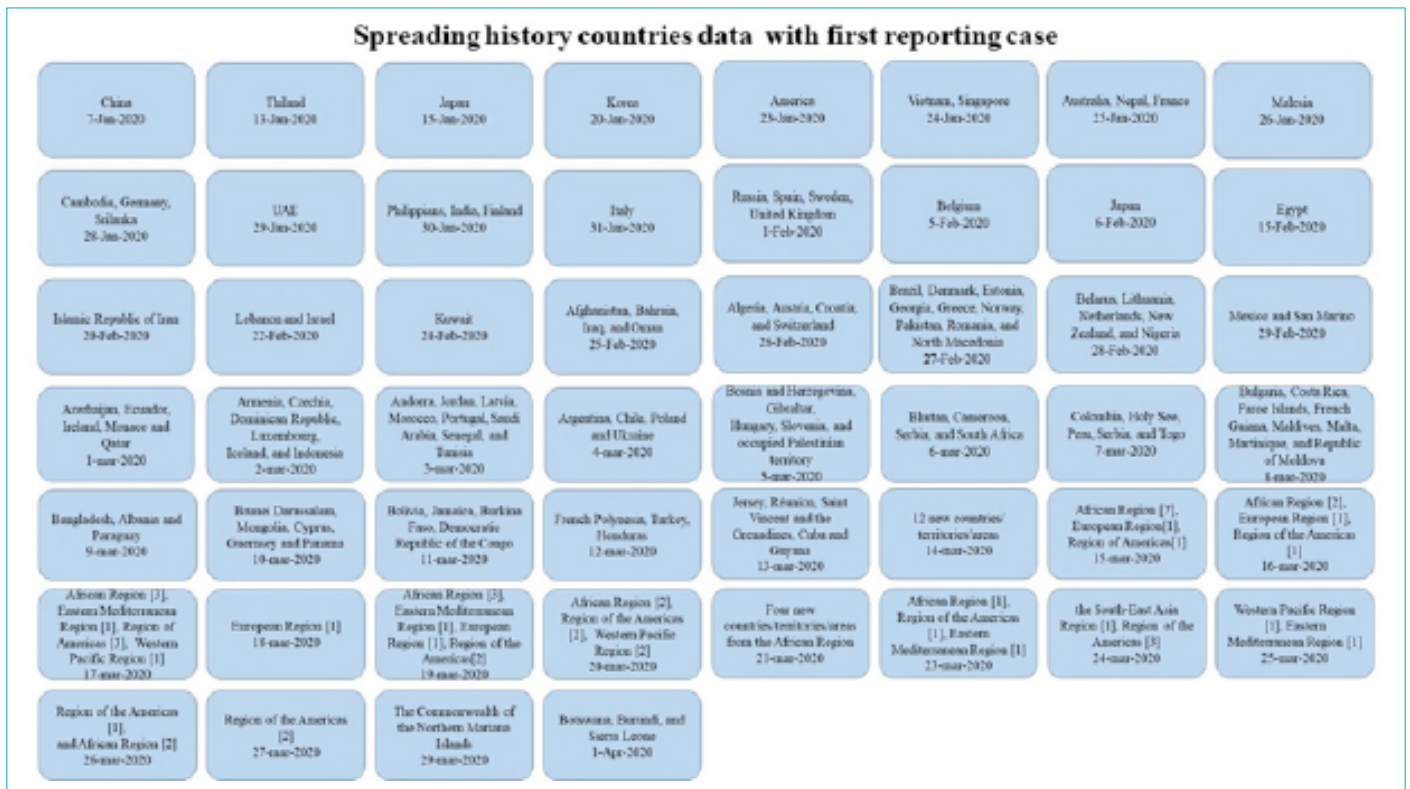


Figure 6. Transmission history of SARS-CoV-2 across the world.

