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Infectious Diseases Beyond COVID-19

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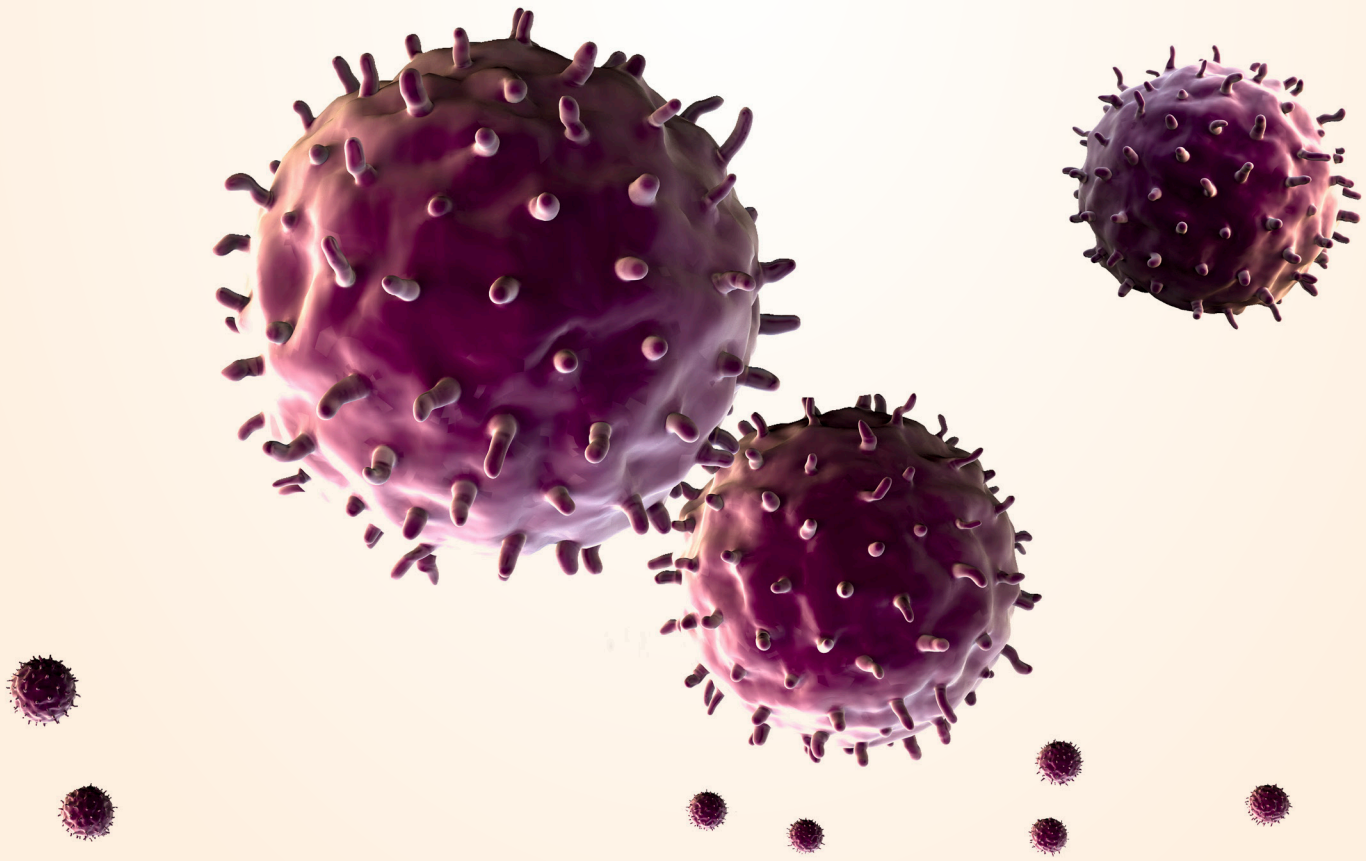

White Paper on

Infectious Diseases Beyond COVID-19

Foreword

With the rapid spread of coronavirus (COVID-19) across the globe, the ability of countries to address and respond to other diseases has been impacted. The virus has caused broad disruptions to health services which is particularly problematic for those living with chronic infectious diseases such as tuberculosis (TB), measles, vector borne diseases, and so on, who need regular care. A complete shift towards catering to COVID-19 patients has led a to disruption in screening, case identification, rehabilitation and referral systems further resulting in a substantial decrease in the diagnosis of Non-Communicable Diseases (NCDs) and an increased burden of care, for example, a reduction in patients being admitted to hospital with acute coronary syndrome led to an increase in out-of-hospital deaths and long-term complications of myocardial infarction. Globally, 2.3 million cancer surgeries and 6.3 million orthopaedic operations have been cancelled or postponed during the peak period of COVID-19.

The major reasons that healthcare services have been hampered were due to the closure of outpatient department services; community level screening programmes for other infectious diseases & NCDs were suspended; and lockdowns hindering access to the health facilities for patients. Due to this there has been lack of proper diagnosis, clinical care, and no access to medications. Furthermore, staff shortages and insufficient logistics have also been among the main causes of disarray to health services.

The global fight against COVID-19 should be treated as a scientific discipline on par with understanding the spread of the disease itself, as change in behaviour is critical to every pandemic response. It requires focusing on vector borne diseases, seasonal diseases, life cycle approaches focusing on diseases from paediatrics to geriatrics along with NCDs. Moreover, capacity building of human resources and Rapid Response Teams (RRT) are important not only at the clinical front but also on the microplanning and inter-sectoral level. Monitoring the access to and continuity of essential health services is required. It is essential to emphasize preparation, alertness and surveillance, developing a robust system to identify such diseases beforehand. Immunization and international foundational programmes and updating of integrated disease surveillance programme portals regularly are important along with strong preventive measures, particularly, those protecting vulnerable groups.

This White Paper highlights the measures needed to tackle other infectious diseases during the current pandemic. Here, we intend to create an awareness among healthcare professionals regarding the need to focus on the other infectious diseases in such unprecedented times, and to minimize the impact of COVID-19 pandemic.

Content

Introductory Background of COVID-19

The novel coronavirus infection (COVID-19) has become a major public health problem and a global pandemic was declared due to the morbidity and mortality resulting from the disease. COVID-19 was first identified in Wuhan, China in December 2019 among a cluster of patients that presented with an unidentified form of viral pneumonia with a shared history of visiting the Huanan seafood market.[1]The virus spread internationally within a month of the first identification and the World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern as of the 1st of February 2020.

Coronaviruses are of zoonotic origin.[2] Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), shows a high sequence identity to some bat CoVs previously detected in *Rhinolophus affinis* (Intermediate horse shoe bat) from Yunnan Province, indicating a bat origin of SARS-CoV-2.[2] Generally, bat habitats are far from human areas of activity, and the virus was probably transmitted to humans by another animal host. Bat SARS like-CoVs cannot directly infect humans unless they undergo mutation or recombination in animal hosts.[2] Regarding the intermediate animal host of SARS-CoV-2, it has been reported that the sequence identity between CoVs of pangolin origin and SARS-CoV-2 is 99%, indicating that pangolins might act as intermediate hosts for SARS-CoV-2.[2,3]

Globally, as of 24th Sep 2021, there have been 230,418,451 confirmed cases of COVID-19, including 4,724,876 deaths, reported to the WHO. In India there have been 33,594,803 confirmed cases of COVID-19 with 446,368 deaths, during this time.[4] It is speculated that numbers might be more than those reported. The WHO reported the situation in various regions as shown in Figure 1 with the maximum confirmed cases in the Americas and least in the Africa. The highest number of cases till 24th Sep 2021 were reported from the USA (42,300,954), followed by India (33,594,803), Brazil (21,283,567), UK (7,565,871), and the Russian Federation (7,376,374) respectively.

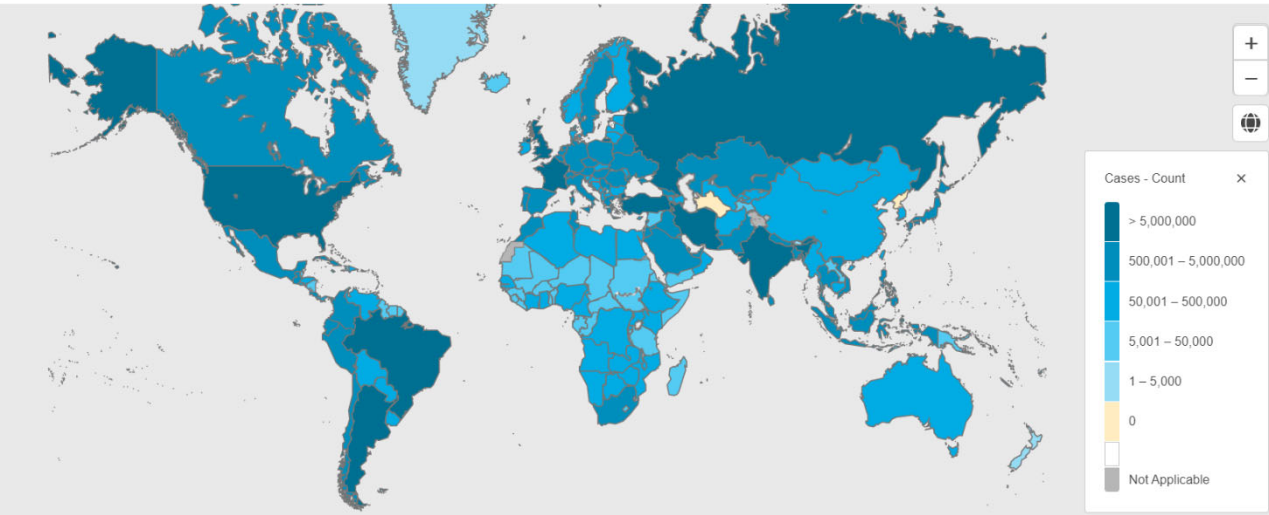

Figure 1 COVID-19 cases globally reported by the WHO till 24th Sep 2021.

The transmission of COVID-19 has been confirmed to occur from human to human, and it spreads through respiratory droplets via coughs or sneezes.[5] The primary cases of COVID-19 have been traced back to the Huanan seafood market, with secondary cases occurring at hospitals among nurses and physicians in Wuhan who had extensive contact with COVID-19 patients.

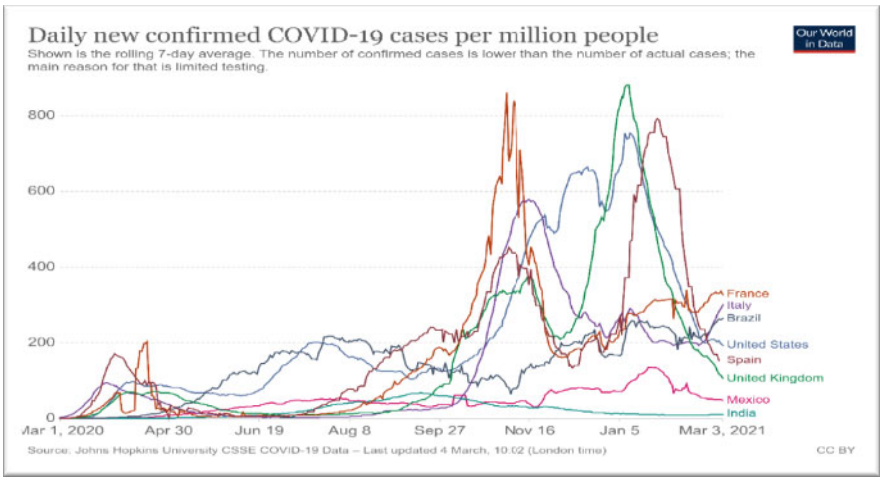

Figure 2: Daily new confirmed cases per million people globally.

Globally governments have implemented five strategies for the prevention and control of the COVID-19 pandemic: namely staying at home (complete lockdown or working from home/and the shutdown of schools), social or physical distancing, quarantine and contact tracing, testing of suspected patients, isolation of confirmed cases. Wearing mask to cover nose and mouth, disinfection of surfaces and hand washing reduces the transmission and prevalence of COVID-19. These measures for the prevention and control of the transmission of COVID-19 have caused people with comorbidities or

immunocompromised people to suffer with other problems such as, difficulty in seeking essential medical care, some are unable (e.g., tuberculosis [TB] patients, HIV patients, etc.) to get the medicines they need, laboratories are not diagnosing other diseases and health systems are overburdened so they cannot look after patients with other infectious diseases. This leads to more infections and delayed treatment for established infections, leading to further increased morbidity and mortality due to causes other than COVID-19.

The objective of this paper is to analyse the factors for the derailment of programmes for the control of the progress of other infectious and the noncommunicable diseases with special reference to vulnerable populations (paediatric and geriatric). Further we suggest methods for preparedness, alertness, and surveillance to deal with COVID-19 along with other infectious diseases during the pandemic.

Epidemiology of COVID-19

Agent

COVID-19 patients were assessed for viral pneumonia and the virus isolated from biological samples (bronchoalveolar lavage samples) was from the beta-coronavirus genus, placing it alongside other diseases such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[1,4] SARS-CoV-2 diseases are enveloped non-segmented positive-sense RNA beta-coronaviruses belonging to the family Coronaviridae (subfamily Orthocoronavirinae), order Nidovirales and realm Roboviria. The virus particle has a diameter of approximately 60–100 nm and appears round or oval. The name is derived from the Latin word ‘coronam’ due to their crown-like appearance in electron micrographs (Fig. 3).[6]

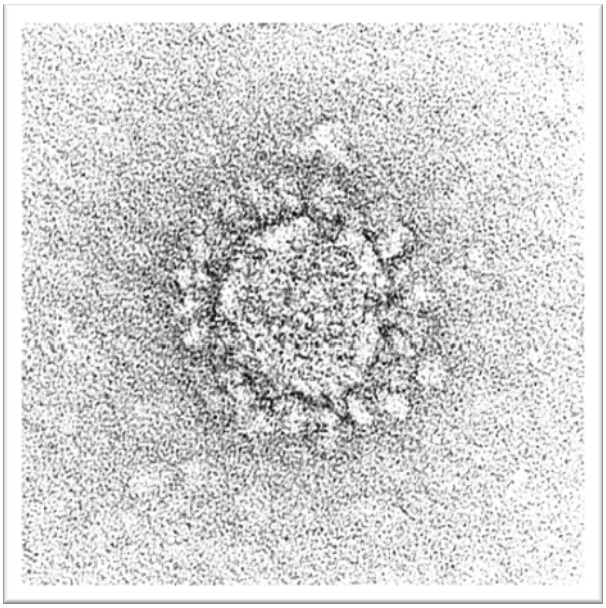

Figure 3 Electron microscopic image of a negatively stained particle of SARS-CoV-2, the causative agent of COVID-19. Note the prominent spikes from which the coronavirus gets its name for 'corona', or crown-like. Source: CDC/ Cynthia S. Goldsmith and A. Tamin. Electron microscopic image of a negatively stained particle of SARS-CoV-2, causative agent of COVID-19. Public Health Image Library (PHIL). [Internet]. [cited 2021 Jan 7]. Available from: https://phil.cdc.gov/Details.aspx?pid=23640

