



## **Novel Corona Virus (nCOVID-19; India): Chain Reaction Disease (CRD); Precaution-Prevention, Treatment A Review**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.*

### **Article Information**

DOI: 10.9734/IJBCRR/2020/v29i930231

Editor(s):

(1) Dr. Prabakaran Nagarajan, The Ohio State University, USA.

Reviewers:

(1) Muhammad Fawad Rasool, Bahauddin Zakariya University, Pakistan.

(2) Pichon Maxime, University Hospital of Poitiers, France.

Complete Peer review History: <http://www.sdiarticle4.com/review-history/56840>

**Review Article**

**Received 21 April 2020**

**Accepted 06 May 2020**

**Published 14 December 2020**

### **ABSTRACT**

Corona virus-2 (nCOVID-19), causes respiratory infection including cold, fever, sneezing and coughing, pneumonia, headache, diarrhea and upper respiratory diseases. It transmitted human to human via airborne droplets. Corona virus enters in human cell through membrane ACE-2 exopeptidase receptor. Corona virus (CV) previously it treated as non-fatal virus (NFV), HCoV-NH, SARS and MERS-CoV and SARS-CoV. It was first isolated from Wuhan market China at December 2019, in world thus its name nCOVID-19. It is a Chain Reaction Disease (CRD) because of tremendously spread through contact human to human. WHO and ECDC advised to avoid public place - social distance and close contact (person-person) to infected persons, airborne droplet

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through sneezing and coughing. Some precautions, preventions and treatment of formerly synthesized anti-malarial, anti-biotic and anti-inflammatory etc drug used on novel corona virus disease.

**Keywords:** *Flue influenza (FE) (1918); flu-like symptoms - CoV (1960); HCoV-NH; MERS-CoV; corona virus or SARS-CoV (2002-2005, 2012-2013); nCOVID-19 (2019); nCOVID-20(2020); chain reaction disease (CRD); treatment and precautions; prevention; India.*

## ABBREVIATIONS

*nCOVID* : Novel corona virus disease

*SARS* : Severe acute respiratory syndrome

*NFV* : Non fatal virus, CV- corona virus

*HCoV-NH* : Heaven new human coronavirus. Precaution, prevention and some treatment

## 1. INTRODUCTION

Over 100 years, since the outbreak of the 1918 influenza pandemic name virus as 'Spanish Flue Enfluenza' (SFE) due to this Crore of people were died in various countries. Corona means Crown shaped, (like crown ether), club shaped, spherical single stranded and covered with glycoprotein enclosed RNA viruses with a very characteristic appearance in electron micrographs (EM) of negatively stained preparations [1,2]. It falls within the same size range (60–140 nm) and spherical shape [3]. It was first discovered in the 1930s when an acute respiratory infection (ARI) of bats, pigs, cats, snake etc animals. In the late 1940s, two more animal coronaviruses, mouse hepatitis virus (MHV) and transmissible gastroenteritis virus (TGEV), were isolated [4]. After twenty year later, human coronaviruses were discovered working with the human strains and a number of animal viruses [5]. First case of corona virus was notified as cold, approximately 500 patients were identified as Flu-like system (fever, chills, sore throat) [6]. Animal studies included, but were not limited to, research that focused on respiratory disorders [7]. Coronavirus OC16, Strain 229E in WI-38 cells these two images was identified by Hamre and Procknow [8] and McIntosh et al. [9]. Severe acute respiratory syndrome (SARS) was first identified in Guangdong Province of the People's Republic of China in November 2002 and spread from there to Hong Kong, United States America (USA), Singapore, Thailand, Vietnam and in Taiwan and then throughout the world [10]. At that time, SARS affected 26 countries and resulted in more than 8,000 cases through animal-to-human transmission (Guangdong, China) [11]. New human coronaviruses (NHCov) have been discovered in

year of 2003-05. Reported discovery of a NHCov isolated from a age of 35 week-old girl bronchiolitis and fever by Van der Hoek et al. [12]. Eleven children's were in the newborn intensive care unit at the time of their sampling and had been hospitalized since birth, related to Kawasaki disease [13,14]. In year 2004, another study report of Hong Kong was confirmed 50 patient of severe acute respiratory syndrome (SARS or SARS-CoV) while 30 of them were confirmed as corona virus (CV) infected [15]. After 8 year (2012), Saudi Arabian reports were presented several infected patient and deaths [16-18]. First cases of Middle East respiratory syndrome Coronavirus (MERS-CoV) infections in France, investigations and implications for the prevention of human-to-human or animals transmission [19]. A number of cases of pneumonia with an unknown origin occurred from Wuhan, China and were reported to the World Health Organization (WHO) on December 31, 2019 [20]. COVID-19 was first identified and isolated from pneumonia patient belongs to Wuhan, China [21,22]. Novel coronavirus (2019-nCoV); forthcoming renamed severe acute respiratory syndrome coronavirus-2 (SARS-2) or nCoV (COVID-2) was confirmed and named coronavirus disease (COVID-19) [23]. Wuhan sea food market also tested positive cases, as a number of cases started increasing exponentially, suggestive of the fact that human-to-human transmission was occurring [24] (Fig. 1).

