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MARSLAND PRESS
Multidisciplinary Academic Journal Publisher

Vaccine

Primarily from Wikipedia, the free encyclopedia
(https://en.wikipedia.org/wiki/Vaccine)

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Abstract: A **vaccine** is a biological preparation that provides active acquired immunity to a particular infectious disease. A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as a threat, destroy it, and to further recognize and destroy any of the microorganisms associated with that agent that it may encounter in the future. Vaccines can be prophylactic (to prevent or ameliorate the effects of a future infection by a natural or "wild" pathogen), or therapeutic.
[Mark Herbert. **Vaccine.** *Researcher* 2021;13(2):7-24]. ISSN 1553-9865 (print); ISSN 2163-8950 (online). http://www.sciencepub.net/researcher. 2. doi:10.7537/marsrsj130221.02.

Keywords: **vaccine;** biology; immunity; disease; microorganism; infection; pathogen; therapeutic

Vaccine

A **vaccine** is a biological preparation that provides active acquired immunity to a particular infectious disease.[1] A vaccine typically contains an agent that resembles a disease-causing microorganism and is often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins. The agent stimulates the body's immune system to recognize the agent as a threat, destroy it, and to further recognize and destroy any of the microorganisms associated with that agent that it may encounter in the future. Vaccines can be prophylactic (to prevent or ameliorate the effects of a future infection by a natural or "wild" pathogen), or therapeutic (to fight a disease that has already occurred, such as cancer).[2][3][4][5]

The administration of vaccines is called vaccination. Vaccination is the most effective method of preventing infectious diseases;[6] widespread immunity due to vaccination is largely responsible for the worldwide eradication of smallpox and the restriction of diseases such as polio, measles, and tetanus from much of the world. The effectiveness of vaccination has been widely studied and verified;[7] for example, vaccines that have proven effective include the influenza vaccine,[8] the HPV vaccine,[9] and the chicken pox vaccine.[10] The World Health Organization (WHO) reports that licensed vaccines are currently available for twenty-five different preventable infections.[11]

The terms *vaccine* and *vaccination* are derived from *Variolae vaccinae* (smallpox of the cow), the term devised by Edward Jenner (who both developed the concept of vaccines and created the first vaccine) to denote cowpox. He used the phrase in 1798 for the long title of his *Inquiry into the Variolae vaccinae Known as the Cow Pox*, in which he described the protective effect of cowpox against smallpox.[12] In 1881, to honor Jenner, Louis Pasteur proposed that the terms should be extended to cover the new protective inoculations then being developed.[13]

There is overwhelming scientific consensus that vaccines are a very safe and effective way to fight and eradicate infectious diseases.[15][16][17][18] The immune system recognizes vaccine agents as foreign, destroys them, and "remembers" them. When the virulent version of an agent is encountered, the body recognizes the protein coat on the virus, and thus is prepared to respond, by first neutralizing the target agent before it can enter cells, and secondly by recognizing and destroying infected cells before that agent can multiply to vast numbers.

Limitations to their effectiveness, nevertheless, exist.[19] Sometimes, protection fails because of vaccine-related failure such as failures in vaccine attenuation, vaccination regimes or administration or host-related failure due to host's immune system simply does not respond adequately or at all. Lack of response commonly results from genetics, immune status, age, health or nutritional status.[20] It also might fail for genetic reasons if the host's immune system includes no strains of B cells that can generate antibodies suited to reacting effectively and binding to the antigens associated with the pathogen.

Even if the host does develop antibodies, protection might not be adequate; immunity might develop too slowly to be effective in time, the antibodies might not disable the pathogen completely, or there might be multiple strains of the pathogen, not all of which are equally susceptible to the immune reaction. However, even a partial, late, or weak immunity, such as a one resulting from cross-immunity to a strain other than the target strain, may mitigate an infection, resulting in a lower mortality rate, lower morbidity, and faster recovery.

Adjuvants commonly are used to boost immune response, particularly for older people (50–75 years and up), whose immune response to a simple vaccine may have weakened.[21]

The efficacy or performance of the vaccine is dependent on a number of factors:

- the disease itself (for some diseases vaccination performs better than for others)
- the strain of vaccine (some vaccines are specific to, or at least most effective against, particular strains of the disease)[22]
- whether the vaccination schedule has been properly observed.
- idiosyncratic response to vaccination; some individuals are "non-responders" to certain vaccines, meaning that they do not generate antibodies even after being vaccinated correctly.
- assorted factors such as ethnicity, age, or genetic predisposition.

If a vaccinated individual does develop the disease vaccinated against (breakthrough infection), the disease is likely to be less virulent than in unvaccinated victims.[23]

The following are important considerations in the effectiveness of a vaccination program:[24]

1. careful modeling to anticipate the effect that an immunization campaign will have on the epidemiology of the disease in the medium to long term
2. ongoing surveillance for the relevant disease following introduction of a new vaccine
3. maintenance of high immunization rates, even when a disease has become rare.