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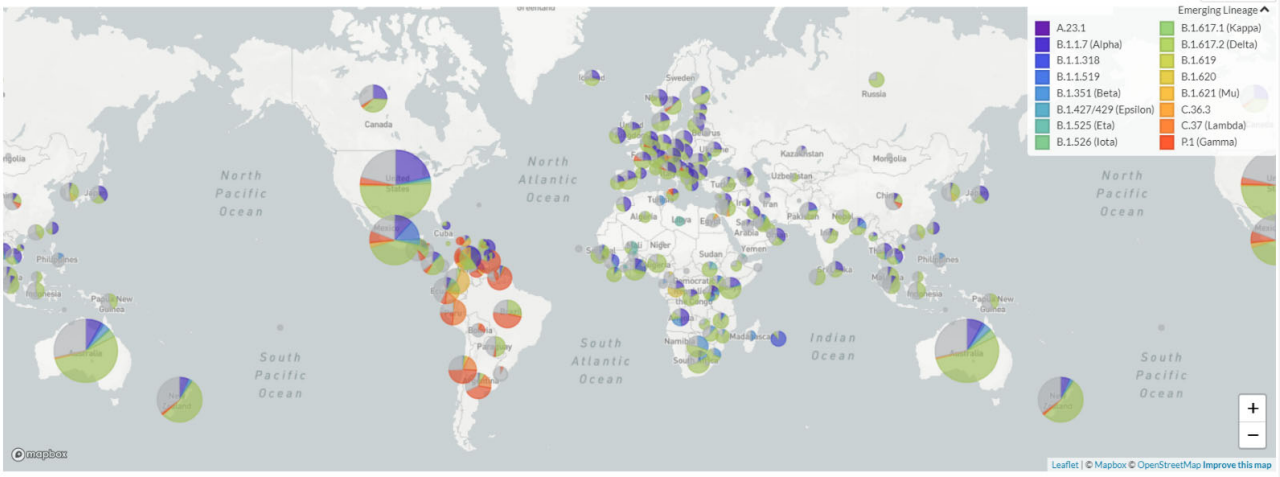
The virus mutates very slowly. When the genetic mutation spectrum was compared amongst viruses isolated from the four countries, namely the USA, Italy, India and Nepal it was found to be different.[8] The Indian strain is reported to be about 99.9% similar to the Wuhan strain of the virus.[9] It is speculated that the presence of a country-specific mutation spectrum may also be able to explain the difference in the current scenario in these countries such as severity of illness, containment of the outbreak, the extent and timing of exposures to a symptomatic carrier and so on.[8] Currently 16 strains of SARS-CoV-2 have been identified globally (Fig. 4).[10]

A virus strain is a 'type of a given virus that is recognizable because it possesses some unique phenotypic characteristics that remain stable under natural conditions'. Such 'unique phenotypic characteristics' are biological properties different from the compared reference virus, such as unique antigenic properties, host range or the signs of disease it causes.[11] This definition is very similar to that of Fauquet and Stanley, who argued that 'strains are viruses that belong to the same species and differ in having stable and heritable biological, serological, and/or molecular characters'.[12]

Van Regenmortel defined a virus variant as an isolate or a set of isolates who's genomic (consensus) sequence(s) differ(s) from that of a reference virus[11], that is, the term 'variant' is often equivalent to 'mutant'. According to Fauquet et al., a virus 'variant is something that differs slightly from the norm, it means a slightly different genome, symptom, or mode of transmission'.[13]



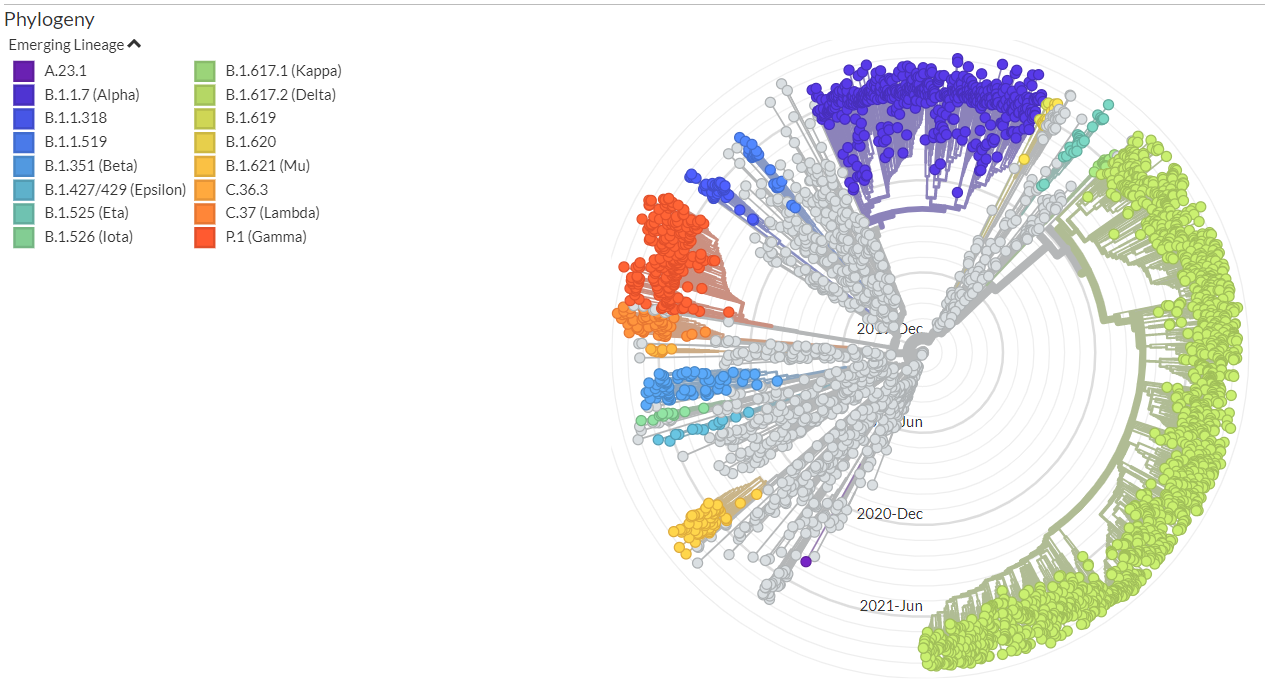


Figure 4 A map of the main known genetic variants of SARS-Co-2 virus that causes COVID-19 disease.

Source: GISAID - NextStrain [Internet]. [cited 2021 Sep 25]. Available from: https://www.gisaid.org/phylodynamics/global/nextstrain/ [100]

Hadfield J, Megill, Bell SM, et al. Nextstrain: real-time tracking of pathogen evolution. Kelso J, editor. Bioinfomatics. 2018;34(23):4121-3.[14]

Given the rapid evolution in SARS-CoV-2 and constant development in our understanding, WHO currently classifies SARS-CoV-2 into following variants[101]:

Variants of Concern (VOC): A SARS-CoV-2 variant that meets the definition of a VOI (see below) and, through a comparative assessment, has been demonstrated to be associated with one or more of the following changes at a degree of global public health significance:

- Increase in transmissibility or detrimental change in COVID-19 epidemiology, OR
- Increase in virulence or change in clinical disease presentation, OR
- Decrease in effectiveness of public health and social measures or available diagnostics, vaccines, therapeutics.

Table: Currently designated Variants of Interest:

WHO label	Pango lineage*	GISAID clade	Nextstrain clade	Additional amino acid changes monitored°	Earliest documented samples	Date of designation
Alpha	B.1.1.7 #	GRY	20I (V1)	+S:484K +S:452R	United Kingdom, Sep-2020	18-Dec-2020
Beta	B.1.351	GH/501Y.V2	20H (V2)	+S:L18F	South Africa, May-2020	18-Dec-2020
Gamma	P.1	GR/501Y.V3	20J (V3)	+S:681H	Brazil, Nov-2020	11-Jan-2021
Delta	B.1.617.2§	G/478K.V1	21A	+S:417N	India, Oct-2020	VOI: 4-Apr-2021 VOC: 11-May-2021

Variants of Interest (VOI): A SARS-CoV-2 variant:

- With genetic changes that are predicted or known to affect virus characteristics such as transmissibility, disease severity, immune escape, diagnostic or therapeutic escape; and
- Identified to cause significant community transmission or multiple COVID-19 clusters, in multiple countries with increasing relative prevalence alongside increasing number of cases over time, or other apparent epidemiological impacts to suggest an emerging risk to global public health.

Table: Currently designated Variants of Interest:

WHO label	Pango lineage*	GISAID clade	Nextstrain clade	Earliest documented samples	Date of designation
Lambda	C.37	GR/452Q.V1	21G	Peru, Dec-2020	14-Jun-2021
Mu	B.1.621	GH	21H	Colombia, Jan-2021	30-Aug-2021

Variants Under Monitoring (VUM, formerly called "Alerts for Further Monitoring"):

A SARS-CoV-2 variant with genetic changes that are suspected to affect virus characteristics with some indication that it may pose a future risk, but evidence of phenotypic or epidemiological impact is currently unclear, requiring enhanced monitoring and repeat assessment pending new evidence.

Table: Currently designated Variants Under Monitoring

Pango lineage*	GISAID clade	Nextstrain clade	Earliest documented samples	Date of designation
B.1.427§ B.1.429	GH/452R.V1	21C	United States of America, Mar-2020	VOI: 5-Mar-2021 VUM: 6-Jul-2021
R.1	GR	-	Multiple countries, Jan-2021	07-Apr-2021
B.1.466.2	GH	-	Indonesia, Nov-2020	28-Apr-2021
B.1.1.318	GR	-	Multiple countries, Jan-2021	02-Jun-2021
B.1.1.519	GR	20B/S.732A	Multiple countries, Nov-2020	02-Jun-2021
C.36.3	GR	-	Multiple countries, Jan-2021	16-Jun-2021
B.1.214.2	G	-	Multiple countries, Nov-2020	30-Jun-2021
B.1.1.523	GR	-	Multiple countries, May-2020	14-July-2021
B.1.619	G	20A/S.126A	Multiple countries, May-2020	14-July-2021
B.1.620	G	-	Multiple countries, November 2020	14-July-2021
C.1.2	GR	-	South Africa, May 2021	01-Sep-2021
B.1.617.1§	G/452R.V3	21B	India, Oct-2020	VOI: 4-Apr-2021 VUM: 20-Sep-2021
B.1.526§	GH/253G.V1	21F	United States of America, Nov-2020	VOI: 24-Mar-2021 VUM: 20-Sep-2021
B.1.525§	G/484K.V3	21D	Multiple countries, Dec-2020	VOI:17-Mar-2021 VUM: 20-Sep-2021

Variant of High Consequence (VOHC)[102]:

A variant of high consequence has clear evidence that prevention measures or medical countermeasures have significantly reduced effectiveness relative to previously circulating variants.

Possible attributes of a variant of high consequence:

In addition to the possible attributes of a variant of concern

- Impact on Medical Countermeasures (MCM)
- Demonstrated failure of diagnostic test targets

- Evidence to suggest a significant reduction in vaccine effectiveness, a disproportionately high number of infections in vaccinated persons, or very low vaccine-induced protection against severe disease
- Significantly reduced susceptibility to multiple Emergency Use Authorization (EUA) or approved therapeutics
- More severe clinical disease and increased hospitalizations

A variant of high consequence would require notification to WHO under the International Health Regulations, reporting to CDC, an announcement of strategies to prevent or contain transmission, and recommendations to update treatments and vaccines.

Currently, there are no SARS-CoV-2 variants that rise to the level of high consequence.

The established nomenclature systems for naming and tracking SARS-CoV-2 genetic lineages by GISAID, Nextstrain and Pango are currently and will remain in use by scientists and in scientific research.

Host Factors

The median age of patients is reported to be from 41 to 57 years and most of the patients are males (50–75%).[5,15,16] Patients with other underlying medical conditions such as diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular diseases, hypertension, malignancy have been noted to have 25.2–50.5% increased chance of being infected with COVID-19.[17] The infection rate in healthcare personnel ranges from 2.1% to 29%.[18]

The median incubation period of COVID-19 infection ranges from 3 to 24 days. Human-to-human transmission is mainly via droplets from coughing or sneezing or through direct contact.[19,20] Some studies suggest faeco–oral transmission of COVID-19 infection.[21] Being infected with COVID-19 does not confer lifelong immunity to further infection and cases of reinfection are being reported.

Environment

SARS-CoV-2 shows significant community spread in regions along a narrow east–west distribution roughly along the 30–50° N′ corridor at consistently similar weather patterns consisting of average temperatures of 5–11°C, combined with low specific (3–6 g/kg) and absolute humidity (4–7 g/m^3).[22] The distribution of significant community outbreaks along restricted latitudes, temperature and humidity are consistent with the behaviour of a seasonal respiratory virus. Besides potentially prolonging the half-life and viability of the virus, other potential mechanisms associated with cold temperature and low humidity include stabilization of the droplet and enhanced propagation in nasal mucosa, as has been demonstrated with other respiratory viruses. Increase in temperature, sunlight and low pH damages the COVID-19 virus. It has been found that when humidity and wind speed increase the prevalence of COVID-19 decreases. (Bhattacharjee,2020; HadiEslami,2020) Many studies suggest that the virus can survive on the surface for many hours. Some studies have suggested that the SARS-CoV-2 can survive

in the sewage. Coronaviruses have been reported to remain in water or wastewater for days or weeks (Qu et al, 2020).

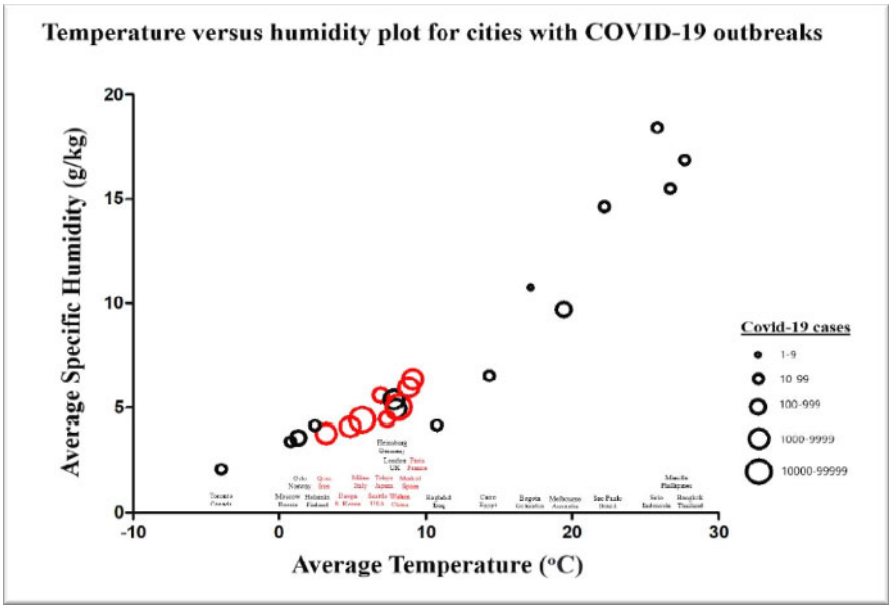


Figure 5 Temperature versus humidity plot for cities with COVID-19 outbreaks.

