CD Alert

National Centre for Disease Control
Directorate General of Health Services, Government of India

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COVID-19

INTRODUCTION

Pandemic (from Greek πᾶν, pan, "all" and δῆμος, demos, "local people" the 'crowd') is an epidemic of an infectious disease that has spread across a large region, for instance multiple continents or worldwide, affecting a substantial number of people. Thus, by definition, *a pandemic is an epidemic occurring on a scale that crosses international boundaries, usually affecting people on a worldwide scale*[1]. A widespread endemic disease with a stable number of infected people is not a pandemic, such as recurrences of seasonal influenza, which are generally excluded as they occur simultaneously in large regions of the globe rather than being spread worldwide.

A disease or condition is not a pandemic merely because it is widespread or kills many people; *it must also be infectious*. For instance, cancer is responsible for many deaths but is not considered a pandemic because the disease is not contagious (i.e. easily transmittable) and not even simply infectious. Throughout human history, there have been a number of pandemics of diseases such as smallpox and tuberculosis. The most fatal pandemic in recorded history was the Black Death (also known as The Plague), which killed an estimated 75–200 million people in the 14th century Fig 1,2. The term was not used yet but was for later pandemics including the 1918 influenza pandemic (Spanish flu). Current pandemics include COVID-19 (SARS-CoV-2) and HIV/AIDS.

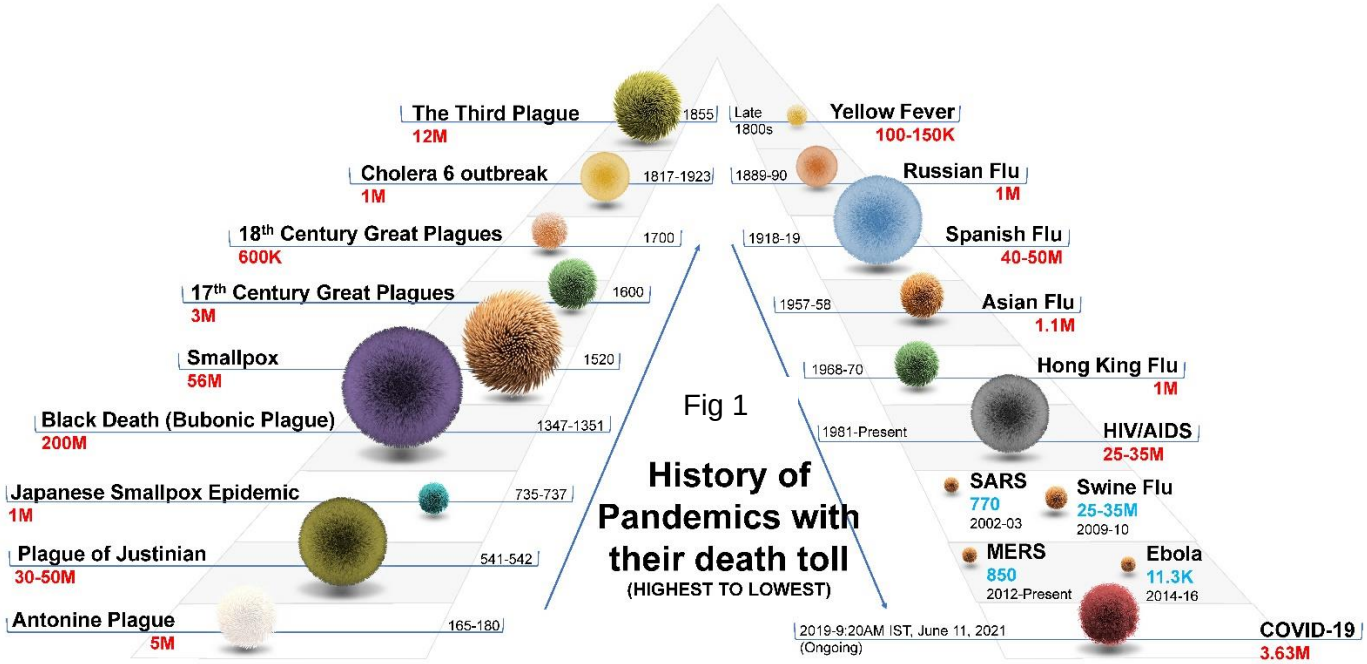
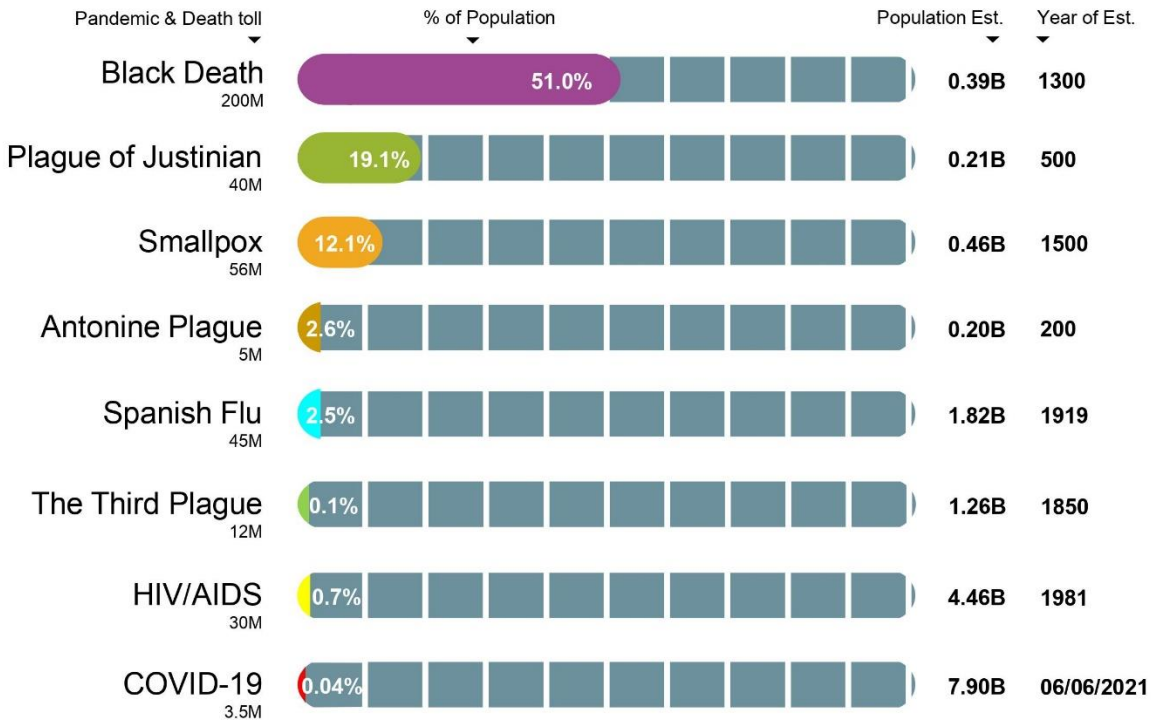


Fig 1

Fig 2 **Death Toll as a percent of the population**



Adapted from www.visualcapitalist.com/history-of-pandemics-deadliest/

HISTORICAL BACKGROUND

On December 31, 2019, hospitals in Wuhan, Hubei province of China, reported a cluster of idiopathic pneumonia cases. The Huanan Seafood Wholesale Market was identified as the origin of the infection, causing the area to shut down. However, a large fluctuation of visitors around the area during the Spring Festival caused the infection to rapidly spread to other regions of China and other countries. With the use of real-time reverse transcription polymerase chain reaction (RT-PCR), on 7th Jan'20, researchers identified the cause being a novel coronavirus (2019-nCoV) which later on 11th Feb was labelled as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and called coronavirus disease 2019 (COVID-19). The number of RT-PCR—positive cases rapidly increased. On January 30, 2020, India confirmed its first case and the World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern (PHEIC). Thereafter on 28 Feb'20, WHO raised its Risk assessment at Regional & global level as VERY HIGH and thereafter declared it as a pandemic on 11th March'2020. More than a year later, despite implementation of the mitigation strategies and the introduction of vaccines, the disease is still surging globally.

EPIDEMIOLOGY

Emergence of any new infectious disease, prompts scientists to work on 5 W's of the disease: what is the disease, what are the factors driving it, what is the source, who has the disease, and why has the outbreak happened. The current pandemic started with Chinese authorities alerting WHO about cases of Pneumonia of unknown etiology on 31 December 2019 detected in Wuhan City, Hubei Province of China. From 31 December 2019 through 3 January 2020, a total of 44

case-patients were reported by the national authorities in China. In this period, causal agent was not identified. Later, the Chinese authorities identified a new type of coronavirus, which was isolated on 7 January 2020 and WHO received further detailed information from the National Health Commission China that the outbreak was associated with exposures in one seafood market in Wuhan. China shared the genetic sequence of the novel coronavirus with the countries to use in developing specific diagnostic kits. The International Committee on Taxonomy of Viruses (ICTV) named the novel virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the coronavirus disease (COVID-19).

