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REVIEW

Epidemiology of coronaviruses, genetics, vaccines, and scenario of current pandemic of coronavirus diseases 2019 (COVID-19): a fuzzy set approach

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ABSTRACT

Human coronaviruses (HCoVs) are associated with a range of respiratory complications. In the last two decades, three major outbreaks have been reported due to HCoVs including the current pandemic. In December 2019, a newly emerged virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan city, China. This paper presents a detailed review of the literature and discusses the uncertain spread of coronavirus disease 2019 (COVID-19) using fuzzy set as classical set theory logic to measure uncertainty and vagueness of COVID-19 in China. Our findings show that both infection and death rate touched the peak (normal fuzzy sets) and have shown a decline. The graphs are not convex, which shows that there remains much uncertainty in the spread of COVID-19. Effective vaccines are clearly needed to control and prevent the COVID-19 pandemic.

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Introduction

Human coronaviruses (HCoVs) are characterized as a main group of coronavirus (CoV) which can cause several respiratory infections of different levels of severity, some of the common manifestations of which are pneumonia, bronchitis, and common cold.[1] In HCoVs, a very rapid evolution occurs by recombination and genome nucleotide substitution.[2] In recent years, the rapid evolution in HCoVs has occurred due to poultry farming and urbanization.[3] These factors have facilitated the regular mixing of species and contribute the genome recombination of HCoVs.[3] The transmission of these highly pathogenic viruses occurs from animals to humans due to their close contacts. Climate changes are also one of the facilitating factors in the transmission of these pathogenic viruses by disturbing the geographical places of viral carrier animals and insects.[4] Seven HCoVs have been identified: HCoV-229E, HCoV-OC43, HCoV-NL63, HCoV-HKU1, Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Among them the first four HCoVs are spread globally in the human population and cause nearly one-third of common cold infections.[5] In immunocompromised patients, HCoV-NL63 and HCoV-229E cause light infection. These two CoVs originate in the bats of Africa.[6,7] HCoV-229E is Camelid, an intermediate host.[8] HKU1 and HCoV-OC43 have origin of rodents and harmless for humans. Rhinolophus-bat CoV HKU2 is a novel strain which is called SADS coronavirus (SADS-CoV) which can cause swine acute diarrhea-syndrome (SADS) and originates from piglets.[9] HCoV-229E and HCoV-OC43 infections accompanied by multiple respiratory and systemic symptoms in the elderly age are frequent, likely causing substantial medical disease burden.[10,11] Infections may lead to some serious complications such as neurological problems.[12,13] Some recent studies suggest that most RNA viruses are likely to have a much more recent human adaptation and evolution.[14,15]

The worldwide spread of recently emerged SARS-CoV-2 is very uncertain. The emerging of such pathogenic viruses is a big challenge for medical science to discover the unknown zoonotic source of zoonotic viruses, to develop rapid diagnostic techniques, and to create drugs and vaccines to treat and control thee deadly infectious viruses. Vaccine and drugs against these highly pathogenic viruses have not yet been developed; thus, only symptomatic therapy is used for infected patients.[4]

The aim of this article is to describe the epidemiology of CoVs, genetics, vaccines, and the current scenario of COVID-19. We also have performed a fuzzy set analysis to measure uncertainty and vagueness of COVID-19 in China.

Genetics of CoVs

CoVs are enveloped RNA viruses, belongs to family *Coronaviridae*, and order Nidovirale. Based on comparison of

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whole viral genome sequences, the International Committee for Taxonomy of Viruses (ICTV) has further divided CoVs into four genera, Alpha, Beta, Gamma, and Delta.[16,17] CoV can cause infection in humans, swine, and avian. HCoVs belong to Alpha or Beta genera. Alpha CoVs include HCoV-NL63 and HCoV-229E, and Beta CoVs include SARS-CoV, MERS-CoV, HCoV-OC43, and HCoV-HKU1. Under electron microscopy, CoV virions have a spherical, pleomorphic shape, and "club-like" projections are present on the outer surface due to spike proteins.[18,19] The virion contains a helical nucleocapsid which protects a positive-sense single-stranded RNA viral genome of 26–32 kilobases.[20] CoVs have four structural proteins named spike, envelope, membrane, and nucleocapsid. Moreover, other accessory overlapping open reading frames (ORFs) are also present. Their number and location are different among CoV species.[21]

According to the sequence databases all HCoVs have a recognized animal origin. SARS-CoV-2, MERS-CoV, SARS-CoV, HCoV-229E, and HCoV-NL63 origin in bats, and HKU1 and HCoV- OC43 in rodents.[22,23] The Phylogenetic relationship of CoVs is presented in Figure 1.