The air pollutants such as sulphur dioxide, nitrogen oxide, carbon monoxides, and so on and particulate matter cause adverse effects on human health.[23] Air pollution is a contributing factor to diseases affecting cardiovascular and respiratory systems according to a study done by Manisalidis et al.[24]. Another study done by Ciencewicki and Jaspers in 2007[25] showed that exposure to air pollution causes oxidative stress leading to the production of free radicals which damage the respiratory system and reduce resistance to infections. Elderly people are more affected by air pollution due to their weaker immune systems.[26,27] There is further evidence that air pollution not only effects the transmission and severity of viral respiratory infections; but it also delays or complicates the recovery of COVID-19 patients. Air pollutants lead to the virus lasting longer in the environment and aids the indirect transmission of COVID-19. This was observed in Northern Italy which has particularly high concentrations of particulate matter (PM2.5 and PM10), where the recovery rates were low.[28] Many studies have suggested that air pollution is an independent co-factor for the transmission and severity of COVID-19.[29-30]

Routes of Transmission

Infection via respiratory droplets or secretions of infected individuals are thought to be the predominant mode of transmission from human to human. Currently, COVID-19 patients are the main source of infection and patients with severe cases are more contagious than those with milder infections. Asymptomatically infected persons or patients who are incubating infection, who show no signs or

symptoms of respiratory infection have been proven to shed infectious virus, and may also be potential sources of infection (also known as super-spreaders).[2,6,31] Recent reports indicate that SARS-CoV-2 can be detected in laboratory stool samples of confirmed patients, implying a risk of faeco–oral transmission. It was found in a study that among the 41 patients (55%) with positive faecal and respiratory samples, respiratory samples remained positive for SARS-CoV-2 RNA for a mean of 16.7 days and faecal samples remained positive for a mean of 27.9 days after first symptom onset.[33] There is still no sufficient evidence that SARS-CoV-2 can be transmitted from mother to baby during pregnancy or childbirth. However, a neonate born to a mother with COVID-19 in China had elevated immunoglobulin M (IgM) antibody levels and abnormal cytokine test results 2 h after birth which might suggest that the neonate contracted the infection in utero as IgM does not get transferred through the placenta.[34] There is no evidence that COVID-19 virus transmits through contaminated drinking water.

Also, SARS-CoV-2 remains viable in aerosols for up to 3 h. Moreover, SARS-CoV-2 also remains viable on plastic for up to 72 h, on stainless steel for up to 48 h, on cardboard for up to 24 h and on copper for up to 8 h thus showing it can spread through fomites.[34] According to a recent study conducted by Goldman published in *The Lancet*, the chances of transmission through inanimate surfaces is very low, and was only found in instances where a COVID-positive patient sneezed or coughed on the surface, and someone touched the same surface soon after this (within 1–2 h).

Incubation Period and Basic Reproduction Number

The symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days. The period from the onset of COVID-19 symptoms to death ranges from 6 to 41 days with a median of 14 days.[6] This period is dependent on the age of the patient and status of the patient's immune system. The secondary attack rate (SAR) was found to be close to 35%.[35]

The basic reproduction number (R0) is an epidemiologic metric used to describe the contagiousness or transmissibility of infectious agents. The R0 for SARS-CoV-2 was assumed to be 2.2 for Wuhan.[2] For Italy however, based on the exponential curve prediction and the assumption that the duration of infection ranges from 15 to 20 days, the basic reproduction number was estimated to range from 2.76 to 3.25, slightly higher than China.[36]

Pathogenicity

Angiotensin-converting enzyme 2 (ACE2) is a common human receptor for both SARS-CoV and SARS-CoV-2 while MERS-CoV uses dipeptidyl peptidase-4 (DPP4) to enter host cells.[37] A higher receptor affinity for ACE2 of SARS-CoV-2 than for SARS-CoV is observed and is hypothesized to cause more severe lung involvement in COVID-19 (Fig. 6).

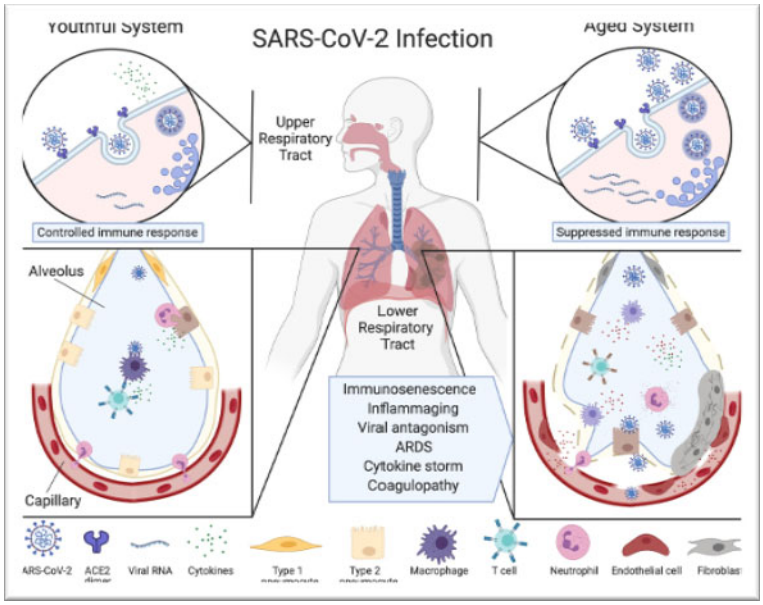


Figure 6 Figure shows that the coronavirus enters lung cells via the ACE2 receptor. Source: Jia H, Look D, Tan P, et al. Ectodomain shedding of angiotensin converting enzyme 2 in human airway epithelia. Am J Physiol Lung Cell Mol Physiol. 2009;297:L84–96.[39]

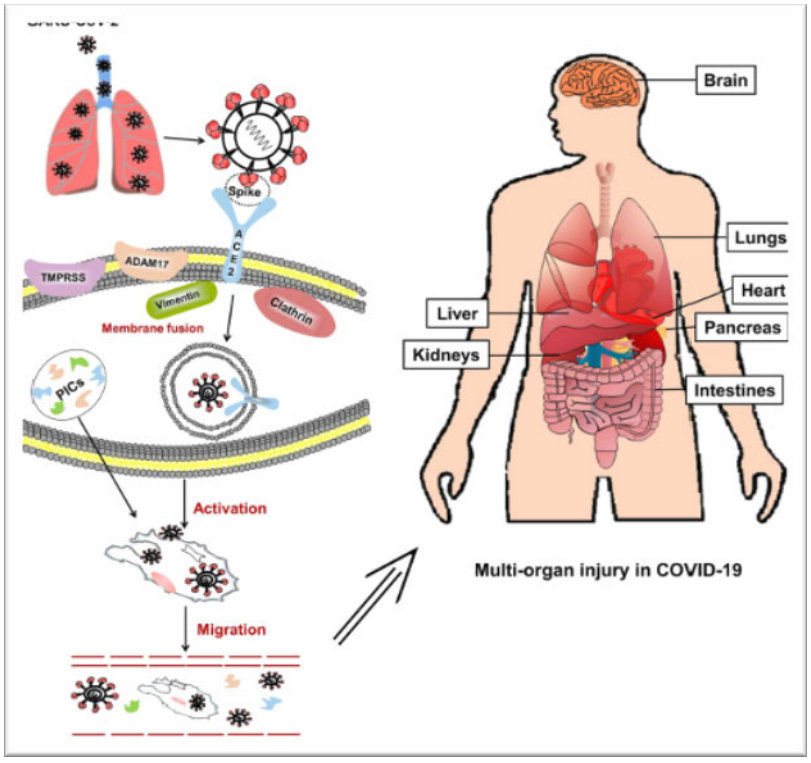
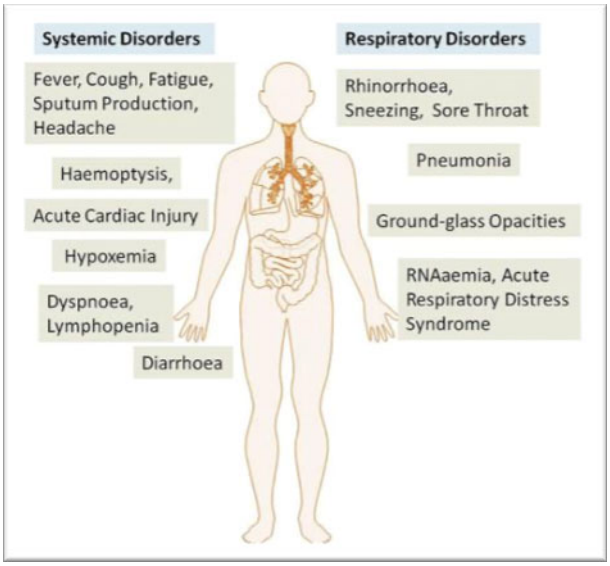


Figure 7 After being phagocytosed the virus then spreads to all the other organs, infecting the ACE-2 expressing cells thus causing multi-organ dysfunction.

Source: World Health Organization (WHO). Coronavirus. 2020. https://www.who.int/health-topics/coronavirus (date last accessed 5 February 2020).[40]

Progression and Spectrum of Disease

As shown in Figure 8, the common signs of COVID-19 infection are respiratory symptoms, fever, cough, shortness of breath and breathing difficulties and serious cases present with pneumonia, SARS, kidney failure and death.[8, 17]



SARS-CoV-2 infection can cause five different outcomes:

asymptomatically infected persons (1.2%)

- mild-to-medium cases (80.9%)
- severe cases (13.8%)
- critical case (4.7%)
- death (2.3% in all reported cases)

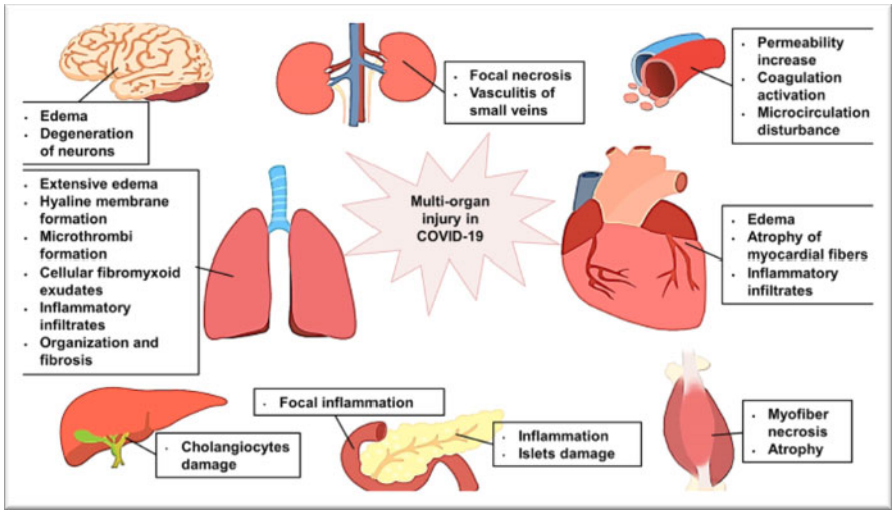
Figure 8 Symptoms of COVID-19.

Case Fatality Rate

The fatality rate due to novel coronavirus infection is estimated to be 2.3%.[18,19] This might be overestimated, only the symptomatic and confirmed cases have been included in the denominator and asymptomatic cases have not been considered. Fatality rates globally are 5.1% ranging from the highest being 11.9% in Italy followed by 9.1% in Spain, 4.1% in China, 2.9% in India and 2.4% in the USA.

Figure 9 The figure below shows the main organs involved in COVID-19.

Source: Ni, W., Yang, X., Yang, D. et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care 24, 422 (2020). https://doi.org/10.1186/s13054-020-03120-0.[43]



COVID-19 and Infectious Diseases

i. COVID-19 and seasonal flu

Seasonal flu annually infects 9% of the world's population with a death rate of around 0.1% (291,000–600,000 deaths each year). The past 100 years have witnessed several outbreaks of viral respiratory infections, mentioned in Box 1.[43]

Box 1: Outbreaks of viral respiratory infections in the last 100 years

- Year 1918: influenza pandemic (500 million infected; 50 million died; mortality rate 10%)
- Years 2002–2004: SARS outbreak (8098 cases; 774 deaths; mortality rate 9.5%)
- Years 2009–2010: H1N1 influenza pandemic (1.649 billion infected, i.e., 24% of the global population [approx. 61 million cases in the USA]; 284,000 died [approx. 12,500 deaths in the USA]; mortality rate 0.02%)
- Years 2012–2020: MERS outbreak (2519 cases; 866 deaths; mortality rate 34.4%)
- Year 2019: currently ongoing COVID-19 pandemic

ii. COVID 19 and other betacoronavirus (MERS, SARS)

Genome sequence analysis has shown that SARS-CoV-2 belongs to the betacoronavirus genus, which includes bat SARS-like coronavirus, SARS-CoV and MERS-CoV.[44] The phylogenetic, pathogenic and epidemiological characteristics of all three viruses are described in Table 1.[45]

Table 1

Phylogenetic, pathogenetic and epidemiological characteristics of SARS-CoV2, SARS- CoV and MERS-CoV

	Phylogenetic origin	Animal reservoir	Intermediate host	Receptor	Case fatality rate	R0
SARS-CoV-2	Clade I, cluster IIa	Bats	Unknown	ACE-2	2.3%	2–2.5
SARS-CoV	Clade I, cluster IIb	Bats	Palm civets	ACE-2	9.5%	1.7–1.9
MERS-Co	Clade II	Bats	Camels	DPP4	34.4%	0.7

Abbreviations: *ACE-2,* angiotensin-converting enzyme 2; *CFR,* case fatality rate; *DPP4,* dipeptidyl peptidase-4; *MERS-CoV,* Middle East respiratory syndrome coronavirus; *R0,* reproductive number; *SARS-CoV-2;* severe acute respiratory syndrome coronavirus 2.

Rates of human-to-human transmission were generally lower for MERS, possibly due to the higher case fatality ratio (CFR) among those diagnosed with the disease. In the case of MERS, primary cases of the virus have been traced to close contact with infected dromedary camels which were identified as the reservoir host for MERS.[46] Fomites, faecal transmission and handling of animals (killing, selling or preparing wild animals) were not the common methods of SARS transmission.[47] The reproductive number (R0) of the CoV-2 is higher than that for SARS (1.7–1.9) and MERS (<1), suggesting that SARS-CoV-2 has a higher pandemic potential.[49-51] The case fatality of COVID-19 is lower than that of SARS (9.5%) and is much lower than that of MERS (34.4%).[48] The clinical features of SARS, MERS and COVID-19 are compared in Table 2.

The median age of the COVID-19 cases is similar to SARS and MERS (49–57 years) and more than half of patients reported a chronic comorbid illness which is slightly lower compared to patients diagnosed with MERS.

Both SARS and MERS patients may deteriorate with the onset of dyspnoea, acute respiratory distress syndrome (ARDS) and the need for invasive mechanical ventilation especially in elderly patients and smokers.[51] Acute kidney injury (AKI) is seen to be rare in SARS and COVID-19 but is a common complication of MERS. The direct renal cytopathic effect induced by the MERS virus can be due to DDP4 receptors largely represented in tubules and glomeruli but it is likely that the high percentage of AKI reported is due to multiorgan failure, frequently observed in MERS compared with other coronavirus infections.

Table 2

Clinical and laboratory features of COVID-19, SARS and MERS

	SARS	MERS	COVID-19
Clinical characters			
Fever	99%–100%	40%–98%	65%–99%
Cough	29%–100%	18%–87%	22%–82%
Myalgia	20%–60%	7%–32%	11%–44%
shortness of breath	20%–60%	27%–72%	4%–35%
Dyspnoea	42%–44%	5%–15%	17%–40%
chill	15%–74%	7%–87%	7%–17%
Diarrhoea	10%–50%	7%–44%	1%–10%
vomiting or nausea	10%–35%	7%–21%	1%–13%
chest pain	30%	15%	2%
Headache	15%–70%	5%–13%	4%–8%
sore throat	11%–30%	4%–11%	4%–26%
runny nose	2%–24%	4%	4%
Laboratory findings			
Leukopenia <4 × 109	7%–34%	6%–14%	17%–25%
Lymphopenia <1 × 109	54%–75%	35%	35%–70%
Thrombocytopaenia	20%–44.8%	17%–36%	21%
Elevated lactate dehydrogenase	71%–87%	47%–49%	40%–98%
Elevated alanine transaminase	23%–56%	11%	17%–31%
Elevated aspartate transaminase	32%–78%	15%–53%	30%–37%
Complications			
Diabetes	5%–40%	28%–87%	6%–34%
Hypertension	11%–30%	22%–34%	19%–57%
chronic lung disease	1%	26%–43%	2%–17%
heart disease	8%–10%	22%–53%	8%–18%
chronic renal insufficiency	1%–5%	5%–53%	1%–8.5%
Smoking	5%–20%	13%–23%	6%–15.6%
malignant disease	6%	2%–23%	0.5%–7%
Abnormal chest radiograph	70%–100%	87%–100%	100%
Critically ill patients	20%–23%	53%–89%	14%–32%
Mechanical ventilation support	13%–50%	70%–78%	29%–89%
Mortality rate	3.6%–30%	60%–65%	4%–28%

Abbreviations: *COVID-19,* coronavirus-19; *MERS,* Middle East respiratory syndrome; *SARS;* severe acute respiratory syndrome coronavirus.