In 1958, there were 763,094 cases of measles in the United States; 552 deaths resulted.[25][26] After the introduction of new vaccines, the number of cases dropped to fewer than 150 per year (median of 56).[26] In early 2008, there were 64 suspected cases of measles. Fifty-four of those infections were associated with importation from another country, although only 13% were actually acquired outside the United States; 63 of the 64 individuals either had never been vaccinated against measles or were uncertain whether they had been vaccinated.[26]

Vaccines led to the eradication of smallpox, one of the most contagious and deadly diseases in humans.[27] Other diseases such as rubella, polio, measles, mumps, chickenpox, and typhoid are nowhere near as common as they were a hundred years ago thanks to widespread vaccination programs. As long as the vast majority of people are vaccinated, it is much more difficult for an outbreak of disease to occur, let alone spread. This effect is called herd immunity. Polio, which is transmitted only between humans, is targeted by an extensive eradication campaign that has seen endemic polio restricted to only parts of three countries (Afghanistan, Nigeria, and Pakistan).[28] However, the difficulty of reaching all children as well as cultural misunderstandings have caused the anticipated eradication date to be missed several times.

Vaccines also help prevent the development of antibiotic resistance. For example, by greatly reducing the incidence of pneumonia caused by *Streptococcus pneumoniae*, vaccine programs have greatly reduced the prevalence of infections resistant to penicillin or other first-line antibiotics.[29]

The measles vaccine is estimated to prevent 1 million deaths every year.[30]

Adverse effects

Vaccinations given to children, adolescents, or adults are generally safe.[31][32] Adverse effects, if any, are generally mild.[33] The rate of side effects depends on the vaccine in question.[33] Some common side effects include fever, pain around the injection site, and muscle aches.[33] Additionally, some individuals may be allergic to ingredients in the vaccine.[34] MMR vaccine is rarely associated with febrile seizures.[32]

Host-related determinants that render a person susceptible to infection, such as genetics, health status (underlying disease, nutrition, pregnancy, sensitivities or allergies), immune competence, age, and economic impact or cultural environment can be primary or secondary factors affecting the severity of infection and response to a vaccine.[35] Elderly (above age 60), allergen-hypersensitive, and obese people have susceptibility to compromised immunogenicity, which prevents or inhibits vaccine effectiveness, possibly requiring separate vaccine technologies for these specific populations or repetitive booster vaccinations to limit virus transmission.[35]

Severe side effects are extremely rare.[32] Varicella vaccine is rarely associated with complications in immunodeficient individuals, and rotavirus vaccines are moderately associated with intussusception.[32]

At least 19 countries have no-fault compensation programs to provide compensation for those suffering severe adverse effects of vaccination.[36] The United States' program is known as the National Childhood Vaccine Injury Act, and the United Kingdom employs the Vaccine Damage Payment.

Types

Vaccines typically contain dead or inactivated organisms or purified products derived from them.

There are several types of vaccines in use.[37] These represent different strategies used to try to reduce the risk of illness while retaining the ability to induce a beneficial immune response.

Inactivated

Some vaccines contain inactivated, but previously virulent, micro-organisms that have been destroyed with chemicals, heat, or radiation.[38] Examples include the IPV polio vaccine, hepatitis A vaccine, rabies vaccine and most influenza vaccines.[39]

Attenuated

Some vaccines contain live, attenuated microorganisms. Many of these are active viruses that have been cultivated under conditions that disable their virulent properties, or that use closely related but less dangerous organisms to produce a broad immune response. Although most attenuated vaccines are viral, some are bacterial in nature. Examples include the viral diseases yellow fever, measles, mumps, and rubella, and the bacterial disease typhoid. The live *Mycobacterium tuberculosis* vaccine developed by Calmette and Guérin is not made of a contagious strain but contains a virulently modified strain called "BCG" used to elicit an immune response to the vaccine. The live attenuated vaccine containing strain *Yersinia pestis* EV is used for plague immunization. Attenuated vaccines have some advantages and disadvantages. Attenuated, or live, weakened, vaccines typically provoke more durable immunological responses. But they may not be safe for use in immunocompromised individuals, and on rare occasions mutate to a virulent form and cause disease.[40]

Toxoid

Toxoid vaccines are made from inactivated toxic compounds that cause illness rather than the micro-organism.[41] Examples of toxoid-based vaccines include tetanus and diphtheria. Toxoid vaccines are known for their efficacy.[39] Not all toxoids are for micro-organisms; for example, *Crotalus atrox* toxoid is used to vaccinate dogs against rattlesnake bites.[42]

