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Theory of COVID-19 vaccines

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Abstract---The causative virus of COVID-19 “SARS-COV2” is an upper respiratory tract pathogen and a member of corona virus family, causes about 15 % of influenza and common cold infections annually. There are several types of viruses that causes influenza to human like orthomyxovirus type A, B, and C. some may cause sever and endemic flu like orthomyxovirus-A, some may be simple and do not spread like endemics.

Keywords---COVID-19, vaccines, influenza, orthomyxovirus.

Introduction

The causative virus of COVID-19 “SARS-COV2” is an upper respiratory tract pathogen and a member of corona virus family, causes about 15 % of influenza and common cold infections annually. There are several types of viruses that causes influenza to human like orthomyxovirus type A, B, and C. some may cause sever and endemic flu like orthomyxovirus-A, some may be simple and do not spread like endemics. One of the main features of influenza viruses specifically and RNA viruses generally that they are show minor and major changes in their outer receptors, usually minor shifting require 2-3 years, while major changes require 5-7 years. Such changes occur due to "genetic rearrangement" i.e. the structural genes rearrange itself to produce different receptors structurally, and that what explain the recurrent infections with influenza annually, and also explain the failure of production of an effective and permanently protective vaccine against influenza virus specifically and against other RNA viruses generally (like HIV, and HCV) so far.

Many non-vaccine options has been tried in Iraq to tackle the diseases, however, most of these options were only conservative therapy. In a uni-center study

conducted by Darweesh et al., 2021, who has reported that using pharmacological therapy has improved the health status for mild-moderately infected patients with only weak impact on severely infected patients, the study also reported few death cases. Despite availability of wide range of drugs which could be considered in COVID-19 either as principle therapy or supportive minerals (Althanoon et al., 2021; Younis et al., 2021) and vitamins (Merkhan et al., 2020) improving the immune system. The needs for vaccine globally is urgent, however, the available vaccines are presented in different types, therefore, in the following review; we do focused on the types of vaccine in the point of view of manufactured form based on our previous knowledge, we also reviewed the mechanism by which our immune system does work and hence their response to foreign invaders.

Immunity to viruses

Immune response to viruses in general include many parts of the immune system, starting from the innate immune system and protective barriers, then triggering of the adaptive immune system which include humoral immune system i.e. B-cells and antibody mediated response; and the cellular immune system i.e. T-cells.

Innate immunity and the virus

Innate immunity has a major role in protection from viral infection, starting from the protective barriers of the upper respiratory tract, the mucus membrane that inhibit viral entrance, along with the presence of local macrophages and lytic enzymes. If the virus entered, the alarming siren will be triggered, i.e. interferon (IFN) which will cause many local and systemic changes to inhibit the viral replication and spreading to other cells and organs; along with activation of other arms of the innate immune system like macrophages, natural killer cells (NK), complement system and many pro-inflammatory cytokines. Innate immunity is swiftly stimulated by viral replication. Interferon (IFN) is antiviral factor excreted by many cells when infected by viruses, virally infected cells are recognized and killed via Natural Killer (NK) cells using cytotoxicity. Viral envelope can be disrupted via complement proteins (MAC) and viral particles can be opsonized by complement for phagocytosis by macrophages (Winn WC., 2006). Interferon is a protein that have several sub classes depending on the source of production, i.e. the releasing cells, like INF-alpha which is produced by virally infected leukocytes, while INF-beta is produced by virally infected fibroblast, and INF-gamma which is produced by triggered lymphocytes (Imanishi J., 1994).

Interferon (IFN) antiviral properties

Interferon prevents continues spreading of the virus to other cells, it binds to IFN-R and inhibits viral proteins synthesis, it also increases MHC class I receptors expression to enhance infected cells destruction via CTLs. INF protects non-infected cells from destruction by NK cells. IFN enhance NK cell search and destruction capabilities specially the search for infected cells with lowered MHC class I receptors or opsonized cells with antiviral antibodies. Natural killer cell is the main lymphocyte of the innate immune system, play a major role in killing

tumor cells and virally infected cells, it is activated early in viral infections, days before the activation of adaptive system lymphocytes, consequently have a primary role in fighting viral infection in the early stage (Abel et.al., 2018).