Source: Adapted from Liu J, Xie W, Wang Y et al. A comparative overview of COVID-19, MERS and SARS: Review article. Int J Surg Lond Engl. 2020 Sep;81:1-8.[53]

iii. COVID-19 and influenza-like illness simultaneous infections

Preliminary observation from Italy[53] showed that two death curves examined for COVID-19, flu and other causes show a completely overlapping profile. The excess mortality reported in the influenza-like illness (ILI) group (in those aged ≥65 years) may be attributable to COVID-19 infection but the uncertainty when considering it as a random sequence of events or a potential relationship between the two viruses require further investigation (Fig. 9).

Box 2: Operational case definition

- Diagnosis of MERS55 by the WHO is defined initially as patients presenting with a fever, cough and hospitalization with suspicion of lower respiratory tract involvement. Patient history is obtained upon hospitalization and prominent considerations for the diagnosis involves a history of contact with probable or confirmed cases of the illness, or a reported history of travel or residence within the Arabian Peninsula.
- A patient was considered to have laboratory-confirmed SARS if there was a positive reverse transcription polymerase chain reaction (RT-PCR) result from two or more clinical specimens, either from different sites or tested in different laboratories, obtained from patients before or after death, or if there was seroconversion by an enzyme-linked immunosorbent assay, indirect fluorescent antibody test or neutralization assay.
- Similar to MERS, serological testing for IgG antibodies was developed for the SARS coronavirus. Treatment of SARS involved a combination therapy of lopinavir and ritonavir and was associated with substantial clinical benefit with fewer adverse clinical outcomes.56 A broad-spectrum antiviral nucleotide prodrug named remdesivir presented potent efficacy for the treatment of MERS coronavirus and SARS coronavirus in preclinical studies.
- There are several similarities between these viruses in their diagnosis and treatment. All three viruses are definitively diagnosed by utilizing cell cultures of respiratory fluids, serum antibody analysis or RT-PCR analysis of respiratory fluids from patients. All three viruses cause pneumonia, and radiography of the lungs is an important diagnostic tool for the preliminary and broad identification of the severity of the disease. Running noses and gastrointestinal symptoms are lesser common symptoms of COVID-19 among infected patients, which are commonplace in MERS and SARS cases. Antiviral treatments as per the recently published trials (WHO Solidarity Trial) indicated that remdesivir, hydroxychloroquine, lopinavir/ritonavir and interferon regimens appear to have little or no effect on 28-day mortality or the in-hospital course of COVID-19 among hospitalized patients.

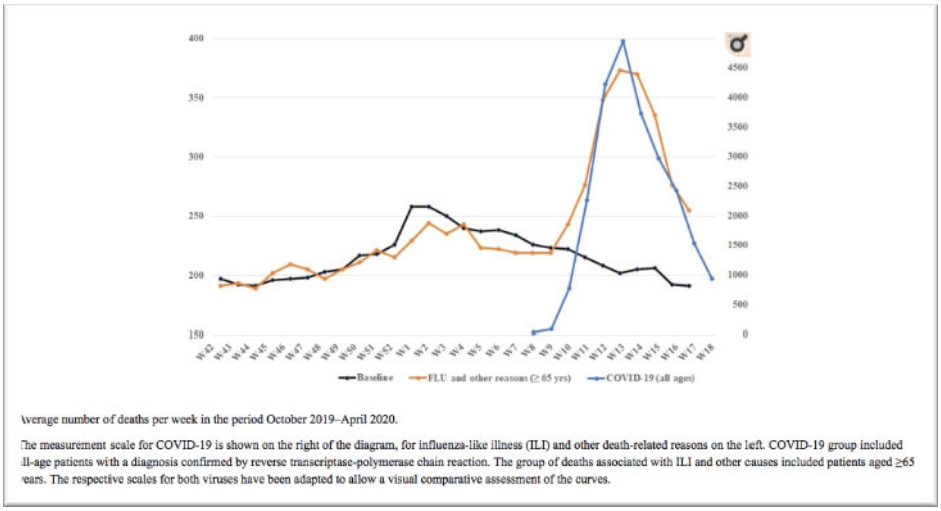


Figure 10 Average number of deaths per week in the period October 2019–April 2020.

Hypothesized mechanism of coinfection: Although influenza and COV-2 though have different binding affinities for their own specific receptors (i.e., sialic acids of glycoproteins or glycolipids and ACE2 for influenza and COVID-19, respectively, both have an elective tropism for the respiratory tract.

Increasingly evidence is appearing that many viruses actively work together, teaming up to coinfect hosts and neutralize antiviral immune procedures. An example of effective viral cooperation was found in several oncogenic genotypes of high-risk and low-risk human papillomavirus.[56] The simultaneous or sequential infection of both viruses (COVID-19 and influenza) leads to strengthening the effectiveness of the single infection, thus this cannot be excluded in the post-COVID era.

COVID-19 and Existing Infectious Killers (HIV, Tuberculosis and Malaria)

Despite the relatively low death rates in India (overall case fatality rate [CFR] is at 1.45)[57] the ongoing surge of COVID-19 poses an unprecedented public health risk. The COVID-19 pandemic has substantially impacted the control of infectious diseases and threatens to undermine the success achieved in established programmes mitigating the burden of HIV, TB and malaria.

Travel Restrictions Imposed Due to the COVID-19 Pandemic and Healthcare Utilization

The current recommendations to curb the pandemic restricts travel and urges people to stay at home. The workforce in the informal sector mainly from the productive age group and those in the formal sector have been rendered unemployed. Thus, enforcement of these measures is likely to pose unprecedented difficulties to lakhs of vulnerable populations in accessing health services due to their

limited disposable income to support transportation expenses as well as other direct and indirect medical costs.

The specific populations facing these critical challenges include:

1) People living with HIV/AIDS (PLWHA) accessing health facilities regularly for antiretroviral and prophylactic drugs
2) Patients under treatment for TB accessing health facilities regularly to access anti-TB drugs
3) Pregnant women exposed to *Plasmodium falciparum* infection who need intermittent preventive treatment for malaria prevention as part of their antenatal care service
4) Children infected with *P. falciparum* who need correct diagnosis and prompt treatment of malaria.
5) Geriatric population

Additionally, COVID-19 control measures in some high burden states include the limitation of the number of passengers using public transportation. This might worsen the availability of means of transportation to reach health facilities by these population sub-groups.

COVID-19 Pandemic and Delayed Access to Healthcare Services

One of the foremost strategies to control COVID-19 including quarantine of suspected cases, isolation of infected patients and contact tracing has poor or limited acceptability in some communities. Many patients with clinical features similar to those of SARS-CoV-2 infection and/or any other diseases with a similar symptomatology are reported to be hesitant to voluntarily seek testing and treatment in a formal health facility.

For continued reductions in vector borne diseases (VBDs) especially malaria death rates, cases need to be correctly diagnosed and promptly treated. The main diagnostic characteristic of VBDs (malaria, dengue) is fever, the similarity of these symptoms to COVID-19 symptoms poses important challenges to the current measures to controlling the pandemic.

Clinically, TB also presents with fever, cough and dyspnoea, among other symptoms. Despite the differences in the duration of incubation and other factors, these three symptoms are also the clinical features observed in most patients with COVID-19, with prevalence of 88.7% (84.5–92.9%), 57.6% (40.8–74.4%) and 45.6% (10.9–80.4%), respectively.

This might result in an increased household transmission of COVID-19 as infected family members will remain in contact with uninfected patients without any protective measures. Transmission of COVID-19 occurs even among asymptomatic and pauci-symptomatic patients. These factors might result in an increased risk of complications and mortality among vulnerable populations because they might delay or avoid seeking care in a formal health facility.

COVID-19 pandemic and the heightened burden on the healthcare force:

The complexities in reducing the burden of infectious disease deaths are further impacted due to the deaths of health

care workers, overwhelmed health facilities and the fear of contracting COVID-19 disease while attending health services. It is already apparent that there will be a need to prioritize the care that healthcare services can deliver. Thus, the focus will mainly be on mitigating the burden of disease (TB/HIV) rather than on prevention.

This is further complicated as the large number of existing TB and HIV workforce is being redirected to manage COVID-19 with the remaining being sick or self-isolating themselves (up to 30% of healthcare staff) due to the concern that too much social contact within a health facility is likely to result in more viral transmission. This reduces contact with patients who are dependent on these systems both for social and medical support. This may result in reduced adherence and poor outcomes especially among those who are least able to self-care (the homeless and socially disadvantaged populations).

Infectious Diseases Post COVID 19 in Children

Up till December 2020, 11% of the 25.7 million of COVID-19 infections globally have been recorded among children and adolescents.[58] Children during and post the COVID-19 pandemic are affected not only by the COVID-19 infection itself but also due to challenges such as the immediate socioeconomic impacts caused by the measures taken to stop the transmission of infection and the long-term effects of deferred execution of the Sustainable Development Goals.

a. Vaccine preventable diseases among children

There are over 80 million children under one year of age, globally in 2020 there has been reported disturbances in routine immunization due to control measures taken to prevent COVID-19 transmission as a result of lockdowns, social/physical distancing, limited access to healthcare centres and the limited availability of personal protective equipment (PPE) kits for healthcare workers. In India, an estimated 20–22 lakh infants are targeted for vaccination in national programmes every month (which translates into approximately 260 lakh children per year) who were not vaccinated due to suspended vaccination sessions.[60] There is a threat of an outbreak of vaccine-preventable disease, which will have a devastating impact on child mortality and morbidity; and may further lead to outbreaks even in susceptible adult populations. Resurgence of these vaccine preventable diseases and a huge backlog of unimmunized children will further burden the health system which is already overburdened battling the COVID-19 pandemic.

Globally, there has been immense progress in the vaccination of children under the age of five years, being 86% in 2018 for three doses of diphtheria, tetanus and pertussis (DPT3) and one dose of measles compared to 72% in 2000 and 20% in 1980. There has been a 99.9% decline in the number of children paralyzed by polio globally. In the WHO South-East region, the Maldives and Sri Lanka, have eliminated rubella and measles well in advance of the 2023 target.

These achievements are minimized due to the decrease in vaccination rates globally resulting from delays or suspensions of scheduled immunization activities because of the COVID-19 pandemic; there has been resurgence of cases of measles, polio, diphtheria, yellow fever and other vaccine preventable diseases. More than 13.5 million children have already missed out on vaccinations for polio, measles, human papillomavirus, yellow fever, cholera and meningitis since the suspensions began.

As COVID-19 infection prevention and control measures, social distancing is being practiced and mass vaccination campaigns go against the idea of social distancing, thus the Global Polio Eradication Initiative has suspended polio vaccination campaigns since 24th March,2020 until the second half of the year. In countries where the polio virus is in circulation this will lead to tragic consequences such as paralysis and the death of children. Measles is extremely contagious and among malnourished children the mortality rates range from 3% to 6%. Disruption of routine immunization activities will lead to an increase in measles infection and deaths due to this easily preventable disease.

Infectious diseases like diphtheria and tetanus may see a resurgence as there is a delay in vaccination and a large proportion of children are not protected.[60]

b. Other infectious diseases such as seasonal flu, chicken pox

Preventive measures adopted for the COVID-19 pandemic resulted in a profound decrease in the diagnosis of common infectious diseases among children. This has resulted either due to the decline in the prevalence of infectious diseases or due to an inhibition to seek health care when the condition occurred.[61] There has been a small decrease in the diagnosis of infectious diseases but not contagious diseases such as urinary tract infections, which suggests there is a change in care-seeking behaviour. Infectious disease transmission has reduced with social distancing, as there is no close contact with other children. According to a study done by Hatoun et al., three of the studied diseases, namely, influenza, croup and bronchiolitis, have disappeared with social distancing.[62] Diagnosis of influenza have increased during the pandemic as compared to 2019, but the spread of influenza has apparently decreased due to social distancing and use of masks. A resurgence of contagious infectious diseases is expected once the pandemic settles down and social interactions increases.

c. Children with TB during and post COVID-19 pandemic

There are 205,000 estimated annual deaths among children living in resource poor settings due to TB.[63] Early diagnosis, timely initiation of treatment, health systems support for the availability of child friendly medication, as well as the prevention of transmission from sputum-smear positive index cases—usually adults—to vulnerable young children in households are crucial for child survival. Resources which are otherwise focused on paediatric care are diverted to deal with adult patients affected by the severe respiratory symptoms of COVID-19, thus leading to missed diagnosis and care of children with TB. The laboratories which previously were involved with the early detection and diagnosis of *M. tuberculosis* are now analysing respiratory specimens for COVID-19 including using the GeneXpert platform. These issues are not limited to childhood TB; the adult TB services are equally affected. Since the timely diagnosis and prompt treatment is most important in childhood TB to avert mortality, this delay in detection, diagnosis and treatment will lead to 20% more deaths due to TB in during COVID.[64]

Challenges such as access to health facilities, as families are hesitant to take an unwell child to the hospital during the initial stages of illness and the overlapping picture of respiratory symptoms leading to misdiagnosis further delays starting correct treatment which will exact a heavy toll. With no regular follow-ups of children by already severely stretched health services during the pandemic there will be a rise in cases of severe illness in children (TB, meningitis) with no provision of isoniazid preventive therapy (IPT) for TB infection in the community, which requires resources to contact trace, screen and eventually implement treatment.

During the COVID-19 pandemic the contact screening for COVID-19 should also include questions regarding TB cases in the household as families are together for longer duration due to the complete lockdown and social distancing leading to more exposure of children and the danger of contacting TB from an infectious case in the family.

d. HIV in children post-COVID-19

Models show that the impact of the novel coronavirus could take 10% more lives due to HIV over the next 5 years due to the pandemic. According to a study conducted by UNICEF, it has been shown that in 2019, 2.1 million pregnant women and children living with HIV had accessed treatment to prevent infection due to other causes. During the COVID-19 pandemic all the control measures were affected for a period of 6 months among 100% of the population when 770,000 fewer children and pregnant women received this treatment leading to more morbidity and mortality among PLHIV. The COVID-19 pandemic reversed the achievements which were gained in past years in terms of the decrease in the number of cases of HIV and the decrease in children and adolescents who will access treatment. The main reason being that people may not get anti-retroviral therapy during the pandemic.[45]

e. Vector borne diseases in children post COVID-19

The vector-borne diseases—malaria, dengue, chikungunya and Japanese encephalitis—will increase during the coronavirus pandemic as activities like integrated vector control measures (such as indoor residual spray, anti-larval measures, etc.) and personal protective methods (like insecticide-treated bed nets) take a back seat. It is predicted that malaria will take 36% more lives during the pandemic. These indirect impacts of the COVID-19 epidemic sound scary, but they are only predictions. An arboviral disease like dengue also presents like COVID-19, and may be misdiagnosed leading to more mortality due to dengue. Health services and governments can take action to avoid these extra deaths. For malaria, mosquito populations must be controlled using the same measures used previoulsy.[65] The implementation of the WHO's Global Vector Control Response (GVCR) 2017–2030 strategy and regional policies for vector control including inter-sectoral coordination, generating awareness among communities and vector control measures which have been interrupted should be implemented as necessary activities even during the COVID-19 pandemic to control the further spread of these vector borne diseases.

f. Large-scale behavioural and social changes

There has been a major impact on our behavioural patterns. We have become very stringent regarding cough etiquette and spitting in public. Our new ways of interacting and socializing with each other have changed majorly doing namaste, saluting or waving instead of handshakes, video conferencing instead of in-person conferences. Our vigilance around things like disinfecting surfaces will probably continue.

g. Overarching factor in children: Poverty and malnutrition

Poverty: Due to the lockdown/social distancing there has been a disruption in the education system as schools are closed. Confinement within homes with no peer group or social network has led to an increase in anxiety and stress even among children and increased cases of domestic violence, thus increasing concerns about mental health issues. The reduced access to healthcare and essential services has only compounded the problems. Even before the COVID-19 pandemic 45% of children were deprived of healthcare, education, nutrition, water and sanitation, and social and child protection services. The pandemic has further magnified these issues.[66] Access to education has been affected as poor children do not have the facilities to attend online classes and there is a digital divide in the society. The ones who have access online may face sexual exploitation and cyber bullying due to unsupervised online Internet use. The economic blows of the pandemic will reverberate for years to come, leading to increased poverty. Globally, it is estimated that there will be an increase of 15% (an additional 150 million children by mid-2020) in the number of children living in poverty, in many aspects such as—health, education, housing, sanitation, nutrition or having access to potable water.