Subunit

Rather than introducing an inactivated or attenuated micro-organism to an immune system (which would constitute a "whole-agent" vaccine), a subunit vaccine uses a fragment of it to create an immune response. One example is the subunit vaccine against hepatitis B virus, that is composed of only the surface proteins of the virus (previously extracted from the blood serum of chronically infected patients, but now produced by recombination of the viral genes into yeast).[43] Another example is edible algae vaccines, such as the virus-like particle (VLP) vaccine against human papillomavirus (HPV), which is composed of the viral major capsid protein.[44] Another example is the hemagglutinin and neuraminidase subunits of the influenza virus.[39] A subunit vaccine is being used for plague immunization.[45]

Conjugate

Certain bacteria have a polysaccharide outer coat that is poorly immunogenic. By linking these outer coats to proteins (e.g., toxins), the immune system can be led to recognize the polysaccharide as if it were a protein antigen. This approach is used in the *Haemophilus influenzae* type B vaccine.[46]

Heterotypic

Heterologous vaccines also known as "Jennerian vaccines", are vaccines that are pathogens of other animals that either do not cause disease or cause mild disease in the organism being treated. The classic example is Jenner's use of cowpox to protect against smallpox. A current example is the use of BCG vaccine made from *Mycobacterium bovis* to protect against tuberculosis.[47]

mRNA Vaccine

An mRNA vaccine (or RNA vaccine) is a novel type of vaccine which is composed of the nucleic acid RNA, packaged within a vector such as lipid nanoparticles. Among the COVID-19 vaccines are a number of RNA vaccines under development to combat the COVID-19 pandemic and some have received emergency use authorization.

The vaccine transfects molecules of synthetic RNA into immunity cells. Once inside the immune cells, the vaccine's RNA functions as mRNA, causing the cells to build the foreign protein that would normally be produced by a pathogen (such as a virus) or by a cancer cell. These protein molecules stimulate an adaptive immune response which teaches the body how to identify and destroy the corresponding pathogen or cancer cells. The delivery of mRNA is achieved by a co-formulation of the molecule into lipid nanoparticles which protect the RNA strands and helps their absorption into the cells.

Reactogenicity, the property of a vaccine of being able to produce common, expected adverse reactions, is similar to that of conventional, non-RNA, vaccines. People susceptible to an autoimmune response may have an adverse reaction to RNA vaccines. The advantages of RNA vaccines over traditional protein vaccines are superior design and production speed, lower cost of production, and the induction of both cellular as well as humoral immunity. A disadvantage in the Pfizer-BioNTech mRNA vaccine for COVID-19 is that it requires ultracold storage before distribution.

In RNA therapeutics, mRNA vaccines have attracted considerable interest as COVID-19 vaccines. By early December 2020, there were two novel mRNA

vaccines for COVID-19 that had completed the required eight-week period post-final human trials and were awaiting emergency use authorization (EUA): Moderna's COVID-19 vaccine (mRNA-1273), and the Pfizer-BioNTech COVID-19 vaccine. On 2 December 2020, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) became the first medicines regulator to approve an mRNA vaccine, authorizing the Pfizer-BioNTech COVID-19 vaccine (Comirnaty) for widespread use. On 11 December in the US the FDA gave EUA for Pfizer-BioNTech's COVID-19 vaccine. On 21 December 2020 the US Centers for Disease Control and Prevention (CDC) recommended emergency use authorization for Moderna's COVID-19 vaccine in adults. This had been approved by the FDA three days earlier.

The use of RNA in a vaccine has been the basis of substantial misinformation circulated via social media, wrongly claiming that the use of RNA alters a person's DNA, or emphasizing the technology's previously unknown safety record, while ignoring the more recent accumulation of evidence from trials involving tens of thousands of people.

Researchers at the Salk Institute, University of California-San Diego, and a US-based biotech company, Vical Incorporated, published work in 1989 demonstrating that mRNA, using a liposomal nanoparticle for drug delivery, could transfect mRNA into a variety of eukaryotic cells. In 1990, the University of Wisconsin, reported positive results where "naked" (or unprotected) mRNA was injected into the muscle of mice. These studies were the first evidence that in vitro transcribed (IVT) mRNA could deliver the genetic information to produce proteins within living cell tissue.

The use of RNA vaccines goes back to the early 1990s. The *in vitro* demonstration of mRNA in animals was first reported in 1990, and use as immunization proposed shortly thereafter. In 1993, Martinon demonstrated that liposome-encapsulated RNA could stimulate T-cells in vivo, and in 1994, Zhou & Berglund published the first evidence that RNA could be used as a vaccine to elicit both humoral and cellular immune response against a pathogen.

Hungarian biochemist Katalin Kariko attempted to solve some of the main technical barriers to introducing mRNA into cells in the 1990s. Kariko partnered with American immunologist Drew Weissman, and by 2005 they published a joint paper that solved one of the key technical barriers by using modified nucleosides to get mRNA inside cells without setting off the body's defense system. Harvard stem cell biologist Derrick Rossi (then at Stanford) read Kariko and Weissman's paper and recognized that their work was "groundbreaking", and in 2010 founded the mRNA-focused biotech Moderna along with Robert Langer, who also saw its potential in vaccine development. Like Moderna, BioNTech also licensed Kariko and Weissman's work.

