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Review Article

Covid-19 Vaccines: Overview, Comparative Analysis and Dynamics

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Abstract

As the mankind experienced the serious situation of COVID-19 that hit the whole world, scientists thought that vaccines are the nearest solution to eliminate this pandemic and minimizes its severity. Therefore, they started the race to develop an effective and safe vaccine, each group in their laboratory working day and night to save the whole world. Vaccines proved their protection roles against many past infections, and here against COVID-19, extensive studied and new technologies were accurately tested. The results came up with several vaccines ready to use and others still under clinical trials, however, fear form vaccines and questions on the best and more safe vaccine are everywhere among people. To be clear, gaining trust in the market became not easy for vaccine production companies, especially in this strong competition after the availability of several vaccine at the same time. By time passage, vaccine distribution and intake will be easier, particularly when people could trust these vaccines and be sure of their safety and efficacy. Many countries could produce vaccines, among of them; China, United States, United Kingdom and Russia and their vaccines spread internationally nowadays. To convince people which vaccine is the best and most safe, it is not easy and this matter will come after long-term of use and experience. However, there is no guarantee that these vaccines will provide 100% protection against COVID-19 and this will be proved also after long-term of use. This review presents comparative analysis of the most common types of COVID-19 vaccines which are already in use in the world market and the dynamics of vaccination over all the world.

Keywords: COVID-19; Vaccines; Types; Efficacy; Safety; Analysis; Dynamics

Introduction

In China, COVID-19 pandemic started in December 2019 when it was diagnosed as pneumonia [1,2]. The viral genome was identified rapidly and published as a new species of SARS-COV-2 virus so it was called COVID-19 referring to the virus species and the year of its appearance [1,3,4]. By March, 2020, COVID-19 spreading occurred over the whole world and it became an international pandemic that threated the whole world not only health, but also economy [3,4]. The sad story is that the discovered therapies for COVID-19 were not as wanted as efficient and still the death rate increasing day by day. As well as hospitals and health cares exposed to high pressure of COVID-19 patients and there were no vacant places to receive further infected patients [5-7]. Therefore, there is an urgent demand on vaccines and it became urgent matter since that time to control that dangerous pandemic [1,6,8]. As known, vaccines can develop immunity against pathogens as they induce

the body immune system to produce antibodies [9]. From here, scientists started their extensive work to develop effective and safe vaccines against COVID-19, thinking that this pandemic cannot be stopped by social distancing, wearing masks, personal hygiene and disinfection practices [10]. Therefore, they worked day and night to achieve phase I studies rapidly and further performed the studies of phase II and III in a parallel way in order to save time and the vaccine be ready to be delivered to the world market [11,12]. However, many vaccines are currently available from different sources and country origin, people still afraid from receiving COVID-19 vaccines, questioning about their safety and adverse effects. Clearly, the evidence on the vaccine efficacy and safety will be proved on a prolonged period after vaccination, however their success in the clinical trial [13]. Similarly, the clear answers for all the questions regarding COVID-19 will not be stated at a short time, it needs a prolonged period for study [12]. This review aims to discuss the main information about COVD-19 Vaccines, their development and immunological strategies and comparatively analyzing the different types currently purchased worldwide. Believing that vaccines is the effective solution to eliminate COVID-19 pandemic over all the world, so it's needed to increase people awareness about its importance, especially at the current period.

Overview on COVID-19 vaccines

Definition

Vaccine is a biological substance used to trigger an immune response towards pathogens to protect human body from future infections [14]. To explain, vaccines have antigen through which the immune response can identify it and form antibodies against this pathogen. That antigen may be part of the pathogen nucleic acid, protein or the dead pathogen capsid. Protection against pathogens including viruses can be assessed through clinical trials which is highly linked with the immune response developed after vaccination [15]. Development of new vaccines depends on finding an immune response against pathogens antigens and this will enrich protection ways towards dangerous pandemics.

