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Review Article

Contemporary COVID-19 Vaccines: The Science and Marketing

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ABSTRACT

Objectives: The viral infection pandemic caused by SARS-CoV-2 has resulted in a flurry of research in the field of immunologicals. Scientific terms like antigen, antibody and immunoglobulins have entered the lexicon of citizens. Ending the pandemic through measures such as double masking, physical distancing and lockdowns have been imposed to break the chain of COVID-19 infection transmission, however, once again it is the vaccines that have proved worthy to improve immunity and halt the march of COVID-19. **Methods:** The vaccination process at optimal levels is aimed at desired antibodies. The impetus provided to vaccine technology commercialization is immense. mRNA vaccines have stolen the march, however, the traditional whole virion inactivated vaccine has made a comeback, new plasmid DNA technology vaccine has made a breakthrough, nasal vaccines are being designed, and recombinant protein subunit vaccine has given new affordability; oral vaccines are in the pipeline. **Conclusion:** Scientists and technologists have proved their worth through innovative vaccine work. This article reviews the science and marketing of COVID-19 vaccines.

Key words: COVID-19, Digital marketing, SARS-CoV-2, Pandemic, Pharmaceutical marketing.

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INTRODUCTION

Beta Coronaviruses have caused two major virus outbreaks in the recent past: SARS (severe acute respiratory syndrome) and MERS (Middle East Respiratory Syndrome).[1] The SARS viral disease with a mortality rate of 11%[2] was first reported in 2002; the MERS viral disease has a mortality rate of 35%[3] and the outbreak occurred in 2012. Belonging to the same genus of beta coronavirus along with these two viruses is the new SARS-CoV-2 that is the causative factor of the COVID-19 pandemic. Beta coronaviruses, along with alpha coronaviruses infect mammals, while gamma and delta coronaviruses infect birds.

COVID-19 is the abbreviation of coronavirus disease 2019.[4] SARS-CoV-2 stands for severe acute respiratory syndrome coronavirus 2.[5] A COVID-19 zoonotic infection has also caused an economic contagion, which has broken consumption cycles, caused partial unemployment, shutting down factories, and even caused negative GDP growth.[6]

The highly contagious Coronavirus disease–19 or COVID–19, has caused a global public health crisis never seen before after the influenza pandemic of 1918.[7] The SARS-CoV-2 positive-sense RNA virus has enveloped the genome and is characterized by high transmissibility, replication, and mutation. The primary receptor of the SARS-CoV-2 virus is ACE2 which stands for angiotensin-converting enzyme 2. Novelty is that ACE2 receptors are mainly bound to cell membranes of respiratory epithelium, tongue, oral cavity, lungs, liver, gut, heart, kidney, and testis, ACE2 receptors are seldom in the unbound soluble form. Strong binding to the ACE2 receptors and fusion with cell membrane causes the entry of the SARS-CoV-2 RNA virus into the host cell to produce COVID-19 viral infection.[8]

IMMUNITY AGAINST COVID-19

The challenge of COVID-19 is the fact that being caused by a novel coronavirus, there is no prior exposure to a similar pathogen; hence, there is no innate immunity towards COVID-19.[9] Therefore, the process of achieving adaptive immunity to SARS-CoV-2 becomes vital. In adaptive immunity the antigen-presenting cells and T and B lymphocytes interact in a complex manner, resulting in immunologic memory and specific antibody production.[10] Certain cells called antigen-presenting cells like dendritic cells, macrophages, and mononuclear phagocytes present the antigen or foreign body to helper and proliferating (killer) T cells (T lymphocytes). Although there are many types of T cells, the two main are: CD4+ T cells or helper T cells and CD8+ T cells or killer T cells or cytotoxic T cells. One interesting thing is that T cells cannot recognize soluble antigens, only those antigens that are bound to receptors or proteins are recognized. T cell disorders are seen in autoimmune diseases and transplant rejections. Thus, T cells are vital for normal adaptive immunity response.

B lymphocytes produce specific antibody proteins that help destroy particular antigens as part of the adaptive immune response. Born from hematopoietic stem cells of bone marrow, continuously produced during the entire life time of a human, the B lymphocytes are critical for adaptive immunity. B lymphocytes have two notable features: ability to discriminate between antigens and non-antigens and also have cell memory. B cells are bursa derived cells. B lymphocytes convert to plasmocytes and produce specific antibodies in response to the antigen epitopes. Thus, the two types of small immune cells (T cells and B cells) of 8 to 10 microns in diameter provide for acquired or adaptive immunity, in which, humoral immunity depends on the B lymphocytes and cell immunity depends on T lymphocytes. Thus protection and strong immunity depends on innate immunity that a person is born with - and adaptive immunity that the individual gains through exposure to various antigens during his lifetime.

