


vaccine development: from concept to licensed product

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DEVELOPING A NEW VACCINE takes a lot more time, effort and scientific expertise than most people realize—rarely less than ten years, and sometimes several decades. While each vaccine is different, the research and development process moves through defined stages that take candidates from a concept to a licensed product. This article gives a quick overview of the whole process. Most of the stages are described in more detail in other chapters.

getting started

Before a vaccine concept can get off the ground, certain basic knowledge is needed. First and foremost, researchers must know what *pathogen* causes the disease and they must be able to grow and isolate it in the laboratory. The more they know about the pathogen, how it works and how the immune system responds to it, the better.

Building on this basic knowledge for HIV, an experimental AIDS vaccine begins with an idea—what scientists call a hypothesis, or an educated guess. Based on their own and others' observations, scientists hypothesize how the human immune system might be stimulated by a vaccine so it can defend the body against HIV infection or disease.

For instance, in the 1990's researchers came to realize that people infected with HIV are able to control the *virus* for a period of years before it begins multiplying more rapidly and destroys their immune system. This temporary control, it turns out, corresponds with a relatively high number of certain immune cells (*T-cells*, or *T-lymphocytes*) that specifically recognize HIV-infected cells. Hence, scientists hypothesized that a vaccine which stimulates these T-cells might not prevent the initial infection but could perhaps control virus *replication*, which in turn might delay or prevent people from getting sick with AIDS. This is the concept behind nearly all the experimental HIV vaccines now being tested.

designing vaccines

Translating a hypothesis into an actual HIV vaccine is a difficult step. A big part of the reason is that we don't understand enough about HIV transmission or our *immune responses* to HIV to know just which parts of the virus to include in a vaccine, and in what form. So vaccine designers have to rely partly on best guesses (the "empirical approach," as it's sometimes called). The next chapter has more information on how vaccines are designed and on the most common designs for HIV vaccines.

Once a candidate has been made in the lab, it is put through a series of tests and gradually improved. If these experiments pan out, the vaccine moves quickly into animals, where its ability to stimulate *immunity* can be tested.

animal experiments

Initial tests are typically conducted in small animals such as mice, guinea pigs or rabbits, and then in monkeys. The aim is to measure the strength and type(s) of immune responses induced by the vaccine. (The stronger these responses are, the more *immunogenic* the vaccine is said to be.) Investigators also look for ways to increase *immunogenicity*, for example, by varying vaccine dosages and *immunization* schedules, or adding certain compounds that may enhance immune responses. Other tests examine the toxicity of the candidate vaccine, including its side effects, to evaluate safety.

Animal testing may also involve so-called “*challenge experiments*” in monkeys to test whether the vaccine actually works. Although monkeys can’t be infected with HIV, they are susceptible to its close relative *SIV (simian immunodeficiency virus)*, which causes the same kind of immune system failure seen in people with HIV, and to a laboratory-made hybrid of HIV and SIV called *SHIV*. In these experiments, small numbers of monkeys are vaccinated and then challenged (that is, deliberately infected) with SIV or SHIV. Scientists then monitor whether vaccinated animals show lower rates of infection or disease, or lower amounts of virus in the blood (called *viral load*), compared with unvaccinated ones. If they do, it is a good sign—although it doesn’t guarantee that the same type of vaccine will protect humans.

Why not? Because animal models are useful, but only up to a certain point. Despite the similarities, monkeys are also biologically different from people. And SIV or SHIV is not HIV. In other words, there is no exact animal model for HIV—a big obstacle in developing an HIV vaccine. So ultimately, the only way to know whether a promising experimental vaccine is safe and effective for humans is to test it in uninfected people, through a lengthy sequence of *clinical trials*.

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big decisions

Only relatively few vaccines make the huge jump from the lab into clinical trials. Although there are no strict criteria for choosing which ones to move forward (except for an excellent safety record), decisions may depend a lot on whether animal data are promising enough to justify the enormous time, expense and use of human volunteers these trials demand. Along with good scientific evidence from the lab (although scientists may disagree about what is “good”), the vaccine should have a strong chance of being acceptable to regulatory agencies and to the general public. There should also be a feasible (and ideally inexpensive) way to manufacture it, although in practice this requirement is sometimes factored in only later for decisions on which candidates should go into large-scale human trials.

clinical trials

Clinical trials are conducted in three sequential phases, each enrolling larger numbers of volunteers and answering somewhat different questions. (For more on the later-stage trials, see chapter 11.)