First imported case of lab-confirmed novel coronavirus (2019-nCoV) from Wuhan, Hubei Province, China was reported by Thailand on 13 January 2020. India reported its first case on 30 January'2020 from Kerala amongst the returnees from Wuhan, China. WHO notified the disease as pandemic on March 11' 2020.

Agent

In Latin corona means "crown." SARS-CoV-2 is a single, positive-stranded RNA virus enveloped in a lipid bilayer. It is a beta coronavirus Fig 3. It has round or elliptic and often pleomorphic form, and a diameter of approximately 60–140 nm. A viral envelope under electron microscopy appears crown-like due to small bulbar projections formed by the viral spike (S) peplomers. Currently bats and pangolins have been implicated as source of its origin although it remains uncertain.

The genome of the SARS-CoV-2 has about 80% nucleotide identity with that of SARS-CoV. The major differences are found in the regions encoding the structural proteins (envelope E, membrane M, nucleo-capsid N, and spike S) and accessory proteins (ORF3a/3b, 6, 7a/7b, 8, and 10), whereas the non-structural proteins (nsp1 to nsp16) are relatively more conserved.[2]

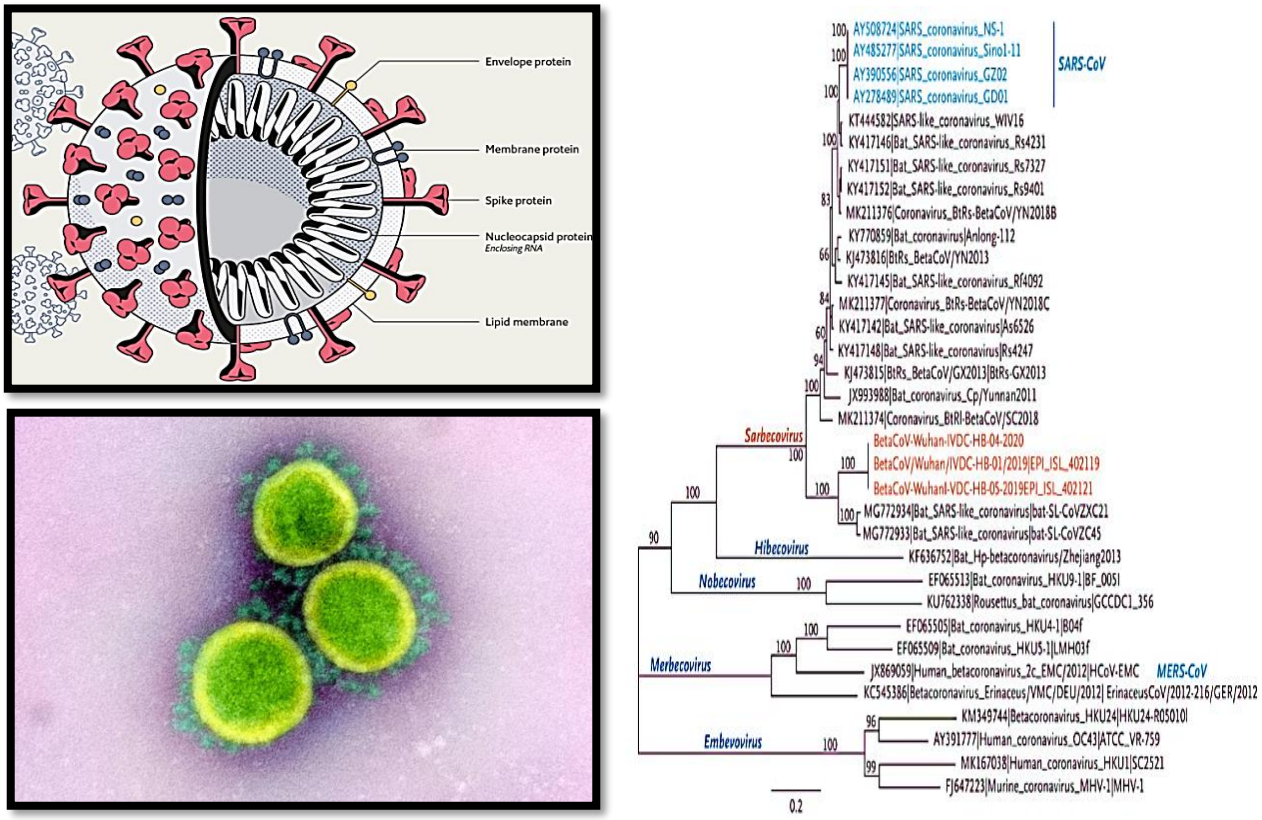


Fig 3: Structural details and phylogenetic tree of SARS-CoV-2 and other coronaviruses

Coronavirus entry into host cells is an important determinant of viral infectivity and pathogenesis. It is also a major target for host immune surveillance and human intervention strategies. To enter host cells, coronaviruses first bind to a cell surface receptor for viral attachment, subsequently enter endosomes, and eventually fuse viral and lysosomal membranes. A virus surface-anchored spike protein mediates coronavirus entry. SARS-CoV S1 contains a receptor-binding domain (RBD) that specifically recognizes angiotensin-converting enzyme 2 (ACE2) as its receptor. Fig 4 The RBD constantly switches between a standing-up position for receptor binding and a lying-down position for immune evasion. Moreover, to fuse membranes, SARS-CoV spike needs to be proteolytically activated at the S1/S2 boundary, such that S1 dissociates and S2 undergoes a dramatic structural change. These SARS-CoV entry-activating proteases include cell surface protease TMPRSS2 and lysosomal proteases cathepsins. These features of SARS-CoV entry contribute to its rapid spread and severe symptoms and high fatality rates of infected patients.

Because ACE2 is highly expressed in various organs and tissues, SARS-CoV-2 not only invades the lungs but also attacks other organs with high ACE2 expression. Fig 5 The pathogenesis of COVID-19 disease is highly complex, with multiple factors involved. In addition to the direct viral effects and inflammatory and immune factors, the down-regulation of ACE2 and imbalance between the RAS and ACE2/angiotensin-(1–7)/MAS axis may also contribute to the multiple organ injuries in COVID-19 Fig 6. [3]

SARS-CoV-2 virus has been mutating and mutation in spike protein of wild corona virus has led to emergence of new strains.

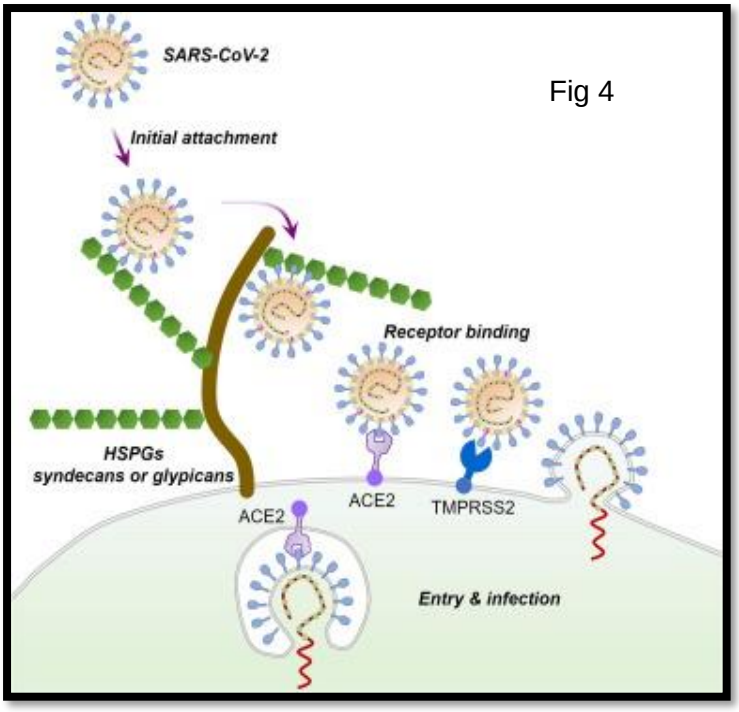


Fig 4

A possible mechanism for SARS-CoV-2 entry and infection: At the early stage of the infection process, SARS-CoV-2 may first interact with the HSPGs on the surface of susceptible cells using the S protein protruding from the virus particle. This initial attachment may promote the subsequent binding of the virus to the high-affinity entry receptor ACE2. The trans-membrane protease serine 2 (TMPRSS2) on host cell surface and other host cell proteases may assist in viral entry by cleaving the S protein at the S1/S2 and/or at the S2' sites [2]

