Review Article

Mapping the footprints of COVID-19 pandemic

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Abstract

The new member of the coronavirus family created havoc in the world in few days of its discovery and was declared as a pandemic by March 2020. The enveloped, single-stranded RNA virus was first identified in a patient with dry cough, pain, and weakness for the past1 week with unknown etiology in Wuhan. The coronavirus soon spread across the globe in the next few weeks. To curb the spread of coronavirus, stringent measures such as lockdown and social distancing were enforced resulted in a declining of cases in various countries. However, unlocking, relaxation of preventive measures, and changing human behaviors led to a drastic increase in the number of COVID-19 cases resulting in the second wave of transmission. This resulted in reimposing of lockdown measures in countries such as Nepal, Italy, France, Netherland, and Germany. At present, the virus has affected over 110.7 million peoples and over 2.4 million deaths across the world, with India having the second-highest number of COVID-19 cases, following the United States of America. Furthermore, a cross-sectional view of the disease states several new strains being reported across the globe at one end and at another end there is rolling out of vaccine against COVID-19. There is still uncertainty related to curbing of the pandemic as effect of vaccine on new strains is undetermined. Thus, it is important to understand the transforming epidemiology of the virus as it helps in planning necessary steps for physicians and policymakers. The present review summarizes the updated information primarily about the epidemiology of COVID-19, from initiation to the present scenario.

Keywords: COVID-19, epidemiology, lockdown, pandemic, social distancing, vaccine

Introduction

The association of coronaviruses with humans was relatively obscure, probably because there was no severe human disease that could be attributed to the virus.[1,2] However, this myth busted with the acquaintance of severe acute respiratory syndrome (SARS)-CoV in 2003, proceeded by Middle East respiratory syndrome (MERS)-CoV in 2012, which served as a great public health threat.[3,4] To replenish and regain its importance in humans, a new member of the family known as SARS-2 (SARS-CoV-2), which caused coronavirus disease-2019 (COVID-19) initially identified by causing pneumonia-like symptoms in a cluster of patients in Wuhan, China in late December 2019.[5,6] The World Health Organization (WHO) initially declared it as a public health emergency of international concern (PHEIC) on the last day of January 2020 and later on March 11, 2020 upgraded its status to a pandemic with more than 118,000 cases spread across 114 countries.[7,8] As of February 21, 2021, it has spread worldwide, causing over 110.7 million cases and over 2.4 million deaths across all the countries.[9] Furthermore, the transmission of the virus initially declined as a result of stringent steps implemented across the globe. However, unlocking, relaxation in lockdown measures, and changing behavior of humans resulted in a spike in coronavirus cases in just a few weeks. In addition to the advent of mutant strains such as Brazil P. 1, the United Kingdom (UK) B.1.1.7, and South Africa B.1.351 strains, cases began to increase because of the increased

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transmissibility of these strains. On the other hand, around 12 vaccines have been rolled out. At present, there is uncertainty regarding the effectiveness of vaccine on the newer strains, hence it is important to continue following stringent preventive measures.[10] Thus, more attention is required for understanding each and every aspect of the virus, so that important strategy can be planned by physicians and policymakers. Moreover, due to ever-evolving nature of this infection, all updates and changes in its epidemiology should be discussed with all physicians, especially those who are involved in primary care, diagnosis, or the ones involved in the treatment of the COVID-19 cases as they are the backbone of the health care delivery system in the periphery. Therefore, through this review, we aim to summarize the updated information of the ever-changing COVID-19 pandemic from initiation to the current status.