Role of Natural Killer (NK) cells in viral infections control

Virally induced down regulation of MHC class I trigger NK cells to kill these infected cells. Infected cells are usually coated with antiviral antibodies and can be recognized by NK cells via Fc portion of the coating antibodies, consequently will be killed by antibody-dependent cell-mediated cytotoxicity mechanism (ADCC) NK cells release more amounts of interferon which will inhibit intracellular viral replication.

Acquired Immunity and Viruses

Acquired immune system is composed of two arms, humoral immune system i.e. B-cells and antibody production, and cellular immune system i.e. T-cells and its classes (Th1, Th2, T-reg., T-cytotoxic). adaptive immune system requires several days for full blown activation, but the main characteristic of this system is the high selectivity and the pin point direction of immune action.

Role of humoral immunity in viral infection control

Viral entrance to the host cells can be prevented via blocking antibodies which will bind to viral ligand and prevent virus from binding to the host cell receptor. If the virus entered into a host cell, viral antigens on the membrane of the infected cell can be recognized via antibodies. These antibodies can cause cell lyses by complement activation or by ADCC through Fc receptors on NK cells.

Role of cellular immunity in viral infection control

Cellular immune responses to viral infection are mandatory to stop the further spreading of virus in the infected cells, and essential for clearing the host cells with established infection, and for destruction of already infected cells and stop the virus from invading new cells. The effector cells are helper T-cells (CD4+) and cytotoxic T-cells (CD8+); CD4+ act by activation of many other immune cells via secreting pro-inflammatory cytokines and activating innate immune system cells and humoral immune system cells with increased chemotaxis while CD8+ act directly on infected cells and induce cell death either by direct releasing perforin/granzym or by induction of internal cell apoptosis by activation of Fas/FasL pathway.

Antiviral cellular immune responses occur in 4 stages

- Activation stage in which the T-lymphocytes proliferate and differentiate in to effector cells, then start to destroy infected cells.
- Induction of apoptosis in already infected cells.
- Silencing stage in which T-helper cells (CD4+) start to release anti-inflammatory cytokines leading to effector cells retrieval, but apoptosis induction is continued.

- Memory cells development stage in which some of CD4+ and CD8+ lymphocytes turn to the dormant stage and remain viable for a long period forming the memory cells.

Dormant or resting memory cells have ability to recognize specific viral antigens; it will proliferate, and lyse infected cells upon re-exposure to the same viral antigen.

Immune compromised patients and COVID-19 infection

Infection with COVID-19 virus in individuals with normal or competent immune system triggers different arms of the immune system with different levels of response, nevertheless such infection still may cause many life threatening complications. The infection with COVID-19 in immune compromised individuals may show unpredicted outcome, this could be due to the type and level of immune compromise, primary immune compromise may show different levels of severity, complement deficiency may cause delayed immune response and consequently delayed appearance of signs and symptoms, IgA deficiency, on the other hand may also cause massive dose infection with the virus due to absence of blocking immunoglobulins on the mucus membranes.

Primary adaptive immune response may cause a prolonged infection time, while the severity of such infection will depend mostly on the efficacy of innate immune system in control and prevention of infection spread to other cells and tissues. Secondary immune deficiency also may show variable outcome to COVID-19 infection but mostly more predictable outcomes, immune deficiency due to HIV infection depends mostly on CD4 count; in patients with advanced stage of AIDS infection, they mostly will show paralyzed immune response to such infection. But in early stage of AIDS, immune system may show a more efficient response. On the other hand, secondary immune deficiency due to certain types of therapy like cytotoxic, corticosteroids, physical radiation, are considered as generalized non-selective immune suppressants that will cause almost total immune suppression resulting in poor immune response to most infections including COVID-19 viruses, and these patients may have bad prognosis for such infection. Figure 1 illustrate the immune response against COVID-19.

