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Vaccines and Covid-19: basic questions

Scientists are working to get potential vaccines against infectious diseases (Font: FCRi).

What is a vaccine and what is it for?

A vaccine is a medical product that simulates or resembles a microbe, and it's manufactured by using various techniques. Its goal is to generate an infection simulation in order to deceive our immune system, which is activated as if it were really infected. If we don't get vaccinated or don't have a vaccine against a germ we'll get a slow and much less effective response when the immune system comes across the real microbe for the first time. The vaccine trains the immune system to have a rapid and powerful reaction to the infection.

What are the different types of vaccines?

There are three classic types of vaccines: those carrying killed germs, as in the case of flu; those carrying attenuated, non-aggressive or defective germs, as in the cases of measles or polio, and those carrying fractions of microbes, proteins or structures of their membrane, as in the cases of hepatitis B, tetanus or pneumococcus. These are the vaccines currently used in the vaccination schedule.

Non-classical vaccines are still in development, and up until Covid-19 there is none yet to tackle infectious diseases. However, other types of vaccines have been used, such as those against tumours. These are the RNA or DNA vaccines. RNA and DNA are the genetic messages that encode genes in microbes. These messages can be isolated, the so-called «naked» RNA or DNA, or can be inserted into another virus that acts as a «molecular bus», i.e. that carries the genes of the microbe we want to use for the vaccine. These vaccines have been developed on an experimental basis against diseases for which we have no others. Such is the case of AIDS, Zika or the new coronavirus. Only the Ebola vaccine has been marketed.

What does a vaccine contain?

The most important element in a vaccine is the microbe we want to fight: the killed, inactivated microbe, or a portion of it. Classical vaccines carry an excipient in which they are solubilised like all medicines, as well as adjuvants, which are chemicals that are not the vaccine itself but enhance its action. Classical vaccines usually contain alum, which is a compound carrying aluminium.

New vaccines, especially those containing RNA, DNA or proteins, also contain some structures we call «vehicles» that protect them and allow them to be recognised by the immune system. Nanoparticles are the most common vehicle, and there are many types of them: lipids, viral pseudo-particles, metals, or sugar structures or even gold structures.

What is the process for developing and distributing a vaccine?

Vaccines go through the following phases:

– Design. It requires defining the part of the microbe that induces an immune response, since not all parts or elements of a microbe do so. These parts of the microbe are usually called «immunogens», as they generate immunity. In general, especially with viruses, immunogens are surface proteins, because they are those accessible to antibodies, which are the protective immune responses to the infection.

– Animal research, by which two aspects are essentially analysed: on the one hand, whether the vaccines are able to induce antibodies and protect against the infection, i.e. its efficacy, and on the other hand, its toxicity.

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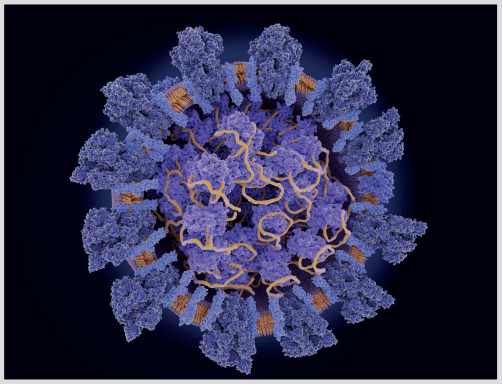
Knowing the structure of the SARS-CoV-2 coronavirus has enabled progress in the design of vaccines to fight it (Font: FCRi).



– Human research. It goes through three phases, and it's always carried out with volunteers:

• In phase 1 both the immunogenicity (antibody induction) and safety of the vaccine are studied. Few subjects, between forty and one hundred, participate in it.

• Phase 2 implies studies aiming to achieve the most appropriate doses, as well as the immunogenicity and safety of the vaccine. A higher number of subjects, between two hundred and one thousand, participate in it.