Description of the Virus

Coronavirus is an enveloped, single-stranded positive-sense RNA virus that is classified within the Nidovirales order and belonged to lineage β-CoVs, subgenus Sarbecovirus. The envelope of the virus is covered with glycoprotein arranged in a typical crown-like appearance under an electron microscope, hence named coronavirus.[11] It is spherical or pleomorphic in shape ranging from 60 nm to 140 nm in diameter. It has four major proteins: spike (S), envelope (E), membrane (M), and nucleo-capsid (N).[12] Though coronavirus is found in several animals, the major natural reservoirs are bats.[13,14]

Origin and Spread of COVID-19 across the World

The first case with unknown etiology was reported in December 2019 in Central Hospital of Wuhan. Following which few more cases of pneumonia with such unknown etiology were identified in Wuhan by the end of 2019. The chronology of the COVID-19 pandemic is explained in Figure 1.[15-18]

According to the WHO Weekly Epidemiological update, there are globally 110,763,898 confirmed cases and 2,455,331 deaths, distributed across six WHO regions [Table 1]. The highest number of confirmed cases and deaths are reported from the Region of Americas, whereas the least number of cases and deaths have been reported from the Western Pacific region.[19]

As of February 21, 2021, more than 70% of the burden is contributed by only 13 countries namely the USA, India, Brazil, Russia, the United Kingdom, France, Spain, Italy, Turkey, Germany, Colombia, Argentina, Mexico, the USA, and India altogether contribute approximately 35% of the total global burden. A similar trend is observed in terms of mortality associated with COVID-19 cases, with 12 countries contributing to more than 70% of the deaths related to the disease globally.[20]

SARS-CoV-2 is an RNA coronavirus that is susceptible to faster mutations, eventually the emergence of various mutated strains

Table 1: Distribution of COVID-19 cases and deaths across six WHO regions

WHO Region	Cumulative cases (%)	Cumulative deaths (%)	Case fatality rate in %
Americas	49, 296, 115 (45%)	1, 171,294 (48%)	2.4
Europe	37, 574, 211 (34%)	838, 761 (34%)	2.2
South-East Asia	13, 345, 590 (12%)	204, 796 (8%)	1.5
Eastern mediterranean	6, 181, 023 (6%)	141, 915 (6%)	2.3
Africa	2, 789, 884 (3%)	70, 332 (3%)	2.2
Western Pacific	1, 576, 330 (1%)	28, 220 (1%)	1.8
Other	745 (<1)	13 (<1)	1.7
Global	110, 763, 898	2 ,455 ,331	2.2

across the globe. In the past couple of months, multiple variants of the virus are reported globally such as UK variant: B.1.1.7, South African variant: B.1.351, and Brazilian variant: P. 1.[21] The UK variant was estimated to be 71% more infectious than previous strain.[22] New variants namely N440K and E484Q have been detected in Maharashtra and Kerala, but there is no direct evidence that suggests the two strains have caused a resurgence of COVID-19 cases in these states.[23]

Epidemic Curve of Infection

The outbreak of the COVID-19 can be well understood by means of the epidemic curve of infection. Different countries of the world exhibit different curve patterns based on their demographics, the readiness of the health system to an epidemic, implementation of preventive measures (lockdown, social distancing), country's reaction time to the pandemic, etc., Different phases may last for a different time period depending upon the above factor. However, the existing data suggest, increasing phase generally lasts for a minimum of 4 to 12 weeks or even more for COVID-19, based upon the measures taken in the particular country. The increasing phase is followed by the plateau phase which describes the stability of incidence cases. The plateau phase was initially achieved by several countries such as China, South Korea, Italy, Germany, France, Spain, Turkey, Belgium, Austria, Australia, Japan, New Zealand, and Malaysia by the month of May.[24] Initially, by June 10, nine countries: New Zealand, Tanzania, Vatican, Fiji, Montenegro, Seychelles, St Kitts and Nevis, Timor Leste, and Papua New Guinea have been declared free from COVID-19, in absence of active cases and following the recovery of their last case. Various countries entered the decreasing phase primarily; however, unlocking, relaxation of preventive measures, and changing human behaviors lead to a drastic increase in the number of COVID-19 cases resulting in a second wave of transmission. This resulted in reimposing lockdown measures in countries such as Nepal, Italy, France, Netherland, and Germany.[25] Furthermore, the discovery of new strains has also significantly contributed to increasing the number of cases.