Immune resonance against COVID-19

Immune resonance against COVID-19

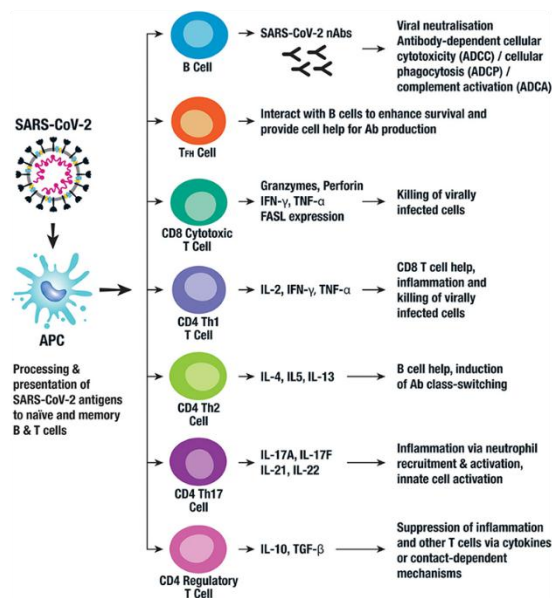
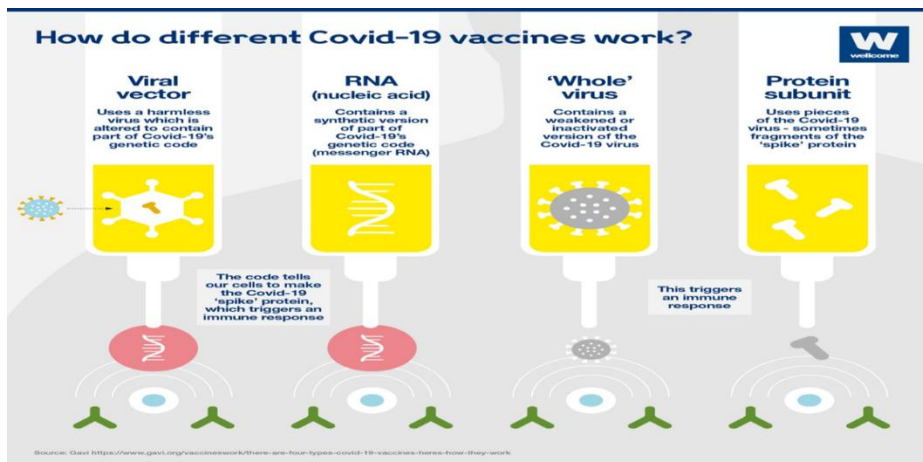


Figure 1. Components of the adaptive immune response to SARS-CoV-2 (Flanagan et al., 2020).

Types of SARS-Cov-2 (COVID-19) vaccines

There are four major groups of vaccines designed for SARS-Cov-2 or COVID-19 and each one work in different mechanism (Figure 2) (Kaur SP, and Gupta V., 2020).



