



Review Article

Recent Updates on Diagnosis and Treatment of SARS-CoV-2: A Review

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Abstract

SARS-CoV-2 (severe acute respiratory syndrome - corona virus-2) emerged as a deadly virus and took approximately 3,422,907 deaths so far globally. The case fatality rate for SARS-CoV-2 is about 3-4% far below in comparison with the previous outbreaks including SARS-CoV and MERS-CoV. So far, the infection has reached in stage 3 i.e., community transmission in most of the countries, globally. The vaccine development is only the way by which the world could get out from this outbreak. Many vaccines have been developed by scientific communities up to the phase 3 trials and expecting some fruitful result out of it. In this review, we have discussed about the current status for COVID-19, the incubation and recovery period of the virus, structure of the virus, biological properties and its mechanism of replication. We have also discussed its health impact and current medicinal drugs including Remdesivir, Hydroxychloroquine, etc. and vaccines which are currently in trial phase, and lastly what could be the future plan to neutralize the effect of this outbreak.

Keywords: SARS-CoV-2, COVID-19, Structure, Strains, Biological Properties, Drugs, Vaccines, ACE2 Receptors.

1. Introduction

The newly emerged virus has left a very deep impact since its arrival and has made all the countries including superpower America to come into a state of emergency. In the emergence situation not only, the human health is affected but several other sectors like entertainment, tourism, restaurants, travel industries, stock market, food supply-chain, etc. are directly affecting the global economy with huge employment losses. During lockdown many suicidal cases reported related to anxiety, mental illness, stress disorders, depression and various psychological issues [1]. At the initial stage, the virus causes more than 90,000 infections and 3000 deaths [2] and now the number of deaths and infections has reached far beyond these numbers globally. The World Health Organization (WHO) named this deadly virus as corona virus (COVID-19) which is basically a family of viruses, specifically the species of current virus is SARS-CoV-2.

The current pandemic is not very much new to us, as if we look into the history of this virus, we come across three type of viruses which belongs to same family i. e. Corona virus. The first virus was SARS-CoV (severe acute respiratory syndrome - corona virus) which caused deadly pneumonia in year 2002, then came MERS-CoV (middle east respiratory syndrome - corona virus) in the year 2012 and lastly the current one SARS-CoV-2 (COVID-19) [2]. Current status globally as of today, a very alarming situation comes i.e. total of 165,069,258 cases confirmed and 3,422,907 deaths [3]. The first case of the novel Covid-19 was reported in Wuhan, China in December 2019 [4].

An incubation and recovery period for SARS-CoV-2 (COVID-19) patients are 2-14 days and 14-56 days, respectively, higher as compared to the patients of SARS-CoV, MERS-CoV and Common Flu as shown in figure 1 [5]. It is clear from incubation and recovery period that, the transmission rate is more in comparison to SARS-CoV, MERS-CoV and Common Flu. However, the transmission for these viruses is human to human as far research is concerned [6]. SARS-CoV emerged as a pandemic in 2002-03 and it was proposed after doing scientific research that this virus was originated from the genome of Bat (Chiroptera), which is similar to SARS-CoV-2 in the context of origin. The

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structure of both these viruses i.e. SARS-CoV and SARS-CoV-2 have their outer membrane made up of S glycoprotein. But there is a difference in the case fatality rate between both these viruses. SARS-CoV has a case fatality rate of 9.7 % with 8098 confirmed cases and 774 deaths, globally reported. For the SARS-CoV-2, case fatality rate is about 3-4 % with 165,069,258 confirmed cases and 3,422,907 deaths as of today globally reported. Also, the reproductive rate for SARS-CoV (2-3%) and for SARS-CoV-2 (2.5 %) are nearly same. In addition, with this, SARS-CoV-2 is not deadly as SARS-CoV and MERS-CoV rather its rate of transmission is very high that makes it worse [7,8].