SARS-CoV

Due to the recombination of bat SARSr-CoVs, a new virus emerged called SARS-CoV.[25] The SARS-CoVs cause epidemics by infecting humans and civets.[4,26] The SARS-CoV outbreak was reported in 2002–3 in China and spread to 37 countries. The number of SARS-CoV confirmed cases were 8273 with 775 (9.4%) deaths.[4] ACE2 is a receptor binding site of the SARS-CoV.[27,28]

MERS-CoV

The occurrence of highly pathogenic CoV in the Middle East, called MERS-CoV, focused attention on HCoVs. MERS-CoV is a highly pathogenic CoV discovered in 2012 in the Kingdom of Saudi Arabia.[29] MERS-CoV infected people in Saudi Arabia, Jordan, Oman, Qatar, Egypt, Jordan, and the United Arab Emirates. Some of the peoples were also infected in European countries who had a history of visit to the Arabian Peninsula or contact with infected peoples. There is evidence of person-to-person transmission of MERS-CoV from infected persons to healthy persons. However, the transmission of MERS-CoV occurs in those who have very close contact with infected persons, like the close contact of health care staff with infected patients. People who are immunocompromised and have secondary infections are more susceptible to MERS-CoV infection.[30]

Studies conducted in Egypt and Oman showed that neutralizing antibodies against MERS-CoV are found in dromedary camels "*Camelus dromedaries*",[31] which shows that the MERS-CoV may have the dromedary camels as intermediate host. A recent study finds that the infected person MERS-CoV RNA matches with that of camels in Qatar.[32] MERS-CoV isolation has not been isolated yet from camels, but it seems that the transmission of MERS-CoV is camel to human. According to phylogenetic analysis MERS-CoV shows close similarity with BtCoV-HKU5 and BtCoV-HKU4 which are the known CoVs.[33] The reservoir of MERS-CoV may be bat as well as the European hedgehog "Erinaceuseuropaeus" in which a MERS-CoV close relative is found.[34]

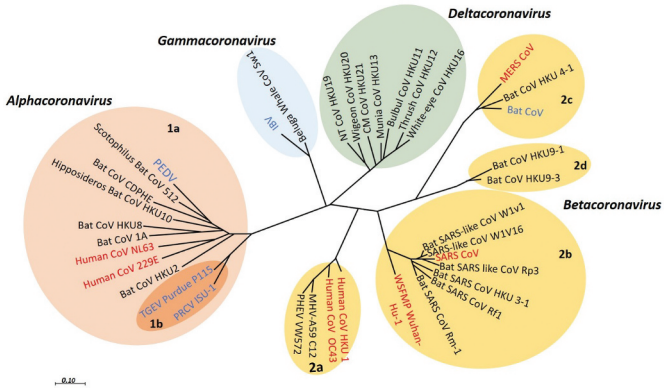

Figure 1. Phylogenetic relationship of CoVs. The phylogenetic tree illustrates the relationship among some HCoVs (red) and animal CoVs (blue) as a reference used in the tree, on the basis of complete genome nucleotide sequences. The viruses are grouped and subgrouped as (prototype shown): Alpha-CoV (pink, subgroup;1a,1b), Beta-CoV (light brown, subgroup; 1a,1b,1 c,1d), Gamma-CoV (light blue), and Delta-CoV (green). This tree is reconstructed with RNA-dependent RNA polymerase-coding region complete sequences of CoVs (with MEGA 7.2 software for maximum likelihood method).[24] Porcine enteric diarrhea virus (PEDV); infectious bronchitis virus (IBV); SARS- CoV; transmissible gastroenteritis virus (TGEV) MERS- CoV; Porcine respiratory CoV ISU-1 (PRCV ISU-1); and Wuhan seafood market pneumonia (Wuhan-Hu-1).