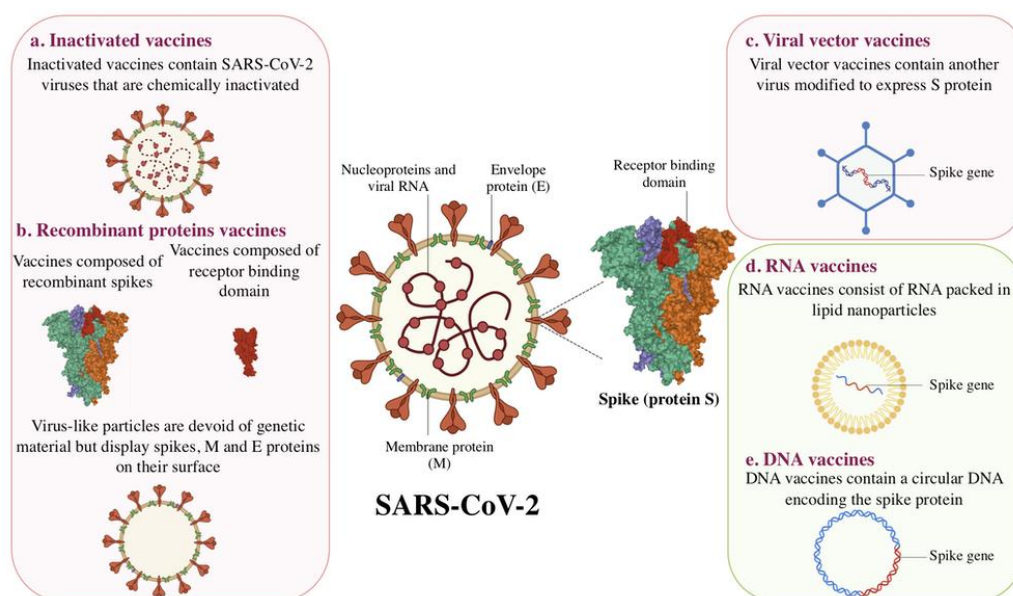


Figure 2. Types of vaccines according to their working mechanism
https://cms.wellcome.org/sites/default/files/styles/image_full_mobile/public/how-do-different-covid-19-vaccines-work.jpg?itok=depMY6O2

Type I: whole virus (live attenuated or killed) vaccines

The vaccine can be prepared by either using a pure isolate of the infecting virus and treated physically, chemically, or both to kill or attenuate the virus rendering it non-virulent i.e. unable to cause active infection; Or, using a virus-like particle i.e. a synthetic particle that highly resemble the original virus, but without any nucleic or genetic material, hence rendering it non-infective particle (Figure 3). The produced vaccines will not cause an infection, but will activate the immune system in the recipient body and provide a protection against the original virus infection in the future. The licenced vaccine for emergency use for COVID-19 virus is sinovac, sinopharm (China). The already licensed vaccine using this technology: Hepatitis A, rabies, polio (all are inactivated type), such vaccine establishes an immune response for all viral antigens and trigger different levels of the immune system as mentioned above, the innate immune stimulation could be manifested as activation of complement, phagocytes, and NK cells, while the adaptive immune stimulation could be manifested as both of B- cells and T-cells activation, and it could provide protection against different strains (Speiser DE, and Bachmann MF., 2020)

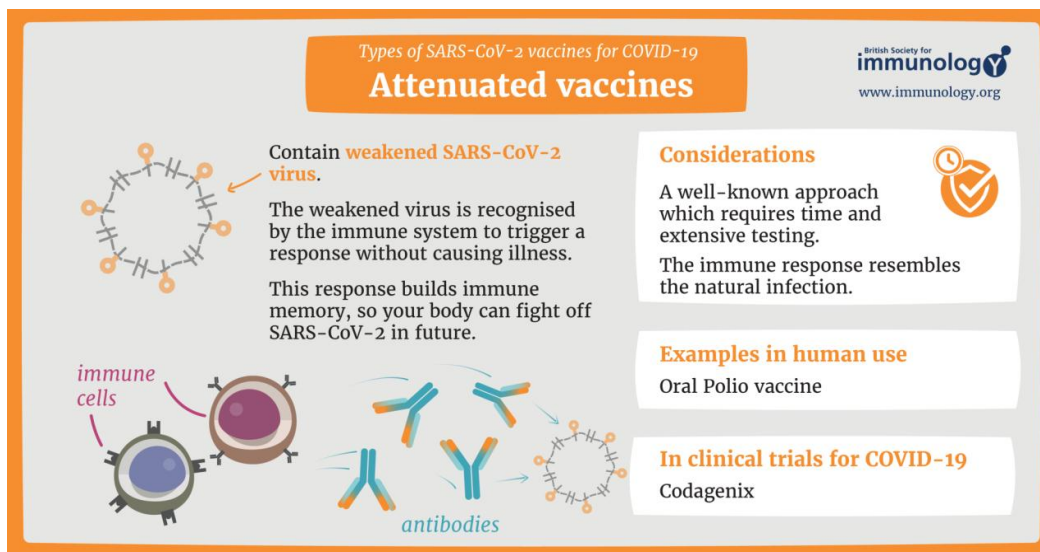


Figure 3. Diagrammatic illustration of attenuated vaccines

https://www.immunology.org/sites/default/files/BSI_attenuated_COVID19_vaccine.png

Type II: nonpathogenic virus with loaded spikes (non-replicative viral vector)