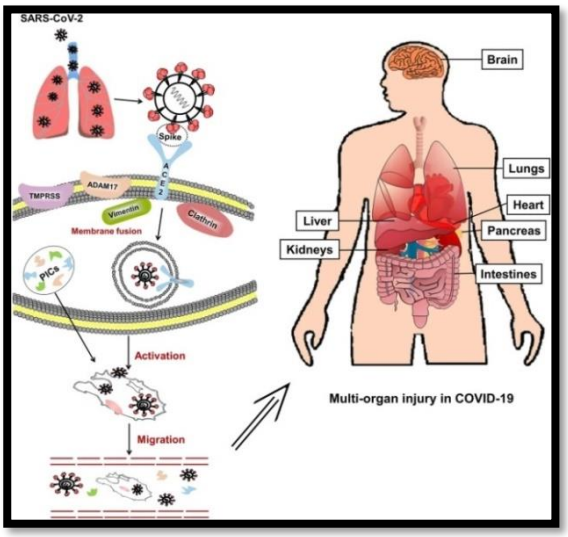


Fig 5

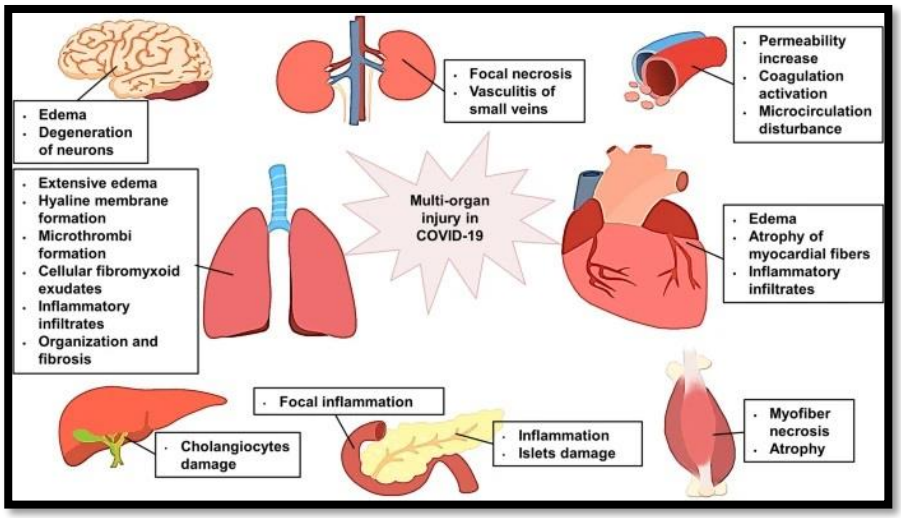


Fig 6

Median incubation period is five to six days, with a range from 2 to 14 days. Mean serial interval is about 3–8 days, presenting sooner than the end of incubation i.e., one becomes contagious about 2.5 days earlier before symptoms present. Thus, asymptomatic (i.e. when the infected person has no symptoms throughout the course of the disease) and pre-symptomatic transmission (i.e. when the infected person develops symptoms after transmitting the virus to another person) plays as the major driver for the growth of the COVID-19 pandemic. Fig 7 According to the study published by the U.S. Centers for Disease Control and Prevention, 60% of coronavirus transmission occurs through people with no symptoms.[4] The new model, published in JAMA Network Open, observed the spread of the virus through three different lenses i.e. by pre-symptomatic, asymptomatic and symptomatic individuals. The study came to the conclusion that 59% of COVID transmission was triggered by asymptomatic people, of which 35% of all new cases came from people who infect others before they show symptoms and 24% from people who never developed symptoms at all.[5]

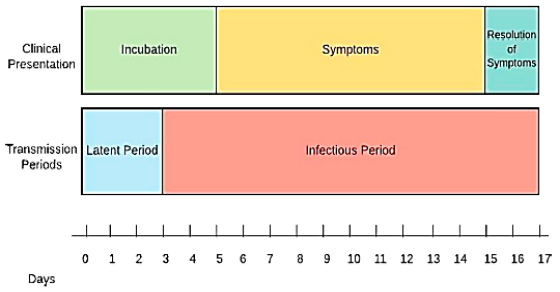


Fig 7: Representation of COVID-19 Clinical and Transmission Periods

Source: Journal of Clinical Virology 127 (2020) 104357

If the transmission takes place during the symptomatic period of the primary case, the serial interval is longer than the incubation period. However, this relationship can be reversed when pre-symptomatic transmission takes place. Furthermore, it is possible that the secondary case may even experience illness onset prior to onset in their infector.

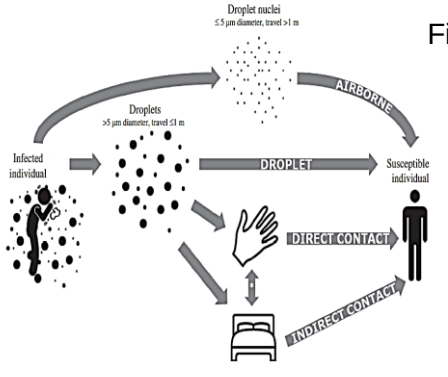
SARS-CoV-2 is primarily transmitted between people through respiratory droplets and contact routes and, to a lesser degree, via contaminated surfaces. Most common mode of transmission is droplets expelled during face-to-face exposure during talking, coughing, or sneezing. Fig 8.

Survivability outside body:

- 1-2 days on nonporous surfaces like metal, glass, laminated wood etc.
- 8-12 hours on porous surfaces like cloth, cardboard, paper etc.
- New studies suggest a shorter survival time on more hydrophilic surfaces, like glass, compared to less hydrophilic surfaces, like some types of plastic [6]

The coronavirus can survive for four days on glass, seven days on plastic, and seven days on stainless steel. But on paper and cloth, the virus survived for only three hours and two days, respectively.[7]

Fig 8



* Transmission routes involving a combination of hand & surface = indirect contact.

Figure 1. Transmission routes: droplet, airborne, direct contact, and indirect contact. (Indirect contact: routes involving a combination of hand and surface.) Definitions of 'droplet' and 'droplet nuclei' are from Atkinson *et al.*[5]

- Infected droplets
  - >5µm, travel <1m
- Aerosols
  - <5µm, travel>1m
- Contact
  - Hands, surfaces, fomites

Airborne transmission is possible in specific settings when aerosols are generated like during suction, dental procedures etc. Further, recent researches have presented strong evidences that SARS-CoV-2 spreads by airborne transmission. Although other routes can contribute, it is now believed that the airborne route is likely to be dominant. If an infectious virus is primarily airborne, someone can potentially be infected when they inhale aerosols produced when an infected person exhales, speaks, shouts, sings, or sneezes. So airborne control measures include ventilation, air filtration, reducing crowding and the amount of time people spend indoors, wearing masks whenever indoors (even if not within 6 feet or 2 meters of others), attention to mask quality and fit, and higher-grade PPE for healthcare and other staff when working in contact with potentially infectious people.[8]

The risk of transmission after contact with an individual with COVID-19 increases with the closeness (distance<1meter) and duration of contact and appears highest with prolonged contact in indoor settings. Most secondary infections occur among household contacts with studies stating secondary attack rate varies widely across countries with lowest reported rate as 4.6% and highest as 49.56%. The rates were unaffected by confounders such as population of the country, lockdown status and geographic location. Review suggested greater vulnerability of spouse and elderly population for secondary transmission than other household members. [9]

Outdoor settings are generally considered lower risk for transmission than indoor settings.

The mean basic reproductive number for COVID-19 (R0)−defined as average number of secondary infections produced by a case of an infection in fully susceptible population with no immunity −2.5. (Fig 9).

When outbreak control interventions are in place and the population cannot be considered as fully susceptible, transmission potential at a given time can be estimated by the effective reproductive number (Re or time-dependent reproductive number). An epidemic is arrested when the R value consistently remains <1. If no infection prevention methods such wearing a mask, hand washing and physical distancing are practiced (non-pharmaceutical interventions NPI), 1 infected person may end up infecting 406 people in 30 days. If we reduce social exposure by 50%, 1 infected person may end up infecting 15 people in 30 days. If we further reduce social exposure by 75%, 1 infected person may end up infecting only 2.5 people in 30 days.