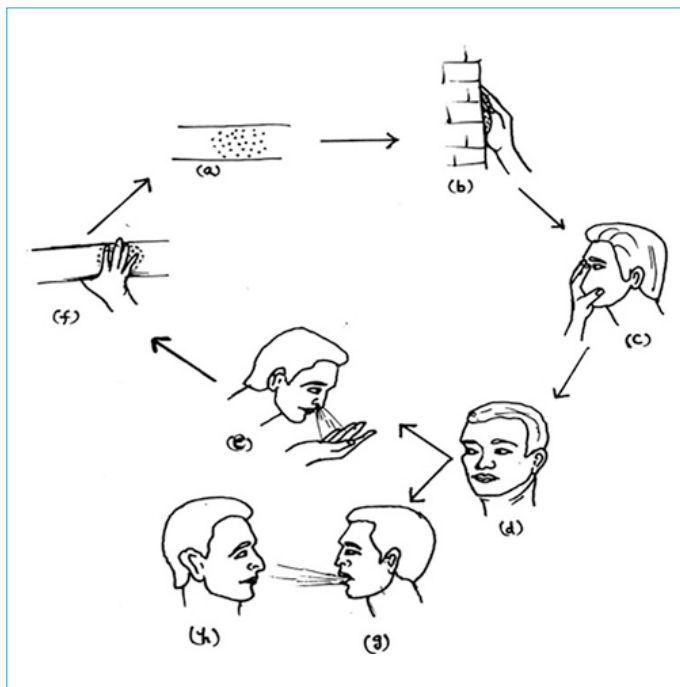


Figure 7. Local transmission among the human population. (a) Droplets containing coronavirus, (b) Person in droplet contact, (c) Virus entry in person through mouth and nasal route, (d) Virus infected person, (e, g) Infected person spread the virus through sneezing or coughing, (h) Person to person transmission of virus through arial droplet, (f) Infected person transfers the viral load on the surface.

Age (in years)	Death Rate (%)
80+	14.80
70-79	8
60-69	3.60
50-59	1.30
40-49	0.40
30-39	0.20
20-29	0.20
10-19	0.20
0-9	No fatalities

Death Rate = (number of deaths/number of cases) = probability of dying if infected by the virus (%). This probability differs depending on the age group. The percentages shown in the table do not have to add up to 100%, as they do NOT represent the share of deaths by age group. Rather, it represents, for a person in a given age group, the risk of dying if infected with COVID-19.

perature, antimalarial drugs and regular BCG vaccination (Fig. 8).^[45-47]

Diagnosis

Covid-19 is pandemic in the human population and causes both upper and lower respiratory tract disease to be associated with more severe illnesses, such as bronchitis, bronchiolitis, pneumonia, exacerbations of asthma, organ fail-

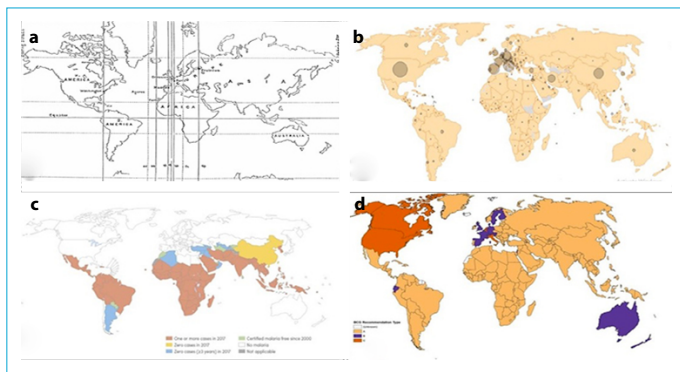


Figure 8. The outcome of comparative study among Malaria, BCG vaccination and Corona infected cases; (a) Geographically world map (b) Corona infected cases depicted by circle (c) Malaria infected cases (denoted by red color) (d) BCG vaccination distribution (Yellow color). From a and b, higher temperature with less patients infected to Covid-19. From (a, c), Malaria infected countries reported less Covid-19 cases. From (a, d), regular BCG administration shows less number of Covid-19 cases.

ure and respiratory distress syndrome. The virus could also invade CNS primarily through the olfactory route which is yet to be subject for further clinical investigation.^[48, 49] Molecular and physiological studies have revealed that SARS-CoV-2 grows better in primary human airway epithelial cells.^[20] Increased level of C-reactive protein (13.9 mg per liter) was observed in covid-19 examination in patients reported from China.^[50] Research findings have shown that lymphocytopenia was present in 83.2% of the patients infected with coronavirus.^[51]

The 14 days period is the incubation time (Table 4) of SARS-CoV-2.^[40] The incubation time was defined by WHO as the interval between the potential earliest date of contact of the transmission source (wildlife or person with suspected or confirmed case) and the potential earliest date of symptom onset (i.e., cough, fever, fatigue, or myalgia). Based on worldwide clinical data it has been established that only 5-15% of infected people face severely ill conditions and develop difficulty breathing. Research findings have shown that older age people with high blood pressure, heart problems or diabetes etc are more likely to develop serious illness and seek medical attention.^[52] Scientific strate-