SARS-CoV-2

Pneumonia cases were reported in December 2019 with an unknown etiological agent. The initial cases were epidemiologically related with the fresh Seafood Market located in Wuhan city, Hubei province, China.[35] Genome sequence of five patients's shows 79.5% identical similarity to SARS-CoV. In addition, on the basis of whole genome sequence, the SARS-CoV-2 is 96% identical with bat CoV. The results of the pairwise proteins sequence analysis of seven conserved nonstructural proteins showed that this novel SARS-CoV-2 belongs to the SARSr-CoV species.[36] The disease caused by SARS-CoV-2 named as COVID-19.

The SARS-CoV-2 was isolated from the patient's bronchoalveolar lavage fluid. As with SARS-CoV, SARS-CoV-2 uses the same receptor called ACE2 for cell entry. SARS-CoV-2 contains six ORFs and other accessory genes. The analysis showed that the genes of SARS-CoV-2 show less than 80% nucleotide sequence similarity with SARS-CoV.[36]

For the classification of SARS-CoV-2, the seven conserved replicase domains of ORF1ab were used, which showed that between SARS-CoV and SARS-CoV-2, the amino acid sequence is 94.6% identical, indicating that SARS-CoV-2 and SARS-CoV belong to the same species. The results of phylogenetic analysis also revealed that SARS-CoV-2 is the closest relative of RaTG13, and it has different ancestry from other SARSr-CoV.[36]

The previously detected bat CoV from *Rhinolophus affine* called "BatCoV RaTG13" from Yunnan province China showed maximum sequence similarity to SARS-

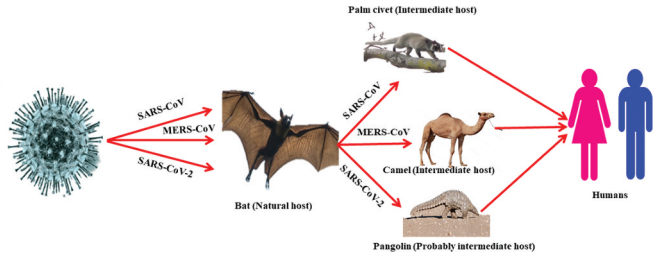

Figure 2. Transmissions cycle of SARS-CoV, MERS-CoV, and SARS-CoV-2.

CoV-2. The results of Simplot analysis showed that RaTG13 genome is very similar to that of SARS-CoV-2, which show 96.2% genome sequence similarity. The gene of receptor spike binding-proteins (S) of SARS-CoV-2 is very different from those of other CoVs, which show <75% nucleotide sequence similarity with the other SARSr-CoVs, while RaTG13 shows 93.1% identity.[36]

The receptor spike binding-protein gene of RaTG13 and the receptor spike binding-protein gene of SARS-CoV-2 are longer than those of other SARSr-CoVs. The main difference in SARS-CoV-2 compared with SARS-CoV is that SARS-CoV-2 has three short insertions in the N-terminal domain, and 4 out of 5 key residues changes in the receptor-binding motif. The recent finding shows close phylogenetic relationship to BatCoV RaTG13, which provides enough evidence for a bat origin of the recent SARS-CoV-2.[36]

By electron microscopy, SARS-CoV-2 is of spherical shape with some pleomorphism and 60–140 nm in diameter. The virus particle consists of unique 9–12 nm spikes, which give the virus an appearance like the solar corona.[37] The cases of COVID-19 have been reported in essentially all countries/regions.[38] Initial COVID-19 cases had a history of travel to China.[39] The transmission cycle of SARS-CoV, MERS-CoV, and SARS-CoV-2 is presented in Figure 2.