Incubation Period

The incubation period of COVID-19 was defined as 6.4 days (95% CI: 5.6–7.7) ranging from 2.1 to 11.1 days.[26] The incubation

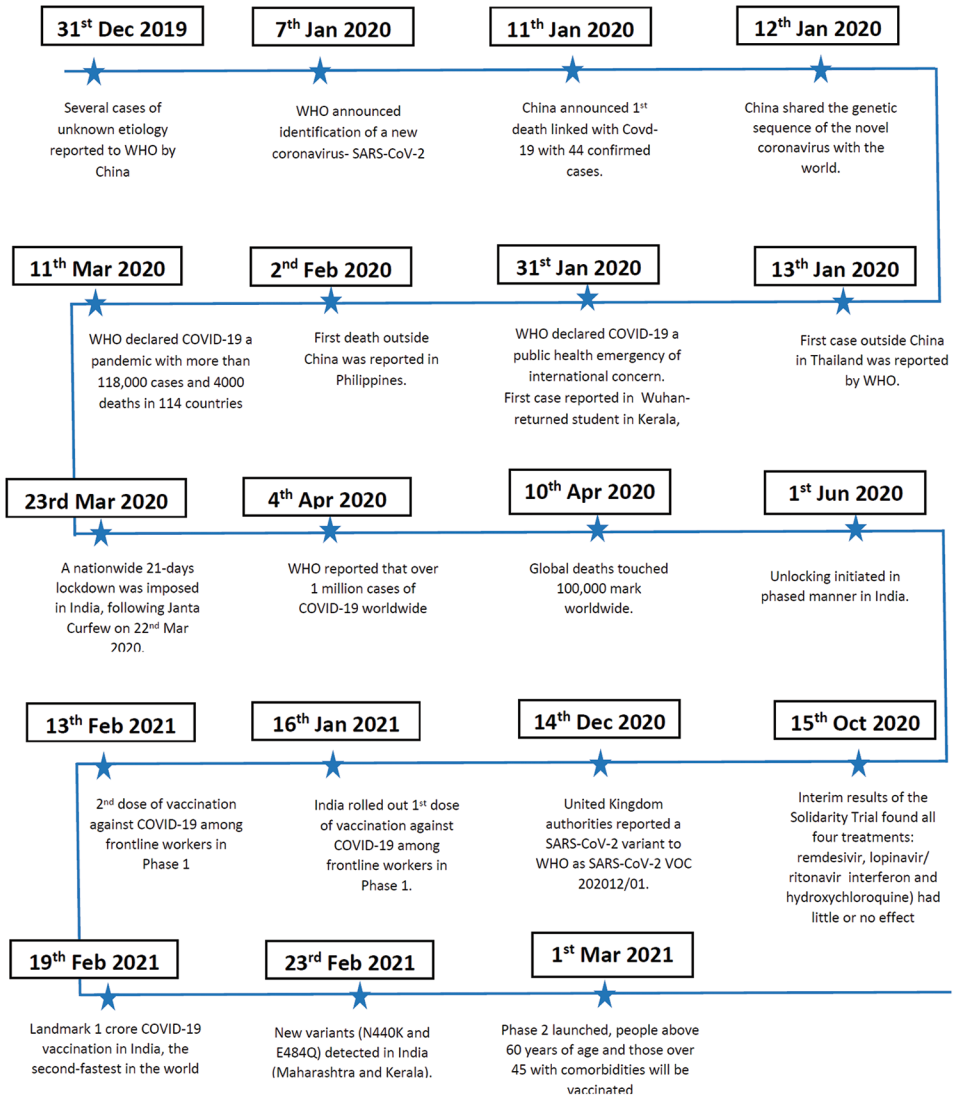

Figure 1: Chronology of the COVID-19 pandemic in the context of India

period averages around 5–6 days, but it ranges between 2 and 14 days.[27,28] The mean incubation period in India is 5 days (ranges from 1 to 14 days).[29]