Malnutrition: Data from 135 countries published by UNICEF indicates that there is a 40% decline in the coverage of services to improve nutrition among women and children.[67] In 161 countries approximately 370 million children are affected due to the disruption of school meals as a daily source of nutrition.[68] Schemes like Anganwadi, providing a mid-day meal (school meal), village health and having a nutrition day have been disrupted in India affecting the daily nutrition of the most vulnerable children. Vitamin A supplementation programmes are being missed by more than 250 million children globally. It is further predicted that 6.7 million children might suffer from malnutrition during the first 12 months of the COVID-19 pandemic: resulting in an additional 120,000 deaths.[69,70] The reasons for disruption in nutrition services are mainly due to a decrease in the demand by caregivers due to a fear of contacting the infection, restricted mobility and closure of schools.

h. Maintaining immunization services during and post COVID-19 Pandemic

When the Democratic Republic of the Congo was fighting the Ebola outbreak, they also witnessed a measles outbreak which took more than 6500 lives and affected more than 340,000 children; caused by the disruption to the immunization services which could have been prevented. During these unprecedented challenging times of the COVID-19 pandemic there have to be systems put in place to ensure strong supply chains, essential health supplies, disease surveillance for vaccine-preventable diseases, providing knowledge and training to health workers and assistance to immunization programmes using rapidly evolving solutions. The following should be implemented: innovative approaches for immunization also ensuring strict infection prevention and control measures such as time slots, mobile vaccination centres, drive-through vaccination centres, catch-up vaccination at homes and campaign modes among others. The health workers who have been going door to door in order to administer lifesaving vaccines are trusted by the communities and can also provide COVID-19 guidance regarding staying safe directly to the people they visit.

Once the pandemic is over, strategies to strengthen routine immunization should be considered and we should be prepared to develop strategies to effectively administer COVID-19 vaccines in the future.[71]

Infectious Diseases Post COVID 19 in the Elderly

Older people, especially those with chronic illness are more susceptible than younger people to COVID-19. The association between the viral load and the severity of COVID-19 has been reported.[72] In fact, while many younger people experience no or mild symptoms of infection, older adults are highly susceptible to life-threatening respiratory and systemic conditions.[73] Those older than 60 years with chronic diseases, such as hypertension, diabetes, COPD, as well as cardiovascular, cerebrovascular, liver, kidney and gastrointestinal diseases, are more susceptible to the infection by SARS-CoV-2 and experience higher mortality when they develop COVID-19.[74]

Many factors are responsible for the higher susceptibility and mortality of older people to COVID-19.

The possible mechanisms of higher severity are:

1. Associated with the decline of the immune system, affecting both the innate and adaptive immune responses[75]
2. Inflammatory cytokines, including tumour necrosis factor (TNF) and interleukin 6 (IL-6), are associated with an increased risk for many diseases, including sarcopenia, osteoarthritis and many infectious diseases[76,77]
3. High IL-18 and IL-1β levels in SARS, MERS and COVID-19 patients, not only in the blood but also in the lungs and lymphoid tissues indicate increased inflammasome activation.

Case fatality and the severity of COVID-19 illness has been directly related to age and immune-compromised states. Almost 15% of the first wave of deaths in China were among the elderly. The Chinese Centre for Disease Control and Prevention (CDC) reported the mortality rate in the 60–69 year age group as 3.6%, 8% for those in their 70s and up to 15% in the 80 years and above age group.[78] In Sweden, for example, 90% of the deaths from COVID-19 were among people more than 70 years of age.80 The New York Times gathered recent data showing that in the USA, at least 28,100 residents and workers have died from a SARS-CoV-2 infection in a nursing home or in another long-term care facility for older people.[79] Overall, more than a third (35%) of all COVID-19 deaths in the USA occurred in long-term care facilities, comprising residents and workers.[79]

An analysis of more than 114,000 COVID-19 associated deaths during May–August 2020, found that 78% of the people who died were aged 65 years and older, and 53% were male; 51% were White, 24% were Hispanic and nearly 19% were Black. COVID-19 remains a major public health concern regardless of age or race and ethnicity.[80] In Belgium, for example, 53% of the country's entire number of COVID-19 deaths occurred in care homes, 62% in Canada, 39.2–51% in France and 67% in Spain.[79] The WHO in its guidelines has recommended strict social isolation for the geriatric population to control the deaths in heavily affected countries. With an increase in vulnerability, there is also rise in fear, panic and apprehension in seniors and their families which has not been spoken about.

Why the Elderly?

There are innumerable changes in the psychological, social and environmental vulnerabilities that comes with ageing. There is increase in the risk of a plethora of infections and diminution of all forms of immune response. The elderly also have multiple comorbidities and increased hospitalizations which increase the chance of contracting the infection during a pandemic. Liu and colleagues[81] reported that progression of illness and risk of death from COVID-19-induced pneumonia is almost three times higher in the elderly than among their younger counterparts. The number of lungs-lobes involved, the need for mechanical ventilation, the chance of blood-gas abnormalities were all higher in the elderly with lower antiviral antibodies and lower C-reactive protein (CRP), a potent marker of inflammation. In another

review, one of the challenges in the COVID-19 pandemic was the nonspecific organ involvement in the elderly as many have died due to congestive cardiac failure and sepsis but had showed no signs of pneumonia. In such cases, factors like iatrogenic infections, polypharmacy and poor mobility also play a role. Besides, older people might have cognitive and sensory deficits which make it difficult for them to comprehend and follow precautions. Many of them are institutionalized exposing them to the risk of overcrowding, poor hygiene, and a lack of adequate supervision. Proper testing is also hampered due to neglect and that increases the risk of them being asymptomatic carriers.

Impact on the Elderly

Pandemics have a significant psychosocial impact. Health anxiety, panic, adjustment disorders, depression, chronic stress and insomnia are the major outcomes. Misinformation and uncertainty can give rise to mass hysteria.[82] The elderly are especially vulnerable. So far only one paper has looked at elderly mental health during these times.[83]

Loneliness is a known factor that negatively affects a person's mental health and well-being, and some older adults were already at a higher risk of experiencing it. Deteriorating health or the death of partner and friends may impede maintaining a healthy social circle. The pandemic and the quarantine heighten this risk of loneliness. What is more, emerging reports have shown that lockdowns increase the risk of abuse among older people.

During the pandemic, older adults have become even more dependent on their caregivers, and, in a pattern similar to the one that has increased the rates of domestic violence, some caregivers have used the pandemic to exercise their control and abuse their elderly patients and family members.

Elder abuse tends to occur more frequently in communities that lack mental health or social care resources. The perpetrators of the abuse also tend to have mental health problems themselves, as well as reporting feelings of resentment with their informal caregiving duties.

According to a recent article appearing in the journal *Aggression and Violent Behaviour*, people who experience 'elder abuse' are more likely to develop mental health problems such as depression, high stress and self-neglect conditions that can only be made worse by lockdowns.

Overall, lockdowns mean that more older people are trapped with their abusers, that some perpetrators of abuse reluctantly find themselves in a caregiving role, and that, as a result, there is a higher need for mental health and community support services.

'Loneliness is a complex, subjective emotion, experienced as a feeling of anxiety and dissatisfaction associated with a lack of connectedness or communality with others'. The article mentions social isolation of the elderly as a 'serious public health concern' due to their bio-psychosocial vulnerabilities. Social distancing, although a major strategy to fight COVID-19, is also a major cause of loneliness, particularly in settings like nursing care or old-age homes, which is an independent risk factor for

depression, anxiety disorders and suicide.[82] Social connectedness is vital during the breakdown of public health services, more so when 'ageism' becomes a factor for stigmatization in this marginalized population. This leads to neglect and therapeutic nihilism. Most seniors are not comfortable with smart phones or media language, hence the precautions for a pandemic need to be explained to them in their own simple terms. Cognitive impairment, and problems like wandering, irritability and psychotic symptoms can worsen the panic and make it difficult for them to follow the precautions of social-distancing and hand hygiene. Furthermore, people with mental health disorders (including the elderly) are more vulnerable and are prone to exacerbations during such a crisis. Discrimination and a lack of healthcare utilization are other factors contributing to their poor care during the COVID-19 outbreak. The substantial stress generated by 'information overload' can lead to paranoia and healthcare-related mistrust which might lead them to avoid quarantining, thus having dire public health consequences.

Mental health is the cornerstone of public health, more so in the elderly. As the need for a 'viral cure' eclipses the importance of mental health, the global panic only aids in increasing the spread of the disease. Lessons learnt from earlier pandemics like SARS have proved that regular telephonic counselling sessions, healthy contact with family, relevant and updated information, caring for the general medical and psychological needs, and respecting their personal space and dignity are important components of mental healthcare in the elderly.[83] This warrants sensitization at all levels for the early detection of mental healthcare needs and planning appropriate interventions, especially for the vulnerable old-age population.

Figure 34 Prevalence (%) of probable major depression based on CIDI-SF among older adults by age in India, LASI Wave 1, 2017-18

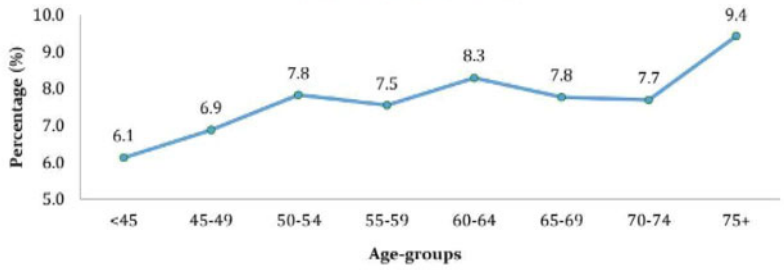
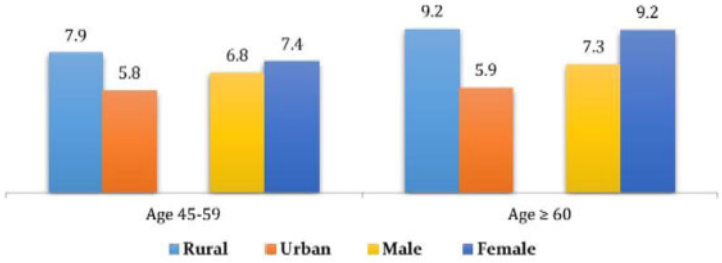


Figure 35 Prevalence (%) of probable major depression based on CIDI-SF among older adults age 45-59 and elderly age 60 and above by place of residence and sex in India, LASI Wave 1, 2017-18



Infectious Diseases Post COVID-19 in Individuals with Comorbidities

Comorbidity: Older adults and people of any age who have serious underlying medical conditions like heart or lung disease or diabetes seem to be at higher risk for developing more serious complications from COVID-19 illness.[84]

An analysis of more than 106,000 patients who survived COVID-19 showed that 9% (9504) were readmitted to the same hospital within two months of discharge, according to the *Morbidity and Mortality Weekly Report*, 9th November, 2020. The odds of hospital readmission increased with age and the presence of five chronic health conditions: COPD, heart failure, diabetes, chronic kidney disease and obesity.[85]

Severe illness from COVID-19 is defined as hospitalization, admission to the intensive care unit (ICU), intubation or mechanical ventilation or death. COVID-19 is a new disease. Currently there are limited data and information about the impact of many underlying medical conditions and whether they increase the risk for severe illness from COVID-19. Based on what we currently know, adults of any age with the following conditions might be at an increased risk for severe illness from the virus that causes COVID-19[86]:

- Cancer
- Chronic kidney disease
- COPD
- Heart conditions, such as heart failure, coronary artery disease or cardiomyopathies
- Overweight and Obesity (body mass index [BMI] of 25 kg/m^2 or higher)
- Pregnancy
- Sickle cell disease
- Smoking
- Diabetes mellitus
- Asthma (moderate-to-severe)
- Cerebrovascular disease (affects blood vessels and blood supply to the brain)
- Cystic fibrosis
- Hypertension
- Immunocompromised state (weakened immune system) from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids or use of other immune weakening medicines
- Neurological conditions, such as dementia

- Liver disease
- Pulmonary fibrosis (having damaged or scarred lung tissues)
- Thalassaemia (a type of blood disorder)

The level of evidence for each condition was determined by CDC reviewers based on the available information about COVID-19. Conditions were added to the list (if not already on the previous underlying medical conditions list [originally released in March 2020]) if evidence for an association with severe illness from COVID-19 met any of the following criteria:

- Strongest and most consistent evidence: Defined as consistent evidence from multiple small studies or a strong association from a large study,
- Mixed evidence: Defined as multiple studies that reached different conclusions about risk associated with a condition, or
- Limited evidence: Defined as consistent evidence from a small number of studies (Table 3).

Table 3

Information for the CDC

Level of Evidence	Condition
Strongest and most consistent evidence	Cancer
	Chronic kidney disease
	COPD
	Heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
	Obesity (BMI >30 kg/m^2)
	Severe obesity (BMI ≥40 kg/m^2)
	Pregnancy
	Sickle cell disease
	Smoking
	Solid organ transplantation
	Type 2 diabetes mellitus
Mixed evidence	Asthma
	Cerebrovascular disease
	Hypertension
	Use of corticosteroids or other immunosuppressive medications
Limited evidence	Bone marrow transplantation
	HIV
	Immune deficiencies
	Inherited metabolic disorders
	Liver disease
	Neurologic conditions

	Other chronic lung diseases
	Overweight (BMI >25 kg/m^2, but <30 kg/m^2)
Level of evidence	
	Paediatrics
	Thalassaemia
	Type 1 diabetes mellitus

Abbreviations: *BMI,* body mass index; *CDC,* Centers for Disease Control; *COPD,* chronic pulmonary obstructive disease.