In 2000, German biologist Ingmar Hoerr published an article on the efficiency of RNA‐based vaccines, which he studied as part of his doctoral degree. After completing his PhD, he founded CureVac together with his PhD supervisor Günther Jung, Steve Pascolo, Florian von der Muelbe, and Hans-Georg Rammensee.

Up until 2020, these mRNA biotech companies had poor results testing mRNA drugs for cardiovascular, metabolic and renal diseases; selected targets for cancer; and rare diseases like Crigler–Najjar syndrome, with most finding that the side-effects of mRNA insertion were too serious. mRNA vaccines for human use have been developed and tested for the diseases rabies, Zika, cytomegalovirus, and influenza, although these mRNA vaccines have not been licensed. Many large pharmaceutical companies abandoned the technology, while some biotechs re-focused on the less profitable area of vaccines, where the doses would be at lower levels and side-effects reduced.

Before the COVID-19 pandemic, no mRNA drug or vaccine was licensed for use in humans. In December 2020, both Moderna and Pfizer/BioNTech obtained emergency use authorization for their mRNA-based COVID-19 vaccines, which had been funded by Operation Warp Speed (directly in the case of Moderna and indirectly for Pfizer/BioNTech). On 2 December 2020, seven days after its final eight-week trial, the UK's Medicines and Healthcare products Regulatory Agency (MHRA), became the first global medicines regulator in history to approve an mRNA vaccine, granting "emergency authorization" for Pfizer/BioNTech's BNT162b2 COVID-19 vaccine for widespread use. MHRA CEO June Raine said "no corners have been cut in approving it", and that, "the benefits outweigh any risk". On 11 December 2020 the FDA gave emergency use authorization for the Pfizer-BioNTech COVID-19 vaccine.

The goal of a vaccine is to stimulate the adaptive immune system to create antibodies that precisely target that particular pathogen. The markers on the pathogen that the antibodies target are called antigens.

mRNA vaccines operate in a very different manner from a traditional vaccine. Traditional vaccines stimulate an antibody response by injecting antigens, an attenuated virus (weakened or harmless virus), or a recombinant antigen-encoding viral vector (carrier virus engineered to have antigens) into muscles. These antigen-containing ingredients are prepared and grown outside the body.

In contrast, mRNA vaccines introduce a short-lived synthetically created fragment of the RNA sequence of a virus into the vaccinated individual.

These mRNA fragments are taken up by dendritic cells – a type of immune system cell – by phagocytosis. The dendritic cells use their own internal machinery (ribosomes) to read the mRNA and produce the viral antigens that the mRNA encodes before destroying the mRNA.

Once the viral antigens are produced by the host cell, the normal adaptive immune system processes are followed. Antigens are broken down by proteasomes, then class I and class II MHC molecules attach to the antigen and transport it to the cellular membrane, "activating" the dendritic cell. Once the dendritic cells are activated, they migrate to lymph nodes, where the antigen is presented to T cells and B cells. This eventually leads to the production of antibodies that are specifically targeted to the antigen, resulting in immunity.

The benefit of using mRNA to have host cells produce the antigen is that mRNA is far easier for vaccine creators to produce than antigen proteins or attenuated virus. Another benefit is speed of design and production. Moderna designed their mRNA-1273 vaccine for COVID-19 in 2 days. Another advantage of RNA vaccines is that since the antigens are produced inside the cell, they stimulate cellular immunity, as well as humoral immunity.

mRNA vaccines do not affect or reprogram DNA inside the cell. The synthetic mRNA fragment is a copy of the specific part of the viral RNA that carries the instructions to build the antigen of the virus (a protein spike, in the case of the main coronavirus mRNA vaccines), and is not related to DNA. This misconception was circulated as the COVID-19 mRNA vaccines came to public prominence, and is a debunked conspiracy theory.

The mRNA should degrade in the cells after producing the foreign protein. However, because the specific formulation (including the exact composition of the lipid nanoparticle drug delivery coating) is kept confidential by the manufacturers of the candidate mRNA vaccines, details and timings have not been researched yet by third parties.

The method of vaccine delivery can be broadly classified by whether the RNA transfer to cells happens within (*in vivo*) or outside (*ex vivo*) the organism.

Dendritic cells are a type of immune cells that display antigens on their surfaces, leading to interactions with T cells to initiate an immune response. Dendritic cells can be collected from patients and programmed with the desired mRNA. Then, they can be re-administered back into patients to create an immune response.