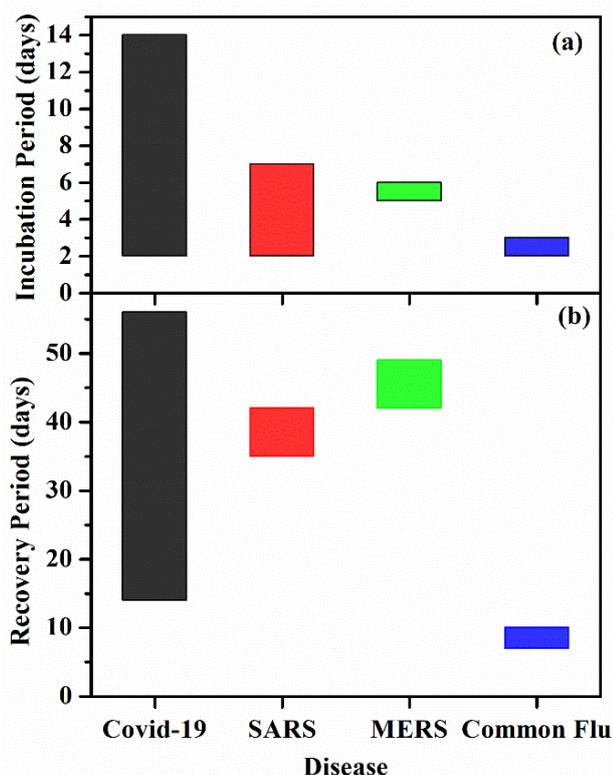


Figure 1: (a) An incubation period (b) Recovery period for different viruses.

Currently the scientific community, all over the world, are working on the vaccine’s development for Covid-19. According to the WHO draft as of September 3rd, 2020 eight vaccines are in their stage 3 trials and many promising candidates for vaccines have come up including mRNA-1273 vaccine, developed by Moderna Laboratories in the USA [9]. Therefore, vaccination is the only solution to the current pandemic and until it comes, the only way is, to follow the government norms and precautions to prevent the world.

2. Current Status of COVID-19

Worldwide, the number of cumulative confirmed cases and deaths are increasing exponentially day by day due to COVID-19 infection. Figure 2, indicates globally

reported confirm cases and deaths until May 20th, 2021 as reported by Worldometer, Johns Hopkins University & Medicine and WHO. Up to 3rd May 2021, cumulative 165.069 million confirmed cases and 3.422 million deaths have been reported.

The data shown in figure 2 seems to be very intuitive, but in principle it’s not as reported through the serological survey by the National Centre for Disease Control (Union Health Ministry and Delhi Government) and Brihanmumbai Municipal Corporation, Mumbai’s Civic Body in India, the picture seems to be clearer. According to the latest Sero survey conducted between August 1st -7th, 2020 in Delhi, data revealed that an approximate 29.1 % of the population have found antibodies against COVID-19 [10], which indicates 5.92 out of 19.81 million of Delhi population, were infected with SARS-CoV-2, however, 0.137 - 0.143 million confirm cases were reported. The similar situation was observed through the serological survey conducted in Mumbai, where in 57 % of slum populations developed IgG antibodies and 17% from non-slums area [11]. Therefore, few take away through the serological survey, i.e. COVID-19 is spreading with very fast rate as shown from the data in figure 2 (a), although testing equipments are adequate many peoples infected with COVID-19 were not registered [12].

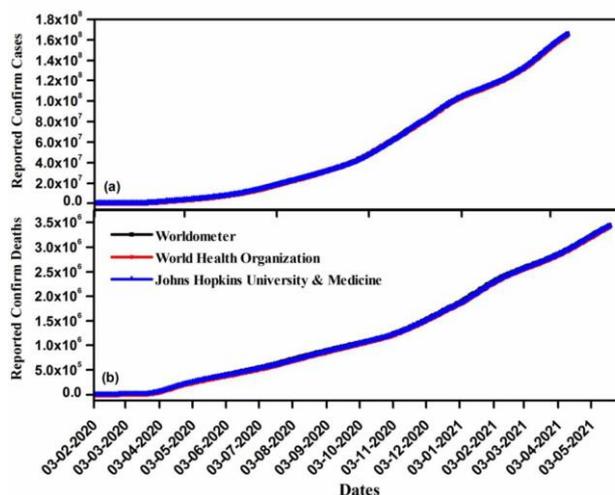


Figure 2: Reported confirmed (a) infected cases and (b) deaths globally.