Role of R0 in Infectious Disease Modelling for public health decision support:

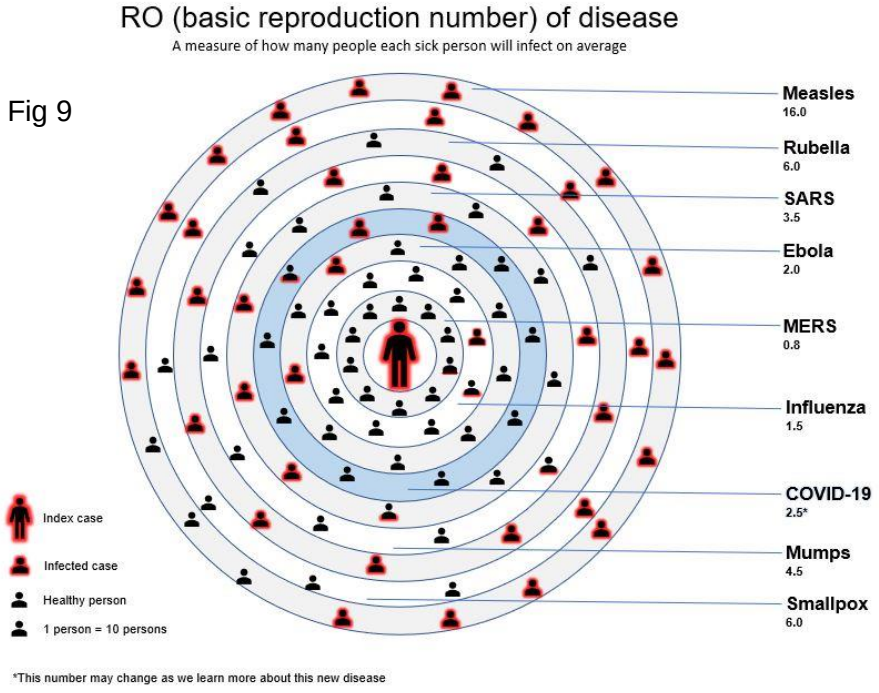
Generally, imposing NPIs reduces R, and lifting them later on increases R. School closure, a public events ban, requirements to stay at home, and internal movement limits—both when being imposed and when lifted had the biggest individual effects, changing R between 3% and 25%.
NPIs in combination are even more effective.

The combined effect of school and workplace closure, a ban on public events and gatherings of more than ten people, internal movement limits, and a stay-at-home requirement reduced R by 52% (95% CI 29–68) 28 days after they were introduced. The R0 value for SARS-CoV-2 lies somewhere between 2 and 3.3 Hence, early pandemic interventions must reduce R by between 50% and 67% to bring it below 1.[10]

However, some NPIs have massive socioeconomic effects. In a similar vein, transmission models that project COVID-19 cases and deaths under different NPI scenarios could be highly valuable for optimizing a country's portfolio of NPIs.
The success of large-scale NPIs requires population adherence.

Host factors: Individuals of any age can acquire severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, although adults of middle age and older are most commonly affected, and older adults are more likely to have severe disease. COVID-19 infections are less frequently observed in children and children usually present with milder symptoms.

Fig 9



CASE DEFINITION

Suspect Case

Acute onset of any one or more of the following symptoms:

1. Fever
2. Cough
3. Loss of taste
4. Loss of smell
5. General weakness/fatigue
6. Headache
7. Myalgia
8. Sore throat
9. Running nose
10. Shortness of breath
11. Loss of appetite
12. Nausea/vomiting
13. Diarrhoea
14. Altered mental status

Probable Case

A. A suspect case who is a contact of a confirmed case
OR
B. An asymptomatic person who is a high-risk contact of a confirmed case
OR
C. All Influenza like illness (ILI) and Severe Acute Respiratory Illness (SARI) cases
OR
D. If clinically suspected by a physician
OR
E. Death following respiratory distress, (cause not known), AND who was a contact of a probable or confirmed case.

High-risk contact: • Lives in the same household as the case • Anyone in close proximity (within 1 meter) of the confirmed case without precautions • Touched or cleaned the linens, clothes, or dishes of the patient. • Had direct physical contact with the body of the patient including physical examination without PPE. • Passenger in close proximity (within 1 meter) of a conveyance with a symptomatic person who later tested positive for COVID-19. • Touched body fluids of the case without appropriate PPE (respiratory tract secretions, blood, vomit, saliva, urine, feces)

Low-risk contact: • Any contact not fitting into the above high risk contact description.

Laboratory Confirmed Case

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

CLINICAL FEATURES

Clinical manifestations: For COVID-19, data to date suggest that 80% of infections are mild or asymptomatic, 15% are severe infection, requiring oxygen and 5% are critical infections, requiring ventilation. Fig 10

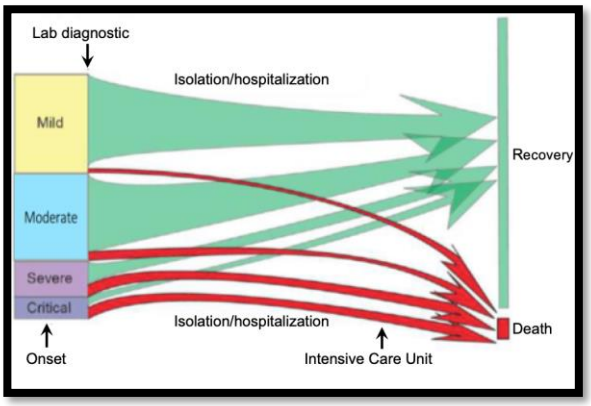


Fig 10 Pattern of Disease Progression

Pneumonia appears to be the most frequent serious manifestation of infection, characterized primarily by fever, dry cough, shortness of breath (dyspnea), and bilateral infiltrates on chest imaging. However, other features, including upper respiratory tract symptoms, muscle pain (myalgia), headache, diarrhea, nausea, vomiting and smell or taste disorders, are also common. Although some clinical features (in particular smell or taste disorders) are more common with COVID-19 than with other viral respiratory infections, there are no specific symptoms or signs that can reliably distinguish COVID-19. However, development of dyspnea approximately one week after the onset of initial symptoms may be suggestive of COVID-19.

The general approach to prevention, evaluation, diagnosis, and treatment of pregnant and lactating women with suspected COVID-19 is largely similar to that in non-pregnant individuals. People of any age with the following conditions are at increased risk of severe illness

from COVID-19:

- Type 2 diabetes mellitus
- Cancer
- Chronic kidney disease
- COPD (chronic obstructive pulmonary disease)
- Immuno-compromised state (weakened immune system) from solid organ transplant or any other cause, steroid intake etc.
- Obesity (body mass index [BMI] of 30 or higher)
- Serious heart conditions, such as heart failure, coronary artery disease, or cardiomyopathies
- Sickle cell disease

Several complications of COVID-19 have been described as:

- Respiratory failure
- Cardiac and cardiovascular complications
- Thromboembolic complications
- Inflammatory complications – Some patients with severe COVID-19 have laboratory evidence of an exuberant inflammatory response, similar to cytokine release syndrome, with persistent fevers, elevated inflammatory markers (e.g. D-dimer, ferritin), and elevated pro-inflammatory cytokines; these laboratory abnormalities have been associated with critical and fatal illnesses

  Other inflammatory complications and auto-antibody-mediated manifestations have also been described. Guillain-Barré syndrome may occur, with onset 5 to 10 days after initial symptoms. A multisystem inflammatory syndrome with clinical features similar to those of Kawasaki disease and toxic shock syndrome has also been described in children with COVID-19.

Secondary infections – Secondary infections like bacterial pneumonia and mucormycosis (black fungus) have been reported, latter being more prevalent in diabetics and with prolonged use of steroids for treatment.

Lately, there has been an upsurge in the number of cases of Candidiasis (white fungus) and *Mucor septicus* (yellow fungus).

Recovery and long-term sequelae: According to the WHO, recovery time appears to be around two weeks for mild infections and three to six weeks for severe disease based on existing data. However, the recovery course is variable and depends on age and pre-existing comorbidities in addition to illness severity.

Covid-19 in children: Majority of children with covid infection may be asymptomatic or mildly symptomatic. Common symptoms include fever, cough, breathlessness or shortness of breath, fatigue, myalgia, rhinorrhea, sore throat, diarrhea, loss of smell, loss of taste etc. Few children may present with gastrointestinal symptoms and atypical symptoms. A new syndrome with name of multi system inflammatory syndrome has been described in children. Such cases are characterized by: unremitting fever > 38oC, epidemiological linkage with SARS CoV-2 and clinical features suggestive of *Multi System Inflammatory Syndrome MIS-C*.

Common symptoms of MIS-C are persistent fever, abdominal pain, vomiting, diarrhea, skin rash, mucocutaneous lesions, fatigue and, in severe cases, trouble breathing, hypotension (low blood pressure) and shock. Blood tests and other laboratory tests show elevated markers of inflammation, and often, markers of heart damage. These symptoms can become more severe and some patients develop myocarditis, cardiac dysfunction, and acute kidney injury.

A majority of children with MIS-C showed all the symptoms of shock. Other symptoms include enlarged lymph nodes, hands and feet erythema/edema, mucous membrane involvement, and conjunctivitis, as well as gastrointestinal symptoms and coagulopathy. Not all children will show the same symptoms.

Long haulers: COVID-19) symptoms can last weeks or months for some people. These patients, given the name "long haulers", have in theory recovered from the worst impacts of COVID-19 and have tested negative. However, they still have symptoms. There seems to be no consistent reason for this to happen.

The most common long hauler symptoms include:

- Coughing
- Ongoing, sometimes debilitating, fatigue
- Body aches
- Recurrent sore throat
- Joint pain
- Shortness of breath
- Loss of taste and smell — even if this didn't occur during the height of illness
- Difficulty sleeping
- Headaches
- Brain fog

Brain fog is among the most confusing symptoms for long haulers. Patient's report being unusually forgetful, confused or unable to concentrate.

