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WHY CAN'T WE DEVELOP VACCINES AGAINST ALL THE GERMS THAT MAKE US SICK?

The World Health Organization (WHO) estimates that immunization alone prevents approximately three million deaths worldwide along with access to safe drinking water, the public health measure that has the greatest impact in terms of reducing mortality.

In response to the COVID-19 pandemic caused by the emerging SARS-CoV-2 coronavirus, two main avenues have been explored: antiviral treatments and vaccines. While the Solidarity clinical trial, set up by the WHO to help find an effective treatment against Covid-19 was unsuccessful, three vaccines against SARS-CoV-2 were developed during 2020: BNT162b2 (BioNTech/Pfizer), mRNA-1273 (Moderna) and ChAdOx1nCoV-19 (Oxford/AstraZeneca).

Within a few months, they were tested in animals and validated in human clinical trials, an absolute record in the history of modern vaccination. Previously, it was considered that an average of eight years was required to have an effective and safe vaccine.

What is the reason for this success? Does it herald a new vaccine revolution which would make it possible to develop vaccines against any pathogen? The reality is more complex.

COVID-19 vaccines: the recipe for success

Attenuated, inactivated, adjuvanted subunit vaccine, viral vector, ribonucleic acid (RNA)… In the face of the health emergency due to the rapid spread of the SARS-CoV-22, all available vaccine technologies have been used without any preconceived ideas in an attempt to develop a vaccine, the objective being to reduce the risk of failure. All stages of development and validation also followed one another without any

pause.

This “all at once” strategy, which was financially very costly and also risky, was only made possible through massive government investment. To date, the United States government has invested more than $18 billion through Operation Warp Speed to fund the development of COVID-19 vaccines. An impressive figure but one that remains negligible compared to the estimated economic cost of the COVID-19 epidemic to the country. If the pandemic is brought under control by the end of 2021, experts estimate that it will have cost the United States between three to five trillion dollars over two years.

This massive investment will not only benefit the management of the SARS-CoV-2 pandemic. In particular, it has made it possible to validate the use of the RNA vaccine technology in humans, which has several major advantages. This technology makes it possible to develop a vaccine directly from the pathogen’s genetic sequence, without needing to go through its culture or the production of its proteins using genetic engineering, and thus saving a considerable amount of time.

In mice, this technology has made it possible to develop protective vaccines against viruses such as the Influenza H1N1 virus or the Ebola virus in just a few months. The new technology enables the production of candidate vaccines to deal locally with emerging infectious agents before they spread and pose a pandemic risk.

Finally, it also paves the way for personalized vaccines against tumors or autoimmune diseases These therapeutic vaccines, produced specifically for a single individual, could revolutionize immunotherapy.

Successes, but also many failures

However, this success and these hopes should not make us forget that there are more than 1,400 pathogens that infect humans and that new ones emerge every year. More than a century has elapsed since Louis Pasteur discovered vaccination but, within this time period, we have only been able to produce effective vaccines for less than 30 infectious diseases.

Of course, we do not need vaccines against all pathogens. Many pathogens only cause benign pathologies and many infections are preventable by simple prophylactic measures. Nevertheless, for decades we have faced repeated failures with several pathogens that represent public health priorities.

The causes of these failures are numerous. One of them is the vaccine funding model. Complex and time-consuming, it often involves numerous public-private partnerships. Yet, the potential market for some vaccines may be deemed insufficient by private investors: for example, when the pathogen infects only a small number of individuals or has a limited geographic distribution.

But money is not everything: considerable investments have been made to fight against the human immunodeficiency virus (HIV) responsible for acquired immunodeficiency syndrome (AIDS), the Mycobacterium tuberculosis bacterium (also known as ‘Koch’s bacillus) that causes tuberculosis, and the protozoan parasite Plasmodium causes malaria, which together are responsible for more than 2.5 million deaths each year. However, these investments have still not led to the development of efficient vaccines. The first hope, a malaria vaccine, RTS, S/AS01 (Mosquirix, GSK), showed significant but partial protection in young children in 2015.

Why are there such difficulties, even when the resources allocated to research for new vaccines are considerable? Will new vaccine technologies, such as RNA vaccines, be able to change this situation?