Few studies have shown longer incubation periods of 19 and 24 days, extended up to 27 days.[30-32] However, the WHO stated that a very long incubation period can be viewed as second exposure. Studies indicate that the incubation period varies greatly from person to person.[33] As compared with other members of the family, the incubation period of COVID-19 was similar to MERS but slightly longer than SARS.[34]

Route of Transmission

The major transmission routes of COVID-19 are through contact transmission and respiratory droplets generated during coughing and sneezing. These respiratory droplets infected with the virus can spread from 1 to 2 meters and can even deposit on surfaces as fomites. Infection is acquired either by inhalation of these virus-infected–droplets or by touching contaminated surfaces and then touching the nose, mouth, and eyes.[35]

Moreover, the viability and stability of the virus also serve as the medium of transmission. The stability of the COVID-19 virus varies from 2 hours to 9 days at 30°C depending upon the surface of contact. The virus can be spotted in aerosols up to 3 h postaerosolization, up to 4 h on copper, up to 24 h on cardboard. The virus exhibits relatively longer viability on surfaces such as plastic and stainless steel as it can survive up to 2-to-3 days.[36,37]

Nevertheless, evidence related to another possible transmission such as airborne transmission[36] and oral-fecal transmission were suspected initially.[38,39] However, later limited airborne transmission is possible as SARS-CoV-2 is viable for up to 3 h.[36] Studies indicated the nonexistence of transmission of COVID-19 via vertical transmission during pregnancy as well as during breastfeeding.[40,41]

Transmissibility and R_0

The basic reproduction number (R_0) of the COVID-19 virus is an indication of the transmissibility of the virus, representing the average number of new infections generated by an infectious person in an unexposed population. The initial reports from China revealed mean R_0 for COVID-19 ranged from 1.4 to 6.49. A study with 14 such studies demonstrated mean R_0 for COVID-19 was 3.28.[42] However, the WHO estimated a considerably lower R_0 as 1.95. Data on real-time monitoring of the transmissibility in Europe suggested real-time R_0 for Italy is 3.1, Germany is 4.43, France is 6.56, and Spain is 3.95.[43] However, different R_0 have been reported in the same geographical region by using different methods and assumptions.

Spectrum of Infection and Clinical Features

COVID-19 is considered a self-limiting infection. Most of the cases with mild symptoms recover within 14 days. The outcomes of the SARS-CoV-2 can be divided into five categories based on the severity of the disease: i) asymptomatically infected persons, ii) mild to medium cases, iii) severe cases, iv) critical case, and v) death.[44]

It is important to note asymptomatic infection or absence of clinical sign of symptoms with positive SARS-CoV-2 results is not latent but a potential source of human-to-human transmission and also contribute informing family clusters.[45,46] Around 1.2% of the total infected cases were reported to be asymptomatic in Chinese studies.[47] However, studies from Diamond Princess and Japan reported an asymptomatic infection rate as high as 18%.[48,49]

Mild and moderate symptoms such as fever, fatigue, myalgia, dry cough, sore throat, runny nose, sneezing, and signs of mild pneumonia are likely to be present in 80.9% of the total coronavirus infected cases and generally do not require hospitalization. Respiratory symptoms such as cough and dyspnea (or tachypnea in children) are likely to be present without signs of severe pneumonia in moderate cases.[45]

Severe cases can be characterized by the presence of severe pneumonia, severe acute respiratory distress syndrome, sepsis, and septic shock. It is present in 13.8% of the cases. Critical cases are found to be 4.7% which suffer respiratory failure, septic shock including multiple organ dysfunction. These cases require critical care and ventilators for management. Death is present in 2.3% of the cases.[47,50]

A recent meta-analysis stated fever (77.6%) and cough (64.8%) as the most common symptoms. In addition to this symptoms such as headache (15.2%), diarrhea (11.8%), olfactory disorders (10.1%), and gustatory disorders (10.0%) were also reported.[51]

Susceptible Population

People of every age group and both genders are susceptible to this transmissible virus. Initially, women were considered to be less susceptible as compared to men, primarily because of different innate immunity, steroid hormones, and factors related to sex chromosomes;[52,53] however, at present no such difference is observed.