Invasion of the human body by pathogenic viruses, bacteria, and other microbes from the environment, is a constant happening. We are able to

cope with this challenge through immunity which includes production of five types of antibodies - these are generated constantly in the body to help destroy the antigens. There is a slight difference between the words antibodies and immunoglobulins. Antibodies are free floating proteins that help destroy the antigens. Immunoglobulins are attached to B lymphocyte cell membrane with the help of transmembrane domains. These domains are not present in free floating antibodies.[11] It should be however reiterated that these words antibody and immunoglobulin are used interchangeably. Both are described as having Y shaped structure.

Immunoglobulins (or antibodies) are heterodimeric in structure, they have two dimers or subunits or chains that are not identical. Each immunoglobulin has two heavy chains (H) and two light chains (L). Immunoglobulins are produced because the immunogen or antigen binds with specific BCR (B cell receptor) on the cell membrane, the nature of immunogen is transcribed to produce the respective immunoglobulin. Further, memory B cells also develop; when subsequent exposure of antigen occurs, these memory B cells quickly differentiate to a plasmocyte that shall produce the specific antibodies.[12]

The innate immunity response is very weak against SARS-CoV-2 as the virus is novel; reliance is heavily on the person's adaptive immunity.[13,14] To develop the adaptive immunity through humoral activity, against the SARS-CoV-2 beta coronavirus, the various proteins of the SARS-CoV-2 are vital. These include: the structural proteins: Spike S protein, Envelope E protein, Membrane M protein, and Nucleocapsid N protein. There are 16 nonstructural proteins.[15] It is vital to appreciate this proteinaceous structure of the COVID-19 virus, since the development of vaccines is based on this profile. A key protein of the SARS-CoV-2 virus is the spike S protein, this protein is responsible for attachment, fusion, entry and transmission of the virus into the host cell. The spike S protein has two subunits S1 and S2.[16] S1 subunit has an N terminal domain (NTD), and a receptor binding domain (RBD) (which docks to the ACE2 receptor). The fusion of the virion to cell membrane is done by the C-terminal S2 subunit of the spike protein.[17]

ACE2 receptor is located on the outer surface of the host cell membrane. The ACE2 receptor is present in the respiratory epithelium including lungs, oral tissue (particularly tongue), liver, heart, intestine, brain, testis and kidneys. ACE2 receptor has a deep channel on top of the molecule with negatively charged ridges, and possibly the site where the positively charged receptor binding domain of the SARS-CoV-2 viruses's S glycoprotein binds.[18]

THE BACKGROUND FOR COVID-19 VACCINE DEVELOPMENT

Vaccination is a life saver process. Eradication of small pox viral disease through the live vaccinia virus vaccine is a marvellous achievement of modern medicine. Small pox that plagued humanity for 3000 years killed 30 crore (300 million) people in the 20th century.[19] An interesting estimate is that for every dollar invested on vaccination, the returns is 44 USD. Vaccines basically stimulate the immune system to produce specific antibodies or particular lymphocytes to work against the invading pathogen on subsequent exposure.[20] One of the interesting points about vaccination is that this process helps prevent more diseases than just the target disease, for instance, the secondary bacterial infections associated to various viral pathogens are also prevented. Seasonal influenza vaccine has been seen to prevent AOM (acute otitis media caused by pathogenic bacteria) since influenza (flu) is associated with AOM. An interesting study report has emerged from Brazil wherein it was observed that influenza vaccination has provided better outcomes in COVID-19 patients pointing to the additional benefit of vaccination process. There appears to be better innate immunity against COVID-19 SARS-CoV-2 virus in patients who have had recent inactivated influenza vaccine. There is an urgent requirement to address the potential and actual havoc of infectious disease through fast development of appropriate vaccines and their distribution to the last patient or recipient. Vaccination is an important approach in endemic, epidemic and pandemic management. It is due thanks to vaccination that small pox has been eradicated and polio is well on the way to get eradicated.[21,22] Vaccination importance is on the spotlight due to COVID-19 pandemic that is said to have started in Dec 2019.