Technical barriers to vaccine development

Upon detection of a pathogenic agent, the immune system rapidly responds through an innate response,

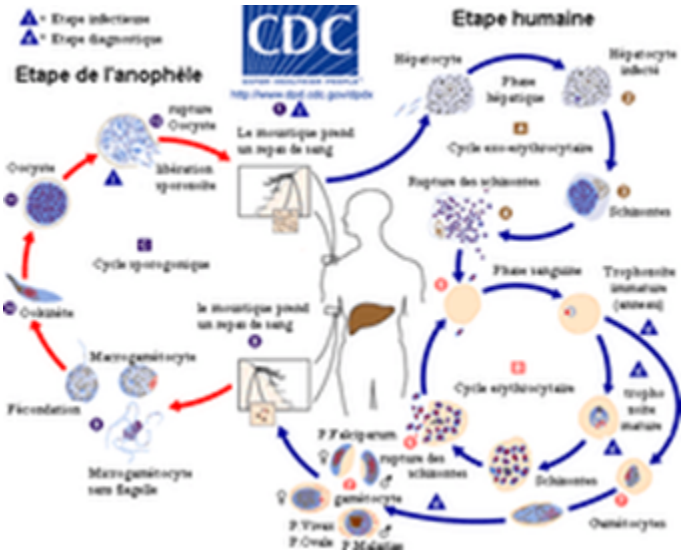
mediated in particular by mucosal cells and macrophages. To infect the host, a pathogen must be able, at the very least, to partially escape this stereotypical response, which is not specific to any given invader. The development of an adaptive response, specific to the pathogen and mediated by the lymphocytes, usually helps the immune system to eliminate the infectious agent and acquire long-term immunity against the germ.

The principle of vaccination consists of copying this adaptive immunity that develops following a natural infection. All vaccines therefore contain information about the structure of the pathogen, known as ‘antigens’ (a term used to describe any foreign element in the body capable of triggering an immune response). Depending on the type of vaccine, antigens may be present in the form of, for example, virus proteins (adjuvanted subunit vaccine) or viral genetic material (vectored vaccine, RNA vaccine). They are essential to induce the development of specific memory lymphocyte populations that will control and eliminate the pathogen.

To develop a vaccine against a pathogen, identifying vaccine antigens is therefore considered a prerequisite. The genome of the majority of viruses contains only a few dozen, or maybe a few hundred, genes. It is therefore fairly easy to identify those corresponding to the antigens most exposed to the immune system, such as the SARS-CoV-2 spike protein.

In bacteria and protozoa, however, it is different: their genome contains several thousand genes. And some parasitic worms have tens of thousands of genes. As a result, identifying vaccine antigens for these highly complex pathogens can be a very time-consuming task.

Figure 1. Plasmodium falciparum: the life cycle of the malaria parasite



Source: CDC

In addition, some pathogens have complex life cycles within their host (the organism they infect). They can change during the course of infection. These changes may be accompanied by different forms of the antigens at each stage of the cycle. This makes it even more difficult to identify the most appropriate antigens to develop an effective vaccine. This is the case, for example, with Plasmodium protozoan, the malaria parasite, with part of its life cycle in the Anopheles mosquito and part in humans. The mosquito vector infects humans with the first form of the parasite which then multiplies in liver cells and transforms into a second form. The second form then infects red blood cells and multiplies into a third form. Each of these forms has distinct antigens.

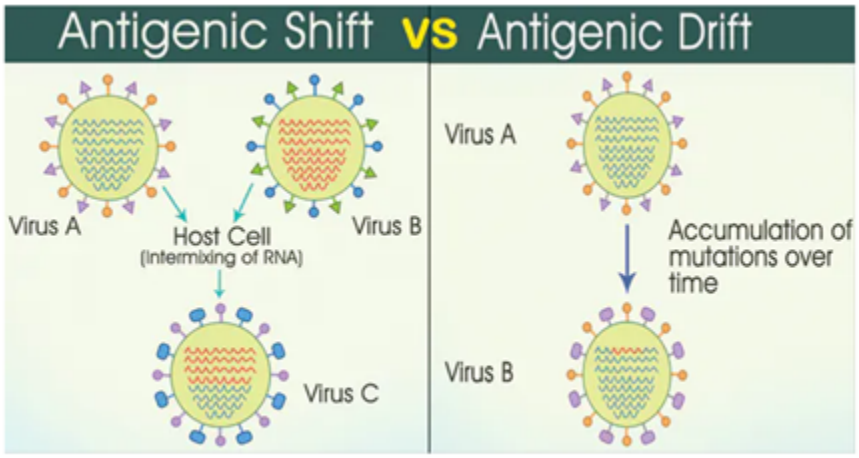
The issue of failure of the immune response

Beyond these difficulties in identifying vaccine antigens, during their evolution many pathogens have also acquired mechanisms that lead to failure in the adaptive immune response. These mechanisms allow them to stay in the host for long periods, sometimes for the host's entire life, thus increasing their chances of transmission. These mechanisms which cause the failure of the immune system primarily result from antigenic variation (antigens change over time, thus thwarting the development of adaptive immunity), stealth or neutralization of the immune system, that sometimes makes vaccine development a nightmare.