• In phase 3 the efficacy of the vaccine is measured, i.e. whether the vaccinated subject is better protected. To prove so, a group of unvaccinated subjects is used so that the resistance to the infection between the two groups can be compared.

Two aspects need to be considered:

– There is the so-called «phase 4». The approval of the vaccine is ensued by a long-term follow-up of the side effects, which must be reported to the health authority.

– Although nowadays it seems normal for these studies to be carried out, in past times many vaccines were not empirically tested, such as the smallpox one, which was developed when the viruses were not yet known to exist, or the polio one, for which a clinical test was never carried out. In Spain, two provinces were vaccinated during the first campaign, and the number of detected cases of the disease in those provinces was compared with the number of cases in a non-vaccinated one. In the United States this was not even done against the health crisis caused by this disease in the 1950s.

How do vaccines work?

Vaccines simulate an infection, a sort of warfare exercise without real fire that makes the immune system react as if it were really infected. This is how the so-called «immunological memory» is provided, since the immune system, just like the nervous system, can remember, and this memory response is very quick and powerful. So the vaccine, which is harmless, prepares the immune system to react very strongly when it's really infected by the microbe. This immune response is complex and it actually raises many responses. The antibodies, which act as specific missiles against a given microbe and are able to neutralise it before it enters the cell, are the most important of these responses. The other type is the cellular response, by which infected cells are recognised and destroyed.

What diseases do vaccines prevent?

Vaccines generally prevent infectious diseases, though others act against allergic reactions –pollen, mites, wasp venom– or against tumours, the latter on an experimental basis.

Vaccines prevent a large number of infectious diseases caused by bacteria and viruses. The bacterial infections they prevent include among others pneumococcal pneumonia, meningococcal meningitis, typhoid fever, cholera, diphtheria, and pertussis, while the viral diseases prevented by vaccines are among others smallpox, which is no longer administered as the virus has been eradicated from the world, polio, rubella, measles, mumps, hepatitis A and B, chickenpox and papillomavirus. When we travel to health risk countries, we get «travel vaccines», such as those against rabies or yellow fever.

Why are there still no vaccines against some infectious diseases?

For three main reasons:

– Because we have very good medicines to fight these diseases, such as broad-spectrum antibiotics or antivirals, as is the case of hepatitis C. However, new vaccines are being developed to face the problem of multidrug-resistant bacteria, like those against Acinetobacter or gonococcus.

– Because microbes are poorly transmitted between humans and do not pose a risk to public health.

– Because some germs are too complex and we have not yet been able to manufacture a vaccine to fight them, despite years of research. Such is the case of the human immunodeficiency virus or plasmodium, the parasite that causes malaria.

Why is it important to get vaccinated?

For two reasons:

– Because vaccines protect vaccinated people from serious and sometimes fatal diseases. Let's think for instance of the terrible diseases and symptoms caused by those microbes vaccines protect us against, or those diseases that very often attack children: smallpox, with its 30% mortality rate, polio and its terrible paralysis, diphtheria, tetanus, rabies, and the like.

– Because individuals protect their community besides themselves by getting vaccinated. This is called «herd immunity». When a significant percentage of the population is vaccinated, the microbe finds nowhere to multiply and then it will very unlikely cause an epidemic. This percentage of herd immunity depends on the infective capacity of the microbe: the more infectious it is, the more individuals ought to get vaccinated.

Why healthy lifestyle is not enough to protect us from certain infectious diseases?

Because germs also infect people who live a healthy lifestyle. It's true that certain infections depend on general hygiene measures too, such as chlorate in water, which prevents hepatitis A, or sewage treatment, which prevents cholera or typhoid fever, and it's also true that malnutrition weakens both our body and immune system, which loses its efficacy in protecting us. These habits are a help, but not enough to protect us from certain infections.

Is the immunity provided by vaccines better than that provided by natural infections?

The immune response to natural infection is often more powerful. The problem is that the infection might turn out to be fatal as a result of the fact that the immune system wasn't able to contain it and stop it on time. Measles natural infection generates a more powerful response than vaccination, but avoiding measles outbreaks that may lead to serious complications is a more important issue.