As on January 30, India reported its first case of COVID-19 in Kerala, which rose to three cases by February 3; all were students who had returned from Wuhan, China [25,26]. The government of Kerala declared high alert from 4 to 8 February and starting 8 March 2020 due to

coronavirus cases being reported from the state [27,28]. As of 9 March, more than 4000 persons are under home or hospital quarantine in Kerala [29]. On 10 March, the government of Kerala shut down all colleges and schools up to grade 7 also urged people to not undertake pilgrimages, attend large gatherings such as weddings and cinema shows [30,31]. As on same date (9 March, 2020) the first positive case of coronavirus in Maharashtra was reported in Pune, where a couple returning from Dubai tested positive [32]. On next day, three more people and were admitted in Naidu Hospital [33]. On 17th of March, first death case were found to the a 64-year-old man at the Kasturba Hospital in Mumbai [34]. On 20 March, Bollywood singer Kanika Kapoor who returned from London tested positive in Lucknow [35]. From Gujrat two cases [36]. Telangana ten new cases [37,38], four people in Lucknow, Uttar Pradesh [39]. Third case was reported in Punjab's Mohali where a 68-year-old women who returned from United Kingdom tested positive [40]. One more person tested positive in Kolkata, West Bengal [41]. three more cases were reported in Maharashtra - one each in Mumbai, Pune and Pimpri-Chinchwad [42]. Two new cases in Himachal Pradesh [43]. Twelve more cases were reported in Kerala five from Ernakulam, six from Kasaragod and one from Palakkad [44]. In Bhilwara, Rajasthan, six people tested positive [45]. After one day, as on 22 March 2020, India observed 14-hour voluntary 'public curfew' at the instance of the prime minister "Narendra Modi". The government followed it up with lockdowns in 75 districts due to COVID cases had occurred in all major cities [46,47]. Further, on 24 March, the prime minister ordered nationwide lockdown for 21 days, affecting the entire 1.3 billion population of India [48,49]. As on 23 March, a 55-year-old man from Kolkata, and a Tibetan refugee from Kangra district in Himachal Pradesh became the eighth and ninth victims of the virus in the country [50,51]. A 68-year-old man from the Philippines died in Mumbai, after initial recovery from the virus [52]. Kerala reported 28 new cases - 19 from Kasaragod district, five from Kannur, one from Pathnamthitta, two from Ernakulam and one from Thrissur [53]. On second day (24 March), a 65-year-old man from Mumbai, the tenth victim of the virus in the country [54], four more cases were reported - three from Pune and one from Satara -Maharashtra [55]. Two more cases were reported in Kozhikode, Kerala having 42-year-old man and 27-year-old person from Cherapuram [56]. Manipur reported its first case in a woman who had returned from the UK [57].

Three more cases were reported in Telangana - one each from Kokapet, Chanda Nagar and Begumpet [58]. Six people tested positive in Punjab, all of whom had come in contact with the 70-year-old who had tested positive for the infection and died of cardiac arrest the previous week [59]. Three cases were reported in Chennai - a 74-year-old male and a 52-year-old female who had returned from the United States US and a 25-year-old female respectively from Switzerland [60]. Mizoram reported its first case in a 50-year-old man with a travel history of Qatar, Amsterdam, Istanbul and Doha [61]. On same day Chief minister announced a statewide lockdown till 31st of march to prevent further spread of Coronavirus and Public transports were shut down. There was no restriction for private vehicles but district to district travels were only allowed with thorough checking [62]. As of 25 March, from Madurai in Tamil Nadu, Indore in Madhya Pradesh and Ahmedabad in Gujarat became the eleventh, twelfth and thirteenth victims of the virus in the country [63]. A 29-year-old from Patna, Bihar, who had returned from Gujarat tested positive [64]. Three more cases were reported in Gujarat [65]. Five cases were reported in Tamil Nadu - Chennai [66]. Six cases were reported in Maharashtra - five from Mumbai and one from Thane [67]. As of 26 March, from Srinagar in Jammu and Kashmir [68], Bhavnagar in Gujarat [69] from Gauribidanur in Karnataka [70], from Navi Mumbai in Maharashtra [71] and in Rajasthan [72] became the fourteenth, fifteenth, sixteenth, seventeenth and eighteenth victims of the virus in the country. Three cases were reported in Goa [73]. Four people tested positive in Lucknow, Uttar Pradesh [74]. Five people tested positive in Telangana [75,76]. Five from Indore, Madhya Pradesh [77]. Three cases were reported in Noida, Uttar Pradesh [78]. Andaman and Nicobar Islands reported its first case [79]. Two more cases were confirmed in Maharashtra from Mumbai and Thane [80]. Three more cases were reported in Bihar from Patna [81,82]. Two positive cases were reported in Andhra Pradesh [83]. On 27 March, Twenty-nine cases were reported in Maharashtra [84,88], other than Maharashtra 53 new cases were observed in India [85,86,87,89,90-97]. As of 28 March, from Ahmedabad in Gujarat [98] and a from Telangana [99] became the twenty-third twenty-fourth, twenty-fifth, twenty-sixth, twenty-seventh, twenty-eighth victims of the virus in the country. Fourteen more cases were registered in Maharashtra - twelve from Mumbai and two from Nagpur [100]. Seventeen more cases were confirmed in Karnataka [101]. Thirteen more