Replication cycle

CoV infection begins when the spike protein S1 domain attaches to the ACE2 receptor. This attachment brings structural changes in the S2 subunit of spike protein, which leads to the mutual membrane fusion of cell plasma membrane and virus resulting in the nucleocapsid entering the cytoplasm. Through ribosomal frameshifting the translation of viral RNA occurs, producing two polyproteins pp1a and pp1ab. Sixteen non-structural proteins (NSPs) are generated from pp1a and pp1ab autoproteolytically processed in the presence of host and viral proteases, and then replicase-polymerase is formed from its assembly. The replicase polymerase is responsible for virus replication, a process by which structural proteins are formed due to replication of genomic RNA and by the transcription and translation of sub-genomic RNA. The viral products assemble in the specific region called ERGIC and form a bud which is a smooth wall vesicle and finally release virus from the cell by a process called exocytosis.[40,41] The replication cycle of SARS-CoV-2 is presented in Figure 3.

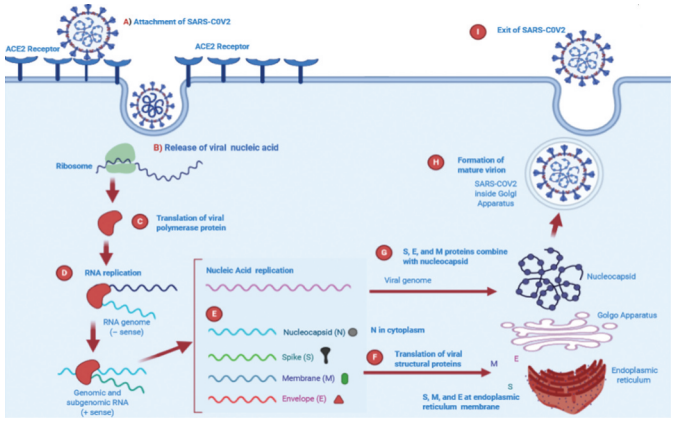

Figure 3. Proposed replication cycle of SARS-CoV-2.

COVID-19 spread in China, a fuzzy set approach

The fuzzy set concept was developed by Zadeh in the mid-60's to account for numerous concepts used in vague and imprecise reasoning, e.g., tall, old, and other similar parameters. It is a very convenient method for the representation of uncertainty. Fuzzy set theory has many applications; it also allows the graduate assessment of membership of element in a set, described with the aid of membership function values in interval [0, 1]. Fuzzy set is capable of measuring uncertainty of certain diseases. Hence it seems quite useful in case of COVID-19, as its spread is very uneven. We can understand it with following example.

Example: Assume that we have the following data which we have extracted from different sources as presented in Table 1.

Now we will use the concept of fuzzy set for which we must find the membership function as shown in Table 2.

By plotting the data we get Figure 4.

If we take only one attribute i.e. a_1 we get Figure 5.

If we take another attribute, a_2 then we get Figure 6.

Figure 4 shows high fluctuation in the data hence no one can predict about the new cases in near or far future. Figure 4 shows the combined effects of series 1 and 2. Series 1 indicates the number of affected individuals while series 2 represents mortality rate. From Figure 5, we observe that until 12/02/2020 the infected touched the peak and after that this rate has been decreasing until now which is a positive sign. From Figure 6, we observe that until 24/02/2020 the rate of deaths in China touched the peak and after that this rate keeps decreasing. The graphs are not convex which shows that a lot of uncertainty exists in the spread of COVID-19.

Diagnosis and treatment

Being the novel CoV, many aspects of the SARS-CoV-2 are still unrevealed. Therefore, a fast and accurate diagnostic method is crucial to diagnose the disease on time to prevent its transmission. Currently different methods are being used such as serological testing, chest computed tomography (CT), nucleic acid

Table 1. Trend of COVID-19 cases in China (01–22-2020 to 04–03-2020).