Efficacy

As known, vaccines induce the immune system to produce antibodies against the virus, however, it can initiate other type of inflammation in human body [16]. Similarly, pain and inflammation may be demonstrated at the place where the vaccine injected. Moreover, symptoms such as fatigue, headache, fever which look like COVID-19 infection may be produced [9]. In normal situations, these moderate symptoms evolved from the body immunity are accepted. However, if the vaccine induced the immune system in animals or even human to produce antibodies, this does not guarantee its efficacy to protect human body against the virus [17]. Basically, before going to clinical studies on human bodies, researchers have to prove first the vaccine efficacy in vivo trials inside laboratories and reveal that the vaccine have protected animals from being infected by the virus after vaccination [18]. The vaccine efficacy can be evaluated through three phases; phase I which concentrates on the study of producing antibodies by upon vaccination, then wider phase II and phase III focus on studying the effect of the vaccine to protect against the virus [13]. To sum up, evaluating the vaccine efficacy and getting obvious evidence and guarantee that vaccine can protect against infection and diseases can be revealed after the third phase of clinical studies.

Safety

Vaccines safety is evaluated during the pre-clinical studies while studying on mice and rats [17]. If the vaccine proved its safety on the animals during that in vivo study and didn't exhibit any disease symptoms, so then clinical studies on human can be initiated. Tests on vaccines can be divided into two phases; In the first phase, small number of people ranging from 10 to 100 persons take the vaccine. The target of this phase is to test the safety of vaccine and be sure it not causing any side effects. In the second phase, larger number of people ranging from 100 to 1000 also are vaccinated, further studies on maintaining the safety of vaccine especially on children, pregnant women and elder people who may suffer from chronic diseases [8,9,19]. If the vaccine showed severe symptoms of inflammation or it demonstrated malfunction of the immune system that could not induce suitable antibodies, so that tested vaccine stops at this stage and cannot be purchased worldwide [9]. A common question spread nowadays whether the vaccine affects the fertility or not, the answer for this question would be from the clinical trials themselves. Extensive studies on developmental and reproductive toxicity revealed that the vaccine has no obstacles regarding pregnancy and does not prevent females from getting pregnant [20,21]. Furthermore, miscarriage frequency was studied and results showed no relation between vaccine and miscarriage in early pregnancy [21]. However, pregnant women in the United

Kingdom, European Union and United States, especially who work in health-cares, hospital and in close contact with COVID-19 patients, have been advised to take the vaccine as its benefits outweigh the possible risks[22]. Many pregnant women were subjected to vaccination these days and by monitoring their babies' health during the coming months, it will provide us with the full image and clear evidence about the safety of vaccines.

Priority

As effective COVID-19 vaccines are currently available and widely spread, it is important to arrange the priority for vaccine receivers to try to put limitations to this pandemic as fast as possible [11]. Joint Committee on Vaccination and Immunization suggested that elder people above 65 years old, and people working in healthcare have the priority to be vaccinated first [11]. However, there are further suggestions for the poor people with low level of education to be prioritized for vaccination against COVID-19 as they suffer from a lot of diseases and have high frequency of hospitalization. Moreover, people living in crowded areas, or homeless, and smokers should be sorted among priority groups to take the vaccines as they can be easily infected and this may lead to uncontrolled pandemic spread in the whole society [11,12]. Furthermore, high risk people those who are suffering from chronic diseases such as diabetes, cardiovascular disease, respiratory allergies, obesity and hypertension have to be prioritized for vaccination against COVID-19 as they can easily infected and their immune systems are not strong enough to resist that viral infection [5,13].

Development of vaccines

Vaccines are used for induction of immune system through stimulating B cells which are mainly responsible for antibodies production as shown in figure 1. Variety of antibodies formed in the body after vaccination is important evidence for vaccine efficacy and protection against many diseases [9,14]. The injection of vaccine antigens into body induces an immune response in which B cell produces specific amounts of antibodies. While the T cell-dependent B cell helps in development of antibody response in which the affinity of antibodies produced increases and induction of different antibodies occurs [3,19,22]. The role of T cells in the immune strategy is not clearly reported yet, however it is known that they may assist maturation of B cell and the production of antibodies in lymph nodes [19].