cases were confirmed in Jammu and Kashmir [102]. Three cases were confirmed in Madhya Pradesh [103]. Four from Rajasthan [104]. Gujarat reported six more cases [105]. Tamil Nadu reported two more case [106,107]. Kerala [108]. Five from Uttar Pradesh [109]. Another case was reported from Uttarakhand, Raipur in Chhattisgarh, Telangana [110-112] from Delhi [113]. Three from West Bengal [114]. As on 29 March, Twenty-two cases were confirmed in Maharashtra - ten from Mumbai, five from Pune, three from Nagpur, three from Ahmednagar and one each from Sangli, Buldhana and Jalgaon [115]. One from Mumbai in Maharashtra [116]. Twenty more cases were reported in Kerala-eight from Kannur district, seven from Kasaragod and one each from Thiruvananthapuram, Ernakulam, Thrissur, Palakkad and Malappuram [117]. Four cases from Bihar [118-120]. Three cases were reported in Telangana [121]. On 30 March, 14 persons was victims and near about 180 positive cases were conformed in India [122-127,128-133]. As of 31 March, one case from Thiruvananthapuram in Kerala [134] from Mohali from Punjab [135] became the forty-eighth and forty-ninth victims of the virus in the country. Sixty-four cases were reported in Maharashtra [136]. Fifty-seven more people tested in Tamil Nadu [137]. In Delhi went up by twenty-three [138]. Another twenty-one persons tested positive in Andhra Pradesh [139]. Nineteen cases were reported in Madhya Pradesh [140]. Three local transmissions were detected in Gujarat [141]. Karnataka reported seven cases [142]. Six cases were reported in Kashmir [143]. Five local transmissions were reported in Bareilly, Uttar Pradesh [144]. Four more cases were reported in Rajasthan [145]. First positive case reported in Jharkhand [146].

As we observed, no single person death upto the 10 march 2020, also the rate of infected person so poor, as the negative rate is satisfactory increased (Fig. 1). WHO declared CoV was pandemic from 12 march 2020. The COVID-19 cases were steadily increased from the 15 march to 31 march 2020 (Fig. 2). It took India to reach 40 days to have its 50 case. After that, just it just five days to reach 100 cases (15 March) and five more days to 200 cases (19 March), Crossed 500 cases on 24 March, 1,000 cases at 30 March (Figs. 2, 3). As on 1-2 April, six cases from Mumbai in Maharashtra [147]. In Maharashtra reported thirty-three more cases - thirty from Mumbai, two from Pune and one from Buldhana [148]. Confirmed cases in Delhi increased by thirty-two [149]. 16 positive cases