The phagocytic activity of immune cells is cellular immunity and antibody production activity of immune cells is humoral immunity. The immunity latent in a person is called innate or natural immunity (this includes the skin and mucous membrane which have self-defense function), and the immunity that a person acquires through interaction with environment and when vaccines are administered is called acquired immunity or specific immunity, this requires time to develop.[23]

The success of any vaccine is measured in terms of the amount and quality of neutralizing antibodies (NAbs) stimulated in a person. If the vaccine fails to produce effective levels of NAbs, then the vaccine is deemed a failure – it has happened with many a HIV vaccine.[24] Neutralizing antibodies are important because they can be transferred from the serum of infected and recovered individual to a patient to speed up recovery, or prevent viral infection. Such therapeutic NAbs or nAB exist for a short time. There are attempts to develop NAb treatments for COVID-19 too.[25] Post COVID-19 infection recovered patients and in the case of COVID-19 vaccinated individuals, serum neutralizing antibodies do appear and remain for several months.[26] In a cohort study on COVID-19 hospitalized patients, RBD (receptor binding domain) specific IgG responses (indicating neutralizing antibodies) were detected 6 days after PCR test confirmation.[27] Generation of NAbs is the goal of vaccination against COVID-19 viral disease (Table 1).

The binding of SARS-CoV-2 betacoronavirus to ACE2 receptor is stronger than the SARS-CoV-1 virus, and this binding is due to the S spike protein studded on the SARS-CoV-2 virus outer surface. Hence, S protein is the target protein in vaccine design and development.[28] All the vaccines as on date are focusing on the viral S spike protein as the immunogen, the idea being that the antibodies that are generated due to S protein will inhibit the viral docking and entry into host cell, thereby the COVID-19 infection.[29] This SARS-CoV-2's S spike protein-centric vaccine design strategy is effective as borne by the fact that there are higher neutralizing antibody levels in those subjects administered the mRNA vaccines: Pfizer vaccine and Moderna vaccine.

Table 1: Important types of immunoglobulins.

Type	IgA	IgM	IgG	IgD
Secreted in	the mucosa such as the nasal and gastric mucosa, and in the tears, saliva, breast milk, and other external organs	primary immunoglobulin produced in the serum due to presence of a pathogen	antibody with highest concentration in blood is that neutralizes toxins and bacteria; crosses the placenta and provides protection to foetus	still not yet established fully

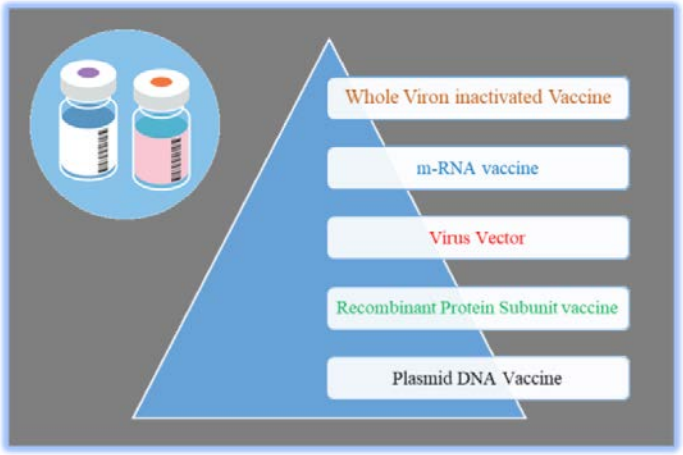

Figure 1: COVID-19 vaccines.

THE COVID-19 VACCINE PLATFORMS

Never before has vaccine science and technology seen so much action and excitement. There are various platforms being experimented with for delivering appropriate amount and type of SARS-CoV-2 antigen to generate neutralizing antibodies.

The contemporary COVID-19 vaccines are using the following technological platforms (Figure 1).