The genome of RNA viruses evolves at an extremely rapid rate. In fact, when these viruses multiply and copy their genetic material, they make many mistakes that lead to the emergence of a large population of variants. This wide variety can make it impossible to identify the vaccine antigens that would allow the entire population to be targeted.

The case of the influenza virus responsible for flu is emblematic in this regard. Its genome can gradually evolve not only through mutation (this phenomenon is called 'antigenic drift') but also by exchanging entire genes with other viruses of the same species (reassortment). Influenza vaccines cannot target all of these antigens; they contain only the most common ones. As a result, they do not protect against all variants of the virus and their composition must be updated annually to reflect the antigens present in the most common circulating viruses.

Figure 2. Antigenic shift versus antigenic drift



Évolution du virus Influenza, agent de la grippe. Différence entre réassortiment (Antigenic Shift) et dérive antigénique (Antigenic Drift)

Some pathogens are even able to alter the most exposed antigens on their surface at such a rate that they generate a large population of variants within the infected host itself. This is the case, for example, with the Helicobacter pylori bacterium, which causes peptic ulcers, or the protozoa Trypanosomabrucei or sleeping sickness. This permanent variability prevents the adaptive immune system from targeting the entire population of invaders and, thus, from neutralizing them.

Other pathogens can make themselves virtually invisible to the immune system by directly neutralizing their activation pathways or by modifying the host cells to build cellular reservoirs that isolate them from the immune response. Viruses of the Herpesviridae family, such as cytomegalovirus, block the presentation of their antigens to the immune system. The Mycobacterium tuberculosis bacterium disrupts microbicidal mechanisms and modifies the metabolism of the macrophages it infects to its advantage.

The partial or total suppression of the immune system, that weakens the host immune system (immunosuppression), is another effective strategy that ensures the persistence of the pathogen. It is likely to invalidate all vaccine strategies. The measles virus reduces the diversity of the host antibody repertoire and deletes the protective immune memory acquired against other pathogens, thus resulting in 'immune amnesia'. As for an infection with Plasmodium protozoan, it induces the production of immunosuppressants, molecules that affect the entire immune system and for a long time they reduce the host's ability to react to infections and to develop immunity following vaccination.

And nothing prevents certain pathogens from accumulating numerous mechanisms that lead to failure. HIV, for example, has a very high mutation rate which is the source of many variants and is capable of integrating itself into the genome of its host cells for a long period, thus becoming undetectable, and destroying CD4 T lymphocytes, ultimately causing severe and irreversible immunodeficiency. This combination of failure mechanisms has so far defied all vaccine strategies.

We should not be blinded by the success of COVID-19 vaccines

There is no doubt that vaccination techniques have considerably evolved in recent decades, thanks in particular to a better understanding of the immune system and advances in molecular biology techniques. Nevertheless, it should be noted that we have been 'fortunate' to be confronted with a relatively 'simple' pathogen, the SARS-CoV-2 coronavirus.

Indeed, while new vaccine platforms make it possible to rapidly produce vaccines based on pathogenic genetic sequencing, it is unlikely that this empirical approach will be sufficient to deal with complex micro-organisms or those that have mechanisms that induce failure in the adaptive immune response. To counter this type of pathogens, it will probably be necessary to finely characterize their multiplication cycle, as well as their interactions with the host immune system, to reveal the chinks in their armour. This may prove to be time-consuming and requires the funding of long-term basic research without a preconceived notion of the expectations, as well as close cooperation between immunologists and microbiologists.

It should also be borne in mind that having an effective vaccine does not mean that the genomic evolution of the pathogen in question does not need to be monitored. Indeed, the relationship between a pathogen and its host follows a 'Red Queen-type' dynamic: pathogens evolve constantly in response to host selection pressures, as shown by the acquisition of resistance to antibiotics, antivirals and certain vaccines.

Numerous mutations of the CoV-2-SARS have already been documented. Will the pressure generated by COVID-19 vaccines identify variants capable of escaping vaccination? Time will tell. One thing is certain, monitoring and understanding the interactions between the pathogen and its host is important for anticipating these potential problems.

Finally, a vaccine is only effective if it is used. Vaccinating the world's population is a challenge, not only logistically because of poor infrastructure in many regions but also because of the high level of vaccine hesitancy. So much so that in 2019 WHO identified vaccine hesitancy as one of the top ten threats to global health.

In conclusion, it remains imperative to invest massively in health systems, scientific communication and. above all, in the prevention of pandemics, by acting on the socio-economic conditions that foster their emergence. For it is now clear that preventing these crises is much less costly than addressing them when they emerge.

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