The virus infects people from all age groups, but more cases were reported from the middle-aged group mainly, probably due to their higher mobility and social connection.[48] The studies have indicated the severity of the disease depends upon the age of the infected person. The proportion of SARS-CoV-2 patients to be hospitalized increases with age up to a maximum of 18·4%, especially in patients above 80 years.[54] The comparative analysis among ICU cases with non-ICU cases from Wuhan suggested the median age of hospitalization was significantly higher in the ICU group (66 years, IQR: 57–78 years vs 51 years, IQR: 37–62 years).[55] In addition to age, the presence of comorbidities also determines the course of infection. The Wuhan study stated ICU patients were more likely to have comorbidities such as diabetes (22.2% vs 5.9%), hypertension (58.3% vs 21.6%), and cardiovascular disease (CVD) (25.0% vs 10.8%) when compared to non-ICU patients.[55]

Case Fatality Rate

The overall case fatality rate is 2.2% according to the WHO Weekly Epidemiological Update as of February 21, 2021.[20] Nevertheless, the mortality rate varies across WHO regions as well as between countries. The exceptionally high mortality was reported from the WHO-European region (4.4%) in the initial few months, majorly contributed by Spain, Italy, France, and the United Kingdom.

Moreover, it was hypothesized that the countries with older population have higher case fatality rates and similarly, the pre-existing comorbid condition can increase fatality rate by 10.5% for CVD, 6.3% for chronic respiratory disease, 6.0% for hypertension, 7.3% for diabetes, and 5.6% for cancer.[47] The initial assessments suggest that mutant strains having similar clinical presentation or severity and are not associated with increased deaths.[21]

Diagnosis

Diagnosis of infection with self-limited nature and mild-moderate symptoms is avoidable, but in the case of the novel coronavirus, it is crucial to identify the etiological agent which is highly contagious. Earlier, the diagnosis of the novel coronavirus was based on the combination of epidemiological risks, clinical features, and laboratory tests. People who had a history of travel from China or close contact with a confirmed or suspected case of COVID-19, and present with clinical symptoms within the incubation period were suspected and administered laboratory testing.

Diagnostic strategies such as nucleic acid amplification of viral antigen through reverse-transcription polymerase

chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP), and microarray-based assays were used as confirmatory tests.[56,57] The nucleic acid can be detected in nasopharyngeal swabs, sputum, lower respiratory tract secretions, blood, and stool.[58,59] Later, increasing cases with local transmission, the WHO guidelines were revised several times.

In addition to the nucleic acid test, other diagnostic tools include CRISPR. It is a genome editing technology developed by the Institute of Genomics and Integrative Biology (IGIB) which has similar accuracy as traditional RT-PCR tests but has a quicker turnaround time and requires less expensive equipment and, hence, better ease of use.[60] At present, many commercial tools such as paper strips which work on antigen-antibody principles have been approved by various organizations. These paper strips work well when the virus is actively replicating i.e. during acute infection.[61]

Recently, a newer test Paper-based RAY (Rapid variant AssaY), which is much quicker than genome sequencing has been identified. It can also identify three variants with the common mutation N501Y from the UK, South Africa, and Brazil.[62]

Treatment

At present, there is no specific treatment available for patients with COVID-19 infection rather it is essentially supportive and symptomatic. However, already existing antivirals lopinavir,[63] ribavirin,[64] and remdesivir[65] and antimalarial drugs-Chloroquine and Hydroxychloroquine[66] approved for other recommendations were considered potential candidates in the treatment of COVID-19. However, the interim results of the Solidarity Trial found all four treatments (remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon) had little or no effect on overall mortality, instigation of ventilation, and duration of hospital stay in hospitalized patients.[67] Over time, the treatment shifted towards use of dexamethasone and ivermectin. Nowadays, a mixed approach is being used to treat the patients of COVID-19.[68] Convalescent plasma transfusion is another technique that has shown significant improvement in the survival of critical patients.[69] Though plasma therapy has shown positive results, its complexity of extracting the plasma restricts its wider clinical application.[70]