The vaccine can be synthesized by modification of a nonpathogenic virus, such modification include addition of selected surface particles from the pathogenic virus to the nonpathogenic virus to attain some structural resemblance, for example: the spike protein of Covid-19 virus. Such vaccine can trigger the immune system to attack the added particles and form a long term memory cells that will identify the original pathogenic virus on later exposure. The licensed vaccines for emergency use against COVID-19 virus are Oxford-AstraZeneca, and Sputnik V. The already licensed vaccines using this technology is Ebola vaccine. Such vaccine could establish an immune response for viral spikes (entrance receptors) mainly; the innate immune stimulation may triggered mostly against the non-pathogenic virus particles. While the adaptive immune stimulation will trigger the antibody mediated and to lesser extend cell mediated immune response, so it may show less chance to provide protection against different strains.

Viral vector vaccine illustrated in figure 4

Two-vector vaccine against coronavirus

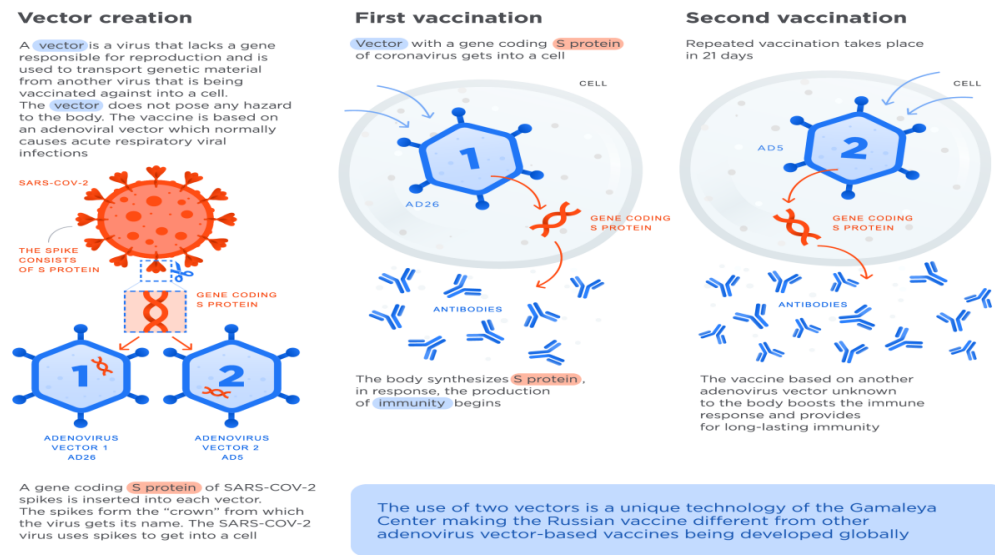


Figure 4. Schematic diagram of two viral vector vaccine

<https://sputnikvaccine.com/local/templates/sputnik/img/infographics/eng.png>

Type III: protein subunits

This vaccine can be synthesized by using genetic bioengineering technology, the same method that is used to synthesize certain hormones or enzymes, and it is conducted by isolation of a genetic fragment of the viral genetic material that is responsible for the synthesis of a surface structural protein (like receptors or spikes) and inserting the selected fragment into specific bacteria or yeast cells, rendering these cells into a factory for synthesis of such structural virus protein (Figure 5).

The synthesized protein then extracted and purified, to form the active ingredient for vaccine synthesis. After injection, the body will learn to recognize the selected viral protein and develop an immune response which protects the recipient from infection. The licensed vaccine for emergency use against COVID-19 virus using this technology is Novavax. The already licensed vaccines using this technology are Hepatitis B, pneumococcal disease, meningococcal disease, and shingles. The protein subunit vaccine contains purified "pieces" or fragments of the selected pathogen rather than the whole pathogen body or particle, and used to trigger an immune response. The innate immune stimulation could be manifested by triggering phagocytes to engulf these particles and presented it to T-helper cells (as antigen presenting cells) but mostly will cause only minor activation of complement system. On the other hand, the adaptive immune stimulation could be manifested by triggering the B-cells and antibody production to block the

foreign particles, but mostly may cause minimal activation of T-cells because such particles will diffuse in extracellular compartments only.