Source: CDC. Coronavirus Disease 2019 (COVID-19) [Internet]. Centers for Disease Control and Prevention. 2020 [cited 2020 Nov 20]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html[87]

Preventive Strategies:

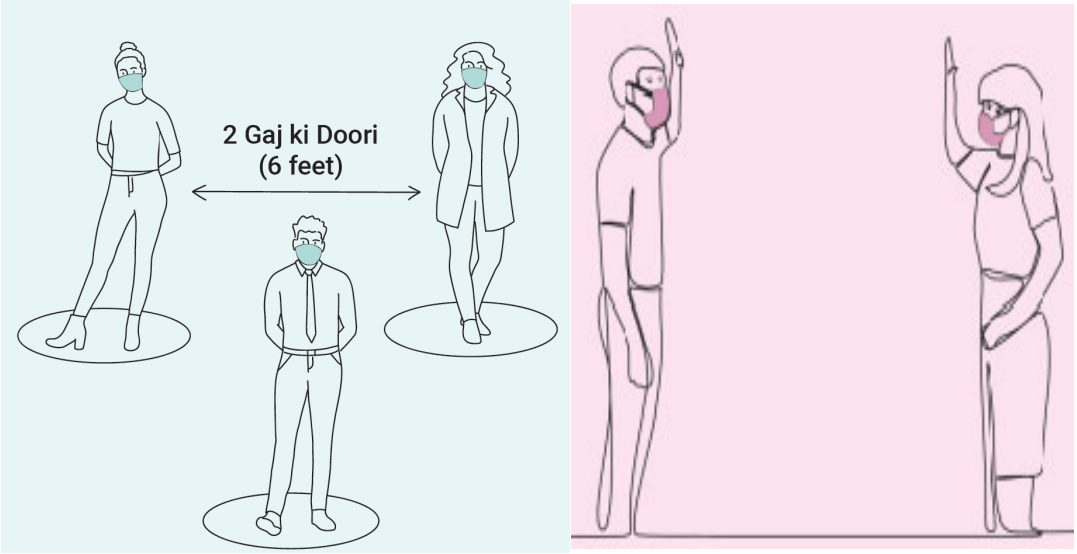
Non-Pharmacological Measures: Till date there is no treatment for COVID-19 infection. Treatment available is for the symptomatic relief. So, there is need to understand the COVID appropriate behaviour and implement the preventive strategies. This will break the chain of transmission, thus decreasing the prevalence of COVID-19 infection. The battle against COVID-19 can be won only when all are included, and everyone behaves responsibly.

- **Face Mask and Face Shields:** Face mask should be always worn when one goes to the public places or essential travel or when in the room with other people or when having cough/cold. Hands must be washed before wearing a mask and after removing a mask. If there is need to travel or in case when there is an infected person who needs care, one must wear mask and also face shield to protect themselves. One may use standard marks or even well fitted face covers made at home with cloth to reduce community transmission.

Source: https://www.mohfw.gov.in/pdf/Illustrativeguidelineupdate.pdf

- **Personal Hygiene, Respiratory hygiene, and hand washing:** It is important to maintain personal hygiene such as hand washing with soap and eye hygiene is recommended to control the spread of infection. Using tissue or handkerchief when one coughs or use for running nose. The cough etiquettes including covering the nose and mouth by bending the elbow during sneezing and coughing is most important. One must avoid touching eyes, noes and mouth, since hands may pick up the virus and transmit it. Hands must be washed properly and thoroughly with soap or sanitize with alcohol-based hand rub. Gloves should be worn when disinfecting the surfaces.
- **Ventilation:** Good ventilation is important to reduce contamination in the closed environments to decrease the transmission of the virus. Some measures taken in the hospitals are use of viral filters, airflow changes and negative pressure to decrease the spread of virus, and installation of Ultraviolet germicidal irradiation (UVGI) for in-duct airborne bioaerosol disinfection.
- **Social Distancing:** There should be at least distance of 6 feet (or 2 Gaj ki Doori) while maintaining social distance in public places when working with other people or doing

shopping for necessities. We should greet each other without any physical contact, such as by Namaste or Salam.

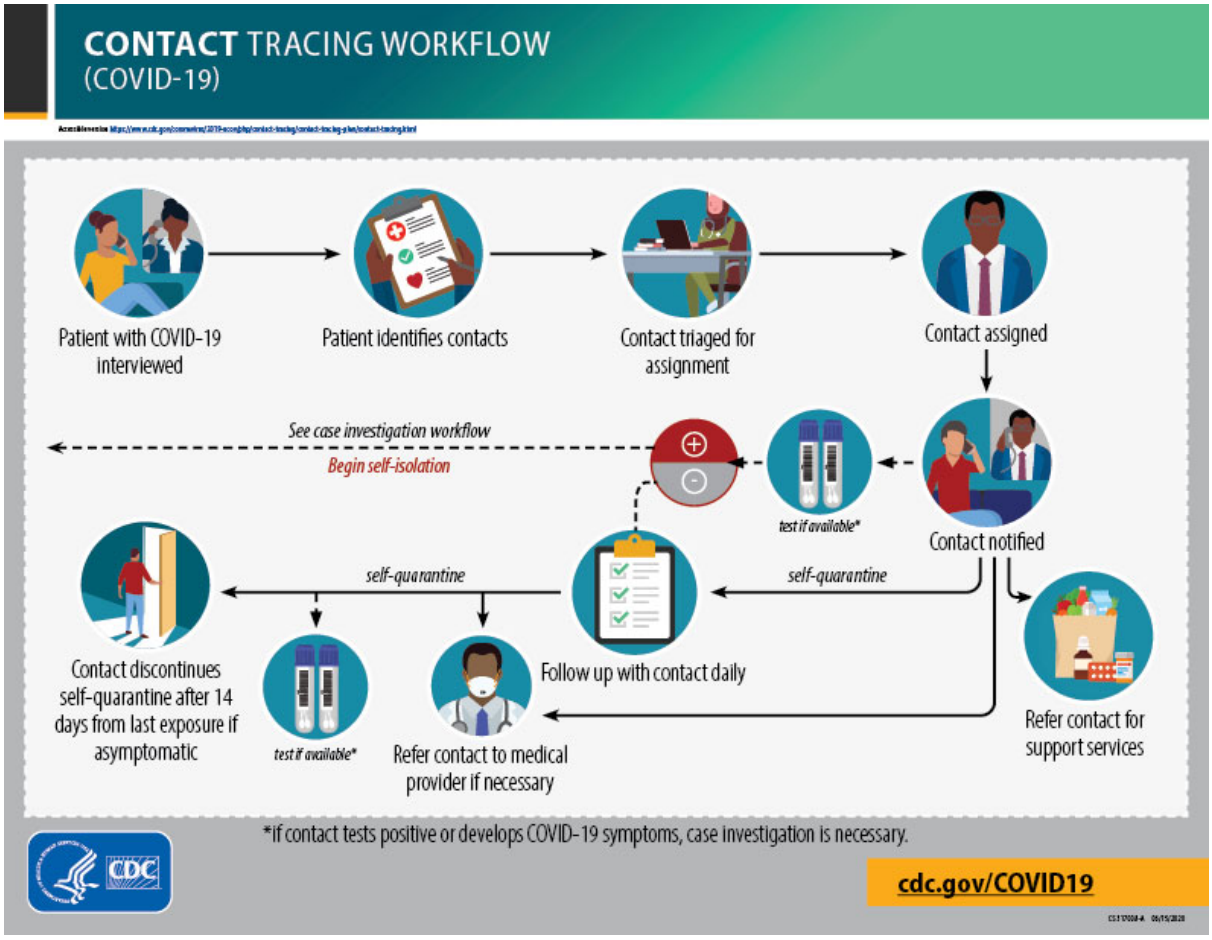


Source: https://www.mohfw.gov.in/pdf/Illustrativeguidelineupdate.pdf

- **Avoiding Public Gathering and unnecessary travel:** One should limit going to public gatherings. Public gatherings for social events like birth, death, marriages, etc should be avoided or the guest list should be kept to minimal. Having tea, coffee or meals together should be discouraged to decrease the spread of infection. Large public gatherings increase the risk of transmission of COVID-19 infection.
- **Surface cleaning and disinfection:** Frequently touched surfaces should be cleaned and disinfected using hydrogen peroxide (0.5%) or Sodium hypochlorite (0.1%) with contact time of 1 minutes. The infected droplets which settle down on the surfaces can be cleaned by practicing good environmental hygiene to make the surroundings safe. One should not spit in the public to avoid putting everyone at risk, especially after having smokeless tobacco.
- **Self-reporting and Self-isolation:** Self reporting of signs and symptoms of cough, cold and flu like symptoms should be encouraged without discriminating towards those who have the disease. The ones who have the symptoms if self-report and get themselves investigated, helps in isolating them. This also helps in contact tracing and further containment of infection. The

employees those who are daily wager or on contractual basis should be encouraged by giving paid leaves during sickness for them to come forward to self-report without any hesitancy. Everyone who has COVID-19 infection should be treated with compassion and support.

- **Balanced nutritious Diet, Exercises and Lifestyle modification:** Balanced nutritious diet helps boost the immunity which helps to fight the infection. Physical exercise helps to reduce obesity, stress and helps to relax. The screen time should be monitored closely and reduced as much as possible.
- **Contact tracing and Monitoring:** Contact tracing is to be done for the close contacts of laboratory- confirmed or probable COVID-19 patients on priority. Close contacts include any individual within 6 feet of an infected person for a total of 15 minutes or more and testing of close contacts is recommended. Those who are found to be positive on testing should be isolated and treated as confirmed cases of COVID-19. Those who are negative on testing and are asymptomatic contacts should self-quarantine for 14 days from their last exposure. (Reference – CDC. Contact Tracing for COVID-19. [103]



Source: https://www.cdc.gov/coronavirus/2019-ncov/php/contact-tracing/contact-tracing-plan/contact-tracing.html)

Information regarding COVID-19 should be taken only from authentic and creditable source. The posts on social media which spread misconceptions/negative/unverified information should not be circulated and one should behave more responsibly. Sources such as your doctors, national toll-free helpline number – 1075, Aarogya Setu app and MOHFW site, are reliable sources latest updates for information. If in any distress or for any anxiety or concerns one must seek help.

Role of Primary Care Physicians in Early Diagnosis and Management of COVID-19

Coronavirus is having a decisive bearing on patients and the healthcare system—including primary care. Primary care clinicians are among the healthcare workers on the front lines during this health catastrophe addressing the prevention of the virus, triaging patients who may be infected, and caring for those who are ill. Primary care physicians can decrease the further burden on the health system due to the COVID-19 pandemic.

The diagnostic challenge of COVID-19 in primary care, especially when facing a concurrent outbreak of an endemic local disease is immense. The early stages of COVID-19 infections are virtually identical to other common viral infections, with many patients initially presenting with mild and undifferentiated symptoms.[87] There is a role for early laboratory investigations and serological testing of local endemic conditions to narrow the list of differentials.[88] A Cochrane review[89] reported that a single sign and symptom is very less sensitive for diagnosing COVID-19 among patients.

Significant thrombocytopenia is atypical for COVID-19 infections, observed in only 5–12% of clinical cases but is a prominent feature of dengue.[5,15,90,91] Most patients with COVID-19 have mild respiratory symptoms although some develop dyspnoea at around 5–7 days from onset of symptoms.[5,16,87,91-93]

Therefore, primary care physicians need to be abreast of current epidemiological trends, case definitions and recognize when there are variations in disease and symptomatology patterns. Within the climate of a novel infectious disease pandemic, we need to be aware of concomitant diseases and false-positive serology. Primary care providers should consider testing patients with persistent fever without a clear source for COVID-19 as earlier identification is key for containment.[88]

In times like these, it is important for Primary care Physicians to rely on reference content written by experts with more exposure to disease variations and treatment modalities. The utilization of such experience based resources in a point of case scenario leads to better outcomes and reduces variation in care standards

Vaccines for COVID-19

SARS-CoV-2 vaccine preparations are progressing with an unparalleled scale and haste. Past evidence from investigating SARS, MERS and Ebola and the accessibility of the next-generation vaccine technology platforms have enhanced the identification of possible candidates and development of new vaccines. A variety of platforms are being tried for the vaccine development.[94] Some of the platforms are drawn from oncology and are relatively newer for vaccine development. As of 4th March, 2020, there have been 258 efforts globally in COVID vaccine development.[94] The vaccines in phase four

development are **CoronaVac** (SARS-CoV-2 vaccine [inactivated] Sinovac Research and Development Co., Ltd), **ChAdOx1-S - (AZD1222)** (Covishield) (AstraZeneca + University of Oxford), **mRNA-1273** (Moderna + National Institute of Allergy and Infectious Diseases [NIAID]) and **BNT162 (3 LNP-mRNAs)** (Pfizer/BioNTech + Fosun Pharma).

Some of the candidate vaccines involve RNA, DNA, inactivated (without and with alum) and nonreplicating viral vectors, all leveraging the platforms used for other viral vaccines.[94-96] Vaccines with attenuated viruses or replicating vectors are targeting the inducement of mucosal immunity to reduce the mucosal infection and viral shedding. The RNA, DNA and subunit vaccines aim to elicit sufficient humoral neutralizing antibodies against proteins (S-protein as primary and M- and N-proteins as secondary targets) or receptor-binding domains to block viraemia and systemic effects. The virus-like particles, subunits, recombinant viral vectors and nucleic acid vaccines provide newer universal vaccine platforms amenable for the introduction of new antigenic targets and are suitable for the new emerging viruses. These agents infect the host cells or induce antigenic proteins to generate both T-cell immune responses and antibodies. Several recombinant vectors from viruses (adenovirus, poxvirus, measles, parainfluenza, etc.) expressing the S- or N-proteins are also being explored. The route of administration will depend on the type of vaccine. The dosage and schedule will be determined by the mechanism, memory B- and T-cell responses and exposure to SARS-CoV-2 infection. As per the available information, the majority of the vaccines are being developed by the private sector and from North America followed by China and Asia including eight Indian companies.[95,97] Paralleling the development and facilitating regulatory adaptations are also being provided.