Date	COVID-19 daily cases	COVID-19 daily deaths
1/22/2020	571	17
1/23/2020	259	8
1/24/2020	457	16
1/25/2020	688	15
1/26/2020	769	24
1/27/2020	1771	26
1/28/2020	1459	26
1/29/2020	1737	38
1/30/2020	1981	43
1/31/2020	2099	46
2/1/2020	2589	45
2/2/2020	2825	57
2/3/2020	3235	64
2/4/2020	3884	65
2/5/2020	3694	73
2/6/2020	3143	73
2/7/2020	3385	86
2/8/2020	2652	89
2/9/2020	2973	97
2/10/2020	2467	108
2/11/2020	2015	97
2/12/2020	14108	146
2/13/2020	5090	121
2/14/2020	2641	143
2/15/2020	2008	142
2/16/2020	2048	105
2/17/2020	1888	98
2/18/2020	1749	136
2/19/2020	391	114
2/20/2020	889	118
2/21/2020	823	109
2/22/2020	648	97
2/23/2020	214	150
2/24/2020	508	71
2/25/2020	406	52
2/26/2020	433	29
2/27/2020	327	44
2/28/2020	427	47
2/29/2020	573	35
3/1/2020	202	42
3/2/2020	125	31
3/3/2020	119	38
3/4/2020	139	31
3/5/2020	143	30
3/6/2020	99	28
3/7/2020	44	27
3/8/2020	40	22
3/9/2020	19	17
3/10/2020	24	22
3/11/2020	15	11
3/12/2020	20	7
3/13/2020	11	13
3/14/2020	20	10
3/15/2020	16	14
3/16/2020	21	13
3/17/2020	13	11
3/18/2020	34	8
3/19/2020	39	3
3/20/2020	41	7
3/21/2020	46	6
3/22/2020	39	9
3/23/2020	78	7
3/24/2020	47	4
3/25/2020	67	6
3/26/2020	55	5
3/27/2020	54	3
3/28/2020	45	5
3/29/2020	0	0
3/30/2020	79	5
3/31/2020	36	7
4/1/2020	35	6
4/2/2020	31	4
4/3/2020	19	4
Total	81639	3326

Table 2. Membership function.

Date = di	a1	a2	a1/am	a2/am
1/22/2020	571	17	0.04	0.113
1/23/2020	259	8	0.02	0.053
1/24/2020	457	16	0.03	0.107
1/25/2020	688	15	0.05	0.100
1/26/2020	769	24	0.05	0.160
1/27/2020	1771	26	0.13	0.173
1/28/2020	1459	26	0.10	0.173
1/29/2020	1737	38	0.12	0.253
1/30/2020	1981	43	0.14	0.287
1/31/2020	2099	46	0.15	0.307
1/2/2020	2589	45	0.18	0.300
2/2/2020	2825	57	0.20	0.380
2/3/2020	3235	64	0.23	0.427
2/4/2020	3884	65	0.28	0.433
2/5/2020	3694	73	0.26	0.487
2/6/2020	3143	73	0.22	0.487
2/7/2020	3385	86	0.24	0.573
2/8/2020	2652	89	0.19	0.593
2/9/2020	2973	97	0.21	0.647
2/10/2020	2467	108	0.17	0.720
2/11/2020	2015	97	0.14	0.647
2/12/2020	14108	146	1.00	0.973
2/13/2020	5090	121	0.36	0.807
2/14/2020	2641	143	0.19	0.953
2/15/2020	2008	142	0.14	0.947
2/16/2020	2048	105	0.15	0.700
2/17/2020	1888	98	0.13	0.653
2/18/2020	1749	136	0.12	0.907
2/19/2020	391	114	0.03	0.760
2/20/2020	889	118	0.06	0.787
2/21/2020	823	109	0.06	0.727
2/22/2020	648	97	0.05	0.647
2/23/2020	214	150	0.02	1.000
2/24/2020	508	71	0.04	0.473
2/25/2020	406	52	0.03	0.347
2/26/2020	433	29	0.03	0.193
2/27/2020	327	44	0.02	0.293
2/28/2020	427	47	0.03	0.313
2/29/2020	573	35	0.04	0.233
3/1/2020	202	42	0.01	0.280
3/2/2020	125	31	0.01	0.207
3/3/2020	119	38	0.01	0.253
3/4/2020	139	31	0.01	0.207
3/5/2020	143	30	0.01	0.200
3/6/2020	99	28	0.01	0.187
3/7/2020	44	27	0.00	0.180
3/8/2020	40	22	0.00	0.147
3/9/2020	19	17	0.00	0.113
3/10/2020	24	22	0.00	0.147
3/11/2020	15	11	0.00	0.073
3/12/2020	20	7	0.00	0.047
3/13/2020	11	13	0.00	0.087
3/14/2020	20	10	0.00	0.067
3/15/2020	16	14	0.00	0.093
3/16/2020	21	13	0.00	0.087
3/17/2020	13	11	0.00	0.073
3/18/2020	34	8	0.00	0.053
3/19/2020	39	3	0.00	0.020
3/20/2020	41	7	0.00	0.047
3/21/2020	46	6	0.00	0.040
3/22/2020	39	9	0.00	0.060
3/23/2020	78	7	0.01	0.047
3/24/2020	47	4	0.00	0.027
3/25/2020	67	6	0.00	0.040
3/26/2020	55	5	0.00	0.033
3/27/2020	54	3	0.00	0.020
3/28/2020	45	5	0.00	0.033
3/29/2020	0	0	0.00	0.000
3/30/2020	79	5	0.01	0.033
3/31/2020	36	7	0.00	0.047
4/1/2020	35	6	0.00	0.040
4/2/2020	31	4	0.00	0.027
4/3/2020	19	4	0.00	0.027
Total	81639	3326		