3. Transmisión of SARS-CoV-2 outbreak

Outbreak transmission due to Covid-19, mainly classified into three categories i. e. community transmission, cluster of cases and sporadic cases. In addition, with these, there are two more categories, which are No cases (Countries/territories/areas without confirm cases in last 30 days) and Pending (the cases which has been identified, but not registered in the data base of governing local bodies). The outbreak distribution type for SARS-CoV-2 in different countries is in figure 3. Community transmission as

the name speaks for itself that transmission istaking place from one community to another community or from one group to another group. The sources of this type of transmission are called herd community. In case of the community transmission large number of cases which are not linked to transmission chains, large number of cases from any laboratory, existence of multiple unrelated disorder found in areas of countries, etc. are also the factors considered by WHO [13]. The cluster of cases type transmission indicates an infection in the given region with times of outbreak. The sporadic cases defined an infection spread in a country or a region imported one place to another place locally. According figure 3 (pie chart) globally i.e. 63.55% of countries possess community transmission, 17.79% countries have cluster of cases, 7.62% countries have sporadic cases, 9.74% of countries possess no cases and rest 1.27% of countries cases are pending.

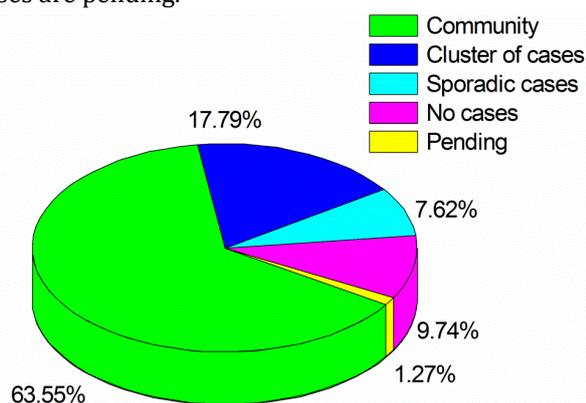


Figure 3: Worldwide type transmission for COVID-19 outbreak.

4. Structure of Novel Corona Virus

SARS-CoV-2 is a new species of corona virus which led to the current outbreak. The virus is having positive strand RNA and crown like shape. This deadly virus belongs to the Coronaviridae family, which can be divided into many sub families in which Ortho-coronavirinae is one of the main sub families. Further, Ortho-coronavirinae sub family can be categorized into 4 sub classes that are alpha, beta, delta and gamma corona virus [14]. figure 4 SARS-CoV-2 belongs to beta class in which most important component is genome that describes the behavior, appearance, etc. of the virus. The genome of SARS-CoV-2 is arranged in the +ssRNA pattern of length of 30Kb (Kilo-base) having structure (5' cap) and a tail (3' poly-A) [14]. The genome of SARS-CoV-2 possesses 4 types of proteins primarily E (Envelope), S (Spike), N (Nucleocapsid) and M (Membrane) protein [6]. The N protein helps in maintaining the structure of capsid. The function of S protein is to act as an inducer to suppress the host cell immune response against the attack of Covid-19.

There is also one special receptor protein i.e. angiotensin-converting enzyme 2 (ACE2) that basically helps in binding of S protein to the host cell [15]. Further S protein is categories in to 3 subunits i.e. Large ectodomain, Single pass Trans membrane anchor and Short intra-cellular tail. The ectodomain is sub-divided into two more units that are thereceptor binding unit and membrane fusion unit [6].

Till now, scientific community has reported 6 types of SARS-COV-2 strains (G,S,L,V,GR and GH) as shown in figure 4, which have been not reported in any peer reviewed Journal but still research is going on. In all these Strains, G strain are the most commonly found in Covid infected humans and GR, GH are mutated from G strain [16]. These 6 strains make SARS-CoV-2 virus more stable and also leads to the increase in its transmission rate due to unpredictable behavior on the human immune system. Based on the mutation, the genome was assembled in to two groups that are changes of amino acid from serine to leucine at position 84 of ORF8 region and from aspartic to glycine at position 614, they are called S and L strains. In addition, these group leads to the formation of spike (S) protein and mutations also help in the strain expression and that is applicable on other strains also [17].