were confirmed in Maharashtra [150]. In Madhya Pradesh [151], Uttar Pradesh [152] 110 people tested positive in Tamil Nadu [153]. 43 cases were reported in Andhra Pradesh [154]. Another more cases In Keral [155]. Guwahati, Assam [156], Rajasthan [157]. 2,000 cases. As on 3 April and over 4,000 cases on 4 April. In India the number of positive cases was observed doubling in every 4 days. Experts believe that India has already started walking on the exponential multiplication phase of the virus. ICMR, while ruling out community transmission scenario in India. As on 5 April, 3,577 positive cases and 83 Deaths in 29 states in India [158]. On 11 April, Two positive cases were reported in Odisha take the state tally to 50 [159]. 92 positive cases were reported in Maharashtra [160]. 7 cases were reported in Karnataka [161]. 54 cases were reported in Gujarat [162]. 117 positive cases were reported in Rajasthan [163]. 2 positive cases were reported in Himachal Pradesh [164]. 1 positive case reported in Patiala District [165]. Later on 2 new cases confirmed in Mohali [166]. 1 more case confirmed in Pathankot [167]. 62 positive cases were reported in Madhya Pradesh [168]. As on 11-12 April 2020, the infected and deaths persons were multiple (8, 447 Confirmed, 2,73 deaths) in 31 different states from India (Fig. 4) [169]. Among these period, in continuation of vaccine preparing on COVID-19 in India, one being ZydusCadila, replicating viral vector and developing DNA plasmid vaccine [170] and other being Hyderabad based 'Bharat Biotech' in collaboration with US based 'FluGen', expecting first clinical trials of a nasal vaccine by late 2020 [171]. Till early second half of February, Serum Institute of India had begun animal trials of its nCOVID vaccine candidates followed by Zydus Cadila in March [172]. After two days later, On 15 April (Total positive cases 12,759 deaths 420), the number of positive cases in India exceeded 11,000 [173]. 39 deaths has been reported [174]. 76 positive cases were reported in Indore [175]. Five positive cases were reported in Dharavi - Mumbai [176]. 56 positive cases were reported in Gujrat [177]. 29 cases reported in Rajasthan [178]. 19 positive cases were reported in Andhra Pradesh [179]. 183 positive cases were reported in Mumbai [180]. only one positive case was reported in Kerala [181]. 15 case were reported in Karnataka [182]. 38 cases reported in Tamil Nadu [183]. As on 16 April, 28 deaths has been reported [184]. 19 positive cases were reported in Agra [185]. 22 positive cases were reported in Andhra Pradesh [186]. 2 positive cases were reported in Bihar [187]. 15 cases were reported in Tamil Nadu [188]. 34 cases were reported in

Karnataka [189]. 107 cases were reported in Mumbai [190]. 7 cases were reported in Kerala [191]. 2 cases were reported in Assam [192]. 6 cases confirmed from Jalandhar District in Punjab [193]. As on 17 April, 32 deaths has been reported [194]. 56 positive cases were reported in Tamil Nadu [195] and new 15 positive cases were reported in Dharavi [196]. Upto the date, total positive 13,835 and deaths cases 452 were observed. On 18 April, According to Ministry of

Health and Family Welfare total deaths 488 cases and total positive 14,378 cases among these 4,291 (29.8%) cases are affected by Nizamuddin Markaz cluster. 84 percent in Tamil Nadu, 63 percent in Delhi, 79 percent in Telangana, 59 percent in Uttar Pradesh and 61 percent in Andhra Pradesh are related to this incident & 1,992 patients has cured till the date, which is overall cure 13.85% of the total patients [197].