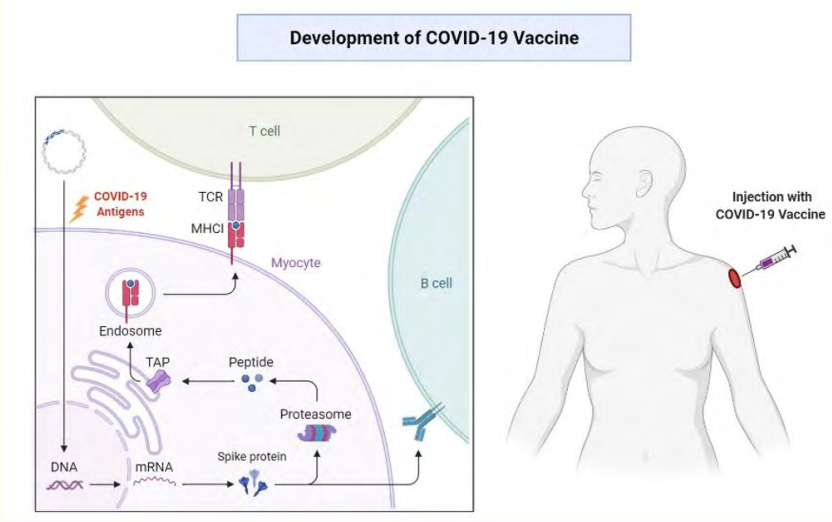

Figure 1: Diagram of COVID-19 Vaccine Development.

Types of COVID-19 vaccines

There are several types of COVID-19 vaccines based on different technology and each type has its own pathway and efficacy, see figure 2.

Inactivated virus vaccines

Developing immune response using inactivated virus as an antigen is still not enough for establishing strong immunogenicity

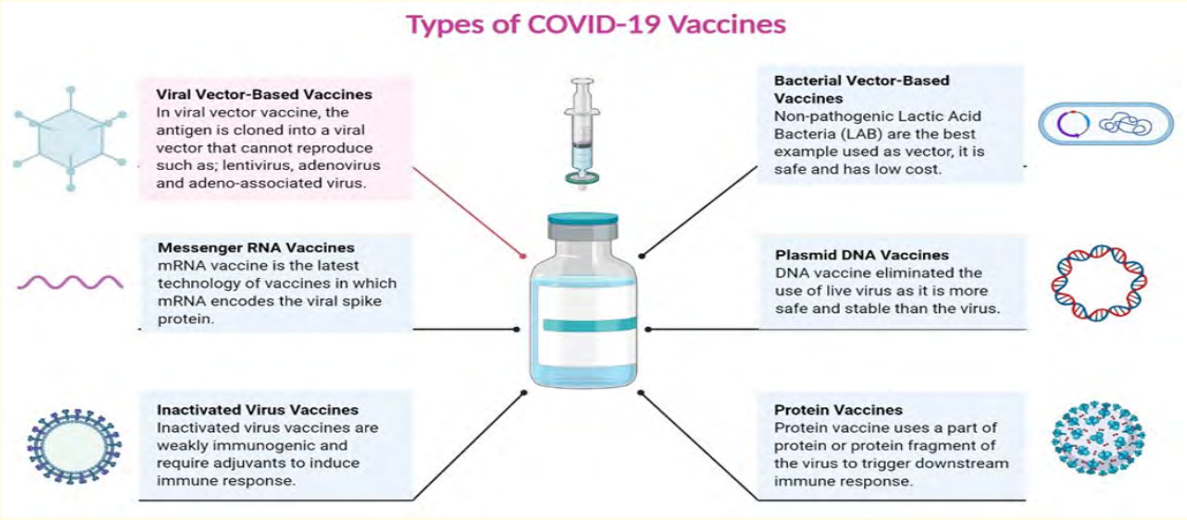

Figure 2: Illustration of Different Types of COVID-19 Vaccines.