As of now there is limited evidence of post-COVID
sequalae and further research is required and is being actively pursued. A holistic approach is required for follow up care and well-being of all post-COVID recovering patients. Refer Post-COVID Follow Up Protocol of MoHFW [11]

Much is still unknown about how COVID-19 will affect people over time, but research is ongoing. Organ damage (heart, lungs, brain, blood vessels etc.) has been caused by COVID-19, therefore researchers recommend that doctors closely monitor people who have had COVID-19 to see how their organs are functioning after recovery. It is advisable to open specialized clinics to provide care for people who have persistent symptoms or related illnesses after they recover from COVID-19. Support groups are helpful.

LAB DIAGNOSIS

COVID-19 tests are available that can test for current infection or past infection.

- A viral test tells you if you have a current infection. Two types of viral tests can be used: nucleic acid amplification tests (NAATs) and antigen tests.
- An antibody test (also known as a serology test) might tell you if you had a past infection. Antibody tests should not be used to diagnose a current infection.

The gold standard test for diagnosis of COVID-19 is Real time RT-PCR test, which is a molecular test recommended by ICMR, to detect the presence of SARS-CoV-2 virus in respiratory clinical samples. Other molecular based tests endorsed by ICMR are TruNAT/CBNAAT.

Although several advanced methods (such as Loop-mediated isothermal amplification methods (LAMP), CRISPR/Cas systems) have been developed for detection of virus nucleic acids with high sensitivity, the virus nucleic acid RT-PCR test has become the standard method for diagnosis of COVID-19 infection from nasopharyngeal swabs. RT-PCR test has a specificity rate of nearly 100 per cent but variable sensitivity ranging from 71-98% which depends on the limit of detection, viral inoculum, timing of testing, sample collection site and proper sample collection and transportation techniques. Fig 11, 12

Rapid Antigen detection kits have also been approved by ICMR and are being used for diagnosis in containment zones and healthcare facilities.

Recently, Home Testing using Rapid Antigen Tests (RATs) has been approved. It is advised only in symptomatic individuals and immediate contacts of laboratory confirmed positive cases. Indiscriminate testing is not advised.

Advisory available on ICMR website.

Fig 13 indicates home based sample collection and testing through RAT.

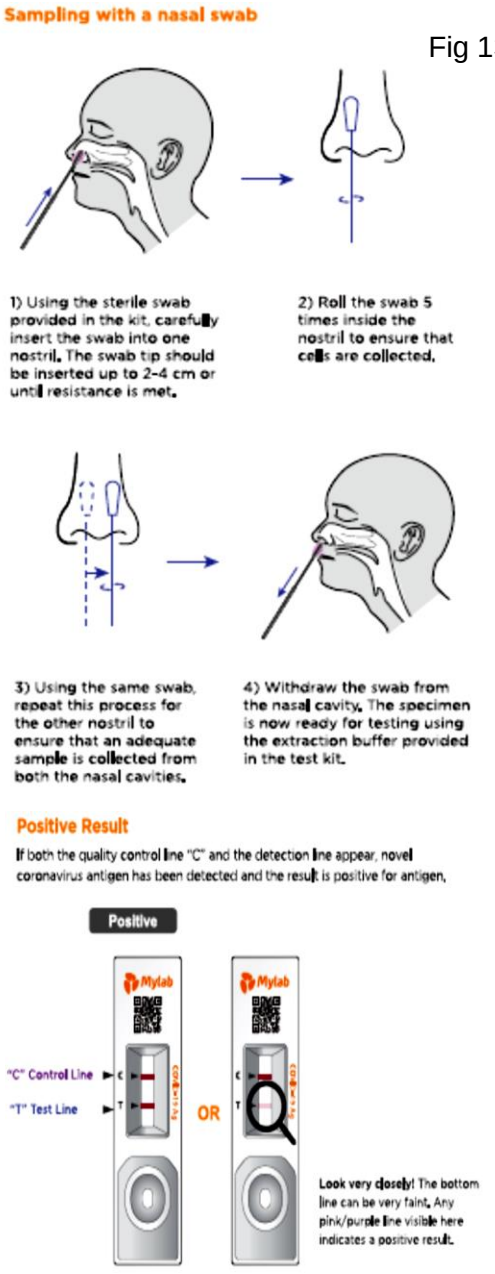


Fig 13

Testing should be done for:

a. All ILI and SARI cases
b. All symptomatic contacts of laboratory confirmed cases including health care workers / frontline workers

Asymptomatic direct and high-risk contacts of a confirmed case including health care workers / frontline workers to be tested once between day 5 and day 10 of coming into contact

a. All asymptomatic high-risk individuals in containment zone
b. Treating doctors based on their clinical judgement may get tested any patient, including those requiring close contact procedures or admission.

Settings:

- RAT: Routine Surveillance, Containment zones, fever clinics, screening at POE
- RT-PCR: Hospitals

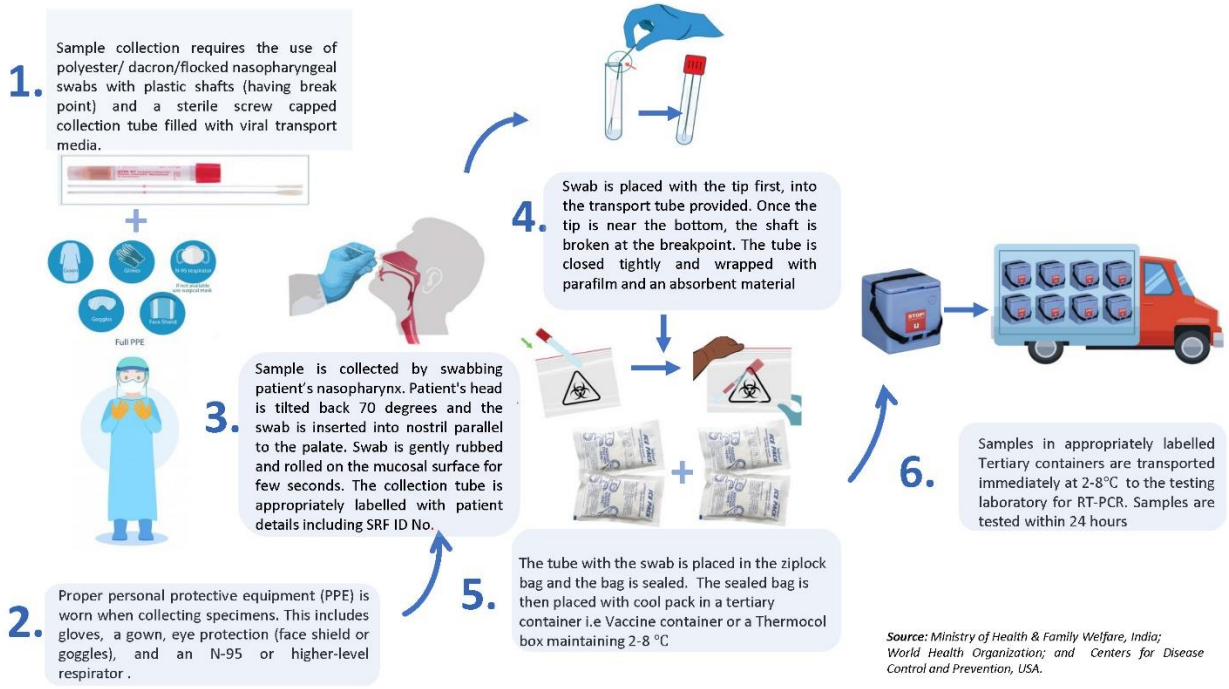
Other investigations which aid the treatment management include: SARS-CoV-2, maintain proper infection control and use recommended personal protective equipment (PPE), which includes an N95 or higher-level respirator (or facemask if a respirator is not available), eye protection, gloves, and a gown.

Respiratory specimens should be collected as soon as a decision has been made to test someone, regardless of the time of symptom onset. Proper specimen collection is the most important step in the laboratory diagnosis of infectious diseases. A specimen that is not collected correctly may lead to false or inconclusive test results.

For initial diagnostic testing for current SARS-CoV-2 infections, it is recommended to collect and test an upper respiratory specimen. Sterile swabs should be used for the collection of upper respiratory specimens. This is important both to ensure patient safety and preserve specimen integrity. The nasopharyngeal and oro-pharyngeal specimens are not appropriate for self-collection.

Testing lower respiratory tract specimens is also an option. For patients who develop a productive cough, sputum can be collected and tested for SARS-CoV-2 when available. However, the induction of sputum is not recommended due to the possibility of aerosol production during the procedure. Under certain clinical circumstances (e.g., for those receiving invasive mechanical ventilation), a lower respiratory tract aspirate or broncho-alveolar lavage specimen can be collected and tested as a lower respiratory tract specimen.[12]

Sample Collection, Storage and Transport to laboratory for COVID-19 testing Fig 11



Source: *Ministry of Health & Family Welfare, India; World Health Organization; and Centers for Disease Control and Prevention, USA.*

Workflow of COVID-19 RT-PCR testing Fig 12

1
Sample collected using nasopharyngeal swab from suspected patients and transported to lab immediately in triple packaging.