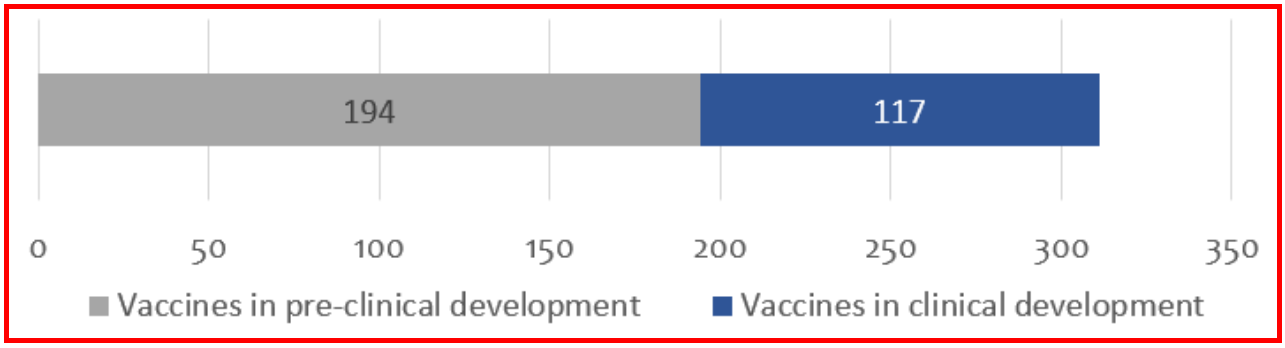


Figure 13 Vaccine for COVID-19 in pre-clinical development and clinical development

Source: World Health Organization. WHO Solidarity Trial—Accelerating a Safe and Effective COVID-19 Vaccine. Geneva: World Health Organization. Available from: https://www.who.int/emergencies/ diseases/novel-coronavirus-2019/global-research-on-novel-coronavir us-2019-ncov/solidarity-trial-accelerating-a-safe-and-effective-covid19-vaccine. [Last accessed on 2021 Sep 17].[95]

Table 4

Platforms for various vaccines in the clinical development for COVID-19

Platform		Candidate vaccines (no. and %)	
PS	Protein subunit	42	36%
VVnr	Viral Vector (non-replicating)	17	15%
DNA	DNA	11	9%
IV	Inactivated Virus	16	14%
RNA	RNA	19	16%
VVr	Viral Vector (replicating)	2	2%
VLP	Virus Like Particle	5	4%
VVr + APC	VVr + Antigen Presenting Cell	2	2%
LAV	Live Attenuated Virus	2	2%
VVnr + APC	VVnr + Antigen Presenting Cell	1	1%
Total		**117**	

Source: World Health Organization. WHO Solidarity Trial—Accelerating a Safe and Effective COVID-19 Vaccine. Geneva: World Health Organization. Available from: https://www.who.int/emergencies/ diseases/novel-coronavirus-2019/global-research-on-novel-coronavir us-2019-ncov/solidarity-trial-accelerating a-safe-and-effective-covid19-vaccine. [Last accessed on 2020 May 02].[94]

Table 5

Details on vaccines in clinical development

Vaccine platform acronym	Vaccine platform description	Type of candidate vaccine	Number of doses	Schedule	Route of administration	Developers	Phase
IV	Inactivated virus	CoronaVac; inactivated SARS-CoV-2 vaccine (vero cell)	2	Day 0 + 14	IM	Sinovac Research and Development Co., Ltd	Phase 4
IV	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell), vaccine name BBIBP-CorV	2	Day 0 + 21	IM	Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products	Phase 4
VVnr	Viral vector (Non-replicating)	ChAdOx1-S - (AZD1222) Covishield	1-2	Day 0 + 28	IM	AstraZeneca + University of Oxford	Phase 4
VVnr	Viral vector (Non-replicating)	Recombinant novel coronavirus vaccine (Adenovirus type 5 vector) Ad5-nCoV	1	Day 0	IM	CanSino Biological Inc./Beijing Institute of Biotechnology	Phase 4
VVnr	Viral vector (Non-replicating)	Ad26.COV2.S	1-2	Day 0 or Day 0 +56	IM	Janssen Pharmaceutical Johnson & Johnson	Phase 4
RNA	RNA based vaccine	mRNA-1273	2	Day 0 + 28	IM	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	Phase 4
RNA	RNA based vaccine	BNT162b2 (3 LNP-mRNAs), also known as "Comirnaty"	2	Day 0 + 21	IM	Pfizer/BioNTech + Fosun Pharma	Phase 4
RNA	RNA based vaccine	mRNA-1273.351. A lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine that encodes for a full-length, prefusion stabilized S protein of the SARS-CoV-2 B.1.351 variant.	3	Day 0 or Day 0 + 28 or Day 56	IM	Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	Phase 4
IV	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell)	2	Day 0 + 21	IM	Sinopharm + China National Biotec Group Co	Phase 3

						+ Wuhan Institute of Biological Products	
VVnr	Viral vector (Non-replicating)	Gam-COVID-Vac Adeno-based (rAd26-S+rAd5-S) Sputnik V COVID-19 vaccine	2	Day 0 + 21	IM	Gamaleya Research Institute ; Health Ministry of the Russian Federation	Phase 3
PS	Protein subunit	SARS-CoV-2 rS/Matrix M1-Adjuvant (Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M) NVX-CoV2373	2	Day 0 + 21	IM	Novavax	Phase 3
PS	Protein subunit	Recombinant SARS-CoV-2 vaccine (CHO Cell)	2-3	Day 0 + 28 or Day 0 + 28 + 56	IM	Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences	Phase 3
RNA	RNA based vaccine	CVnCoV Vaccine	2	Day 0 + 28	IM	CureVac AG	Phase 3
IV	Inactivated virus	SARS-CoV-2 vaccine (vero cells)	2	Day 0 + 28	IM	Institute of Medical Biology + Chinese Academy of Medical Sciences	Phase 3
IV	Inactivated virus	QazCovid-in® - COVID-19 inactivated vaccine	2	Day 0 + 21	IM	Research Institute for Biological Safety Problems, Rep of Kazakhstan	Phase 3
DNA	DNA based vaccine	nCov vaccine	3	Day 0 + 28 + 56	ID	Zydus Cadila	Phase 3
IV	Inactivated virus	Whole-Virion Inactivated SARS-CoV-2 Vaccine (BBV152); Covaxin	2	Day 0 + 14	IM	Bharat Biotech International Limited	Phase 3
PS	Protein subunit	VAT00002: SARS-CoV-2 S protein with adjuvant	2	Day 0 + 21	IM	Sanofi Pasteur + GSK	Phase 3
IV	Inactivated virus	Inactivated SARS-CoV-2 vaccine (Vero cell)	2	Day 0 + 28	IM	Shenzhen Kangtai Biological Products Co., Ltd.	Phase 3
PS	Protein subunit	SCB-2019 + AS03 or CpG 1018 adjuvant plus Alum adjuvant (Trimeric subunit Spike Protein vaccine)	2	Day 0 + 21	IM	Clover Biopharmaceuticals Inc./GSK/Dynavax	Phase 3
PS	Protein subunit	COVAX-19® Recombinant spike protein + adjuvant SPIKOGEN®	2	Day 0 + 21	IM	Vaxine Pty Ltd./CinnaGen Co.	Phase 3
PS	Protein subunit	MVC-COV1901 (Spike-2P protein + adjuvant CpG 1018)	2	Day 0 + 28	IM	Medigen Vaccine Biologics + Dynavax + National Institute of Allergy and Infectious Diseases (NIAID)	Phase 3
PS	Protein subunit	FINLAY-FR-2 anti-SARS-CoV-2 Vaccine (RBD chemically conjugated to tetanus toxoid plus adjuvant)	2	Day 0 + 28	IM	Instituto Finlay de Vacunas	Phase 3
PS	Protein subunit	EpiVacCorona (EpiVacCorona vaccine based on peptide antigens for the prevention of COVID-19)	2	Day 0 + 21	IM	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector"	Phase 3
PS	Protein subunit	RBD (baculovirus production expressed in Sf9 cells) Recombinant SARS-CoV-2 vaccine (Sf9 Cell)	2	Day 0 + 28	IM	West China Hospital + Sichuan University WestVac Biopharma Co., Ltd.	Phase 3
RNA	RNA based vaccine	SARS-CoV-2 mRNA vaccine (ARCoV)	2	Day 0 + 14 or Day 0 + 28	IM	Academy of Military Science (AMS), Walvax Biotechnology and Suzhou Abogen Biosciences	Phase 3
PS	Protein subunit	CIGB-66 (RBD+aluminium hydroxide)	3	Day 0 + 14 + 28 or Day 0 +28 + 56	IM	Center for Genetic Engineering and Biotechnology (CIGB)	Phase 3
IV	Inactivated Virus	VLA2001	2	Day 0 + 21	IM	Valneva, National Institute for Health Research, United Kingdom	Phase 3
PS	Protein subunit	Recombinant Sars-CoV-2 Spike protein, Aluminum adjuvanted (Nanocovax)	2	Day 0 + 21	IM	Nanogen Pharmaceutical Biotechnology	Phase 3

IV	Inactivated Virus	ERUCOV-VAC, inactivated virus	2	Day 0 + 21	IM	Erciyes University, Turkey	Phase 3
PS	Protein subunit	GBP510, a recombinant surface protein vaccine with adjuvant AS03 (aluminium hydroxide)	2	Day 0 + 28	IM	SK Bioscience Co., Ltd. and CEPI	Phase 3
PS	Protein subunit	Razi Cov Pars, recombinant spike protein	3	Day 0 + 21 +51	IM and IN	Razi Vaccine and Serum Research Institute	Phase 3
DNA	DNA based vaccine	INO-4800+electroporation	2	Day 0 + 28	ID	Inovio Pharmaceuticals + International Vaccine Institute + Advaccine (Suzhou) Biopharmaceutical Co., Ltd	Phase 2/3
DNA	DNA based vaccine	AG0301-COVID19	2	Day 0 + 14	IM	AnGes + Takara Bio + Osaka University	Phase 2/3
VVnr	Viral vector (Non-replicating)	GRAd-COV2 (Replication defective Simian Adenovirus (GRAd) encoding S)	1	Day 0	IM	ReiThera + Leukocare + Univercells	Phase 2/3
PS	Protein subunit	UB-612 (Multitope peptide based S1-RBD-protein based vaccine)	2	Day 0 + 28	IM	Vaxxinity	Phase 2/3
VLP	Virus like particle	Coronavirus-Like Particle COVID-19 (CoVLP)	2	Day 0 + 21	IM	Medicago Inc.	Phase 2/3
VVr	Viral vector (Replicating)	rVSV-SARS-CoV-2-S Vaccine (IIBR-100)	1	Day 0	IM	Israel Institute for Biological Research	Phase 2/3
IV	Inactivated Virus	COVID-19 inactivated vaccine	2	Day 0 + 14	IM	Shifa Pharmed Industrial Co	Phase 2/3
RNA	RNA based vaccine	mRNA-1273.211. A multivalent booster candidate combining mRNA-1273 plus mRNA-1273.351.	1	Day 0	IM	ModernaTX, Inc.	Phase 2/3
VVnr	Viral vector (Non-replicating)	AZD2816; adenoviral vector ChAdOx platform and based on the Beta (B.1.351) variant	2	Day 0 + 28	IM	AstraZeneca + University of Oxford	Phase 2/3
RNA	RNA based vaccine	ARCT-154 mRNA Vaccine	2	Day 0 + 28	IM	Arcturus Therapeutics, Inc.	Phase 2/3
RNA	RNA based vaccine	ARCT-021	NR	NR	IM	Arcturus Therapeutics	Phase 2
PS	Protein subunit	FINLAY-FR1 anti-SARS-CoV-2 Vaccine (RBD + adjuvant)	2	Day 0 + 28	IM	Instituto Finlay de Vacunas	Phase 2
VVr	Viral vector (Replicating)	DelNS1-2019-nCoV-RBD-OPT1 (Intranasal flu-based-RBD)	2	Day 0 + 28	IN	University of Hong Kong, Xiamen University and Beijing Wantai Biological Pharmacy	Phase 2
VVr + APC	Viral vector (Replicating) + APC	Dendritic cell vaccine AV-COVID-19. A vaccine consisting of autologous dendritic cells loaded with antigens from SARS-CoV-2, with or without GM-CSF	1	Day 0	IM	Aivita Biomedical, Inc. National Institute of Health Research and Development, Ministry of Health Republic of Indonesia	Phase 2
RNA	RNA based vaccine	MRT5500, an mRNA vaccine candidate	2	Day 0 + 21	IM	Sanofi Pasteur and Translate Bio	Phase 2
VLP	Virus like particle	SARS-CoV-2 VLP Vaccine Vaccine-Wuhan; Vaccine-Alpha variant; Vaccine-Wuhan+Alpha variant	2	Day 0	SC	The Scientific and Technological Research Council of Turkey	Phase 2
PS	Protein subunit	Recombinant SARS-CoV-2 Fusion Protein Vaccine (V-01)	2	Day 0 + 21	IM	Guangdong Provincial Center for Disease Control and Prevention/Gaozhou Center for Disease Control and Prevention	Phase 2
PS	Protein subunit	SCB-2020S, an adjuvanted recombinant SARS-CoV-2 trimeric S-protein (from B.1.351 variant)	2	Day 0 + 21	IM	Clover Biopharmaceuticals AUS Pty Ltd	Phase 2
DNA	DNA based vaccine	GX-19N	2	Day 0 + 28	IM	Genexine Consortium	Phase 1/2
PS	Protein subunit	KBP-COVID-19 (RBD-based)	2	Day 0 + 21	IM	Kentucky Bioprocessing Inc.	Phase 1/2
VLP	Virus like particle	RBD SARS-CoV-2 HBsAg VLP vaccine	2	Day 0 + 28	IM	Serum Institute of India + Accelagen Pty + SpyBiotech	Phase 1/2
PS	Protein subunit	IMP CoVac-1 (SARS-CoV-2 HLA-DR peptides)	1	Day 0	SC	University Hospital Tuebingen	Phase 1/2

VVnr + APC	Viral vector (Non-replicating) + APC	LV-SMENP-DC vaccine. Dendritic cells are modified with lentivirus vectors expressing Covid-19 minigene SMENP and immune modulatory genes. CTLs are activated by LV-DC presenting Covid-19 specific antigens.	1	Day 0	SC & IV	Shenzhen Geno-Immune Medical Institute	Phase 1/2
VVnr	Viral vector (Non-replicating)	Human Adenovirus Type 5: hAd5 S+N bivalent vaccine (S-Fusion + N-ETSD). E2b- Deleted Adeno.	1-2	Day 0 + 21	SC or Oral or SL	ImmunityBio, Inc	Phase 1/2
PS	Protein subunit	CIGB-669 (RBD+AgnHB)	3	Day 0 + 14 + 28 or Day 0 +28 + 56	IN	Center for Genetic Engineering and Biotechnology (CIGB)	Phase 1/2
PS	Protein subunit	BECOV2	2	Day 0 + 28	IM	Biological E. Limited	Phase 1/2
VVnr	Viral vector (Non-replicating)	AdCLD-CoV19 (adenovirus vector)	1	Day 0	IM	Cellid Co., Ltd.	Phase 1/2
DNA	DNA based vaccine	GLS-5310	2	Day 0 + 56 or Day 0 + 84	ID	GeneOne Life Science, Inc.	Phase 1/2
PS	Protein subunit	Recombinant protein vaccine S-268019 (using Baculovirus expression vector system)	2	Day 0 + 21	IM	Shionogi	Phase 1/2
PS	Protein subunit	SARS-CoV-2-RBD-Fc fusion protein	1-2	NR	SC or IM	University Medical Center Groningen + Akston Biosciences Inc.	Phase 1/2
PS	Protein subunit	COVAC-1 and COVAC-2 sub-unit vaccine (spike protein) + SWE adjuvant	2	Day 0 + 28	IM	University of Saskatchewan	Phase 1/2
DNA	DNA based vaccine	COVID-eVax, a candidate plasmid DNA vaccine of the Spike protein	2	Day 0 + 28	IM or IM + electroporation	Takis + Rottapharm Biotech	Phase 1/2
IV	Inactivated virus	Inactivated (NDV-based) chimeric vaccine with or without the adjuvant CpG 1018	2	Day 0 + 28	IM	The Government Pharmaceutical Organization (GPO); PATH; Dynavax	Phase 1/2
VLP	Virus like particle	VBI-2902a. An enveloped virus-like particle (eVLP) of SARS-CoV-2 spike (S) glycoprotein and aluminum phosphate adjuvant.	2	Day 0 + 28	IM	VBI Vaccines Inc.	Phase 1/2
PS	Protein subunit	EuCorVac-19; A spike protein using the recombinant protein technology and with an adjuvant.	2	Day 0 + 21	IM	POP Biotechnologies and EuBiologics Co.,Ltd	Phase 1/2
RNA	RNA based vaccine	DS-5670a, mRNA vaccine	2	NR	IM	Daiichi Sankyo Co., Ltd.	Phase 1/2
VVnr	Viral vector (Non-replicating)	COVIVAC. Newcastle Disease Virus (NDV) expressing membrane-anchored pre-fusion-stabilized trimeric SARS-CoV-2 S protein +/- adjuvant CpG 1018	2	Day 0 + 28	IM	Institute of Vaccines and Medical Biologicals, Vietnam	Phase 1/2
PS	Protein subunit	Recombinant SARS-CoV-2 Vaccine (CHO cell)	2	Day 0	IM	National Vaccine and Serum Institute, China	Phase 1/2
RNA	RNA based vaccine	EXG-5003; a temperature-sensitive self-replicating RNA vaccine expressing the receptor binding domain of the SARS-CoV-2 spike protein.	1	Day 0	ID	Elixirgen Therapeutics, Inc	Phase 1/2
IV	Inactivated Virus	Inactivated COVID-19 vaccine	2	Day 0 + 28	IM	KM Biologics Co., Ltd.	Phase 1/2
VVnr	Viral vector (Non-replicating)	Modified Vaccinia Virus Ankara (MVA) vector expressing a stabilized SARS-CoV-2 spike protein	2	Day 0 + 28	IM	German Center for Infection Research	Phase 1/2
PS	Protein subunit	QazCoVac-P - COVID-19 Subunit Vaccine	1-2	Day 0 + 21	IM	Research Institute for Biological Safety Problems	Phase 1/2
DNA	DNA based vaccine	AG0302-COVID19	2-3	Day 0 + 14 + 28	IM	AnGes, Inc	Phase 1/2
PS	Protein subunit	Recombinant protein RBD fusion dimer adjuvanted vaccine (COVID-19 Vaccine Hipra)	2	Day 0 + 21	IM	Laboratorios Hipra, S.A.	Phase 1/2
PS	Protein subunit	Versamune-CoV-2FC vaccine, recombinant S1 antigen	3	Day 0 + 28	NR	Hospital do Coracao	Phase 1/2
PS	Protein subunit	SII B.1.351 + Matrix-M1 adjuvant, a monovalent SII SARS-CoV-2	2	Day 0 + 21	IM	Novavax	Phase 1/2

