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Mini Review

Process for the Production of Vaccines in Basic Steps

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Abstract

Understanding the complexity and cost factors associated with vaccine production is essential for informing decision-making by companies, governments, and policymakers considering investments in vaccine manufacturing for immunization and outbreak response. Top multinational companies are well aware of the complex manufacturing processes, the high technological and R&D barriers to market entry and the costs associated with vaccine production. Policymakers in developing countries, donors and investors, however, may not be aware of the factors that continue to limit the number of new manufacturers and have led to attrition and consolidation among existing manufacturers. Through providing a general and consolidated overview of these requirements, we aim to raise awareness in the global community of the benefits and costs of vaccine manufacturing and the challenges associated with maintaining a constant supply.

Every year, vaccines save millions of lives, but what exactly constitutes a vaccine, and how is it manufactured? Also, how do we know they're safe? This is where we talk about all aspects of vaccines. A vaccine is made up of a whole bacteria or virus or parts of it, often a protein or sugar. It is these active components of the vaccine, called antigens, that trigger an immune response in the body. Since vaccines are biological products, most conventional viral vaccines must be grown on biological material, for example, on chicken eggs for influenza vaccines, on mammalian cells for hepatitis A vaccines, or on yeast for hepatitis B vaccines. It is a rather tedious and slow process. For example, in flu vaccines, the live virus is injected into an embryonated egg, then once the virus has replicated, the viral material is collected, purified, and inactivated. More recent RNA vaccines can be produced from a DNA template, which is much cheaper and faster than conventional vaccine production. The manufacturing process of vaccines can be a complex one, but we can simplify these processes

The vaccine production process involves the following steps:

- Breeding of the pathogens against which the vaccine is to be effective, or genetic engineering of the desired antigens or of the appropriate antigenic construct
- "Harvesting" of the antigens, for example of viruses from cell cultures or of antigens from yeast cells, or of the genetic blueprint, and subsequent preparation
- Adding further components, e.g. to enhance the vaccine effect (adjuvants), and combining the components in the case of combination vaccines
- Packaging and filling

The manufacturing process

From the immunological point of view, however, it is worth discussing the production-related aspects of vaccines:

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Vaccination trains the immune system to combat pathogens that may cause severe or fatal diseases. This could be a virus, a bacterium, or even a parasite (in the case of malaria, for example). Hours after receiving a dose of vaccine, the specialized white blood cells of the immune system - B cells and T cells - are already activated [1]. After approximately two weeks, the B cells release antibodies into the bloodstream that can bind to the vaccine target. A few of these antibodies neutralize the microbe to prevent it from entering human cells. In addition, T-cells (called "killers") come into play to eliminate the microbes so that they cannot cause disease or complications [2]. For the immune system to produce B and T cells that are effective against a given microbe, it must learn to recognize certain elements that are characteristic of that microbe: often these are specific proteins present on the surface of the microbe. Each vaccine contains at least these characteristics of the target microbe, and these characteristics can be presented to the immune system in several ways [3].

Vaccine manufacturing process

Depending on the nature of the vaccines, the following manufacturing principles are relevant: Immunization contains the entire microbe in an attenuated form. An "attenuated" form is when the microbe is manipulated to make it less aggressive, such as by reducing its ability to multiply. It is the most effective method, but also the one that requires the most care. Attenuated live vaccines mimic natural immunity, and trigger a stronger and more prolonged immune response: after one or two doses, there is no need for a booster vaccination. The main disadvantage is that they cannot be given (except in exceptional cases) to people with weakened immune systems due to certain diseases or medical treatments [4].

Some vaccines contain the entire microbe in an inactivated form, rendering it incapable of multiplication or causing disease. Inactivated whole vaccines are generally less effective than live attenuated vaccines and often require multiple doses or boosters. The main advantage of inactivated vaccines is that they have very few side effects and can be given even to people with weakened immune systems [5].

Vaccines are purified and contain only one or more fragments of the microbe. Such vaccines contain only those elements of the microbe that are necessary for the immune system to recognize it and provide protection. The advantage of these vaccines is that they stimulate the immune system in a very targeted way. They are therefore very well tolerated, but booster shots are often necessary [6].

Conjugated vaccines that contain only the complex sugars (polysaccharides) of the microbe's capsule, attached to a transport protein to be better recognized by the immune system. Multiple injections may be required to achieve immunity, which may last only a few years [7].

Vaccines "by vector": A large piece of the microbe is inserted into a virus or bacteria that does not cause disease in humans. These 'vectors' are chosen so that their multiplication is impossible (e.g. ChAdOx1) or limited (e.g. rVSV) in the human body so as not to cause infection. It is a recent technique that has already proved its worth in vaccinating against Ebola disease and certain cancers. With viral vector vaccines based on an adenovirus (Astra Zeneca/Oxford University or Janssen/Johnson vaccines), the gene code of the adenovirus is modified (truncated DNA) so that the virus cannot replicate in the human body. Therefore, it is biologically impossible for it to cause a modified adenovirus infection. DNA from these adenoviruses used as vectors can enter cell nuclei, but incorporation into human cell DNA is made impossible by modification of its DNA strand ends. Adenovirus DNA is transcribed into messenger RNA in the nucleus and then expelled into the cytoplasm where it is translated into proteins (Figure 1).