2
On receipt of samples in lab, first step of sample inactivation is done in BSL2 lab.

3
Post inactivation, sample is subjected to viral RNA isolation via automated or manual methods.

4
Once the viral RNA is extracted, RNA is subjected to RT-PCR using ICMR/ US FDA approved COVID-19 detection RT-PCR kits. Viral RNA extracts from samples are added in PCR plates in dedicated extract loading area.

5
After addition of the RNA extracts and controls (Positive and Negative) to the PCR plates, plates are subjected to RT-PCR reaction conditions as per kit protocol in a real-time PCR thermal cycler.

6
Real-time PCR cycler detects the fluorescence signal generated by primer-probe complex in the reaction during thermal cycling. Result are analysed after comparing the Ct values of Negative, Positive and internal controls as per kit manufacturer's instructions

TREATMENT

Two main processes are thought to drive the pathogenesis of COVID-19. Early in the clinical course, the disease is primarily driven by replication of SARS-CoV-2. Later in the clinical course, the disease appears to be driven by a dysregulated immune/inflammatory response to SARS-CoV-2 that leads to tissue damage. Based on this understanding, it is anticipated that antiviral therapies would have the greatest effect early in the course of the disease, while immunosuppressive/anti-inflammatory therapies are likely to be more beneficial in the later stages of COVID-19. No therapy has been proven to be beneficial in outpatients with mild to moderate COVID-19 who are not at high risk for disease progression

Thus, the treatment of Covid-19 is driven by pathogenesis. The severity of the disease is defined by the changing spectrum due to viral replication and further cytokine response of the body. Treatment protocols vary for mild, moderate and severe disease. With investigation supporting every stage, medical therapies vary at every stage. Ant-inflammatory or immune-modulatory therapy has been warned with judicious use in moderate disease. It is very important to diagnose the disease and start its treatment without any delay.

Anti-coagulant therapy has been proven beneficial because of thrombotic nature of the disease. However, irrational use of medicines does not help in reducing morbidity and mortality of the disease. Post-covid complications of the disease and their treatment are becoming a challenge. Rare complications of over-use of steroids are mucormycosis (black fungus) candidiasis (white fungus) and yellow fungus(Mucor septicus) which are becoming prevalent.

The spectrum of medical therapies to treat coronavirus disease 2019 (COVID-19) is growing and evolving rapidly but there is no specific treatment of the disease till date. Current clinical management of COVID-19 consists of infection prevention and control measures and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated. Early effective treatment of any disease can help avert progression to more serious illness, especially for patients at high risk of disease progression and severe illness, with the additional benefit of reducing the burden on healthcare systems. Treatment protocols are regularly updated by Indian Council of Medical Research and DGHS[13], MoHFW, Govt. of India. Fig 14, 15, 16.

Fig 14

Directorate General of Health Services, MoHFW, GOI
Comprehensive Guidelines for Management of COVID-19 patients

COVID-19 Symptoms at a glance box

Symptoms*	Asymptomatic	Mild	Moderate	Severe
• Fever	✕	+	++	+++
• Cough	✕	+	+	++
• Sore Throat/Throat irritation	✕	+	+/-	+/-
• Body ache/ Headache	✕	+	+	++
• Malaise/Weakness	✕	+	+	++
• Diarrhoea or gastro-intestinal upset	✕	+	+	+
• Anorexia/ Nausea/ Vomiting	✕	+/-	+/-	+/-
• Loss of Smell and/or Taste	✕	+/-	+/-	+/-
• Shortness of breath/breathlessness	✕	✕	++	+++
• Respiratory rate/min	12-16	May be raised but less than 24	24-30	≥ 30/min
• SpO_2 on room air	≥95%	≥ 94%	90%-93%	< 90%

The possible symptoms, signs and finding have been enlisted and patients in each category may have one or many of these

Fig 15

Directorate General of Health Services, MoHFW, GOI

Comprehensive Guidelines for Management of COVID-19 patients

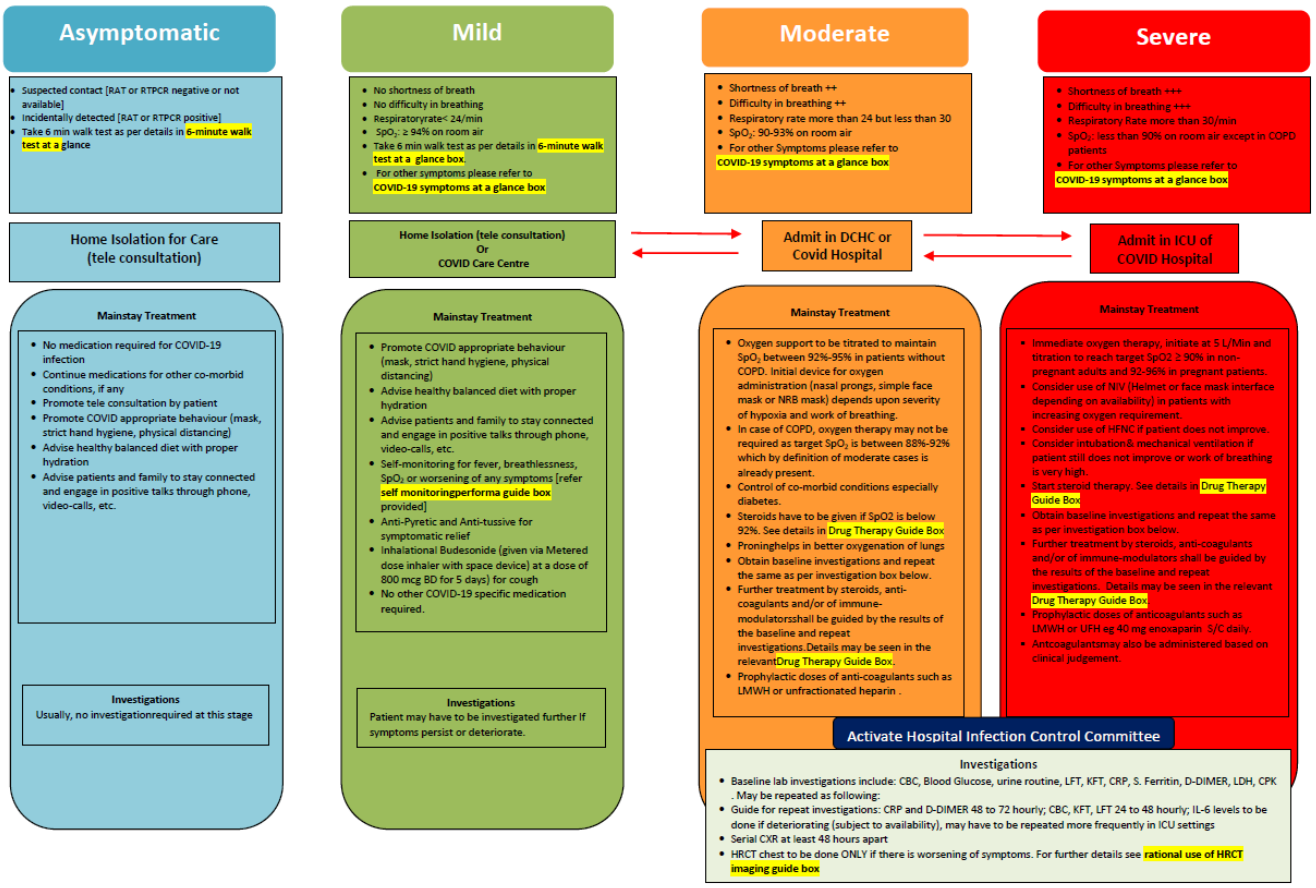


Fig 16

Directorate General of Health Services, MoHFW, GOI

Comprehensive Guidelines for Management of COVID-19 patients

COVID-19 Treatment/What-to-do at a glance box

Do's/Treatment	Asymptomatic	Mild	Moderate	Severe
Wearing Mask	✓	✓	✓	✓
Physical distancing	✓	✓	✓	✓
Hand hygiene	✓	✓	✓	✓
Cough etiquettes	✓	✓	✓	✓
Anti-pyretic (PCM)	✗	✓	✓	✓
Anti-tussive SOS	✗	✓	✓	✓
Inhalational Budesonide	✗	✓	✗	✗
Oxygen Support#	✗	✓	✓	✓
Anti-inflammatory/ Immunomodulatory therapy#	✗	✗	✓	✓
Anticoagulation#	✗	✗	✓	✓
Monitoring (CXR/ HRCT/ Lab investigations)*#	✗	✗	✓	✓

*Please see detailed guidelines for HRCT

To be done in hospital setting as per the guidance of treating physician.