Since the discovery that introducing *in vitro* transcribed mRNA leads to expression *in vivo* following direct administration, *in vivo* approaches have become more and more attractive. They offer some advantages over *ex vivo* methods, particularly by avoiding the cost of harvesting and adapting dendritic cells from patients, and by imitating a regular infection. There are still obstacles for these methods to overcome for RNA vaccination to be a potent procedure. Evolutionary mechanisms that prevent the infiltration of unknown nucleic material and promote degradation by RNases need to be circumvented in order to initiate translation. In addition, RNA is too heavy to move around on its own inside the cell via diffusion, making it vulnerable to being discovered and eliminated by the host cell.

A naked injection means that the delivery of the vaccine is simply held in a buffer. This mode of mRNA uptake has been known for since the early 2000s. The first worldwide clinical studies (Tübingen, Germany) used intradermal injections of naked mRNA for vaccination.

The use of RNA as a vaccine tool was discovered in the 1990s in the form of self-amplifying mRNA. The two main categories of mRNA vaccines are non-amplifying (conventional, viral delivery), and molecular self-amplifiying mRNA (non-viral delivery). When mRNA is delivered non-virally it enters the cell's cytoplasm and can amplify and express the antigenic protein.

It has also emerged that the different routes of injection, such as into the skin, blood or to muscles, resulted in varying levels of mRNA uptake, making the choice of administration route a critical aspect of delivery. One study showed, in comparing different routes, that lymph node injection leads to the largest T cell response.

The mechanisms and consequently the evaluation of self-amplifying mRNA may be different, as self-amplifying mRNA is fundamentally different by being a much bigger molecule in size.

Cationic polymers can be mixed with mRNA to generate protective coatings called polyplexes. These protect the recombinant mRNA from ribonucleases and assist its penetration in cells. Protamine is a natural cationic peptide and has been used to encapsulate mRNA for vaccination.

The first time the FDA approved the use of lipid nanoparticles as a drug delivery system was in 2018, when the agency approved the first siRNA drug, Onpattro. Encapsulating the mRNA molecule in lipid nanoparticles was a critical breakthrough for producing viable mRNA vaccines, solving a number of key technical barriers in delivering the mRNA molecule into the host cell. Principally, the lipid provides a layer of protection against degradation, allowing more robust translational output. In addition, the customization of the lipid's outer layer allows the targeting of desired cell types through ligand

interactions. However, many studies have also highlighted the difficulty of studying this type of delivery, demonstrating that there is an inconsistency between *in vivo* and *in vitro* applications of nanoparticles in terms of cellular intake. The nanoparticles can be administered to the body and transported via multiple routes, such as intravenously or through the lymphatic system.

In addition to non-viral delivery methods, RNA viruses have been engineered to achieve similar immunological responses. Typical RNA viruses used as vectors include retroviruses, lentiviruses, alphaviruses and rhabdoviruses, each of which can differ in structure and function. Clinical studies have utilized such viruses on a range of diseases in model animals such as mice, chicken and primates.

Reactogenicity is similar to that of conventional, non-RNA vaccines. However, those susceptible to an autoimmune response may have an adverse reaction to RNA vaccines. The mRNA strands in the vaccine may elicit an unintended immune reaction. To minimize this, mRNA sequences in mRNA vaccines are designed to mimic those produced by host cells.

Strong but transient reactogenic effects were reported in trials of novel COVID-19 RNA vaccines; most people will not experience severe side effects which include fever and fatigue. Severe side effects is defined as that which limits everyday activity.

Before 2020, no mRNA technology platform (drug or vaccine) had been authorized for use in humans, so there was a risk of unknown effects. The 2020 coronavirus pandemic required faster production capability of mRNA vaccines, made them attractive to national health organisations, and led to debate about the type of initial authorization mRNA vaccines should get (including emergency use authorization or expanded access authorization) after the eight-week period of post-final human trials.

Because mRNA is fragile, the vaccine must be kept at very low temperatures to avoid degrading and thus giving little effective immunity to the recipient. The BNT162b2 mRNA vaccine has to be kept between −80 and −60 °C (−112 and −76 °F). Moderna says their mRNA-1273 vaccine can be stored between −25 and −15 °C (−13 and 5 °F), which is comparable to a home freezer, and that it remains stable between 2 and 8 °C (36 and 46 °F) for up to 30 days. In November 2020, *Nature* reported, "While it's possible that differences in LNP formulations or mRNA secondary structures could account for the thermostability differences [between Moderna and BioNtech], many experts suspect both vaccine products will ultimately prove to have similar storage requirements and shelf lives under various temperature conditions."

RNA vaccines offer specific advantages over traditional protein vaccines. Because RNA vaccines are not constructed from an active pathogen (or even an inactivated pathogen), they are non-infectious. In contrast, traditional vaccines require the production of pathogens, which, if done at high volumes, could increase the risks of localized outbreaks of the virus at the production facility. RNA vaccines can be produced faster, more cheaply, and in a more standardized fashion (with fewer error rates in production), which can improve responsiveness to serious outbreaks.