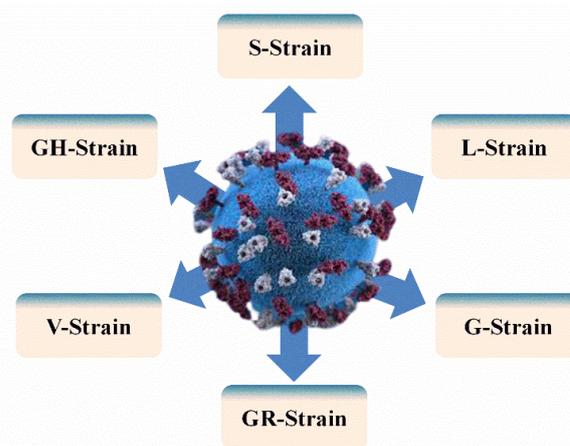


Figure 4: Types of strains for SARS-CoV-2 (Covid-19).

5. Biological Properties of SARS-CoV-2

Replication mechanism is the most important biological property for the survival of viruses in the host cell. SARS-CoV-2, required some ingredients such as ORF's (open reading frames), rep1a and rep1ab (replicase genes), a slippery sequence (5'-UUUAAAC-3') and pp1a, pp1ab (polyproteins) to perform replication in the host cell [6]. There are some special kinds of proteins present in viruses, are called non-structural proteins (replicase enzyme), whose main function is to guide the virus for the process of replication. Two main types of non-structural proteins (Nsp) i.e. Nsp1-11 and Nsp1-16 found in corona virus.

In addition, Nsp-15 also exists in ACE2 receptor, which performs both the functions of binding as well as affecting the immune system of the host cell. Collectively, these Nsp forms RTC complex (Reverse Transcriptase Complex) that helps in replication of SARS-CoV-2. Nsp also provides templates for the mRNA layering by using the negative side of RNA genome and, additionally, results in the formation of structural proteins i.e. M, S, N, and E. The function of Nsp doesn't end here, there is one more important function of Nsp i.e. assembly of genomic RNA in a helical twisted manner in the host cell [6].

6. Health Impact of Covid-19 (SARS-CoV-2)

SARS-CoV-2 has been emerged as a pandemic and took many lives. In case of death there could be two reasons, one is due to severe Covid-19 infection only and, another one may be due to other medical complications before getting infected with Covid-19. The primary organs that are affected after having Covid positive are lungs. It sounds very intuitive as SARS-CoV-2 is respiratory syndrome that will indirectly or directly affect the lungs. In some cases, lungs get infected which results to ARDS (acute respiratory distress syndrome) and, eventually death. Some studies, claims that about 80 % cases of Covid-19 show mild symptoms, 14% shows signs of pneumonia, 5 % suffers from septic shock and organ failure (mostly lungs) and 2 % of the cases were approaching fatality [18] but according to WHO fatality rate is 3-4 %. Most of the ARDS patients were facing breathing difficulties with increasing heart rate. In addition to these, there may be some other complications such as;

Acute cardiac injury: In this injury either the patient suffers from serious cardiac problem including breathlessness, chest pain, high/low blood pressure, etc. after getting Covid positive or after recovery.

Secondary infection: It is possible that the patient may get some secondary infection depending on his/her immunity, ranging from common flu to other contagious viruses [18].

Sepsis: In case of septic shock or sepsis condition, organ failure may occur (most probably kidney failure) [19].

Blood Clots: Some Covid-19 patients were also diagnosed with disseminated intravascular coagulation (DIC) [20] which leads to blood clotting including organs failure and brain hemorrhage.

7. Drugs Used for COVID-19 Treatment

Worldwide there are no appropriate approved clinical drugs to treat Covid-19 patients till date, however, some of the following antiviral drugs are being used.