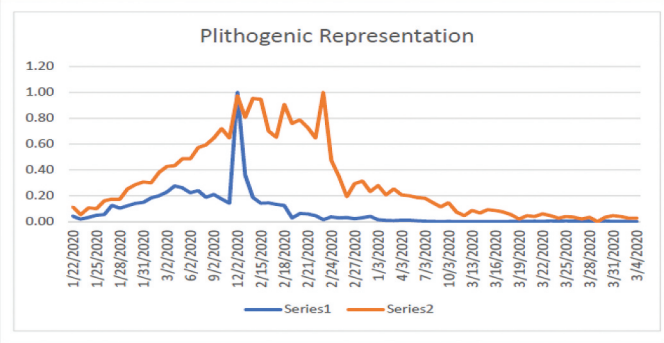

Figure 4. Plithogenic representation of COVID-19 cases in China from 01/22/2020 to 03/04/2020.

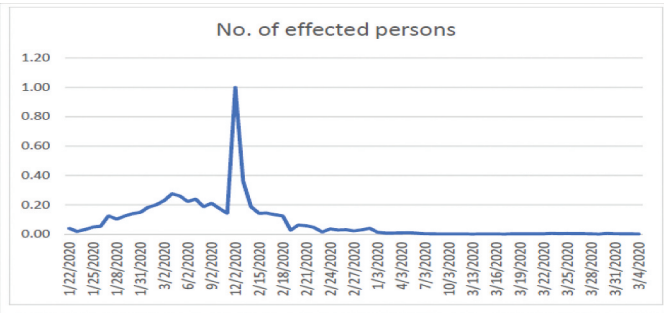

Figure 5. Number of infected person from COVID-19 in China.

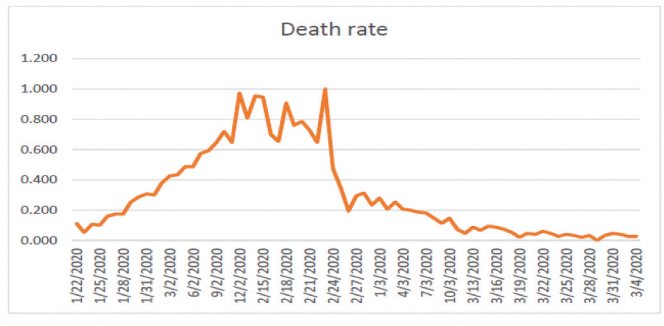

Figure 6. Death rate due to COVID-19 in China.

amplification tests (NAAT), viral sequencing, and viral culture.[42] There is no specific antiviral treatment of SARS-CoV-2. Ribavirin with recombinant interferons show limited effects against CoV infection.[43] Many researchers have developed different agents after the epidemic of SARS-CoV and MERS-CoV against of their polymerases, entry proteins, and proteases but till now none of them proved to be helpful.[44–46] It is proposed that for the treatment of COVID-19 the antibody and plasma of recovering patients can be used.[47] In addition, convalescent plasma therapy is an experimental treatment which shows a potential therapeutic effect and low risk in the treatment of severe COVID-19 patients.[48] For the treatment of COVID-19 infection, only remdesivir or in combination with interferon beta or chloroquine was found active; this approach has not triggered any significant adverse effects.[49–51] To confirm the effects of remdesivir more investigation is necessary. Common therapeutic objectives can be of more significance as CoV shares significant genomic features. The best approach for the treatment of COVID-19 may be therapeutic agents to target the viral nucleic acids, nucleotides, nucleosides, and enzymes which are involved in the transcription and replication of CoV.[52]