In addition to sharing the advantages of theoretical DNA vaccines over established traditional protein vaccines, RNA vaccination offers other benefits. The mRNA is translated in the cytosol, so there is no need for the RNA to enter the cell nucleus, and the risk of being integrated to the host genome is averted. Modified nucleosides (for example, pseudouridines, 2'-O-methylated nucleosides) can be incorporated to mRNA to suppress immune response stimulation to avoid immediate degradation and produce a more persistent effect through enhanced translation capacity. The open reading frame (ORF) and untranslated regions (UTR) of mRNA can be optimized for different purposes (a process called sequence engineering of mRNA), for example through enriching the guanine-cytosine content or choosing specific UTRs known to increase translation.

An additional ORF coding for a replication mechanism can be added to amplify antigen translation and therefore immune response, decreasing the amount of starting material needed.

The use of RNA-based vaccines has been the basis of substantial misinformation circulated in social media, wrongly claiming that the use of RNA somehow alters a person's DNA, or emphasizing the technology's previously unknown safety record, while ignoring the accumulation of recent evidence from trials involving tens of thousands of people.

In November 2020, *The Washington Post* reported on novel mRNA vaccine hesitancy amongst healthcare professionals in the United States, citing surveys that "some did not want to be in the first round, so they could wait and see if there are potential side effects".

It is unclear why the novel mRNA COVID-19 vaccines from Moderna and Pfizer/BioNTech have shown potential efficacy rates of 90 to 95 percent, when the prior mRNA drug trials on pathogens other than COVID-19 were not so promising and had to be abandoned in the early phases of trials. Physician-scientist Margaret Liu stated that it could be due to the "sheer volume of resources" that went into development, or that the vaccines might be "triggering a nonspecific inflammatory response to the mRNA that could be heightening its specific immune response, given that the modified nucleoside technique reduced

inflammation but hasn't eliminated it completely", and that "this may also explain the intense reactions such as aches and fevers reported in some recipients of the mRNA SARS-CoV-2 vaccines". These reactions though severe were transient and another view is that they were believed to be a reaction to the lipid drug delivery molecules.

Unlike DNA molecules, the mRNA molecule is a very fragile molecule that degrades within minutes in an exposed environment, and thus mRNA vaccines need to be transported and stored at very low temperatures. Outside the cell, or its drug delivery system, the mRNA molecule is also quickly broken down by the host. This fragility of the mRNA molecule is a hurdle to the efficacy of any mRNA vaccine due to bulk disintegration before it enters the cells, that could lead people to believe, and act, as if they are immune when they are not.

Experimental

A number of innovative vaccines are also in development and in use:

- Dendritic cell vaccines combine dendritic cells with antigens in order to present the antigens to the body's white blood cells, thus stimulating an immune reaction. These vaccines have shown some positive preliminary results for treating brain tumors [52] and are also tested in malignant melanoma.[53]
- DNA vaccination – The proposed mechanism is the insertion and expression of viral or bacterial DNA in human or animal cells (enhanced by the use of electroporation), triggering immune system recognition. Some cells of the immune system that recognize the proteins expressed will mount an attack against these proteins and cells expressing them. Because these cells live for a very long time, if the pathogen that normally expresses these proteins is encountered at a later time, they will be attacked instantly by the immune system. One potential advantage of DNA vaccines is that they are very easy to produce and store.
- Recombinant vector – by combining the physiology of one micro-organism and the DNA of another, immunity can be created against diseases that have complex infection processes. An example is the RVSV-ZEBOV vaccine licensed to Merck that is being used in 2018 to combat ebola in Congo.[54]
- T-cell receptor peptide vaccines are under development for several diseases using models of Valley Fever, stomatitis, and atopic dermatitis. These peptides have been shown to modulate cytokine production and improve cell-mediated immunity.
- Targeting of identified bacterial proteins that are involved in complement inhibition would neutralize the key bacterial virulence mechanism.[55]
- The use of plasmids has been validated in preclinical studies as a protective vaccine strategy for cancer and infectious diseases. However, in human studies, this approach has failed to provide clinically relevant benefit. The overall efficacy of plasmid DNA immunization depends on increasing the plasmid's immunogenicity while also correcting for factors involved in the specific activation of immune effector cells.[56]

While most vaccines are created using inactivated or attenuated compounds from micro-organisms, synthetic vaccines are composed mainly or wholly of synthetic peptides, carbohydrates, or antigens.