7.1 Remdesivir

Remdesivir is one of the antiviral drug whose structure is shown in figure 5, which is being in use for the

treatment of Covid-19 symptoms, it is also known as GS-5734. This drug was synthesized by Gilead Sciences in 2017 as a broad-spectrum antiviral agent that was used to cure the Ebola virus infection [21]. A study revealed that Remdesivir can effectively severe the lungs function in animals which were affected by the MERS-CoV [22]. It is designed to prevent the replication of genetic materials of the virus enzyme. It can be integrated into the virus RNA chain as the RNA polymerase (RdRp) substrate cause mature termination of the virus by inhibiting the genome replication [23].

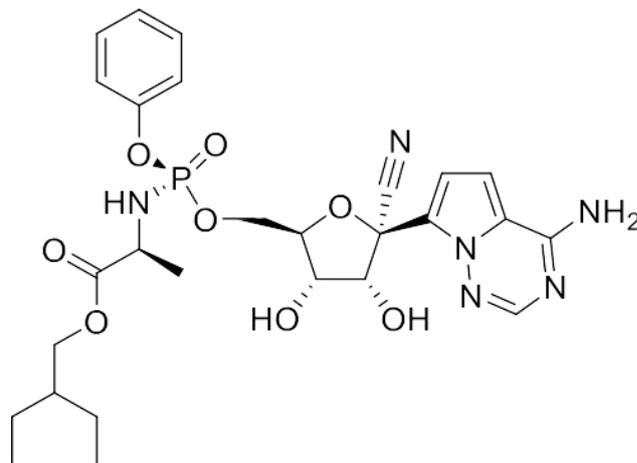


Figure 5: Structure of Remdesivir.

It has been clinically proven that Remdesivir can strongly interfere with the accomplishment of the SARS-CoV-2 life cycle in the host cells [24]. A randomized Phase 3 clinical trial was started in China on February 5th, 2020 to examine the effectiveness and safety of drug. In an experimental group, patients were given an initial dose of 200 mg followed by 100 mg for 9 consecutive days in intravenous infusion. Now, the current recommendation of Remdesivir dose is 200 mg on 1 day followed by 100 mg per day for 9 days [25,26]. After, clinical trial it has been approved by the European Medicines Agency (EMA) for the Covid treatment in European Union (EU). A randomized trial conducted by Dr. John Beigel and reported in the New England Medicine on one thousand patients and observed that, Remdesivir exhibits the best therapeutic effect for lower risk groups as compare to the patients who are on ventilator [27]. The latest report revealed that Remdesivir has been proved to be effective in clinical trials to treat severe Covid-19 patients. During the clinical trials, some side effects were also observed, such as hypotension, increased hepatic enzymes, renal impairment, etc. however, there is no reason known for the side effect of this drug, till date [28]. As a result, Remdesivir has been proved to be promising to treat Covid-19 infection [29].

7.2 Hydroxychloroquine and Chloroquine

Chloroquine is old and safe antiviral drug which was

first used for the treatment of infection caused by *Plasmodium falciparum* (parasite) [30,31], It inhibits the parasite penetration and genome replication by increasing the endosomal pH. Hydroxychloroquine and Chloroquine (figure 6) lead to increase in body pH which results in the inhibition of toll-like receptor 7 (TLR7) and 9 (TLR9), hence results in to the worse host cell immunity [32]. It has been noticed in clinical trials that chloroquine is able to stop the replication of Covid-19 *in vitro* with an EC50 of 1.13 μM [24,33]. Chloroquine phosphate is recommended to use for the treatment of novel coronavirus [34]. Along this, Hydroxychloroquine with an EC50 of 5.47 μM was found to be more effective than chloroquine towards Covid-19. On the basis of PBPK model, hydroxychloroquine recommended dose for CoV-2 infection is 400 mg twice a day followed by 200 mg maintenance dose twice a day for 4 days is proved to be 3 times more effective as compare to a dose of 500 mg Chloroquine phosphate twice a day for 5 days [35].