Prevention

As there are no approved treatments for this infection, hence, prevention is a crucial and necessary step. However, asymptomatic nature, non-specific and overlapping feature of the disease, its contagious nature during the incubation period, and prolonged duration of the illness are some peculiar characteristics of the virus that makes prevention difficult. These properties re-emphasize the importance of prevention.[71,72]

At the personal level, isolation of confirmed or suspected cases from apparently healthy individuals. Use of any type of mask, following respiratory etiquettes, and hand hygiene are highly recommended for all, irrespective of the case or noncase of COVID-19.[73] Cleaning the frequently used surfaces with surface disinfections such as 62%–71% ethanol, 0.5% hydrogen peroxide, or 0.1% sodium hypochlorite can efficiently inactivate the virus.[37] Apart from this, social distancing should be maintained.[71,72] At the community level, avoidance of crowded areas and postponement of nonessential travel to places should be avoided.

Several countries have taken legislative steps to curb the disease by restricting the flights from affected areas, screening people at airport and seaports, closing down nonessential services, and announcing a complete lockdown in the country. A nationwide 21-days lockdown was implemented in India on March 23, 2020 and with the incessantly increase in cases, an extended phase two of lockdown was imposed till May 3, 2020, which subsequently prolonged till May 17, 2020 and later continued till May 31, 2020. To make the lockdown and social distancing effective, India also levied the quarantine law under the Epidemic Disease Act, 1897.[74-76] The unlocking was done in a phased manner with having continued lockdown in a modified manner in certain parts of the country such as weekend restrictions, movement limitation after a particular time, or closure of some services like continuing closing of educational institutes. However, a drastic decrease has been seen in the number of cases as of February 21, 2020, which has eventually resulted in the opening of the above-mentioned services. With a dearth of specific treatment, movement restriction and social distancing still hold immense importance in the containment of the spread of novel coronavirus.

In addition to the above-mentioned preventive measures, the development of a safe and effective vaccine against COVID-19 has been a breakthrough event in less than a year, a process known to take a decade or more. The normal time frame for vaccine development was greatly squeezed because of the raging pandemic, and there has been a total paradigm shift from the traditional approach in clinical trials, approvals for public deployment, and subsequent production.

To date more than 200 vaccine candidates are in the development phase, out of which more than 60 are in the clinical development phase, and 12 vaccines have been approved and rolled out in several countries [Table 2].[77] As per the update on February 26, 2021, more than 225 million doses of COVID-19 vaccine have been administered across 100 countries with a rate of approximately 6 million doses per day.[78] There is limited data available with respect to the safety of the vaccine; however, no conclusive evidence on adverse effects following immunization has been generated to date.[79] Furthermore, the status of effectiveness of these vaccines is unclear with respect to newer strains.[11]

Conclusion

This novel virus pandemic has been a public health challenge to the entire world over 1 year of its origin. The trends have

Table 2: Description of approved COVID-19 Vaccine[80]