Some vaccines generate very powerful responses. For instance, people vaccinated against smallpox get lifelong memories. The same is true for hepatitis B, for instance, which is a more modern vaccine. In general, we need to get revaccinated throughout life, which is something we not always do. In this case we are protected by herd immunity.

When is the right time to get vaccinated?

It depends on the microbes, and when they pose a health problem and may cause a serious disease. Most of the vaccines are administered during childhood, as they prevent very serious diseases in children, though others are given to adults or elderly people, as in the case of flu or pneumococcus, which causes a serious illness in the elderly or in people who suffer from other diseases. And finally, as already mentioned, when we travel to endemic countries because of other microbes we ought to be given the «travel vaccines», such as those against yellow fever, rabies, and the like.

Who can get vaccinated?

In principle, everybody can, though precautions should be taken to protect two groups of people: pregnant women, for whom attenuated vaccines are not recommended, as they carry live viruses, somewhat stunned, but live anyway, and people who suffer from immunosuppression, which is caused by certain diseases or treatments, such as those using corticosteroids or chemotherapy. These people can be given vaccines carrying killed viruses or virus proteins, but never inactivated viruses.

Do we need to get vaccinated against rare diseases in our community or country?

No. We need so only when we travel to risk countries because of a microbe that does not exist in ours or when we get in contact with a traveller carrying an imported disease, but the latter case is rare.

Have the necessary steps been taken to ensure a safe vaccine in the case of Covid-19?

Yes. The fact that these steps have necessarily been taken quickly does not compromise safety. Vaccines imply three types of serious side effects:

– The immediate ones, which are usually pain in the injection area, fever, discomfort, and muscle pain. These effects are not significant and appear between forty-eight and seventy-two hours after the vaccination has been administered. Allergic reactions to components of the vaccines are immediate too, though they are rare and can be prevented. For instance, flu vaccine is grown in eggs, so people who suffer from egg allergies should not get it.

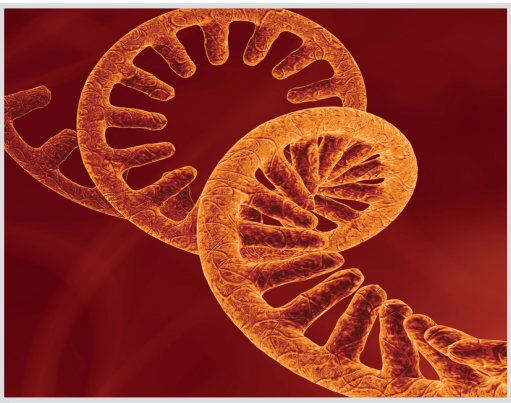
– Major adverse reactions because of a cross-reacted or misguided immune response that attacks an organ or system. These reactions occur in the first two months after the vaccine has been administered, and as during phase 3 trials patients were followed up for at least six months the effects would have been detected.

– Very rare effects occur in the long term. They are exceptional and difficult to be predicted. This is why all marketed medicines and vaccines are always monitored. If any serious and incomprehensible health effects occur, it must be reported to the health authority, the medicines agency, to check out whether or not is related to the vaccine. These effects are seldom related to the vaccine, but even so a part of the population is very much concerned in some cases. Such is the case of the fear of the relation between vaccines and autism, which is false.

Why have Covid-19 vaccines arrived so much sooner than those against other diseases?

There are three things to be considered here:

– The progress achieved in new vaccines research over the last five years. All this prior knowledge allowed applying in the case of coronavirus what was done before with other microbes. We can say that, despite all the pain and the health, economic, and social crisis, we have been lucky that Covid-19 has arrived now, in a moment when science was ready to provide a response. One lesson we should learn from the pandemic is that disinvestment in science comes at a high price and that research cannot be improvised. That is why only countries with a solid



Coronavirus RNA chain
(Font: FCRi).

science and biotechnology base have succeeded in developing a vaccine in record time.