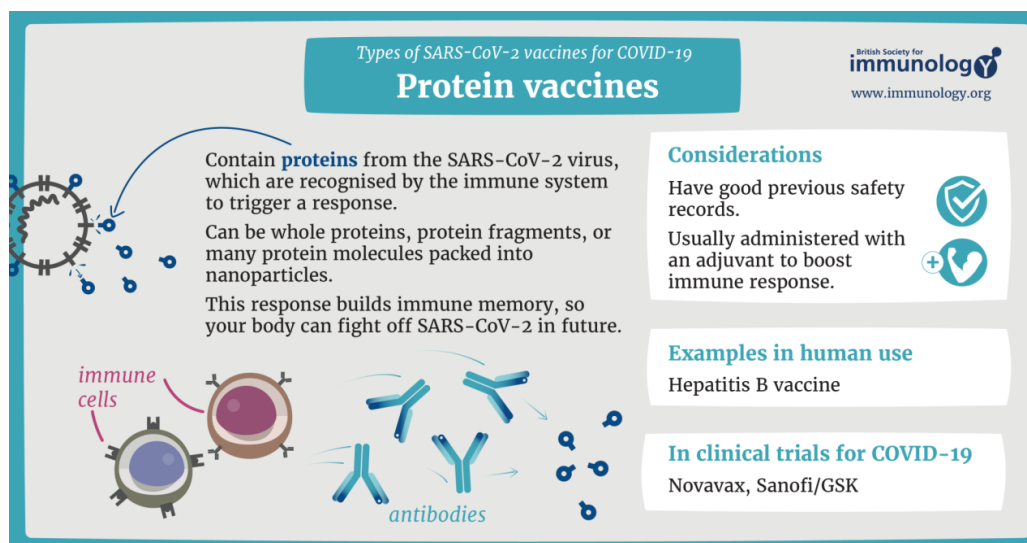


Figure 5. Diagrammatic illustration of protein vaccines

https://www.immunology.org/sites/default/files/BSI_protein_COVID19_vaccines.png

Type IV: RNA or mRNA vaccine

Messenger RNA (mRNA) is a genetic code sequence used by the cell to construct, repair, and maintain function. mRNA is the expression of cell function level. The novel idea of using a specifically designed fragment of synthesized mRNA fragment to introduce a new function to body by interfering with the genetic machinery of the affected cells has many implications. Applying this novel idea to produce a whole new generation of vaccination methodology and introducing it to the practical application worldwide without long duration studies and follow up on a wide spectrum of volunteered population may implicate the continuity of this method application for other medical problems. The newly synthesized vaccine can be prepared by development of a synthetic version of viral RNA. When this synthetic mRNA version is injected into the body, cells start to recognize it as an instruction to build the relevant viral protein, for example 'spike' protein of Covid-19 virus. This will trigger the immune system to respond, and develop assumed protection against Covid-19 infection.

The licensed vaccines for emergency use against COVID-19 virus using this technology are Pfizer-BioNTech, Moderna. The already licensed vaccines using this technology for other infectious diseases are none. The introduced RNA fragment will be engulfed by cells, and the fragment will be translated to the encoded protein, then the synthesized protein will be released extracellularly to the interstitial compartment. The newly synthesized and released protein will trigger the immune system in order to provide an accepted level of immunity to provide a protection against COVID-19 virus infection (Figure 6) (Lee P., 2021)

The immune response may be manifested as following: Innate immune stimulation will trigger phagocytes to engulf the foreign protein then present it to specialized T- helper lymphocytes, but there will be minimal complement system activation.

On the other hand adaptive immune stimulation will be higher than expected, such foreign protein will trigger mainly the T-helper cells and B cells, T-cell may start targeting the protein producing host cells and consider it as "infected cells" and start triggering apoptosis protocol in these cells considering them as defective cells; while B-cells will be also on high alert to produce blocking antibodies in order to prevent the spreading of the foreign protein to other cells (Bettini E, and Locci M., 2021). Consequently, such activation could not be totally safe for receiving individuals.