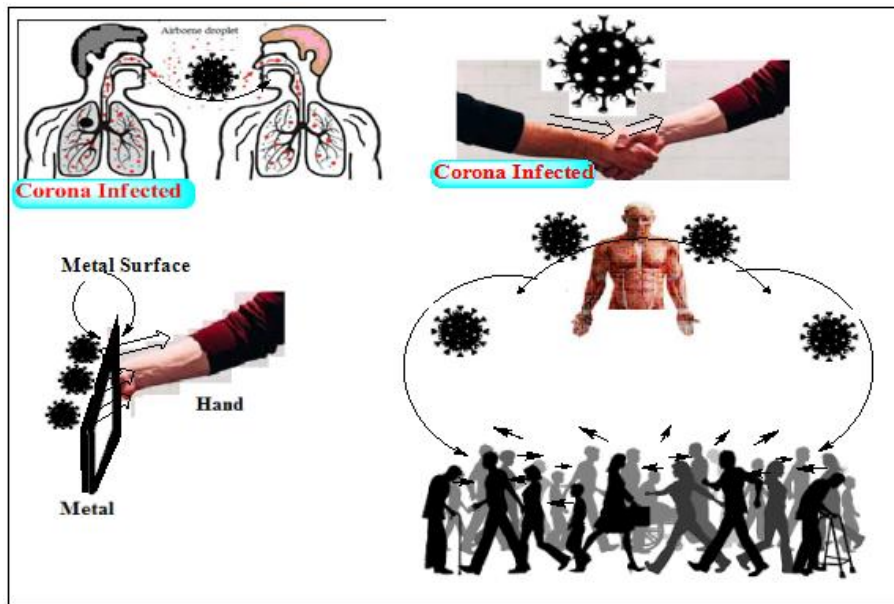


Fig. 1. Transmission of nCOVID-19 via airborne droplet, handshake, public place

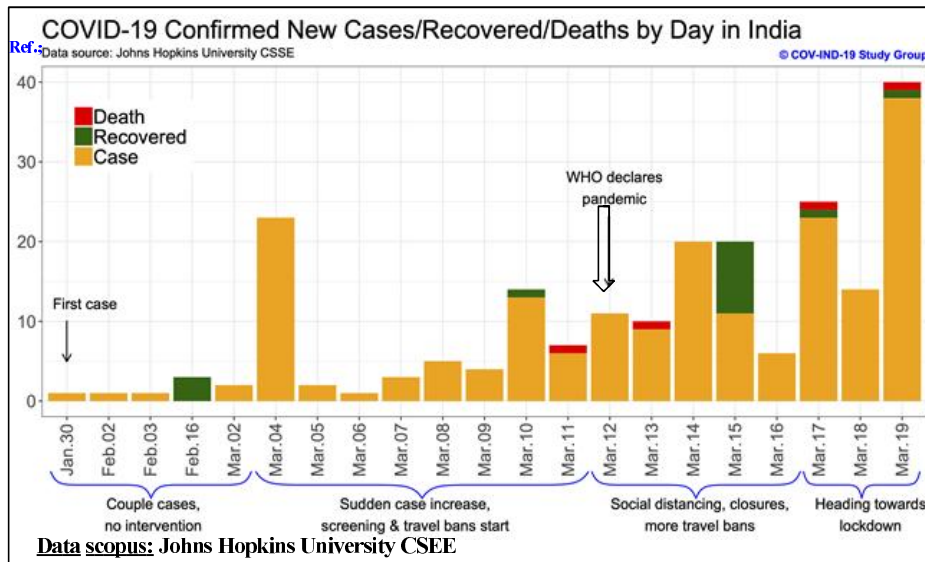


Fig. 2. nCOVID-19 confirmed new cases, recovered and death by day in India

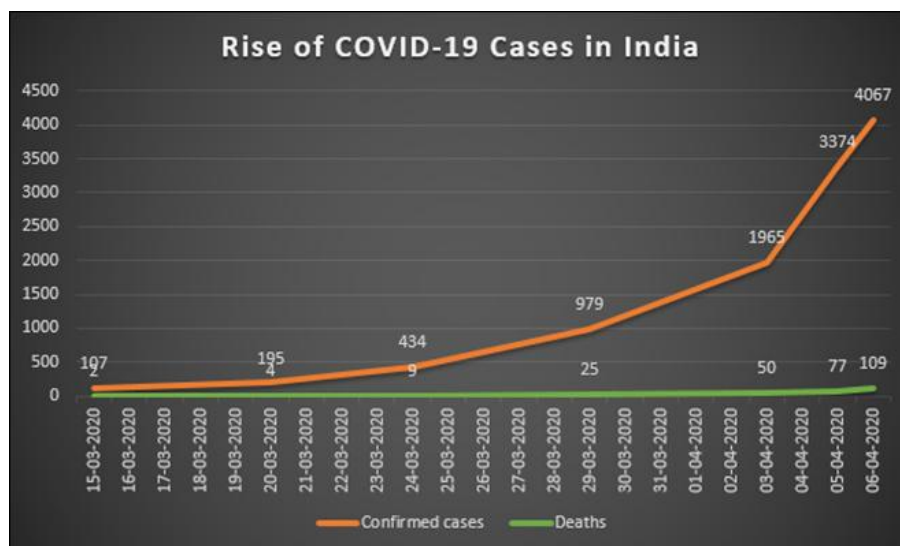


Fig. 3. Rise of nCOVID-19 Cases in India

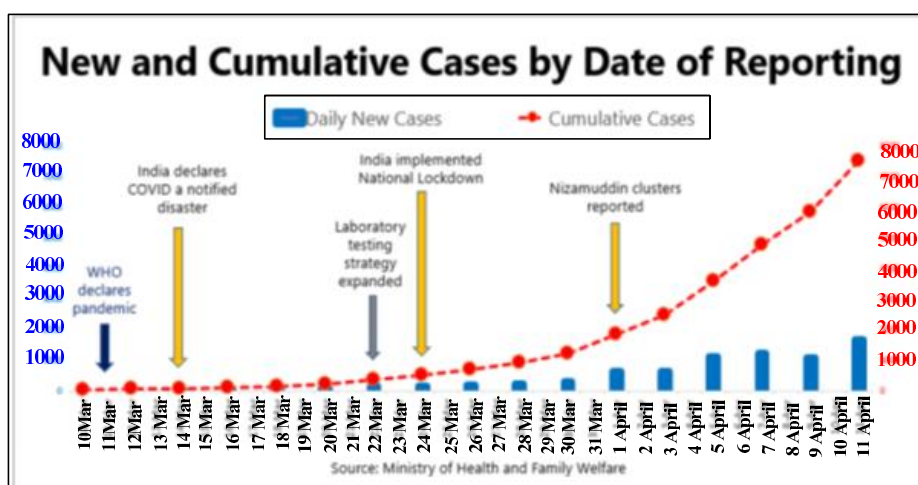
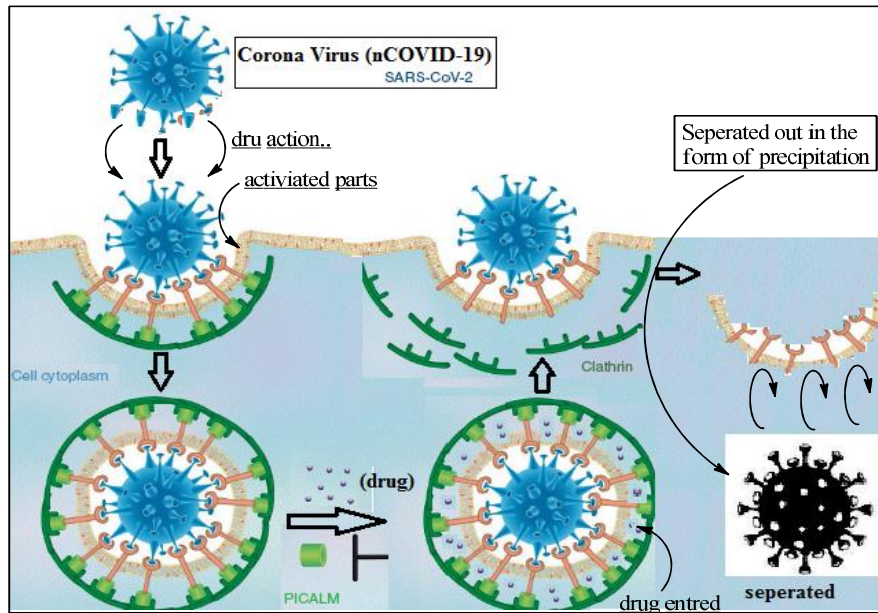


Fig. 4. New & cumulative cases by date of reporting (12 – April, 2020)

## 2. DRUG MECHANISMS OF ACTION [198-200]

The mechanistic action; corona virus (non-living) if it is come contact with human body specially mouth, nose, eye etc. then it becomes or we can say 'plays as living thing' and goes to drug action target (Fig. 5). The drug may act to reduce SARS-CoV-2 infections are of considerable interest, as this information could be valuable for identifying new prophylactic and therapeutic candidates. Drug becomes entrapped in membrane-enclosed low pH organelles, interfering with their acidification [198]. In which drug treatment leads to an increase in lysosomal pH. Speculation on chloroquine-induced antiviral

effects include inhibition of pH-dependent viral fusion/replication and prevention of viral envelope glycoprotein as well as host receptor protein glycosylation [198]. In malaria-causing plasmodium parasites, drug accumulates in the digestive vacuole where it is thought to prevent pH-dependent detoxification of heme, which is produced upon parasitic consumption of haemoglobin to obtain free amino acids [199]. Additionally, it is probable that drug exhibits