[7]. These inactivated cells still require an adjuvant to be immunogenic and provide border against disease infection [23,24]. Here, Sinovac vaccine for COVID-19 depends on this method using aluminum hydroxide Al(OH)3 as an adjuvant [25].

Recombinant protein vaccines

Recombinant protein vaccine utilizes protein fragment of a part from protein for immunogenicity. Once injected inside the body, the antigen protein goes to the endosome for digestion and the small produced fragments bind to the major histocompatibility complex (MHC) II molecules which induces immune response and antibodies production [22,23]. There are some drawbacks of protein vaccines which are that the vaccine sometimes initiates specific immune responses and then produces partial immunogenicity [16]. To increase the protection against disease infection, adjuvants are needed for this type of vaccines [22]. A good example of protein vaccines for COVID-19 is Novavax vaccine which uses this technology [26].

Viral vector-based vaccines

In this type of vaccines, the antigen is being cloned inside a vector and this vector is virus. Lentiviruses, adenoviruses and adeno-associated viruses are the typical examples of viral vectors [3,9,10]. Here, the viral vector can induce infectious status inside the body and then immune response development which is considered to be stronger than protein vaccines [23]. Sputnik V vaccine is the typical example for COVID-19 vaccines from this type as its vector is the adeno-associated virus [27].

Bacterial vector-based vaccines

This type is from vector-based vaccines and the commonly used bacterial vector is the non-pathogenic lactic acid bacteria (LAB) which is the most effective vaccine vector [28]. What makes LAB unique vector for many vaccines is that they are safe as food as well as the cost of manufacturing is low [23,29]. The COVID-19 vaccine candidate Symvivo (bacTRL-Spike) which is currently in the clinical trials, depends on LAB as the vector.

Plasmid DNA vaccines

The plasmid DNA vaccines replaced the use of live viruses for vaccination hence it has higher safety as well as the DNA molecule is more stable than the virus and able to storage for long periods by freezing [30]. The COVID-19 vaccine uses this technology is INOVIO which is currently under clinical trials which requires electroporation device to transfer the vaccine into body [31].

Messenger RNA vaccines

The mRNA vaccine is the latest technology of vaccines in which the antigen is expressed inside the target host cell into specific proteins according the codes on the mRNA [13,17].

There is no high risk from using this technology as mRNA used is totally synthetic even in the case of dangerous pathogens such as COVID-19. Moderna vaccine against COVID-19 is mRNA vaccine which encodes the S protein as the virus antigen [32].