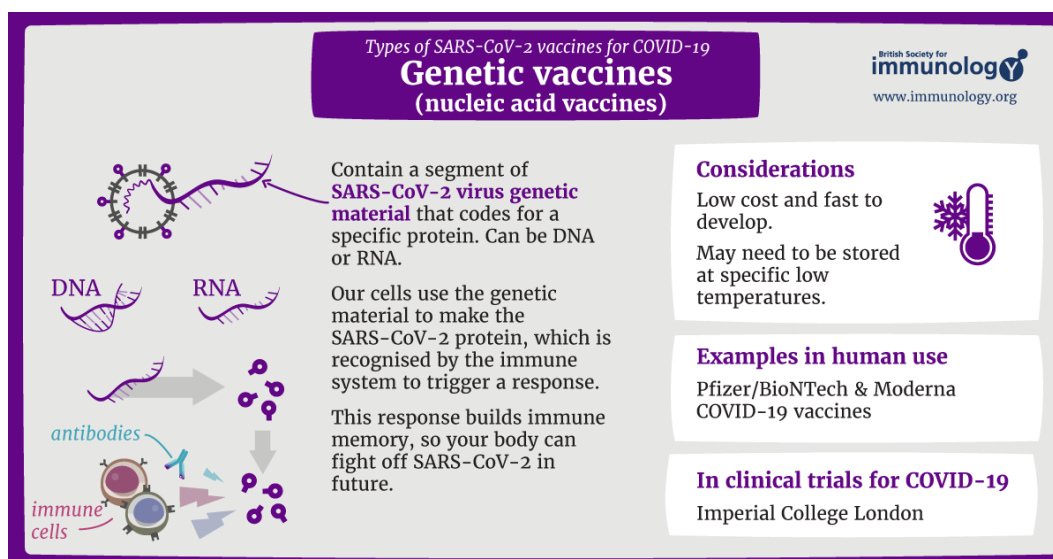


Figure 6. Diagrammatic illustration of genetic vaccines

https://www.immunology.org/sites/default/files/BSI_genetic_COVID19_vaccines.png

Reported side effects

The reported side effects on many official sites like CDC, NHS and WHO can be classified to local and systemic side effects and such side effects varied from mild and previously recorded side effects accompanied with previously and routinely used vaccines and newly recorded side effects accompanied with new COVID-19 vaccines. Local and mild side effects may include pain, redness, and swelling at site of injection could be accompanied with systemic but also mild side effects like tiredness, headache, muscle pain, chills, fever, and nausea. Most of the mentioned features are expected with most previously known vaccines. Some other systemic and more serious side effects are reported with COVID-19 vaccines like allergic reactions, blood clotting, and myocarditis; such side effects mostly correlated with the new technique for synthesis of mRNA based vaccines.

Most commonly reported side effects

- Blood and lymphatic system disorders
- Cardiac disorders
- Gastrointestinal disorders
- Immune system disorders
- Nervous system disorders
- Respiratory disorders
- Vascular disorders

Expected efficacy versus approved efficacy

The early expected efficacy of vaccines was much higher than the actual efficacy after public administration started with 60-75% for sinopharm , 85-89% for sputnik V and 90-95% for Biontek Pfizer vaccine, but after mass administration the level of efficacy dropped to a much lower levels (Vergara et al., 2021).

Conclusion

- Establishing a long term immunity for RNA viruses is quite difficult and not been approved yet, considering the longtime of discovery and analysis of previously known chronic and highly fatal RNA viruses i.e. Human Immune Deficiency virus (HIV) and Hepatitis C virus (HCV), to whom there is no effective, and lifelong protective vaccines.
- Already approved vaccines for Orthomyxovirus which is RNA virus of influenza and common cold can provide a short term protection which lasts only for one or two consecutive years, this is due to the change in the outer portentous receptors structure caused by viral genetic rearrangement process.
- The more resemblance of the vaccine action to the actual infection action in triggering multi-step in the immune system, the more efficacy and multi-step protective mechanisms will be developed by the immune system, and provide multi-levels protection.
- The newly generated vaccines require further studies and follow up for the reported efficacy and reported side effects that can appear in different population due to variation in age, gender, ethnicity, hypersensitivity, and other diseases, that may interfere with the vaccine action or side effects.
- Further studies are required to obtain a full knowledge about the differences in immune response to the different mechanisms of vaccines, and to assess the risks or side effects of such vaccines on long term.

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