VACCINATION

Numerous vaccine candidates have been evaluated and launched for prevention of COVID-19 including:

- Inactivated or recombinant protein vaccines (Covaxin)
- Viral-vector vaccines, (Covishield Oxford Astra Zeneca, Sputnik V, Johnson & Johnson Janssen)
- Nucleic acid-based (mRNA and DNA) vaccines (eg. Moderna & Bio N tech Pfizer)

The different vaccine platforms vary in their potential safety and immunogenicity, speed and cost of manufacturing, and other features important for meeting global demand. Several of these vaccines have induced binding antibodies, neutralizing activity, and T cell responses in healthy adults during trials.

Immunity and risk of reinfection: Antibodies to the virus are induced in those who have become infected. Antibodies are detected by ELISA in most patients by 14 days following the onset of symptoms; Fig 17 IgM and IgG are 'binding' antibodies which physically bind their Y-shaped structure to the proteins on the virus, flagging it and causing macrophage cells to destroy it. They can also attract natural killer cells to come and destroy cells that are infected with the virus. They simply act as markers and may not interfere with the infectivity of the virus.

A subset called 'neutralizing' antibodies can affect the virus' ability to infect cells by preventing it from undergoing the structural changes required to enter a host cell. Protection against infections occurs in the form of blocking viral infection and/or replication.

For Covid-19, at the moment, it is not known which antibody protects against the virus, and to what extent, but experts say it is likely to be neutralizing antibodies. A majority of neutralizing antibodies are IgG.

There is no standardized test available today that can measure neutralizing antibodies, and thus, protection against virus.

It is unknown whether all infected patients mount a protective immune response and how long any protective effect will last.

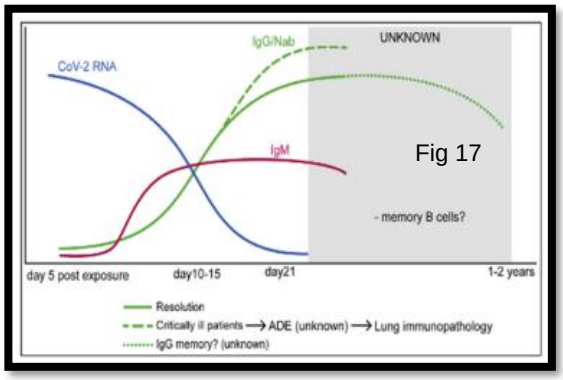


Fig 17

Studies have also identified SARS-CoV-2-specific CD4 and CD8 T cell responses in patients who had recovered from COVID-19 and in individuals who had received an investigational SARS-CoV-2 vaccine, which suggest the potential for a durable T cell immune response. There are concerns that humoral immunity against SARS-CoV-2 may not be long lasting in persons with mild illness, who compose the majority of persons with Covid-19.

As per recent study of care home residents and staff by University College London (UCL) scientists, previous Covid-19 infection substantially reduces the risk of a new infection for up to 10 months afterwards. The study, published in The Lancet Healthy Longevity on Thursday, found that care home

residents who had been previously infected with Covid-19 were approximately 85% less likely to be infected than those who had not been infected. For staff, those with a past infection were around 60% less likely to become infected again. Reinfection does occur – so protection is not complete. It is still expected that natural infection should protect against more severe infection, but there is still not enough data to know this. Hence it's vital to continue Covid appropriate behavior after recovery, and vaccination is still necessary to boost immune response and reduce disease transmission.

While viral RNA shedding declines with resolution of symptoms, it may continue for days to weeks. However, the detection of RNA during convalescence does not necessarily indicate the presence of viable infectious virus.

Cross reactivity with Dengue: both COVID-19 and Dengue may co-exist hence Dengue antibodies can cross-react with SARS-CoV-2 and vice versa-Antibody detection kits can give false-positive results for both viruses in regions in such cases.

SERO-SURVEY

Role of sero-survey in Covid-19

Sero-survey examines how many people in a population have been infected with COVID-19 and recovered from the same. It is done to gauge the prevalence of the virus in a particular area. These are the blood tests conducted on selected set of population to look at antibodies against the SARS-CoV-2 virus. These studies particularly focus on IgG antibodies which usually develop after two weeks of infection and remains in body for sustained longer duration. These studies give us an indication of how many people in the study group in a population have been exposed to the virus, taking into account that many infections occur without any symptoms and people may not have sought care or they may not have had a test done at all. It can also help provide information on place distribution like low income, highly crowded, urban settlements versus rural areas, to see if there is a difference in exposure or which group of population are more exposed or have had higher rates of infection like health care workers, frontline workers, any specific age group. If we do these surveys repeatedly over a period of time, the local public health authorities get an idea of how infection rates are progressing in that particular area and help in assessing how the measures that have been put in place are actually having an impact in keeping the infection rates under control. If the survey is repeated in the same group of people over a period of time, it helps us in understanding more about the immunity against this virus.

Antibody tests in the market today indicate the presence of IgM or IgG antibodies, and sometimes IgA, which are produced after IgM and play a key role in protecting mucous membranes around the body.

These antibodies, in turn, reveal past exposure or immune response after vaccination. These tests measure binding antibodies, and are used in sero-surveys to measure exposure.

Types of antibody tests

Test sensitivity is the ability of a test to correctly identify those with the disease (true positive rate), whereas test specificity is the ability of the test to correctly identify those without the disease (true negative rate). Thus, the 'sensitivity' of a test is its ability to pick up antibodies, while its 'specificity' is the ability to pick up the correct antibodies produced in response to the SARS-CoV-2 virus (and not other coronaviruses). A low sensitivity provides false negatives, while a low specificity gives false positives.

Antibody tests for SARS-CoV-2 have a low specificity within the first week of exposure and increase in the second and third weeks. Many antibody tests have a high false negative rate and studies evaluating them tend to have a high risk of bias for participant

selection, thus incorrectly reporting the accuracy of such antibody tests.

There are four major types of antibody tests: Rapid diagnostic tests (RDT), which are growing in popularity; enzyme-linked immune-sorbent assays (ELISA), neutralization assays, and chemi-luminescent immunoassays. The non-rapid tests are all lab-based and require at least 2-3 days for processing.

Rapid tests detect antibodies against antigens or the four structural proteins of the virus — spike (S), envelope (E), membrane (M) and nucleocapsid (N) — within minutes. Of these, S and N are considered to be more immunogenic, or able to invoke an immune response.

INSACOG and Whole Genome Sequencing

Mutations in SARS CoV2 are common and occur during the process of replication. Some mutations may result in alteration of transmissibility, immunogenicity and pathogenicity of the virus. These may also adversely affect COVID 19 countermeasures related to testing kits, vaccines and treatment measures like monoclonal antibodies. The UK experienced a second wave of COVID 19 in November December 2020 due to emergence of a new variant B.1.1.7 in South England. To strengthen preparedness for early detection of SARS CoV2 variants, India established a SARS CoV2 whole genome sequencing surveillance programme in December 2020.

A network of ten regional genome sequencing laboratories (RGSLs) were identified under the **Indian SARS-CoV-2 Genomics Consortium (INSACOG)** to undertake this activity with NCDC as the nodal agency. The overall aim of the INSACOG is to monitor the genomic variations in the SARS-CoV-2 on a regular basis through a multi-laboratory network.

Since its inception, the 10 labs have sequenced more than 19,000 SARS CoV-2 samples as on 19 May 2021. The sequencing for SARS COV2 was initiated under following three modules:

1. International travellers & contacts

A point of entry screening for international passengers who arrive to India from UK, Brazil or South Africa or transit through UK, Brazil or South Africa and contacts (screened for COVID-19 by RT-PCR and found positive) are sequenced at RGSLs. Samples of all passengers and their contacts who test positive for RT-PCR, are sent for whole genome sequencing to detect variant of concern.

Community Samples:

a. **Retrospective surveillance:** Five percent of all the RT-PCR positive SARS CoV-2samples in the State/UT before December 2020 were sequenced in RGSLs to retrospectively identify transmission of any variants of interest or concern in the community.

b. Prospective surveillance

i. **Sentinel Surveillance:** This is an ongoing surveillance activity across India. Each state has identified ten sentinel sites (5 RT PCR labs and 5 tertiary health care facility) and sends SARS CoV 2 samples for sequencing. The samples from health care facility are collected from patients with severe illness, vaccine breakthrough infections, long haulers and other atypical clinical presentations, etc.

ii. **Special Surveillance:** A representative number of samples targeting COVID clusters of reinfection, vaccine breakthrough, super-spreader events, high mortality clusters etc.

iii. 3. **Current Status of VOCs**

Currently, VOCs are distributed in about 146 districts in 35 states and UTs. States of Punjab, Maharashtra, Telangana, Delhi, Andhra Pradesh, Haryana and West Bengal are among the districts with maximum proportion. Four strains of SARS COV2 have been detected in India, which are of public health importance. (The public health importance of variants is given in para 1)

1. B 1.1.7 variant (Alpha)
2. B.1.351 variant (Beta)
3. P.1 variant (Gamma)
4. B.1.617.2 variant (Delta)

iv **Current Status of other variants:** Following other mutations has also been observed in various districts / States: -

- L452R
- E484K/Q
- L452R+E484Q combination found in B1.617
- N501Y
- N440K

New nomenclature: The World Health Organization (WHO) has announced Greek alphabetical labels to identify different strains of Covid-19 that have emerged across the world. Fig 18.