Comparative analysis of Covid-19 vaccines

As shown in table 1, the University of Oxford/AstraZeneca vaccine AZD1222 was made of a single recombinant, which are chimpanzee adenovirus vector a replication deficient encode with the virus S glycoprotein. In the vaccine, the S immunogen of the virus is designed to be translated for trimeric prefusion, however the coding sequence had not been changed for the stability of S-protein expression in the prefusion conformation. The double stranded DNA single copy of the genome include the adenoviruses non-encapsulate with icosahedral particles (virions). The expressed cassette for the SARS-Cov-2 spike protein which is bounded with plasminogen activator sequence which used to modify a bovine growth hormone polyadenylation and human cytomegalovirus promoter sequence. The human embryonic kidney 293 cells are used to produce the vaccine which genetically modified with composition of 0.5 ml ChAdOx1-S viral particles with the L-histidine hydrochloride monohydrate, excipients L-histidine, magnesium chloride hexahydrate, disodium edetate dihydrate ethanol, polysorbate 80, sodium chloride, sucrose, and water for injection. The Shelf-life is proposed to 6 months while the stability in use up to 48 hours in 2 - 8ºC in refrigerators for the first needle punctures. However, the product may use up to 6 hours in one time in the temperature of 30 ºC. The Efficacy report reflects from the data collection, till to 7th December, 2020, of the two optimal doses with any interval between both doses. The efficacies against COVID-19 with the Vaccine efficacy were 51.91%, 95%, and the confidence interval 59.98% to 85.54%. The safety profile was found to be the same in both the vaccine and control groups. The Adverse reactions majorities of vaccines ranged from mild to moderate and they generally were resolved within few days after the vaccination. The common were headache, myalgia, nausea, arthralgia, injection site pain, injection site tenderness, injection site pruritus, injection site warmth, fatigue, feverishness, malaise, and chills [33]. Various studied were focused to identify the thromboembolic diseases. Where no clear causal effect confirmed [34]. Pfizer-BioNTech (BNT162b2 vaccine) and Moderna vaccine (mRNA-1273vaccine) approved by the US Food and Drug administration, are the mRNA vaccines the BNT162b2 Pfizer-BioNtech vaccine which were made of the SARS-CoV-2 spike glycoprotein S antigen that is encoded with the mRNA while lipid nanoparticles are used in the composition which showed 90% effectiveness in the older volunteers and the 16 years age people within 2 to 21 days. These types of vaccines show mild adverse reactions same to AstraZeneca vaccine. On the other hand, the Moderna/NIAID vaccine mRNA-1273 the mRNA was encoded with the S-2P antigen which consists of SARS-CoV-2 glycoprotein and attached to the anchor of trans-membrane, while the intact of S1-S2 sites for cleavage which enclosed with the 4 subunits of lipid nanoparticles. However both vaccines were observed by the neutralizing of antibodies titers and further the T cells response, the safety and efficacy level were so far satisfactory as the BNT162b2 Pfizer-BioNtech vaccine demonstrated, and the adverse reactions of the moderna vaccines are mild to moderate as they sharing the same symptoms with AstraZeneca vaccine [35,36]. CanSino Biological Inc./Beijing Institute of Biotechnology vaccine which Replication-defective 5 Ad human type which encode full-length of spike protein which were cloned on bases of wuhan-hu-1 gene bank with the tissue plasminogen activator a signal peptide gene which deleted the Ad5 vector into E1 and E3, and the covid-19 vaccine that was made by the Ad5 vector showed the same adverse reaction like the other vaccines which were mild to moderate [37]. The vaccine efficacy is 90.07% and with the shelf life of 12 months as well as it can be stored in 2 - 8ºC [36,38]. Sinovac's Corona Vaccine is an inactivated vaccine against COVID-19 while the SARS-CoV-2 (CN02 strain) with adjuvant Aluminum hydroxide and the excipients are Disodium hydrogen phosphate dodecahydrate, sodium dihydrogen phosphate monohydrate, and sodium chloride [39]. The efficacy level of the vaccine was 83.5% and 65.3% and these vaccines are safe with mild to moderate adverse reaction sharing same with above mentioned vaccine. The shelf life of the vaccine was 20 months and it can be stored in 2 - 8 ºC [40]. Novavax NVX-CoV2373 is protein subunit vaccine and the efficacy of the vaccine is 95.06%. In these types of vaccines, the immunogenic virus-like nanoparticles based on recombinant expression. The S-protein made by Novavax' recombinant nanoparticle technology while the purified protein is encoded by the SARS-CoV-2 spike (S) protein genetic code as it is translated inside the host cells. Furthermore, this sequence is safe and cannot cause viral infection, it is also stable from 2 to 8°C as it can be easily transferred by shipping in a liquid solution [41]. The adverse reaction of Novavax starting from mild to moderate, and sharing the same with above mentioned vaccines. Herein, Sputnik V Covid19 vaccine requires