Whole virion inactivated vaccine

Covaxin from Bharat Biotech (India) is a whole virion inactivated vaccine. The genes, spike protein and the entire virion is inactivated through treatment with beta propiolactone. This inactivated vaccine is administered intramuscularly. India's first indigenously produced COVID-19 vaccine Covaxin is the whole virion SARS-CoV-2 inactivated vaccine having 6 micrograms per vial of the strain NIV-2020-770, this vaccine is also called Bharat Biotech COVID-19 vaccine (Covaxin). Covaxin's phase 3 clinical trial data shows 81% efficacy. Inactivated vaccines have low potential for toxicity. Excipients like aluminium hydroxide in the vial augment the immunogenicity. Covaxin is given in two doses, 28 days apart. The vero cell (monkey kidney cell line) platform is used and requires BSL-3 compliant facility for manufacturing.

mRNA vaccines

In the mRNA vaccine technology, the messenger ribose nucleic acid (mRNA) coding for the spike genes is presented in a nanolipid. On injection the mRNA enters the host cell and is translated straight away by ribosomes (protein factories) that synthesize the spike protein. This comes to the surface of host cell, and on sensing this foreign presence, the antigen presenting cells such as macrophages attack the virus. The broken down cells and the spike proteins further primes B lymphocytes to produce antibodies that help destroy the spike protein bearing cells. The spike proteins come up to the surface of the host cells, T cells destroy the abnormal cell, the released spike protein antigen stimulates appropriate antibody production by B lymphocytes in the host body.[30] mRNA vaccines are also two dose vaccines (in the Pfizer vaccine the two doses are given three weeks apart). The mRNA from mRNA vaccines do not enter into the host cell nucleus, the vaccine mRNA is transcribed directly in host cell ribosome, hence a lower vaccine dose is required and this is considered advantageous.[31]

The mRNA vaccine 1273 is the Moderna vaccine, and this vaccine has shown 94.10% efficacy at preventing COVID-19 illness, including severe COVID-19 disease in a phase 3 trial. The Pfizer BioNtech mRNA vaccine BNT162b2 offers 95% protection against COVID-19.

Virus vector vaccine

Sputnik the Russian vaccine and Covishield (from Serum Institute of India) are GMO products. Covishield is the same as AZ-Oxford vaccine or AstraZeneca Oxford vaccine. Sputnik and the AZOxford vaccine (Covishield in India) are adenovirus vector vaccines.[32]

In Covishield (AZ-Oxford vaccine), the DNA virus adenovirus is used as a vector or carrier of the RNA gene that produces spike protein of SARS-CoV-2. In Covishield (AZ-Oxford vaccine) vaccine, the DNA of the adenovirus that is found in chimpanzees is taken, genetically engineered with help of special enzymes, so that only the viral RNA gene portion that codes for the spike protein of the SARS-CoV-2 virus, gets fused into the chimpanzee adenovirus DNA. This is recombinant technology at work. The resulting adenovirus that acts as a vector is a GMO or genetically modified organism. Thus, the Covishield vaccine contains GMO. The generic name of Covishield is ChAdOx nCoV-19 corona virus vaccine (recombinant). Each dose of Covishield is 0.5 ml, and each dose provides ChAdOx nCoV-19 corona virus vaccine (recombinant) 5×10^{10} viral particles (vp). ChAdOx refers to the chimpanzee adenovirus, Ox is Oxford, and nCoV-19 is novel coronavirus 19. This is a monovalent vaccine, using only one type of adenovirus for both the doses. (Sputnik V uses two types of adenovirus for each dose of the two doses).

After Covishield is injected into a person, the adenovirus gets into the human host cell. The virus is broken down and the recombinant DNA gets into the nucleus of the host cell. There the adenovirus recombinant DNA produces the corresponding mRNA (messenger RNA, photocopy of DNA), which goes to the ribosome (protein factory) of the host cell. The spike protein is manufactured by the host cell ribosome and this goes to the surface of the host cell. Immediately, the antigen presenting cells present this abnormal host cell, to the killer cytotoxic T lymphocyte cells that break down the abnormal host cell with spikes, and further the spike protein fragments stimulate B lymphocytes to produce specific antibody immunoglobulins M and G that help destroy the spike protein antigen. Thus, when a vaccinated individual is exposed to the SARS-CoV-2 virus in society, the B lymphocytes produce corresponding antibodies that help destroy the SARS-CoV-2 virus that has entered the human body. Hence, vaccinated individuals almost never suffer severe COVID-19 and hospitalization.

Covishield contains non-replicating adenovirus, hence there is no danger. Adenovirus is chosen as a vector because this DNA virus is commonly present in the respiratory system of humans. Adenovirus cause non-fatal common cold infection. The adenovirus vector technology is a 50 year old technology, hence, there is high confidence on the same.