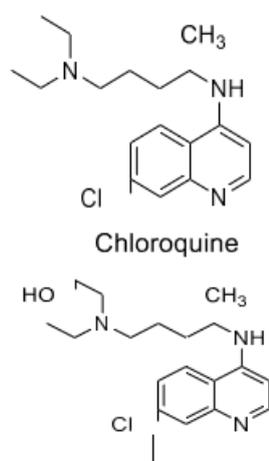


Figure 6: Structure of Chloroquine and Hydroxychloroquine.

7.3 Lopinavir-Ritonavir

Lopinavir and Ritonavir (figure 7) are HIV-1 inhibitor which are using in combination for treatment of Covid-19 symptoms by inhibiting the 3-chymotrypsin-like protease [36,37]. After giving doses of Lopinavir and Ritonavir in combination to the patients of Covid-19 in Korea, it was observed that the Covid-19 viral load decreased between 7 to 14 days [38]. The health department of different countries suggested the doses of this combination drugs such as National Health Commission of China recommend a dose of 200 mg/ 50 mg capsule of Lopinavir and Ritonavir, twice a day for less than 10 days. Ministry of Health & Family Welfare, Government of India, has recommended that 2 tablets of 200 mg Lopinavir and 50 mg Ritonavir twice a day, or 400 mg Lopinavir and 100 mg ritonavir, 5ml suspension (for Those persons who are unable to take orally) twice a day for 7 or 14 days leads to the cure of

Covid-19 symptoms [39].

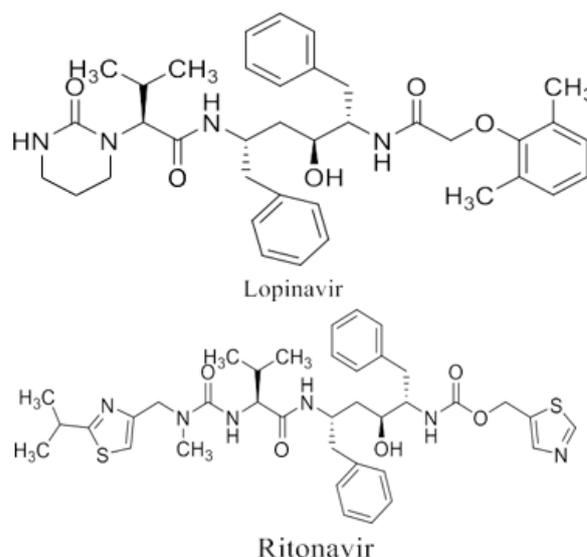


Figure 7: Structures of Lopinavir and Ritonavir.

7.4 Dexamethasone

Dexamethasone as structure presented in figure 8, is a corticosteroid used to treat the inflammation such as allergic disorder by inhibiting the release of anti-inflammatory hormones that is responsible for inflammatory conditions in the body [40]. Now, it is being in use for treatment of symptoms caused by the Covid-19. On the basis of ongoing study, it is proved to be the most effective drug for the critical condition of Covid-19 patients, and it also reduces the mortality rate. A recovery study was done on 12000 patients in which 15% patients were admitted in UK hospitals for trials, and it was found that 1 out of 8 patients on the ventilator was recovered by the use of dexamethasone drug [41]. In a trial, which was organized by a team of Oxford University, 2000 patients were provided Dexamethasone drug and 4000 were not for 10 days. It was observed that, this drug reduces the death risk for patients who are on ventilators from 40 % to 28 % and for patients who need oxygen from 25% to 20% [42].

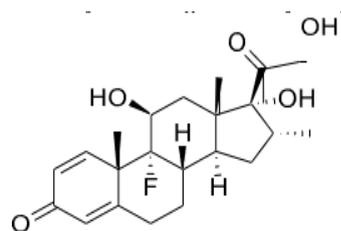


Figure 8: Structure of Dexamethasone

7.5 Favipiravir

The structure of Favipiravir drug is shown in figure 9, is an antiviral drug developed by the industry of Japan

(Fujifilm Toyama Chemical) in 2014. This Prodrug having pyrazine carboxamide structure and works as RNA polymerase inhibitor. This drug was used to treat the symptoms caused by RNA virus (influenza, Ebola) [43]. Recent studies revealed that the Favipiravir can be used for the treatment of novel corona virus patients. The drug has been proved to be effective for Vero E6 cells that are infected by SARS-CoV-2 with half-maximal effective concentration (EC₅₀) of 61.88 μ M and half-cytotoxic concentration (CC₅₀) at over 400 μ M, suggesting that high concentration is required for cautious and effective treatment [24]. The clinical results from China shows that the patients who are given Favipiravir has been recovered with a high rate (71.43%) [44].