Name	Mechanism	Doses	Efficacy	Storage	Status
Pfizer-BioNTech: Comirnaty (also known as tozinameran or BNT162b2)[81]	mRNA	2 doses, 3 weeks apart	95%	Freezer storage only at –13°F to 5°F (–25°C to –15°C)	Approved in Bahrain, Brazil, New Zealand, Saudi Arabia, Switzerland. Emergency use in other countries (Argentina, Australia, Canada, Chile, Colombia, Costa Rica, Ecuador, European Union, Hong Kong, Iceland, Iraq, Israel, Japan, Jordan, Kuwait, Lebanon, Malaysia, Mexico, Moldova NEW, Mongolia, Norway, Oman, Panama, Peru, Philippines, Qatar, Serbia, Singapore, Tunisia, United Arab Emirates, United Kingdom, United States)
Moderna: mRNA-1273[82]	mRNA	2 doses, 4 weeks apart	94.5%	30 days with refrigeration, 6 months at –4°F (–20°C)	Approved in Switzerland. Emergency use in Canada, European Union, Iceland, Israel, Mongolia, Norway, Qatar, Singapore, United Kingdom, United States.
Gamaleya: Sputnik V (also known as Gam-COVID-Vac)[83]	A combination of two adenoviruses Ad5 and Ad26.	2 doses, 3 weeks apart	92%	Freezer storage. Developing an alternative formulation that can be refrigerated.	Early use in Russia. Emergency use in other countries (Algeria, Argentina, Armenia, Bahrain, Belarus, Bolivia, Bosnian Serb Republic, Egypt, Honduras, Gabon, Ghana, Guatemala, Guinea, Guyana, Hungary, Iran, Kazakhstan, Kyrgyzstan, Lebanon, Mexico, Moldova NEW, Mongolia, Montenegro, Myanmar, Nicaragua, Pakistan, Palestinian Authority, Paraguay, San Marino, St. Vincent and the Grenadines, Serbia, Syria NEW, Tunisia, Turkmenistan, United Arab Emirates, Uzbekistan, Venezuela.)
Oxford-AstraZeneca: AZD1222 (Covishield in India)[84]	ChAdOx1	2 doses, 12 weeks apart	82.4% for doses separated by 12 weeks.	Stable in the refrigerator for at least 6 months	Emergency use in U.K., E.U., other countries.
CanSino: Convidecia (also known as Ad5-nCoV)[85]	Adenovirus Ad5	1 dose	65.3%	Refrigerated	Approved in China. Emergency use in Pakistan, Mexico.
Johnson & Johnson: Ad26.COV2.S[86]	Ad26	1 dose	72% in the United States, 64% in South Africa, 61% in Latin America	Up to two years frozen at –4° F (–20°C), and up to three months refrigerated at 36-46°F (2-8°C).	Emergency use in Bahrain, United States.
Vector Institute: EpiVacCorona[87]	Protein	2 doses, 3 weeks apart	Unknown	Stable in the refrigerator for up to two years	Early use in Russia
Novavax: NVX-CoV2373[88]	Protein	2 doses, 3 weeks apart	89.3% against most variants including South African strain	Stable in refrigerator	Agreement with Serum Institute of India to 2 billion doses a year. Agreement to supply to other countries: United States, United Kingdom, Canada, Australia, and South Korea.
Sinopharm: BBIBP-CorV[89]	Inactivated form of the coronavirus	2 doses, 3 weeks apart	72.5%	-	Approved for use in Bahrain, China, United Arab Emirates. Emergency use in Argentina, Cambodia, Egypt, Guyana, Hungary, Iraq, Jordan, Nepal, Pakistan, Peru. Limited use in Serbia, Seychelles.
Sinovac: CoronaVac (formerly PiCoVacc)[90]	Inactivated form of the coronavirus	2 doses, 2 weeks apart	50.38%	Refrigerated	Approved for use in: China. Emergency use in Azerbaijan, Brazil, Chile, Colombia, Ecuador NEW, Hong Kong, Indonesia, Laos, Mexico, Philippines, Thailand, Turkey, Uruguay.
Bharat Biotech: Covaxin (also known as BBV152 A, B, C)[91,92]	Inactivated form of the coronavirus	2 doses, 4 weeks apart	78%	At least a week at room temperature	Emergency use in India
CoviVac[93]	live attenuated vaccine	2 doses, 2 weeks apart	Unknown	2 to 8 degrees Celsius (35.6 to 46.4 Fahrenheit)	Approved for use in Russia

suggested the unlocking in absence of preventive measures can drastically increase the COVID-19 cases. Thus, there is a need to reemphasizing hand hygiene and respiratory etiquettes and continuing the practice of preventive measures even after the

advent of the vaccine is important in containing the new strains of the coronavirus. The coming days will suggest how the new strains of the virus will impact our lives; however, the primary care physicians need to be aware of the updated knowledge about the ever-changing pandemic for better prevention, diagnosis, and management of the disease.

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Conflicts of interest

There are no conflicts of interest.

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