Covishield is given in two doses, the second dose is after 6 to 8 to 12 weeks after the first dose. Covishield efficacy rate is generally reported as 73.43% but some studies have said it is upto 100%. With dose interval of 12 weeks efficacy rate of Covishield is 78.79%, as reported.

Sputnik 5 COVID-19 vaccine invented by Gamaleya National Center of Epidemiology and Microbiology, Russia, which is a leading center for virus research, has its competency on adenovirus vector technology, they have initially extracted the adenovirus from human adenoids. Sputnik V is the first human adenoviral vector technology COVID-19 vaccine.[33] This is a recombinant gene technology product. Sputnik V is a GMO product (GMO = genetically modified organism). However, Sputnik V uses the human adenovirus and not the chimpanzee adenovirus. Sputnik V vaccine is also known as GAM-COVID-Vac using a heterologous recombinant approach, two adenovirus strains are used: Ad26 and Ad25. Use of two different strains of adenovirus helps in overcoming any previous adenovirus immunity, the vectors carry the spike protein

gene.[34] As such, the adenoviruses are commonly occurring microbes in human respiratory, oral and gastrointestinal systems. Adenoviruses are DNA viruses and are known to cause common cold and humans have learnt to co-inhabit with adenovirus. The Sputnik V vaccine uses two types of non-replicating adenoviruses as vectors for the coronavirus gene coding the spike protein.

Sputnik V is a two dose vaccine (the second dose uses a different adenovirus vector than the first dose to enable better efficacy), dose interval is 3 weeks. Randomized controlled phase 3 clinical trial has established the safety and efficacy of Sputnik V. The efficacy claim of Sputnik V is reported from 91% to 97.6% at preventing infection. Single dose COVID-19 vaccine Sputnik Light is the first dose of Sputnik 5 based on Ad26 vector, storage condition at 2 to 8 deg centigrade, and is also said to generate good level of antibody production for protective effect from COVID-19, to be used for booster dose and in cases of acute outbreaks of COVID-19.[35] Both Sputnik V and Covishield (AZ-Oxford vaccine) use non-replicating adenovirus technology. As such, adenovirus vector vaccine technology products are known to produce strong cellular and humoral immunity, and can offer good amount of genetic payload and is cost effective.[36]

Recombinant protein subunit vaccine

Biological Evans, Hyderabad, India is on the verge of launching an antigen recombinant protein (subunit of the spike protein), based vaccine, in collaboration with Baylor College of Medicine, USA. The projected cost makes this vaccine highly affordable. This too is a two dose vaccine (28 days apart). The brand name of this vaccine is Corbevax. These vaccine is also called a RBD (receptor binding domain) protein based vaccine. Such CoV RBD vaccines are second generation and production is using the yeast.[37] As such to make recombinant protein vaccines, the SARS-CoV-2 virus has four main structural proteins, including, S spike protein, M membrane or matrix protein, E envelope protein, and N nucleocapsid protein. These are four important vaccine antigen candidates, the RBD component is from the S spike protein.[38] There is also an option of creating a full length S protein antigen based vaccine.[39] Other companies including Sanofi are experimenting to produce recombinant protein vaccines through various routes such as *E. coli*, yeast and insect cells.

Plasmid DNA vaccine

Zydus Cadila is using plasmid DNA technology platform, in a BSL-1 compliant facility. The plasmid DNA vaccine technology platform is well – suited for vaccine production against viral mutations too. The spike protein RNA gene is combined into the circular plasmid DNA of certain bacteria – the recombinant plasmid vector thus created is injected interdermally. The brand name of this three dose vaccine is Zy-CoV-D. This vaccine is stored between 2°C to 8°C. The plasmid is a circular DNA present in bacteria outside the main nuclear DNA. The phase 3 trials are currently on for this vaccine candidate in children and adults.[40] The DNA vaccine technology is attractive due to stability, storage and producibility, and that this approach will generate both humoral and cellular immunity against COVID-19.[41] The myocytes and antigen presenting cells are crucial for the work of this vaccine, the DNA enters the host cell nucleus, to manufacture the RNA and then the spike protein is synthesized in the ribosomes. The Zydus Cadila ZyCoV-D vaccine is the first ever plasmid DNA vaccine for human use. The ZyCoV-D vaccine trials are being conducted in 12 years and above age group.[42]