		B.1.351 (Beta) variant vaccine					
PS	Protein subunit	SII Bivalent + Matrix-M1 adjuvant, a bivalent SII vaccine containing antigen for both the ancestral strain and B.1.351 (Beta) variant of SARS-CoV-2	1	Day 0	IM	Novavax	Phase 1/2
PS	Protein subunit	SII B.1.617.2 + Matrix-M1 adjuvant, a monovalent SII SARS-CoV-2 B.1.617.2 (Delta) variant vaccine	1-2	Day 0 +/- 21	IM	Novavax	Phase 1/2
VVnr	Viral vector (Non-replicating)	ChAdOx1-S - (AZD1222) Vaxzevria	1-2	Day 0 + 28	IN	University of Oxford	Phase 1
VVnr	Viral vector (Non-replicating)	VXA-CoV2-1 Ad5 adjuvanted Oral Vaccine platform	2	Day 0 + 28	Oral	Vaxart	Phase 1
VVnr	Viral vector (Non-replicating)	MVA-SARS-2-S	2	Day 0 + 28	IM	University of Munich (Ludwig-Maximilians)	Phase 1
RNA	RNA based vaccine	LNP-nCoVsaRNA	2	NR	IM	Imperial College London	Phase 1
VVr + APC	Viral vector (Replicating) + APC	Covid-19/aAPC vaccine. The Covid-19/aAPC vaccine is prepared by applying lentivirus modification with immune modulatory genes and the viral minigenes to the artificial antigen presenting cells (aAPCs).	3	Day 0 + 14 + 28	SC	Shenzhen Geno-Immune Medical Institute	Phase 1
PS	Protein subunit	AdimrSC-2f (recombinant RBD +/- Aluminium)	NR	NR	NR	Adimmune Corporation	Phase 1
DNA	DNA based vaccine	Covigenix VAX-001 - DNA vaccines + proteo-lipid vehicle (PLV) formulation	2	Day 0 + 14	IM	Entos Pharmaceuticals Inc.	Phase 1
DNA	DNA based vaccine	CORVax - Spike (S) Protein Plasmid DNA Vaccine	2	Day 0 + 14	ID	Providence Health & Services	Phase 1
RNA	RNA based vaccine	ChulaCov19 mRNA vaccine	2	Day 0 + 21	IM	Chulalongkorn University	Phase 1
DNA	DNA based vaccine	bacTRL-Spike oral DNA vaccine	1	Day 0	Oral	Symvivo Corporation	Phase 1
VVnr	Viral vector (Non-replicating)	COH04S1 (MVA-SARS-2-S) - Modified vaccinia ankara (sMVA) platform + synthetic SARS-CoV-2	1-2	Day 0 + 28	IM	City of Hope Medical Center + National Cancer Institute	Phase 1
LAV	Live attenuated virus	COVI-VAC	1-2	Day 0 or Day 0 + 28	IN	Codagenix/Serum Institute of India	Phase 1
PS	Protein subunit	MF59 adjuvanted SARS-CoV-2 Sclamp vaccine	2	Day 0 + 28	IM	The University of Queensland	Phase 1
DNA	DNA based vaccine	COVIGEN	2	Day 0 + 28	ID or IM	University of Sydney, Bionet Co., Ltd Technovalia	Phase 1
VVnr	Viral vector (Non-replicating)	BBV154, Adenoviral vector COVID-19 vaccine	1	Day 0	IN	Bharat Biotech International Limited	Phase 1
RNA	RNA based vaccine	PTX-COVID19-B, mRNA vaccine	2	Day 0 + 28	IM	Providence Therapeutics	Phase 1
RNA	RNA based vaccine	CoV2 SAM (LNP) vaccine. A self-amplifying mRNA (SAM) lipid nanoparticle (LNP) platform + Spike antigen	2	Day 0 + 30	IM	GlaxoSmithKline	Phase 1
PS	Protein subunit	SK SARS-CoV-2 recombinant surface antigen protein subunit (NBP2001) + adjuvanted with alum.	2	Day 0 + 28	IM	SK Bioscience Co., Ltd.	Phase 1
VVnr	Viral vector (Non-replicating)	Chimpanzee Adenovirus serotype 68 (ChAd) and self-amplifying mRNA (SAM) vectors expressing spike alone, or spike plus additional SARS-CoV-2 T cell epitopes.	2-3	Day 0 + 14 + 28 or Day 0 +28 + 56 or Day 0 + 112	IM	Gritstone Oncology	Phase 1
PS	Protein subunit	SpFN (spike ferritin nanoparticle) uses spike proteins with a liposomal formulation QS21 (ALFQ) adjuvant.	2-3	Day 0 + 28 + 180	IM	Walter Reed Army Institute of Research (WRAIR)	Phase 1
IV	Inactivated virus	Inactivated SARS-CoV-2 vaccine FAKHRAVAC (MIVAC)	2	Day 0 + 14 +/- 21	IM	Organization of Defensive Innovation and Research	Phase 1

LAV	Live attenuated virus	MV-014-212, a live attenuated vaccine that expresses the spike (S) protein of SARS-CoV-2	1	Day 0	IN	Meissa Vaccines, Inc.	Phase 1
PS	Protein subunit	ReCOV: Recombinant two-component spike and RBD protein COVID-19 vaccine (CHO cell).	2	Day 0 + 21	IM	Jiangsu Rec-Biotechnology	Phase 1
IV	Inactivated Virus	Koçak-19 Inactivated adjuvant COVID-19 viral vaccine	2	Day 0 + 21	IM	Kocak Farma, Turkey	Phase 1
VVnr	Viral vector (Non-replicating)	SC-Ad6-1, Adneviral vector vaccine	1-2	Day 0 +/- 21	IM	Tetherex Pharmaceuticals Corporation	Phase 1
VLP	Virus like particle	ABNCoV2 capsid virus-like particle (cVLP) +/- adjuvant MF59	2	Day 0 + 28	IM	Radboud University	Phase 1
RNA	RNA based vaccine	HDT-301: Self-replicating mRNA vaccine formulated as a lipid nanoparticle.	2	Day 0 + 28	IM	SENAI CIMATEC	Phase 1
IV	Inactivated Virus	Adjuvanted inactivated vaccine against SARS-CoV-2	2	Day 0 + 21	SC	The Scientific and Technological Research Council of Turkey (TÜBITAK)	Phase 1
RNA	RNA based vaccine	mRNA-1283	2	Day 0 + 28	IM	ModernaTX, Inc.	Phase 1
IV	Inactivated Virus	Live recombinant Newcastle Disease Virus (rNDV) vector vaccine	2	Day 0 + 21	IM or IN	Laboratorio Avi-Mex	Phase 1
RNA	RNA based vaccine	mRNA COVID-19 vaccine	2	TBD	IM	Shanghai East Hospital and Stemirna Therapeutics	Phase 1
PS	Protein subunit	CoVepiT vaccine: SARS-CoV-2 multi-target peptide vaccine (targeting Spike, M, N, and several non-structural proteins)	1-2	Day 0 +/- 21	SC	OSE Immunotherapeutics	Phase 1
PS	Protein subunit	CoV2-OGEN1, protein-based vaccine	1-2	Day 0 +/- 14	Oral	USSF/Vaxform	Phase 1
RNA	RNA based vaccine	LNP-nCOV saRNA-02 vaccine; Self-amplifying RNA (saRNA) encapsulated in lipid nanoparticles (LNP)	2	Day 0 + 28	IM	MRC/UVRI and LSHTM Uganda Research Unit	Phase 1
PS	Protein subunit	RBD protein recombinant SARS-CoV-2 vaccine	3	Day 0 + 21 + 35	IM	Bagheiat-allah University of Medical Sciences/AmitisGen	Phase 1
PS	Protein subunit	Baiya SARS-CoV-2 VAX1, a plant-based subunit vaccine (RBD-Fc + adjuvant)	2	Day 0 + 21	IM	Baiya Phytopharm Co., Ltd.	Phase 1
VVnr	Viral vector (Non-replicating)	PIV5 vector that encodes the SARS-CoV-2 spike protein	1	Day 0	IN	CyanVac LLC	Phase 1
PS	Protein subunit	202-CoV; SARS-CoV-2 spike trimer protein + adjuvant, CpG7909.	2	Day 0 + 28	IM	Shanghai Zerun Biotechnology + Walvax Biotechnology + CEPI	Phase 1

(Green highlighted are currently in Phase 4, Vaccines whose further development have been discontinued are highlighted in red)

Source: Adapted from World Health Organization. WHO Solidarity Trial – Accelerating a Safe and Effective COVID-19 Vaccine. Geneva: World Health Organization. Available from: https://www.who.int/emergencies/ diseases/novel-coronavirus-2019/global-research-on-novel-coronavir us-2019-ncov/solidarity-trial-accelerating-a-safe-and-effective-covid19-vaccine. [Last accessed on 2021 Sep 17].

Role of primary care physicians during COVID-19 vaccination[98]

Well-supported primary care teams can make vaccination distribution programmes more successful for five reasons:

- The established relationships between primary care teams and their patients are a powerful resource for building the trust—a rare commodity these days—necessary for vaccine outreach and acceptance.
- Primary care providers are best positioned to identify and contact people in high-risk categories, as well as monitor and advise patients on the best vaccine regimens.
- Primary care practices already have communication pipelines to patients via telephone contacts, newsletters and online messaging systems and have management in place to oversee vaccination efforts.
- Primary care practices provide longitudinal care for the patient and are well situated to counsel and integrate COVID-19 vaccination into adult immunization schedules.
- Primary care practices can document information on administered vaccines so that healthcare personnel have accurate and timely information on patients' vaccination status to ensure continuity of care.

Box 3: Roles of community health workers to maintain the surge in existing services:

- Maintain routine primary healthcare services, for example, vaccinations and integrated community case management of young children with malaria, pneumonia or diarrhoea.
- Codesign workflow modifications necessary to continue primary healthcare delivery while being responsive to changing pandemic conditions and patient and health worker safety.
- Introduce safe means of requesting and accessing care in the event of community-level COVID-19 spread.
- Postpone nonessential services to alleviate capacity constraints on the existing health workforce.
- Monitor patients for clinical deterioration and support rapid referral of individuals who require hospitalization, reinforcing links between the health system and communities.
- Harness digital technology to receive requests for care, proactively check in with families, follow up with patients, assess symptoms and establish care plans.
- Support preparation of health systems and communities for the eventual introduction of still-in-development COVID-19 vaccines and treatments, including outreach to high-risk groups.
- Implement or support disinfection of high-risk surfaces in communities using appropriate infection prevention and control supplies and procedures.

Roles of community health workers to shield the vulnerable:

- Support self-isolation and monitor patients in the community while ensuring delivery of food, social and medical support.
- Combat misinformation, fear and mistrust by acting as a bridge to the formal health system and national authorities. Inspire positive behaviour change and collective action.
- Identify and educate at-risk populations (elderly, immunocompromised, those with underlying conditions) to reduce their exposure to COVID-19.

Source: Adapted from Ballard M, Bancroft E, Nesbit J, et al. Prioritising the role of community health workers in the COVID-19 response. BMJ Glob Health. 2020 Jun 1;5(6):e002550.[99]

The Way Forward

- **Assessment of caseload**—The synergistic effect of COVID-19 and ILI on overall mortality needs to be carefully evaluated using robust data collection platforms and thus establishing a national sentinel influenza surveillance system for early reporting and diagnosis of ILI. Both viruses are likely to circulate simultaneously (during the flu season), and thus a national level study needs to be planned specifically aimed at establishing the predominant risk factors of virus-related death. Detailed characterization of deaths attributed to flu and coronavirus by cross-linking data stored in a countrywide database is needed to ensure high intrinsic quality of the analysis and reduce systematic bias.

- This must be coupled with the identification and targeted prevention of people at very high risk of mortality due to an overlapping or combination of risk factors especially those aged ≥65–70 years who suffer from hypertension or diabetes and especially those with metabolic syndrome or with two to three comorbidities. Building capacity for longitudinal electronic health records with a predetermined time interval for each individual is essential to plan retrospective analysis of administrative and demographic databases.

- **Case management and control**—There is no specific treatment available for COVID-19. Many drugs such as chloroquine, hydroxychloroquine, remdesivir, ritonavir, lopinavir and azithromycin; and immunomodulators (convalescent plasma, plasma therapy and Igs) have being tried with varying success. Measures such as quarantine, face masks, hand washing, personal protective measures, contact tracing and environmental disinfection requires community engagement for the prevention and control by reducing transmission.

- Support for the management of COVID-19 by Centre to severely affected states must be combined with support for malaria, TB and HIV treatment and prevention programs as it is likely that the achievements made under these programmes will suffer until COVID-19 is brought under control. Therefore, COVID-19 responses at the country level should be tailored to local social, epidemiological and economic profiles. These should include measures to protect underserved and vulnerable populations, in particular PLWHA, communities living in malaria endemic settings, pregnant women, people undergoing treatment for TB and other relevant segments of society. These populations need protection not only from the pandemic, but also from the consequences of its control measures.

- **Using innovative delivery systems**—Government should continue to advocate exclusive breastfeeding and complementary feeding among children <2 years of age. Immunization services and micronutrient supplementation should continue, and mop-up rounds should be planned. Communities should be made self-reliant or self-sufficient (e.g., Atmanirbhar Bharat)—by strengthening local supply chains for vegetables, fruits and other perishable foods. Hand

washing, social distancing, proper nutrition and exercising should be advocated. By ensuring emergency food distribution and cash transfer programmes for the vulnerable population as beneficiaries to provide adequate nutrition, health and basic necessities. Policies to generate employment will help in fighting poverty during the COVID crisis.

- **National communication campaigns for mental health of children**—Care givers of children and adolescents should have access to mental health services through 24 × 7 help lines. Children should be protected against child abuse and neglect. Children should be able to safely navigate on the Internet.

- Healthcare Professionals training and involvement The unprecedented workload faced by Clinical Departments has created a gap in the training of residents and support staff while their exposure to other non Covid based infections has also reduced significantly. Use of more digital resources and expert opinions is required at the point of care to assist quick and accurate decision making

- **Research**—There should be a strong foundation of research (Self-reliant India Mission) along with political commitment to use it for the best interest of global community.

- Efforts to find vaccines— Globally vaccines for COVID-19 are being developed very rapidly. Many of the new vaccine technologies are now being utilized. New vectors and platforms are being used. Eight of the vaccines have entered phase four trials.

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