Valence

Vaccines may be *monovalent* (also called *univalent*) or *multivalent* (also called *polyvalent*). A monovalent vaccine is designed to immunize against a single antigen or single microorganism.[57] A multivalent or polyvalent vaccine is designed to immunize against two or more strains of the same microorganism, or against two or more microorganisms.[58] The valency of a multivalent vaccine may be denoted with a Greek or Latin prefix (e.g., *tetravalent* or *quadrivalent*). In certain cases, a monovalent vaccine may be preferable for rapidly developing a strong immune response.[59]

When two or more vaccines are mixed together in the same formulation, the two vaccines can interfere. This most frequently occurs with live attenuated vaccines, where one of the vaccine components is more robust than the others and suppresses the growth and immune response to the other components. This phenomenon was first noted in the trivalent Sabin polio vaccine, where the amount of serotype 2 virus in the vaccine had to be reduced to stop it from interfering with the "take" of the serotype 1 and 3 viruses in the vaccine.[60] This phenomenon has also been found to be a problem with the dengue vaccines currently being researched, where the DEN-3 serotype was found to predominate and suppress the response to DEN-1, −2 and −4 serotypes.[61]

Adjuvants

Vaccines typically contain one or more adjuvants, used to boost the immune response. Tetanus toxoid, for instance, is usually adsorbed onto alum. This presents the antigen in such a way as to produce a greater action than the simple aqueous tetanus toxoid. People who have an adverse reaction to adsorbed tetanus toxoid may be given the simple vaccine when the time comes for a booster.[62]

In the preparation for the 1990 Persian Gulf campaign, whole cell pertussis vaccine was used as an adjuvant for anthrax vaccine. This produces a more rapid immune response than giving only the anthrax

vaccine, which is of some benefit if exposure might be imminent.[63]

Preservatives

Vaccines may also contain preservatives to prevent contamination with bacteria or fungi. Until recent years, the preservative thiomersal (A.K.A. *Thimerosal* in the US and Japan) was used in many vaccines that did not contain live virus. As of 2005, the only childhood vaccine in the U.S. that contains thiomersal in greater than trace amounts is the influenza vaccine,[64] which is currently recommended only for children with certain risk factors.[65] Single-dose influenza vaccines supplied in the UK do not list thiomersal in the ingredients. Preservatives may be used at various stages of production of vaccines, and the most sophisticated methods of measurement might detect traces of them in the finished product, as they may in the environment and population as a whole.[66]

Many vaccines need preservatives to prevent serious adverse effects such as *Staphylococcus* infection, which in one 1928 incident killed 12 of 21 children inoculated with a diphtheria vaccine that lacked a preservative.[67] Several preservatives are available, including thiomersal, phenoxyethanol, and formaldehyde. Thiomersal is more effective against bacteria, has a better shelf-life, and improves vaccine stability, potency, and safety; but, in the U.S., the European Union, and a few other affluent countries, it is no longer used as a preservative in childhood vaccines, as a precautionary measure due to its mercury content.[68] Although controversial claims have been made that thiomersal contributes to autism, no convincing scientific evidence supports these claims.[69] Furthermore, a 10–11 year study of 657,461 children found that the MMR vaccine does not cause autism and actually reduced the risk of autism by 7 percent.[70][71]

Excipients

Beside the active vaccine itself, the following excipients and residual manufacturing compounds are present or may be present in vaccine preparations:[72]

- Aluminum salts or gels are added as adjuvants. Adjuvants are added to promote an earlier, more potent response, and more persistent immune response to the vaccine; they allow for a lower vaccine dosage.
- Antibiotics are added to some vaccines to prevent the growth of bacteria during production and storage of the vaccine.
- Egg protein is present in the influenza vaccine and yellow fever vaccine as they are prepared using chicken eggs. Other proteins may be present.
- Formaldehyde is used to inactivate bacterial products for toxoid vaccines. Formaldehyde is also used to inactivate unwanted viruses and kill bacteria that might contaminate the vaccine during production.
- Monosodium glutamate (MSG) and 2-phenoxyethanol are used as stabilizers in a few vaccines to help the vaccine remain unchanged when the vaccine is exposed to heat, light, acidity, or humidity.
- Thiomersal is a mercury-containing antimicrobial that is added to vials of vaccine that contain more than one dose to prevent contamination and growth of potentially harmful bacteria. Due to the controversy surrounding thiomersal it has been removed from most vaccines except multi-use influenza, where it was reduced to levels so that a single dose contained less than 1 micro-gram of mercury, a level similar to eating 10 g of canned tuna.[73]

Nomenclature

Various fairly standardized abbreviations for vaccine names have developed, although the standardization is by no means centralized or global. For example, the vaccine names used in the United States have well-established abbreviations that are also widely known and used elsewhere. An extensive list of them provided in a sortable table and freely accessible, is available at a US Centers for Disease Control and Prevention web page.[74] The page explains that "The abbreviations [in] this table (Column 3) were standardized jointly by staff of the Centers for Disease Control and Prevention, ACIP Work Groups, the editor of the *Morbidity and Mortality Weekly Report* (MMWR), the editor of *Epidemiology and Prevention of Vaccine-Preventable Diseases* (the Pink Book), ACIP members, and liaison organizations to the ACIP."[74]