Oral and nasal vaccines

Vaccination is undoubtedly the way forward for disease prevention and control, as it is economical and effective. The allure of oral vaccination approach is due to ease of administration and distribution, and likely safe, effective and affordable.[43] The challenge of oral vaccines is to make the vaccine stable on administration due to the challenging enzyme laced environment of gastrointestinal tract. Improved compliance through ease of administration implies that herd immunity can also be achieved more efficiently through oral vaccination approach.[44] Injectable vaccines boost adaptive immunity through systemic route, in which antibody production happens at the serum level, whereas the fact is systemic infection takes place only after pathogens break through the mucosal barrier, for example the diarrhea causing pathogens break through the intestinal barrier to cause fatal diarrhea.[45] Hence, the prudent approach is to build the mucosal immunity through oral vaccination route, thereby build the mucosal antibody IgA level at the mucosal surface, ensure effective cell-mediated (T cell) immunity and antibody IgG level in the bloodstream.[46] In fact this is also the method of approach in nasal route vaccination where the target area is the nasal mucosa.

Mucosal route of immunization is a good preventative strategy – the intramuscular route of immunization is not the only way to provide circulating antibodies that protect from COVID-19.[47,48] The idea is that both mucosal immunoglobulin IgA and systemic immunoglobulin IgG can be generated through the mucosal immunization approach in the oral and nasal routes of administration.

Historically, needle-free vaccination route has been tried mainly through oral route for managing communicable diseases, and there is a fascination to make needle-free vaccination a reality and oral vaccines are perceived patient-friendly.[49] Vaccine technology mimics the exposure of natural primary pathogen but the antigen in the vaccine does not cause infection, although it primes the immune system to generate self-defensive antibody production and T cell activity. Mucosal vaccine developers bear in mind MALT (mucosal associated lymphoid tissue) to create oral or nasal vaccines.

GAVI the vaccine alliance holds forth the promise of nasal route vaccination as the nasopharyngeal area is where the coronavirus first infects.[50] Bharat Biotech is actively working on nasal vaccine development (BBV 154), using a chimpanzee adenovirus vector that has a modified recombinant genome, the SARS-CoV-2 gene that codes for the spike protein is inserted into the chimpanzee adenovirus genome. On administration of a single dose of this nasal vaccine – the vaccine shall potentially avoid COVID-19 infection in the lower and upper respiratory tracts, and transmission of infection is also stopped.

A company by name ORAVAX (Israel – India partnership), is creating an oral vaccine with a triple antigen VLP (virus like particle).[51] The three antigens of this VPL are: spike protein (S), membrane protein (M) and small membrane protein (E).

A blessing in disguise has been the fact that SARS-CoV-1 and SARS-CoV-2 share the same ACE2 receptor on the outer surface of the host cell membrane, and genetically SARS-CoV-2 is 79% similar to SARS-CoV-1. This has helped in faster understanding of the disease, also the speedier development of vaccines, and development of passive immunization strategy through monoclonal antibodies.[52]

DISCUSSION

Vaccination is a most effective method to control mortality and morbidity. Vaccination has reduced mortality by 97% to 99% in cases of various diseases like measles, polio, mumps, hepatitis, tetanus and diphtheria. Vaccines market has been traditionally smaller than the larger non-vaccine pharmaceutical market. As per 2001 analysis, vaccines are just 1.50% of the pharmaceutical market, and when vaccine supply disruptions occur, it affects the childhood immunization programs adversely. To develop a vaccine, 20 million USD to 30 million USD are

Table 2: Various Covid-19 vaccines and their manufacturer.

