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Coronavirus: current method of control and protection. Vaccination.

In 2019, coronavirus infection started actively growing in popularity; by 2020, coronavirus has assumed pandemic status. Active efforts were initiated to find means to control, protect, and prevent the growth of coronavirus infection. A vaccine is the only reliable way to avoid infection or a complicated course of the disease. Vaccination is used against many infections and, more recently, against the COVID-19 coronavirus. Even if a vaccinated person gets sick, there is little or no chance of complications or a severe course of the disease.

All current covid vaccines are biphasic, which means that a second dose is required for maximum protection. This tactic has been used in medicine for many decades. A second dose, called a "booster," allows for a more pronounced immune response and maintains protection against infection for a longer period of time.

According to the WHO, there are several types of vaccines.

The first, traditional, is a live, weakened virus that should not develop into a disease, but can induce an immune response. The second type are vaccines that use harmless protein fragments or protein envelopes that mimic the virus to safely create an immune response. The third are vaccines with a viral vector, and these include Sputnik V. They use a genetically engineered virus, so it cannot cause disease, but it produces coronavirus proteins to safely create an immune response. And the fourth type is the most advanced approach, which uses genetically engineered RNA or DNA from the virus to create a protein that itself safely triggers an immune response.

When the immune system first encounters a vaccine, it triggers two types of immune cells: B and T cells. B cells actively produce antibodies, but without a second dose of the vaccine, the number of these immunoglobulins decreases dramatically after just a few weeks. T-lymphocytes are the main weapon of the immune system. It is these cells that find the danger and destroy the pathogen. The main problem with T-cells is that

after the first stage of vaccination, the immune system creates very few T-lymphocytes, and the body remains unprepared to meet the virus.

The second - booster - dose of the vaccine triggers the second part of the immune response, resulting in the body producing more T cells and forming long-term immune memory. This process also "trains" the B cells to respond more quickly to viral invasion, to divide more quickly, and to produce more effective antibodies.

The results of major medical studies of all the COVID-19 vaccines available today show that a second dose increases protection several times over. Israeli scientists concluded that the level of antibodies in patients who received both doses of the coronavirus vaccine was 6-12 times higher than in those who were vaccinated once. As we can see, the second stage of vaccination is fundamentally important for reliable protection.

The COVID-19 vaccines that scientists around the world are working on are developed on different technological platforms, each with advantages and disadvantages.

Inactivated vaccines are produced by growing SARS-CoV-2 in cell culture, usually on Vero cells, followed by chemical inactivation of the virus. They can be produced relatively easily, but their yield may be limited by the productivity of the virus in cell culture and the need for production facilities with a high level of biosafety. These vaccines are usually administered intramuscularly and may contain alum (aluminum hydroxide) or other adjuvants. Since the entire virus is presented to the immune system, the immune response is likely to target not only the SARS-CoV-2 spike protein but also the matrix, envelope and nucleoprotein. Examples of registered inactivated vaccines include CoronaVac (Sinovac, China), Covaxin (Bharat Biotech, India), Sinopharm (Sinopharm/Institute of Biological Products Wuhan, China), CoviVac (Chumakov Center, Russia), BBIBP-CorV (Sinopharm/Beijing Biological Products Institute, China).

Live attenuated vaccines are produced by creating a genetically attenuated version of the virus that replicates to a limited degree without causing disease, but inducing an immune response similar to that induced by natural infection. Weakening can be achieved by adapting the virus to unfavorable conditions (e.g., growth at lower

temperatures, growth in non-human cells) or by rationally modifying the virus (e.g., deoptimizing codons or deleting genes responsible for countering recognition of innate immunity). An important advantage of these vaccines is that they can be administered intranasally, after which they induce an immune response of the mucous membranes of the upper respiratory tract, the main entry gate of the virus. In addition, because the virus replicates in the vaccinated individual, the immune response is likely to affect both structural and nonstructural viral proteins through antibody and cellular immune responses. However, disadvantages of these vaccines include safety issues and the need to modify the virus, which is time-consuming if done by traditional methods, and technical difficulty if reverse genetics is used. Examples of live attenuated vaccines include the BCG vaccine (University of Melbourne/University of Nijmegen, Netherlands/US/Australia) and COVI-VAC (Codagenix/Serum Institute of India, USA/India), which are in clinical trials.

Vector-derived, non-replicating vaccines (including adenovirus vaccines) represent a large group of vaccines in development. Such vaccines are usually based on another virus that has been engineered to express a spike protein and has been switched off from replication in vivo due to deletion of parts of its genome. Most of these approaches are based on adenovirus vectors (AdV), although modified Ankara[de] viruses (MVA), human parainfluenza virus vectors, influenza virus, adenoassociated virus and Sendai virus are also used. Most of these vectors are injected intramuscularly, penetrate vaccinated human cells and then express a spike protein to which the host immune system responds. These approaches have many advantages. There is no need to deal with live SARS-CoV-2 during production, there is considerable experience in producing large quantities of some of these vectors (a primary booster vaccine based on Ad26-MVA against the Ebola virus was created many years ago), and the vectors show good stimulation of both B-cell and T-cell responses. The disadvantage is that some of these vectors are affected and partially neutralized by already existing vector immunity. This can be avoided by using vector types that are either rare in humans, derived from animal viruses, or using viruses that do not themselves induce special immunity (for example, adenoassociated viruses). In addition, immunity to vectors can

be problematic with prime-boosting schemes, although this can be avoided by using priming with one vector and boosting with another vector. Examples of reported nonreplicating vector vaccines include Gam-Covid-Vac (Sputnik V) (Gamaleya Center, Russia), Convidicea (CanSino Biologics, China), AZD1222 (Oxford/AstraZeneca) (AstraZeneca/Oxford University, Sweden/United Kingdom), COVID-19 Vaccine Janssen (Johnson & Johnson, Netherlands/USA).