VARIANTS OF CONCERN

Established to have attributes that make them 'fitter' than the first version of the virus

NEW WHO LABEL	PANGO LINEAGE (MOST COMMONLY USED CODE)	FIRST FOUND IN	DATE OF DESIGNATION	CONCERN BECAUSE
ALPHA	B.1.1.7	UK (Kent); September, 2020	Dec 18, 2020 VOC)	Spreads more rapidly than predominant virus
BETA	B.1.351	South Africa; May, 2020	Dec 18, 2020	Shows significant resistance
GAMMA	P.1	Brazil; November 2020	Jan 11, 2021	Shows some resistance, enhanced infectivity
DELTA	B.1.617.2	India; October, 2020	May 11, 2021	Significantly more transmissible; somewhat resistant

VARIANTS OF INTEREST

These are being investigated by scientists at present

NEW WHO LABEL	PANGO LINEAGE (MOST COMMONLY USED CODE)	FIRST FOUND IN	DATE OF DESIGNATION	CONCERN BECAUSE
EPSILON	B.1.427/B.1.429	US (California); March, 2020	March 5, 2021	May be more transmissible
ZETA	P.2	Brazil; April, 2020	March 17, 2021	May be more resistant
ETA	B.1.525	Multiple countries; Dec, 2020	March 17, 2021	May be more resistant to vaccines
THETA	P.3	Philippines; Jan, 2021	March 24, 2021	Has some of the same mutations as the other VOCs
IOTA	B.1.526	US (New York); Nov, 2020	March 24, 2021	May be more resistant
KAPPA	B.1.617.1	India; October, 2020	April 4, 2021	May be more resistant, spread more readily

PREVENTION & MITIGATION

- Covid appropriate behavior:
  - Physical distancing by avoiding crowds and maintaining a distance of six feet (two meters) from others when in public
  - Individuals to wear masks when out in public
  - Hand hygiene,
  - Respiratory hygiene (e.g., covering the cough or sneeze).
  - Avoiding touching the face (in particular eyes, nose, and mouth)
- Cleaning and disinfecting objects and surfaces
- Adequate ventilation of indoor spaces

Other mitigation strategies are stay-at-home orders, school, venue, and nonessential business closure, ban on public gatherings, travel restrictions, aggressive case Identification and isolation, contact tracing and quarantine, health system strengthening (isolation wards, medical supplies), and public risk communication for adequate community engagement.

MASKS

Masks are a simple barrier to help prevent your respiratory droplets from reaching others and are the mainstay of protection from coronavirus. Studies show that masks reduce the spray of droplets when worn over the nose and mouth. Correct and consistent mask use is a critical step everyone can take to prevent getting and spreading COVID-19. Masks work best when everyone wears them, but not all masks provide the same protection. When choosing a mask, one should look at how well it fits, how well it filters the air, and how many layers it has. Different types of face masks have their different levels of effectiveness in containing droplet spread from coughs, sneezes, and conversation. According to an article published in *The Journal of Family Practice*, single-layer masks may only provide 1% particle filtration. A two-layer cotton mask filters out about 35% of small particles, so they offer personal protection to the wearer. A typical cloth face mask "is probably at least 50%" protective, while "high quality masks could be 80-95% protective, and even low-quality masks made of very thin materials could still be 10-20% protective. Disposable surgical masks are flat, thin, paper-like masks

are usually white and light blue. According to a 2013 study published in *Aerosol Science and Technology*, surgical face masks can filter out about 60% of smaller, inhaled particles. N95 face respirators offer the most protection against novel coronavirus and other respiratory diseases. N95s protect the person wearing the mask because they filter out 95% of particles from the air breathed in Fig 19. [14]

Double masks to prevent COVID-19 is another protective measure that you can make use of, to reduce your chances of getting infected. Double masks refer to the practice of wearing two masks, helping create a stronger barrier against COVID-19.

Studies done by the US Centers for Disease Control and Prevention (CDC) states that double masking can reduce your exposure to the COVID-19 virus by up to 95%

Mask management

For any type of mask, appropriate use, storage and cleaning, or disposal are essential to ensure that they are as effective as possible and to avoid any increased risk of transmission. Adherence to correct mask management practices varies, reinforcing the need for appropriate messaging (7).

WHO provides the following guidance on the correct use of masks:

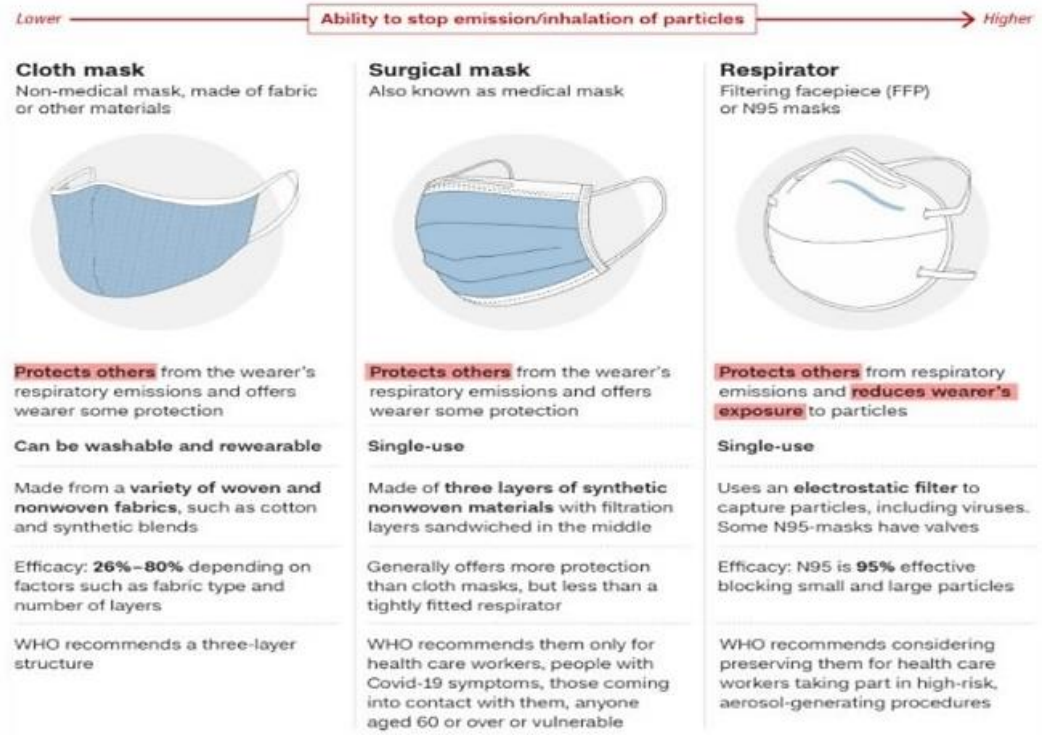
- Perform hand hygiene before putting on the mask
- Inspect the mask for tears or holes, and do not use a damaged mask.

Place the mask carefully, ensuring it covers the mouth and nose, adjust to the nose bridge and tie it securely to minimize any gaps between the face and the mask. If using ear loops, ensure these do not cross over as this widens the gap between the face and the mask.

Avoid touching the mask while wearing it. If the mask is accidently touched, perform hand hygiene. • Remove the mask using the appropriate technique. Do not touch the front of the mask, but rather untie it from behind.

- Replace the mask as soon as it becomes damp with a new clean, dry mask.
- Either discard the mask or place it in a clean plastic resealable bag where it is kept until it can be washed and cleaned. Do not store the mask around the arm or wrist or pull it down to rest around the chin or neck.
- Perform hand hygiene immediately afterward discarding a mask.
- Do not re-use single-use mask.
- Discard single-use masks after each use and properly dispose of them immediately upon removal.
- Do not remove the mask to speak.
- Do not share your mask with others.
- Wash fabric masks in soap or detergent and preferably hot water (at least 60° Centigrade/140° Fahrenheit) at least once a day. If it is not possible to wash the masks in hot water, then wash the mask in soap/detergent and room temperature water, followed by boiling the mask for 1 minute.

Fig 19



CONCLUSION

The COVID-19 pandemic is rapidly spreading. Case rates and CFRs continue to change. Prompt identification of infected through rapid testing, clinical characteristics & radiological investigations, isolation of the patient, meticulous contact tracing, development & improvisation of pertinent diagnostic criteria, provision of effective treatment & care, more research into diagnostics/therapeutics, use of AI and IT, risk communication/IEC, accelerated vaccination drives for entire eligible population along with enforcement of Covid-appropriate behavior through community engagement and enabling environment are vital for overcoming the pandemic. Global cooperation is critical to bring Covid-19 pandemic to a halt because no one is safe till everyone is safe.

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