Sr. No.	Name of vaccine	Vaccine source
1	Vaxzevria / Covishield	AstraZeneca, University of Oxfprd
2	Comirnaty	Pfizer- BioNTech German company
3	Janssen COVID-19 vaccine	Johnson and Johnson COVID-19 vaccine Janssen Pharmaceuticals
4	Vaccine Moderna	American company Moderna
5	Sinopharm COVID-19 vaccine	Sinopharm,s Beijing Institute of Biological Products
6	Sputnik V /Gam-COVID-Vac/ Sputnik Light	Gamaleya Research Institute of Epidemiology and Microbiology , Russia
7	CoronaVac /Sinovac COVID-19 vaccine	Sinovac Biotech Ltd, Chin
8	Covaxin	Bharat Biotech International Limited (BBIL), India
9	Convidecia	CanSino Biologics , Chin
10	WIBP-CorV	Sinopharm, China National Pharmaceutical Group Corporation (CNPGC)
11	EpiVacCorona	State Research Center of Virology and Biotechnology VECTOR, Russia
12	ZIFIVAX or RBD-Dimer	Anhui Zhifei Longcom in collaboration with the Institute of Microbiology at the Chinese Academy of Sciences, Chin
13	Abdala technical name CIGB-66	Center for Genetic Engineering and Biotechnology, Cuba
14	CoviVac	Russian Academy of Sciences, Russia
15	QazCovid-in	Kazakh Biosafety Research Institute and in clinical trials, Kazakhstan
16	Minhai COVID-19 vaccine/ KCONVAC	Shenzhen Kangtai Biological Products , Beijing Minhai Biotechnology Co., Ltd.
17	COVIran Barekat	State-owned Shifa Pharmed Industrial Group, Iran
18	IMBCAMS COVID-19 vaccine	Institute of Medical Biology, Chinese Academy of medical Sciences, Beijing, China
19	Soberana 02 or Soberana 2, FINLAY-FR-2	Finlay Institute, Cuba
20	MVC-COV1901 / MVC COVID-19 vaccine	Medigen Vaccine Biologics in Taiwan, National Institute of Health, Bethesda Maryland.

required. The global vaccine market has shown exponential growth, as per Statista website, the global vaccine market revenues from 2014 to 2020 shall grow from 30 billion USD (2014) to 60 billion USD (2020).[53] In 2013, the global infectious disease vaccine market is estimated to be 25 billon USD. The major companies are GSK, Merck, Novartis, Pfizer and Sanofi.[54]

The essence of vaccination process has contributed to the growth and relevance of vaccine industry. As such, humans and viruses have a history of conflict and assimilation too! Of the 22000 genes in a human cell, around 8% of the human DNA is estimated to be of virus origin, assimilated into our genome through evolution, and derived from infectious retroviruses.[55] Thus, in vaccination process, a suitable viral biological entity is introduced into the body, the antigen presenting cell (an immune cell like the macrophages) engulfs the antigen, activates the helper T cells, and in turn the helper T cells will stimulate the B lymphocytes to produce antibodies and also stimulates cytotoxic T cells or killer T cells to destroy the antigen through phagocytosis.

The commercial allure of the vaccine market can be understood by the fact that Pfizer's COVID-19 vaccine (Comirnaty in EU) has already made 3.5 billion USD revenues, with profits of 900 million USD in the first three months of 2021. In the USA projected COVID-19 vaccine market is 10 billion USD per annum (2020). In 2021, the expected sales of Pfizer COVID-19 vaccine and Moderna COVID-19 vaccine is expected to be 25.20 billion USD. The stage is set for a lucrative COVID-19 vaccine market.

The projected COVID-19 global vaccine market for 2021 is 75.75 billion USD.[56] Nevertheless the challenge is to ensure access of COVID-19 to low income countries too, as COVID-19 is a pandemic. There are 289 experimental vaccine candidates as on 3.2.2021, and it is difficult to get regulatory approval, further more doses of COVID-19 vaccine are required compared to any vaccine in immunization history.[57] Manufacturing of vaccines is not evenly distributed across the globe, this causes distribution and access challenges, there is concentration of plants in some markets.[58] In low and middle income countries, there is a challenge of affordability and purchasing power, about 85% of the population will have this challenge.[59] To improve compliance to COVID-19 vaccination one has to overcome vaccine hesitancy and vaccine refusers. Counselling shall help vaccine hesitant parents to comply for vaccination to their children. Overcoming the production and vaccine hesitancy related issues will grow the COVID-19 vaccine market even further.[60]

CONCLUSION

The vaccine science has exploded as never before and so has the vaccine market. Each pharmaceutical marketer is aware that the COVID-19 vaccine market is a zero sum game, since the market will require billions of doses and booster doses, there will be many types of vaccines at various price points. WHO says the minimum COVID-19 vaccine efficacy requirement is 50% and several players are into the fray. Revenues generated by the COVID-19 vaccine market will funnel into development of other vaccines for diseases like cancer. The COVID-19 contagion is a game changer and transformational event that has provided impetus to development of vaccine science (including for mRNA anticancer vaccines) and the broader vaccine market. The market is also facing the challenge of COVID-19 vaccine hesitancy in some quarters.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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