- › *Phase I trials*
typically involve several dozen volunteers at low risk for HIV infection and focus on safety issues, but usually also look at whether the vaccine is immunogenic. Often several Phase I studies will be done in succession, to test different vaccine doses or immunization schedules.
- › *Phase II trials*
involve several hundred volunteers, often including some with a high infection risk, and gather both safety and immunogenicity data.
- › *Phase III (efficacy) trials*
enroll several thousand volunteers or even more, and to *statistically* determine whether the vaccine works—that

is, does it protect some vaccinees from either infection or HIV/AIDS disease? Very few of the vaccines tested in Phase I will go all the way to Phase III testing. So far there have been dozens of different HIV vaccines in Phase I trials, but only three types have made it into Phase III.)

Alongside these traditional categories, HIV vaccine developers are adding a fourth one to the process: so-called *Phase IIb* trials, also called “proof of concept” trials. The idea is to look for preliminary evidence of efficacy in smaller, shorter and much less expensive trials before launching a full-fledged Phase III study.

For HIV vaccines, it's highly likely that *Phase IV* studies will also be done. These are studies conducted after a vaccine has been licensed, to determine its true effectiveness outside the *controlled* conditions of a clinical trial, to measure how long protection lasts and to look for any late-emerging or very rare side effects. A Phase IV study can involve up to many thousands of people.

Since vaccine trials involve giving a new substance to healthy people, scientists need advance approval from various regulatory bodies in the country where the vaccine is produced and the countries where it is to be tested. (For more information on regulatory review and safety, see chapter 14.)

licensing

Before a vaccine can be distributed and used by the public, it has to be licensed by the regulatory body that monitored the clinical trials and by those in countries where it will be used. Licensing decisions involve careful review of Phase III trial data by the regulators, who look closely to make sure the vaccine is safe and that it offers a clinical benefit. There's no fixed standard for how much of a benefit is necessary for licensing an HIV vaccine. In practice it could even end up that countries might make different decisions, depending on factors such as the severity of their epidemic.

Obviously, a vaccine that is safe and highly successful in preventing HIV infection or disease would be licensed. But HIV vaccines may raise some difficult issues for regulators. One is how to recognize, let alone license, vaccines that delay disease without blocking infection—an outcome that can't be fully measured in the 3–4 year time span of an efficacy trial. Another type of dilemma would arise if the first HIV vaccines work in only a relatively small proportion of people—say, 30%. Is this enough to merit licensure? (For a discussion of partially effective vaccines, see chapter 9.) Complicating the decision-making process even more, differences in regulatory procedures from country to country could lead to a bureaucratic mess over licensure, especially since some developing countries are short of capacity and expertise in this area.

manufacturing

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At first glance, manufacturing a vaccine may seem straightforward, but in practice it's usually difficult, expensive and time-intensive. Vaccine makers therefore have to start their planning as early as possible in a product's development. Yet making a major investment in manufacturing capacity before efficacy trials have shown that the vaccine works is a very expensive gamble. (This dilemma is discussed further in chapter 36.)

Problems making a new vaccine can arise even with the (relatively) small amounts needed for clinical trials. But the bigger problems come later, in finding ways to produce hundreds of millions of doses (if the vaccine proves to be effective)—methods that usually take time and practice to work out. It also takes years to build and equip the high-tech factories that can make such huge amounts of vaccine, and to have them approved by regulators. Ideally, construction should begin while a vaccine is still in clinical trials so there is no delay in having enough available if it gets licensed.

Vaccine manufacture must meet strict standards set by governmental regulatory agencies. These standards ensure, for example, that each vaccine lot is identical to the others, that the vaccine doesn't have impurities and that its chemical composition remains stable over time. The plants themselves must follow what is called *GMP (Good Manufacturing Practice)*, which controls everything from the cleanliness of the facility to the source of the raw materials and the production, packaging and storage of the final product.

access for all

HAVING A LICENSED HIV VACCINE in hand is still a long way from getting it quickly to people who need it, especially those in poor regions of the world (see chapter 36 on vaccine access.) Typically, new vaccines are available only in wealthy countries for a decade or more (and at high prices) before they are slowly introduced into poor countries. Making sure this doesn't happen for an HIV vaccine will be a huge challenge, to say the least, and will take money, greatly expanded health care infrastructure, public education campaigns, and above all, strong global advocacy and political will.