host effects, independent of direct viral action, by attenuating the expression of pro-inflammatory factors and receptors [198], which can induce acute respiratory distress syndrome, which is primarily responsible for coronavirus-associated mortality [200].



**Fig. 5. Possible mechanism by which drug exerts therapeutic effects against COVID-19(SARS-CoV-2)**

### 3. PRECAUTION [201], PREVENTION [202-207]

- ◆ nCOVID-19 (nCOVID-20 in India) virus is expelled as droplets from the respiratory tract of an infected individual (for example during coughing and sneezing) directly onto a mucosal surface of a susceptible individual(s) or environmental surface(s).
- ◆ some studies suggest that droplets could travel on long and short distance; a distance of at least 1-2 meters has been used for deploying droplet precautions; however, this distance should be considered as the minimum rather than an absolute, ten ways to make sure you to avoid corona virus disease [201];

1. Avoid close contact with people who are sick. Maintain at least two to three feet distance between yourself and anyone who is coughing or sneezing.
2. Avoid touching your eyes, nose, and mouth.
3. Stay home, Stay safe.
4. Cover your cough or sneeze with a tissue, then dispose of the tissue safely.
5. Clean and disinfect frequently-touched objects and surfaces using a regular household cleaning spray or wipe.
6. Wearing a mask is not necessary unless you are taking care of an infection. The

Centers for Disease Control (CDC) does recommend that only infected people wear masks to prevent the spread of the virus.