special precautions in handling and transfer to conserve its effectiveness. These vaccines are divided in two Components; the first component is the 1st Dose in which the volume of each dose is 0.5 ml and it contains the Serotype 26 Recombinant Adenovirus particles as well as the protein S gene of SARS-COV-2 virus. The second component is the 2nd Dose which also of 0.5 ml and contains Serotype 5 Recombinant Adenovirus particles with the virus protein S gene [27]. Moreover, the Sputnik vaccine can be stored by freezing where the shelf life of the two vaccine components (I and II) is 6 months and can be kept in dark places at -18°C. However, in the solid or lyophilized powder formula of the vaccine, it can be stored at 2-8°C [42]. The adverse reactions are mild to moderate as shared by other vaccines and these safe vaccine can be strongly recommended for use against covid-19 because of their high efficacy of 91.6% [43]. However, the development of the Sputnik V vaccine has been criticized for unseemly haste, an absence of fair and transparency are still there [44].

Vaccine	Types of vaccine	Composition	Storage	Shelf-life	Efficacy	Safety	Adverse reactions	Ref.
University of Oxford/ AstraZeneca	Non-replicating viral vector vaccines	ChAdOx1-S (recombinan)	2-8ºC	6 months	95%,	No difference in vaccinated and control group	Mild to moderate	[33]
BioNTech/Pfizer	RNA-based vaccines	SARS-CoV-2 spike antigen glycoprotein encoded with lipid nanoparticles	-70ºC	6 months	95%	Safe	Mild to moderate	[35,36]
CanSino Biological Inc./Beijing Institute of Biotechnology	Non-replicating viral vector vaccines	Replication-defective human type 5 Ad encoding a full-length spike protein	2-8ºC	12 months	90.07%	Safe	Mild to moderate	[37,38,45]
Moderna/NIAID	RNA-based vaccines	SARS-CoV-2 glycoprotein, a transmembrane anchor, intact S1–S2 cleavage site with 4 subunit lipid nanoparticles	2-8ºC	6 months	95%	Safe	Mild to moderate	[35,36]
Sinovac's CoronaVac	Inactivated virus	Inactivated SARS-CoV-2 virus, and the adjuvant is aluminium hydroxide.	2-8ºC	12 months	83.5% and 65.3%	Safe	Mild to moderate	[39,46]
Novavax	Protein subunit	Immunogenic virus-like nanoparticles based on recombinant expression of the S-protein	2-8ºC	12 months	95.6%	Safe	Mild to moderate	[47,48]
Sputnik V vaccine	Viral vector-based vaccine	rAd5 and rAd26	-18°C	6 months	91.6%	Safe	Mild to moderate	[27,42,43]

Table 1: Types of Vaccines with Their Properties.

Dynamics of Covid-19 vaccination

As the covid-19 third wave is ongoing on, which severely affects many countries with high death ratio, high positive numbers of new cases have been reported. To overcome these situations, the above vaccine is too convenient to use against the covid-19 which may lead to control these serious situations, but some of them are trial base and some were approved by the WHO. The world getting vaccinations with huge number with passing of the time, here we focus on those regions which were facing higher number of cases and further prioritizing them for vaccine distribution.

First or single dose vaccination drive

In these situations, the vaccination distribution started from the date of 20th December, 2020 when North America received the vaccine with 0.09% and at that time, the world only stands with 0.01% which was only single dose. After that on 20th January, 2021 North America vaccination rate reached to 2.61%, Europe and European Union with 1.76, and 1.58%, respectively. On the other side, Asia received only 0.09%, South America with 0.08% and India with 0.06% while the total world with single dose was 0.43%. On 20th February, 2020 North America, Europe and Europe Union expressed with higher numbers of single dose vaccine as shown in table 2 and figure 3 by the ratio of their percentage. Till now, world 1.59 billion pollution get the first dose vaccine [49].