Table 4. Incubation time for different coronaviruses including COVID-19	
Virus Name	Incubation Period (Typical Cases) in Days
COVID-19	2-14
SARS	2-7
MERS	2-14
Swine Flu	1-4
Seasonal Flu	1-4

gies for diagnosis of viruses are in the public domain such as RT-PCR based methods, paper-strip tests associated with CRISPR, viral RNA genome sensing based techniques. Researchers have revealed that the antibody based algorithms should have been implemented for SARS-CoV-2 in samples collected from throat swabs and serum.^[53] Worldwide clinical studies have suggested the use of oseltamivir and oxygen therapy, mechanical ventilation, systemic glucocorticoids to severe patients.^[54]

Treatment and Prevention

Physical distancing is an alternative way to restrict the viral spread, applied by various countries. It includes isolating ill persons (including voluntary isolation at home), quarantine suspected people, school closures, and telecommuting where possible. In public health practice, “quarantine” refers to the separation of persons (or communities) who have been exposed to an infectious disease and “isolation,” in contrast, applies to the separation of persons who are known to be infected.^[55] Researchers have suggested potential drug therapies including antiviral medication of interferon-1 β , the RNA polymerase inhibitor remdesivir, chloroquine, and a variety of traditional medicine. Doctors have treated covid-19 patients with combination of drugs being used in HIV, Swine flu and malaria; lopinavir–ritonavir (200 mg and 50 mg, respectively) twice a day for 14 days, Oseltamivir, Chloroquine are used in swine flu and malaria treatment, respectively.^[56, 57] In-silico methods should be employed for the development of vaccines and potential targets are subjected to find out.^[58] Day by day case dynamics has revealed that the most problematic situation will be the urgent requirement of mechanical ventilation. So far, data on case fatalities have shown that 5%-6% patients require ventilators.^[59] Telemedical innovations and electronic intensive care

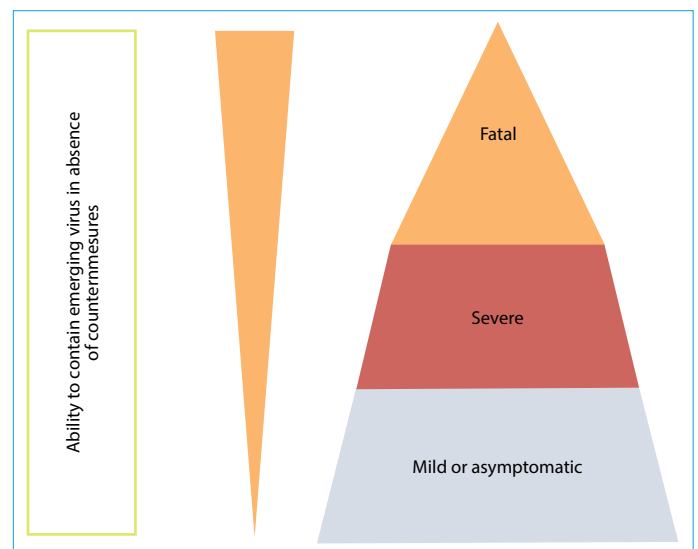


Figure 9. Surveillance Pyramid and Its Relation to Outbreak Containment.

unit (e-ICU) monitoring programs are ideal to fight Covid-19.^[60] Epidemiologic investigations, risk assessment, surveillance, rapid diagnostic tests and vigilance (Fig. 9) are required by all countries to combat the potential outbreak.^[61] In this pandemic, specific recommendations have been suggested for allocating medical resources such as maximize benefits, prioritize health workers, be responsive to evidence and recognize research participation.^[62]

Conclusion

Both N and S proteins are the most abundant proteins in SARS-CoV-2 and can be potential targets of covid-19. Combined studies on antimalarial drugs, regular administration of BCG vaccine, and geographical variation in temperature can help researchers to find potential solutions to combat Covid-19. The Covid-19 pandemic caused worldwide shortage of hospital beds, ICU beds, and ventilators. More and more epidemiologic studies are needed to address risk factors for infection, severity of disease and the efficacy of infection-control measures. These types of studies should help us refine and focus our efforts to control and treat Covid-19. The SARS-CoV-2 has a large economic and social impact on the human population. Several aspects of the covid-19 outbreak are not yet fully understood, including transmission dynamics and the full spectrum of clinical illness. We need to save lives now while also improving the way we respond to outbreaks in general. Governments and industries will need to come to an agreement: during a pandemic, vaccines and antivirals can't simply be sold to the highest bidder. Prevention is the ultimate solution for saving lives from such a pandemic.

Disclosures

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Conflict of Interest: None declared.

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