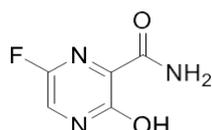


Figure 9: Structure of Favipiravir.

8. Types of Vaccines and its Current Status

According to draft publish by WHO on Covid-19, there are total 34 candidates for SARS-CoV-2 vaccines which are in development until September 3rd, 2020. As of now these vaccines are in clinical trials proposed by different renowned institutes all over the world [45]. These vaccines are broadly classified into 11 categories that are RNA vaccines, DNA vaccines, Protein subunits, Viral vectors, VLP's (viral like particles), Inactivated virus, Live attenuated virus, Lentiviral minigene vaccine (LMV), Pathogen specific vaccines, Replicating viral vector and non-replicating viral vector [46]. In all these 34 candidates, eighteen vaccines are in phase 1, six vaccines are in phase 2 and eight vaccines are in phase 3 trials, however, remaining two vaccines are in phase 1/2. In addition, Ad26COVS1 (non-replicating viral vector type) vaccine developed by Janssen Pharmaceutical Company, of Belgium is waiting for clinical trial approval.

Till date ChAdOx1-S (University of Oxford), Adenovirus Type 5 Vector (Beijing Institute of Biotechnology), rAd26-S+rAd5-S (Gamaleya Research Institute), Non-Replicating viral vector type vaccines, Inactivated type vaccines (Sinovac), Wuhan Institute of Biological Product and Beijing Institute of Biological Products, LNP-encapsulated mRNA (Moderna) and 3 LNP- mRNAs (BioNTech) are in phase 3 trial [45].

9. Conclusions

SARS-CoV-2 is a zoonotic virus, derived from bats (Chiropteran) in China and belongs to the same family of SARS-CoV and MERS-CoV. Structure of Covid-19 has two main components; one is S-glycoprotein and another ACE2 receptor, these helps in the binding of the virus to the target site and in mutation, respectively. The only difference between Covid-19 and its

ancestors is of fatality rate. SARS-CoV possess fatality rate of 7-9.7 %, MERS-CoV (34 %) while SARS-CoV-2 (3-4 %), with similar reproductive rate. The incubation and recovery period of Covid-19 is 2-14 and 14-56 days, respectively. Lungs are main targeting organs due to Covid-19 exposure along with the kidney failures and other multiple complications. For clinical treatment of Covid-19 patients, mainly Remdesivir, Hydroxychloroquine and Chloroquine, Hydroxyquinone, Lopinavir-Ritonavir, Dexamethasone, and Favipiravir antiviral drugs have been used. Presently, 34 vaccine candidates are under clinical trial including eight vaccines that are in stage 3 trial. The serological survey of some places indicates that the spreading of virus is far more than the actual reported data globally. As of now Covid-19 transmission is in stage 3 (Community transmission, more than 50 %) in most of the countries worldwide.

10. Futuristic View for Covid-19

Three pillars for Covid-19 need to be addressed presently and in future i.e. more testing, complete isolation and precautions are required. These three will be the main soldiers in our route towards future prevention from spreading the virus infection.

The patients that are recovered from Covid-19 need to protect themselves from reinfection as to block the second wave of virus may come if proper measures are not taken.

The impact on the human body after getting Covid-19 infection, regarding to the response towards immune system is an important aspect that need to be delayed.

SARS-CoV-2 mutates different strains and vaccine for one particular strain may not be effective in an analogous manner with other strain.

Cleanliness and social distancing are the only tools to curtail of SARS-CoV-2 infection, which in turns lead to economic development, reducing the economic burden of the country, providing more opportunities and self-employment to the upcoming youth.

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