Vaccines

Vaccines are immediately required to control and prevent infrequent viral outbreaks and epidemics which occurred due to newly emerging viruses like the recent outbreak due to SARS-CoV-2. In 2003 the SARS-CoV was controlled, similarly MERS-CoV later as well. The current SARS-CoV-2 pandemic is spreading constantly with a continuous increase in infection and mortality rate. So effective vaccine is required to control SARS-CoV-2. For SARS-CoV, live-attenuated vaccines designed may be assessed for infected individuals as well.[49]

Many strategies are used for the vaccine development of CoV such as viral vector-based vaccines, inactivated viruses, subunit vaccines, inactivated viruses, recombinant proteins, live-attenuated viruses, and DNA vaccines, and these all were tested in animal models.[53,54] Given the conserved RBDs of SARS-CoV and bat SARSr-CoVs, some anti-SARS-CoV strategies in development, such as anti-RBD antibodies or RBD-based vaccines, could be tested against bat SARSr-CoVs. Recent studies demonstrated that anti-SARS-CoV strategies worked against only WIV1 and not SHC014 (rEFs71,88,89). Some strategies are being used to develop vaccine against SARS-CoV and recombinant SARSr-CoV by using the anti-receptor binding domains antibodies or receptor binding domain-based vaccine.[43,55,56] The different strategies of vaccine development are presented in Figure 7.

Moreover, protein cage nanoparticles and rhesus θ-defensin -1 are innate immune-modulators with great anti-SARS-CoV ability.[57,58] A protein cage nanoparticle which is prepared for SARS-CoV can be assessed for SARS-CoV-2 based on the SARS-CoV-2 and SARS-CoV higher resemblances and phylogenetic similarity. In the meantime, following the related approaches applied for SARS-CoV, novel protein cage nanoparticles identified for novel CoV can be prepared on an emergency basis. Based on the current situation of COVID-19 pandemic, vaccination approaches based on viral-like particles, recombinant protein,

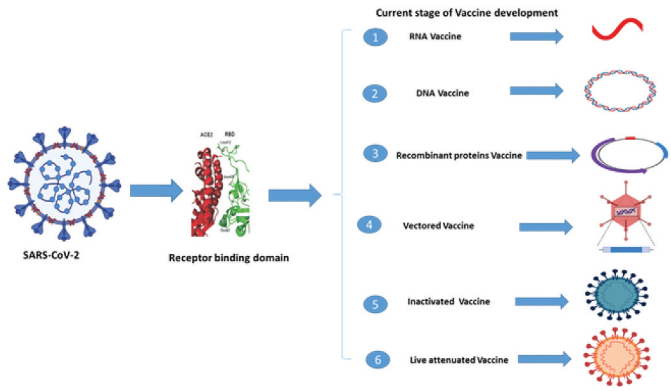

Figure 7. Different strategies of vaccine development against SARS-CoV-2.

and viral vectors which have been established for MERSS or SARS can be reformed for application against SARS-CoV-2.[59]

Limitations of study

This study has certain limitations. It discusses the different aspects of COVID-19 with respect to China only, hence data from other regions or countries are not applicable.

Conclusions

Since the start of the COVID-19 pandemic the morbidity and mortality rate keeps increasing with an alarming and uncontrolled conditions worldwide. There has been an imperative need to accelerate the research and development of COVID-19 candidate vaccine (s) and drugs.

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Authors' contributions

FMK and TA: Study design and wrote the manuscript. TA: Data collection and compilation. MG and WC: Preformed the analysis. TA, MK, and JH: Edited and reviewed the manuscript. All the authors read and approved the final manuscript for publication.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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