7. Wash your hands often with soap and water for at least 30 seconds, especially after going to the bathroom, before eating, and after blowing your nose, coughing, or sneezing.
8. If soap and water are not readily available, use an alcohol-based hand sanitizer with at least 60% alcohol. Always wash hands with soap and water when hands are visibly dirty.
9. Breathing exercise, use to drink hot water with turmeric, 2-5 times in daily.
10. If you have a fever, cough and difficulty breathing, seek medical attention immediately.

According to WHO and US Centers for Disease Control and Prevention (CDCP) have issued advice on preventing further spread of COVID-19 [201,202]. They recommend avoiding travel to high-risk areas, contact with individuals who are symptomatic, and avoid the consumption of food, vegetable, meat etc from regions with known COVID-19 outbreak. Basic hand hygiene (sanitization) measures are also recommended, including frequent hand washing and the use of PPE such as face masks or two to three folded handkerchief. One of the Japanese-based company 'Bespoke Inc' has also launched an

artificial intelligence-powered Chabot (Bebot) that provides up-to-date information regarding the coronavirus outbreak, preventative measures as well symptom checker [203]. A infectious disease. It is paramount to implement infection control practices by infection source controlling, transmission route blocking, and susceptible population protection [204-207].

#### **4. DISESES AND TREATMENT (PAST AND PRESENT)**

##### **4.1 MERS-CoV**

The Middle East respiratory syndrome coronavirus (MERS-CoV).

Treatment [208]: A combination of ribavirin and interferon therapy was used for the treatment of MERS-CoV-positive patients.

##### **4.2 SARS-CoV**

Severe acute respiratory syndrome-Corona Virus.

Treatment [209-217]: Ribavirin alone or with interferon [209-217] severe acute respiratory syndrome with lopinavir/ritonavir [218].

##### **4.3 nCoV or CoV-2 or SARS-nCOVID-19 or nCOVID-19**

Novel corona Virus-19 or severe acute respiratory syndrome Novel corona Virus-19. (Biological Weapons). As on present surge, number of peoples going to death due virus name as "nCOVID-19" in world (nCOVID-20 in INDIA).

Treatment [219-226]: Some infected person by corona virus were recovered by using anti-malarial, anti-biotic anti-inflammatory naming as hydroxychloroquine (HCQ) (Fig. 6-a), chloroquine (CQ) (Fig. 6-b), azithromycine (Fig. 6-c). rheumatologists and dermatologists to treat immune-mediated diseases or immune-mediated condition, antiviral activity against SARS-CoV-2 in vitro and in small, poorly controlled or uncontrolled clinical studies [219-223]. The data support, drugs used in vitro activity against several viruses, including coronaviruses and influenza, but previous randomized trials in patients with influenza have been negative. In COVID-19, nonrandomized study from France, China in patients with mild to moderate nCOVID-19 found no difference in recovery rates [224-226]. As per literature surge still there is no specific vaccine on corona virus.

##### **4.4 Antiviral Therapy**

Based on our clinical research and experiences of using interferon- $\alpha$  in treating bronchiolitis, viral pneumonia, acute upper respiratory tract infection, hand foot mouth disease, SARS, and other viral infections in children.

Treatment [227-240]: Interferon- $\alpha$  nebulization: interferon- $\alpha$  200,000–400,000 IU/kg or 2–4  $\mu$ g/kg in 2 mL sterile water, nebulization two times per day for 5–7 days; 2. Interferon- $\alpha$ 2b spray: applied for high-risk populations with a close contact with suspected 2019-nCoV infected patients or those in the early phase with only upper respiratory tract symptoms. Patients should use 1–2 sprays on each side of the nasal cavity, 8–10 sprays on the oropharynx, the dose of interferon- $\alpha$ 2b per injection is 8000 IU, once every 1–2 hours, 8–10 sprays/day for a course of 5–7 days.

##### **4.5 Lopinavir/Ritonavir**

Lopinavir/ritonavir (Fig. 6-d) is sold under the brand name *Kaletra* among others, it combines lopinavir with a low dose of ritonavir. It is generally recommended for use with other antiretrovirals. It may be used for prevention after a needlestick injury or other potential exposure. It is taken by mouth as a tablet, capsule, or solution [241]. As of 2006, lopinavir/ritonavir forms part of the preferred combination for HIV first-line therapy recommended by the US United States Department of Health and Human Services in 2006 [242].

Treatment [227,243,244]: Lopinavir/ritonavir has been tried to apply to the treatment of adult patients for nCoV pneumonia, but its efficacy and safety remain to be determined.