– The health and economic urgency, which pushed the states and companies to invest no less than 500 million euros to support research groups that due to their experience could make these vaccines. Powerful research, solid biotechnological base, strong support from the states, and the commitment of pharmaceutical companies to promising prototypes are gathered behind all the vaccines to be administered.

– The adoption by companies and regulatory agencies of a three-tiered acceleration strategy:

• The very rapid generation of prototypes. This was possible owing to the research already underway and the choice of the new vaccines, which allow high safety and large-scale manufacturing in a short time.

• The combination of animal and human subject research, which was carried out simultaneously rather than successively. This is possible and ethical too, since new prototypes, such as RNA vaccines, are very safe and allow this strategy, which is not possible, for instance, in the case of attenuated vaccines.

• The start of vaccines large-scale manufacturing before having the results of the efficacy trial or phase 3. This poses a great risk to companies, as they lose a huge investment when trial brings no profit. Political authorities acted as insurers here by buying the vaccines before their efficacy was proved. Their commitment was paying for them even if in the end they didn't work. This allowed the risk to be taken.

What types of vaccines are being developed to tackle Covid-19?

In the case of classic vaccines:

– Killed or inactivated vaccines. There are several prototypes of them, mainly those produced in China, which are already used in that country to immunise the population. These are very safe vaccines, but have low efficacy, as the induced immune response is generally weak. They have been most rapidly developed by Sinovac and Sinopharm, though many other companies are working on this type of vaccines at earlier stages.

– Attenuated vaccines. They are not recommended for this type of infection, as the attenuated virus can result in a less attenuated or weakened one. One variant of them are the so-called «replicons», which are attenuated viruses that multiply but don't spread from cell to cell. They are more difficult and slower prototypes to achieve, as they require a lot of safety testing before being tested on humans.

– Protein subunit vaccines. Novavax-Sanofi has already a very promising prototype in phase 3. These are safe vaccines, and this one in particular induces a very potent response when combined with an adjuvant.

In the case of new vaccines:

– RNA vaccines. Despite the technical difficulty and the novelty they involve, they were the first to achieve the goal. The Moderna and Pfizer-Biontech prototypes were the ones to be approved first. They are very safe vaccines and their efficacy is extraordinary. They are delivered in liposomes and lipid nanoparticles.

– DNA vaccines. In this case, a SARS-CoV-2 gene is inserted into another virus that acts as a «molecular bus». The most developed ones are based on adenoviruses: adenovirus 5, as in the case of Chinese Cansino; chimpanzee adenovirus, AstraZeneca; adenovirus 26, Janssen, and the combination of adenoviruses 5 and 26, used by the Russian Gamaleya. Published results are good, though vaccines based on adenovirus 5 are less effective in elderly people and there is controversy about the recommended dosage in the case of the AstraZeneca vaccine. They will probably be the second line of approval. The Russian and Chinese ones have already been approved and they are actually being administered.

– Other replicons or self-replicating RNA –another type of vectors that use the attenuated smallpox virus, the measles virus or even attenuated bacteria, such as the tuberculosis one– are being developed.

Will new vaccines for Covid-19 continue to appear in the coming months?

The basic problem here is that as ten approved prototypes will be available by the first quarter of 2021, those under development have very little chance of reaching the final stages, since carrying out phase 3 trials will be almost impossible.

To begin with, they cannot have a placebo group and will need to be compared with an effective marketed vaccine at a time when these vaccines will be in high demand because of the vaccination of the general population.

On the other hand, recruiting volunteers will be a difficult task, as they will have to choose between a vaccine with a proven 90% efficacy and one which efficacy is unknown.

Moreover, for ethical reasons, the at-risk population, such as the elderly or people who suffer from pathologies, cannot be included in these trials, and so demonstrating how these prototypes act on these groups of people will be practically impossible.

And finally, companies will very unlikely invest hundreds of millions of euros in these prototypes due to the high risk in terms of demonstrating their efficacy in phase 3.

PARLAMENT DE CATALUNYA

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