Time interval	North America	South America	Asia	Europe	Europe Union	India	Africa regions	World Wide
Dec-20-2020	0.09	0	0	0	0	0	0	0.01
Jan-20-2021	2.61	0.08	0.09	1.76	1.58	0.06	0	0.43
Fab-20-2021	7.64	2.15	0.56	5.07	3.97	0.72	0.19	1.55
Mar-20-2021	15.01	4.76	1.57	10.32	9.24	2.69	0.42	3.4
Apr-20-2021	26.58	10.25	3.69	18.16	19.57	0	0.85	6.68
May-20-2021	34.19	15.55	5.14	28.26	33.76	10.62	1.41	9.48

Table 2: Dynamics of First Dose Divided Through (%) in Vaccinated Regions.

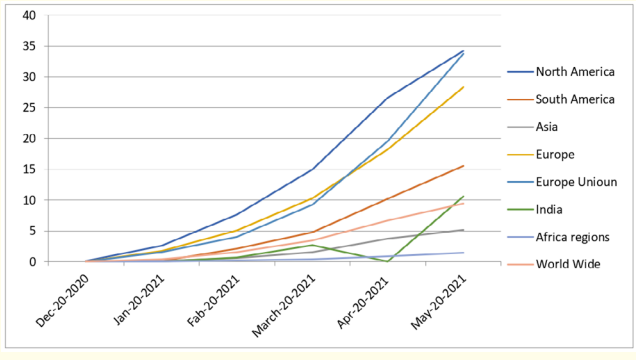

Figure 3: Monthly Divided Vaccination Drive According to First Dose.

Fully or second dose vaccination drive

The fully vaccinated populations in world, which take the first and second doses of vaccine in various regions with high percentage, the drive of vaccinations is just started from 10th January, 2021. Hence, Europe 0.05%, and Asia with 0.01%, and the total world with 0.01%. Till to 20th May, 2021 these drives were increased with higher number to reach in North America 23.98%, South America 7.74%, European Union 14.36%, Europe 13.35%, Asia 2.03% and 4.83% of the world population get fully vaccinated against Covid-19. The statistics were shown in the table 3 and figure 4 by percentage ratio [49].

Time interval	North America	South America	Asia	Europe	Europe Union	India	Africa regions	World Wide
Jan-10-2021	0	0	0.01	0.05	0	0	0	0.01
Fab-10-2021	1.83	0.07	0.06	0.91	1.39	0	0	0.27
Mar-10-2021	5.77	1	0.33	2.47	3.16	0.34	0.08	0.94
Apr-10-2021	12.49	3.06	0.78	5.64	6.07	0.92	0.34	2.18
May-20-2021	23.98	7.74	2.03	13.35	14.36	2.99	0.49	4.83

Table 3: Second Dose Dynamics Divided by (%) in Vaccinated Regions.

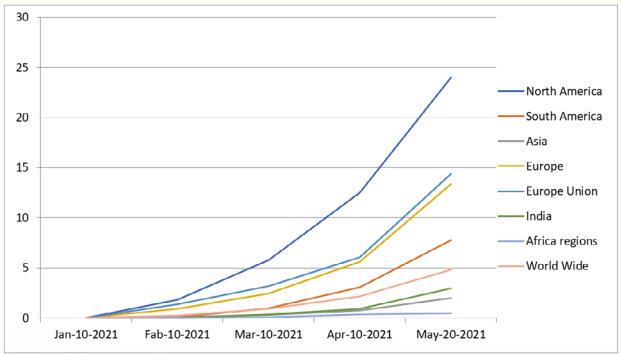

Figure 4: Monthly Divided Vaccination Drive According to Second Dose.

Conclusion and Future Perspectives

After demonstrating the possible data around COVID-19 vaccines safety, efficacy and dynamics, great effort has to be performed towards people awareness by the importance of vaccinations in these situations, especially in developing nations with less educated people. Further studies regarding vaccines safety on the babies inside their mother's uterus during pregnancy has also be investigated after the birth. The current data proves the safety, efficacy and availability of COVID-19 vaccines which are present currently in the world market. However, scientists are looking forward for the new updates, in particular around the vaccines efficacy and full protection of COVID-19 during the coming months.

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