Vector-replicating viruses usually come from attenuated or vaccine strains of viruses that have been engineered to express a transgene, in this case a spike protein. In some cases, animal viruses that do not multiply and do not cause disease in humans are also used. This approach can lead to a more sustained induction of immunity, since the vector spreads to some degree in the vaccinated individual and often also induces a strong innate immune response. Some of these vectors can also be administered through mucosal surfaces, which can induce an immune response. As an example, an influenza virus-based vector being developed by the Beijing Institute for Biological Products. DelNS1-2019-nCoV-RBD-OPT1 (Xiamen University, China) is currently in development and is not registered.

Vector-derived, inactivated. Some SARS-CoV-2 candidate vaccines currently in development are based on viral vectors that display a spike protein on their surface but are then inactivated before use. The advantage of this approach is that the inactivation process makes the vectors safer because they cannot replicate even in an immunocompromised host. Using standard viral vectors, it is not easy to control the amount of antigen that is presented to the immune system, but in vaccines with inactivated vectors it can be easily standardized, as in the case of vaccines with inactivated or recombinant proteins. These technologies are currently in the preclinical stage.

DNA vaccines are based on plasmid DNA, which can be produced in large quantities in bacteria. Typically, these plasmids contain mammalian expression promoters and a gene encoding a spike protein that is expressed in the vaccinated individual upon delivery. A big advantage of these technologies is the possibility of large-scale production in E. coli and the high stability of the plasmid DNA. However, DNA

vaccines often exhibit low immunogenicity and must be administered using delivery devices to make them effective. This requirement for delivery devices, such as electroporators, limits their use. There are no registered DNA vaccines, with INO-4800 (Inocio Pharmaceuticals, USA/South Korea), AG0301-COVID19 (AnGes Inc., Japan), ZyCoV-D (Zydus Cadila, India), for example, in clinical trials.

RNA vaccines are relatively recent. Similar to DNA vaccines, genetic information about the antigen is delivered instead of the antigen itself, and the antigen is then expressed in the cells of the vaccinated person. Either mRNA (modified) or self-replicating RNA can be used. Higher doses are required for mRNA than for self-replicating RNA, which amplifies itself, and RNA is usually delivered via lipid nanoparticles. RNA vaccines have shown great promise in recent years, and many are in development, such as those against Zika virus or cytomegalovirus. Promising preclinical trial results have been published as potential vaccines against SARS-CoV-2. The advantages of this technology are that the vaccine can be produced entirely in vitro. However, the technology is new, and it is unclear what problems will be encountered in terms of large-scale production and stability during long-term storage, since ultra-low temperatures are required. In addition, these vaccines are administered by injection and are therefore unlikely to induce strong mucosal immunity. Comirnaty (Pfizer/BioNTech/Fosun Pharma, USA/Germany/China) and Moderna (Moderna/NIAID, USA) are registered and actively used, and five more vaccines are in clinical trials.

Recombinant protein vaccines can be divided into recombinant vaccines based on spike proteins, recombinant vaccines based on RBD (Receptor-binding domain) and vaccines based on virus-like particles (VLP, virus-like particle). These recombinant proteins can be expressed in a variety of expression systems, including insect cells, mammalian cells, yeast and plants; it is likely that RBD-based vaccines can also be expressed in Escherichia coli. The yields as well as the type and degree of posttranslational modifications vary depending on the expression system. In particular, for recombinant spiked protein-based vaccines, modifications-such as deletion of the multi-base cleavage site, inclusion of two (or more) stabilizing mutations and inclusion

of trimerization domains, and method of purification (soluble protein versus extraction through the membrane)-can affect the evoked immune response. The advantage of these vaccines is that they can be produced without handling the live virus. In addition, some vaccines based on recombinant proteins, such as the FluBlok influenza vaccine, have been licensed and there is considerable experience in their production. There are also drawbacks. Spike protein is relatively difficult to express, and this is likely to affect productivity and how many doses can be obtained. RBD is easier to express; however, it is a relatively small protein when expressed on its own, and although strong neutralizing antibodies bind to RBD, it lacks the other neutralizing epitopes that are present on a full-length spike. This may make RBD-based vaccines more susceptible to antigenic drift than vaccines containing the full-length spike protein. Like inactivated vaccines, these candidates are usually administered by injection and are not expected to result in sustained mucosal immunity. Examples of recombinant protein vaccines are EpiVacCorona (Vector Center, Russia) and ZF2001 (Institute of Microbiology, China).

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