1. In the lab, we extract the RNA sequence of the coronavirus that contains the information to make its surface protein Spike (dark-shaded).
2. The RNA Spike sequence is converted into a DNA Spike sequence.
3. The Spike-DNA sequence is inserted into the chromosome of an adenovirus.
4. Modified adenovirus carries the Spike surface protein on its surface, but is unable to multiply.
5. Immunization: modified adenovirus is injected into the arm of a person.
6. Modified adenovirus enters a human cell, and transfers its DNA into the cell nucleus. The vaccine DNA is modified so that it does not integrate into the genome.
7. Within the nucleus, the DNA-Spike sequence is transcribed into messenger RNAs that then exit the nucleus.
8. The human cell's tools read the messenger RNAs, make Spike proteins, and release them into the body - this will alert the immune system and allow the body to produce antibodies against the Spike protein. If a coronavirus enters the body 2-3 weeks after vaccination, the immune system will be able to recognize it quickly

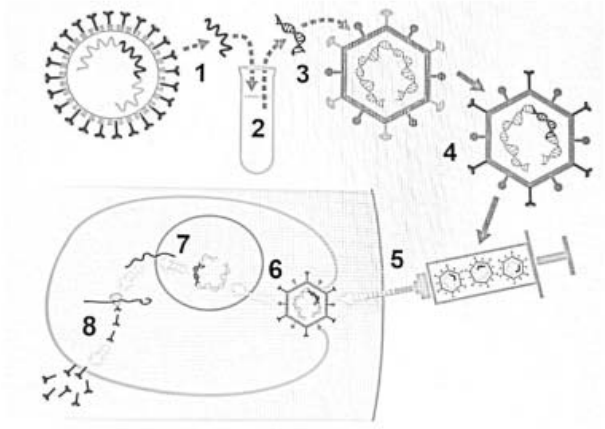

Figure 1: Production methods for vector vaccines.

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and neutralize it, including antibodies against the Spike protein [8,9].

Messenger RNA vaccines, through direct injection of a fragment of the microbe's genetic material (m-RNA), are encapsulated in nanoparticles composed of various lipids (liposomes). The messenger RNA vaccine technology has been known for about ten years, but despite its attractiveness (simplicity of concept, speed of development, easy production) it did not benefit from the necessary investments before the mobilization resulting from the COVID-19 pandemic. A comparison of natural coronavirus infection and vaccination with messenger RNA (Figure 2).

A. Natural Infection:

1. A coronavirus SARS-CoV-2 enters the human body and binds to a cell with its nail-like surface proteins (in English, this protein is called Spike).
2. It releases its RNA (genetic code that contains all the information needed to make the virus) into the cell.
3. The cell uses its own tools to read the viral RNA and to manufacture, in spite of itself, all the parts of the virus (different kinds of proteins + viral RNA).
4. New viruses can self-assemble and then be released into the human body to continue the contamination... In order to stop the reproduction of the virus, it is necessary to wait several days so that the immune system of the body reacts, and finally produces antibodies [10].

B. Immunization with viral messenger RNA (Figure 3):

1. In the lab, messenger RNAs encoding only the Spike protein of the coronavirus are made. Messenger RNAs are inserted into small fat bubbles.
2. During the vaccination, fat bubbles are injected into the muscle of the arm, and then they are absorbed by human muscle cells: the messenger RNAs are released.
3. Human cells use their own tools to read the messenger RNA and make only Spike proteins. These proteins alone are not dangerous for the organism.
4. Cell releases viral Spike proteins into the body - which will alert the immune system and allow the body to produce antibodies against the Spike protein then after 2-3 Weeks after vaccination, if a coronavirus enters the body, the immune system will quickly recognize and neutralize it, especially with antibodies against the Spike protein [11,12].

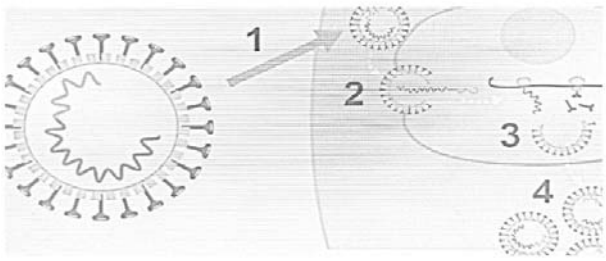

Figure 2: Production method natural coronavirus vaccination.

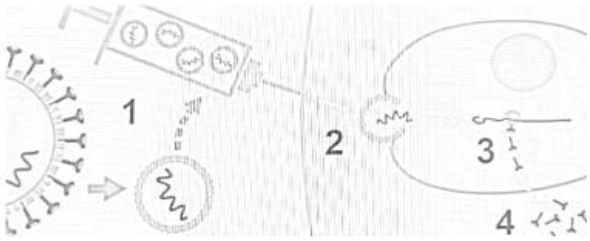

Figure 3: Immunization with viral messenger RNA.

Conclusion

Vaccines are developed, evaluated, and controlled in a similar way to other drugs. In general, vaccines are tested even more thoroughly than other drugs because the number of subjects in clinical trials for vaccines is usually larger. In addition, public health agencies responsible for approving vaccines are intensively involved in monitoring vaccines once they are approved.

Expanding vaccine production capabilities in developing countries presents a significant opportunity to enhance global health security. Although inequitable access to vaccines is the catalyst for finally accelerating efforts to scale up production, it is long overdue. Improving health security by ensuring the supply of vaccines against both pandemics and endemic and epidemic infectious diseases is of great benefit to current and future generations. Moreover, the ability to produce pandemic vaccines during the next crisis depends on the availability of high-quality and productive vaccine manufacturing capacity capable of responding. Building this "warm" capacity in the period between pandemics can build a long-term industry and provide an economic boost to developing countries while benefiting overall health worldwide. Innovations ranging from the development of artificial interfering drives to personalized vaccines and new delivery methods will shape the future of vaccine research. But overcoming preclinical limitations remains a major hurdle. For example, ex vivo human models and platforms offer an innovative approach to accelerate vaccine development while improving human relevance. Additionally, as the field continues to evolve, the integration of advanced preclinical models will be essential for the development of safer and more effective vaccines.

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