##### **4.6 Antiviral Western Medicine Treatment**

At present, the treatments of patients with nCOVID or SARS-CoV-2 infection are mainly symptomatic treatments.

Treatment [245]: *Remdesivir* (Fig. 7) was recently reported as a promising antiviral drug against a wide array of RNA viruses. Holshue et al. for the first time reported that treatment of a patient with nCOVID-19 used remdesivir and achieved good results [245], remdesivir effectively in the control of nCoV-19 infection in vitro. In the meantime, also found that chloroquine has an immune-modulating activity and could effectively inhibit in this virus *in vitro* [246].



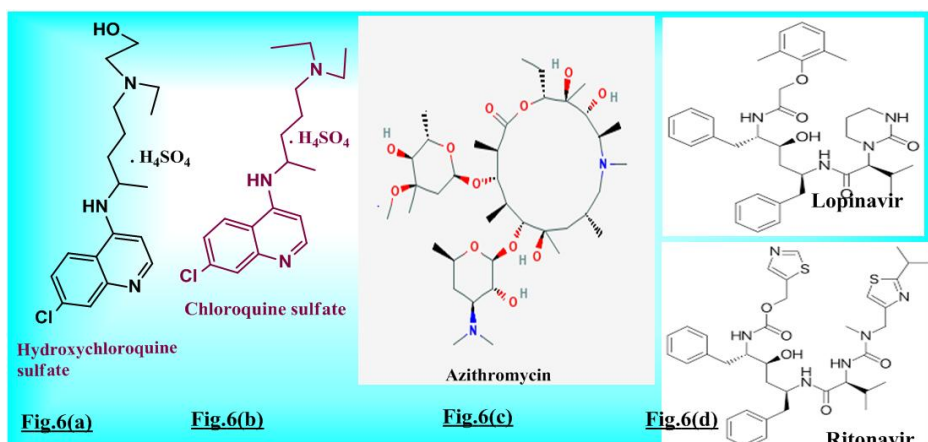


Fig. 6(a,b,c,d). Chemical structure of anti-malarial & anti-biotic etc.

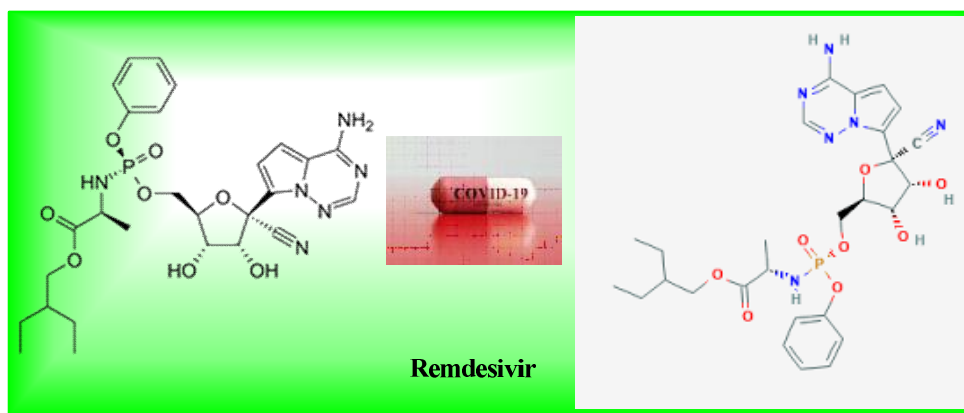


Fig. 7. Chemical structure of antiviral medication (Remdesivir)

## 5. CONCLUSION

We systematically explained pandemic virus, in past before 100 years ago Flue Like Symptoms (FLS). Slowly the symptoms were changes MERS to CoV (CoV) and now strong symptoms appearing in virus is the novel corona virus. The FLS, MERS, CoV, SARS and SARS-2 (nCOVID-19) are the same family Virus. The SARS-2 or (nCOVID-19) is transmission by human to human (Chain Reaction Disease) *via* airborne droplets generating by coughing, kissing, sneezing and smooching by infected person.

So avoid these activities by isolate, keep social distance as per WHO and ECDC guideline. Explained some prevention and precautions of corona virus advised by ICMR, WHO. Specially in India, day by day the ratio of infected and deaths persons were increases due to nCOVID-19 virus. Upto the date, ratio of infected and death persons are going increases in

Maharashtra state than other state. The infected (positive case) person also cured by using previously synthesized anti-malarial (hydroxychloroquine, Chloroquine, azithromycin, remdesivir etc), anti-biotic, anti-inflammatory as per medical expertise and using ICMR rules and guidelens. Still there are no anti-corona virus vaccine on nCOVID-19 or SARS-2. Future research needed to fight with corona virus disease.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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