Some examples are "DTaP" for diphtheria and tetanus toxoids and acellular pertussis vaccine, "DT" for diphtheria and tetanus toxoids, and "Td" for tetanus and diphtheria toxoids. At its page on tetanus vaccination,[75] the CDC further explains that "Upper-case letters in these abbreviations denote full-strength doses of diphtheria (D) and tetanus (T) toxoids and pertussis (P) vaccine. Lower-case "d" and "p" denote reduced doses of diphtheria and pertussis used in the adolescent/adult-formulations. The 'a' in DTaP and Tdap stands for 'acellular,' meaning that the pertussis component contains only a part of the pertussis organism."[75]

Another list of established vaccine abbreviations is at the CDC's page called "Vaccine Acronyms and Abbreviations", with abbreviations used on U.S. immunization records.[76] The United States Adopted Name system has some conventions for the word order of vaccine names, placing head nouns first and adjectives postpositively. This is why the USAN for "OPV" is "poliovirus vaccine live oral" rather than "oral poliovirus vaccine".

Schedule

In order to provide the best protection, children are recommended to receive vaccinations as soon as their immune systems are sufficiently developed to respond to particular vaccines, with additional "booster" shots often required to achieve "full immunity". This has led to the development of complex vaccination schedules. In the United States, the Advisory Committee on Immunization Practices, which recommends schedule additions for the Centers for Disease Control and Prevention, recommends routine vaccination of children against[78] hepatitis A, hepatitis B, polio, mumps, measles, rubella, diphtheria, pertussis, tetanus, HiB, chickenpox, rotavirus, influenza, meningococcal disease and pneumonia.[79]

The large number of vaccines and boosters recommended (up to 24 injections by age two) has led to problems with achieving full compliance. In order to combat declining compliance rates, various notification systems have been instituted and a number of combination injections are now marketed (e.g., Pneumococcal conjugate vaccine and MMRV vaccine), which provide protection against multiple diseases.

Besides recommendations for infant vaccinations and boosters, many specific vaccines are recommended for other ages or for repeated injections throughout life—most commonly for measles, tetanus, influenza, and pneumonia. Pregnant women are often screened for continued resistance to rubella. The human papillomavirus vaccine is recommended in the U.S. (as of 2011)[80] and UK (as of 2009).[81] Vaccine recommendations for the elderly concentrate on pneumonia and influenza, which are more deadly to that group. In 2006, a vaccine was introduced against shingles, a disease caused by the chickenpox virus, which usually affects the elderly.

Economics of development

One challenge in vaccine development is economic: Many of the diseases most demanding a vaccine, including HIV, malaria and tuberculosis, exist principally in poor countries. Pharmaceutical firms and biotechnology companies have little incentive to develop vaccines for these diseases because there is little revenue potential. Even in more affluent countries, financial returns are usually minimal and the financial and other risks are great.[82]

Most vaccine development to date has relied on "push" funding by government, universities and non-profit organizations.[83] Many vaccines have been highly cost effective and beneficial for public health.[84] The number of vaccines actually administered has risen dramatically in recent decades.[85] This increase, particularly in the number of different vaccines administered to children before entry into schools may be due to government mandates and support, rather than economic incentive.[86]

Patents

The filing of patents on vaccine development processes can also be viewed as an obstacle to the development of new vaccines. Because of the weak protection offered through a patent on the final product, the protection of the innovation regarding vaccines is often made through the patent of processes used in the development of new vaccines as well as the protection of secrecy.[87]

According to the World Health Organization, the biggest barrier to local vaccine production in less developed countries has not been patents, but the substantial financial, infrastructure, and workforce expertise requirements needed for market entry. Vaccines are complex mixtures of biological compounds, and unlike the case of drugs, there are no true generic vaccines. The vaccine produced by a new facility must undergo complete clinical testing for safety and efficacy similar to that undergone by that produced by the original manufacturer. For most vaccines, specific processes have been patented. These can be circumvented by alternative manufacturing methods, but this required R & D infrastructure and a suitably skilled workforce. In the case of a few relatively new vaccines such as the human papillomavirus vaccine, the patents may impose an additional barrier.[88]

Production

Vaccine production has several stages. First, the antigen itself is generated. Viruses are grown either on primary cells such as chicken eggs (e.g., for influenza) or on continuous cell lines such as cultured human cells (e.g., for hepatitis A).[89] Bacteria are grown in bioreactors (e.g., *Haemophilus influenzae* type b). Likewise, a recombinant protein derived from the viruses or bacteria can be generated in yeast, bacteria, or cell cultures.[90][91]

After the antigen is generated, it is isolated from the cells used to generate it. A virus may need to be inactivated, possibly with no further purification required. Recombinant proteins need many operations involving ultrafiltration and column chromatography. Finally, the vaccine is formulated by adding adjuvant, stabilizers, and preservatives as needed. The adjuvant enhances the immune response to the antigen, stabilizers increase the storage life, and preservatives allow the use of multidose vials.[90][91] Combination vaccines are harder to develop and produce, because of potential incompatibilities and interactions among the antigens and other ingredients involved.[92]

The final stage in vaccine manufacture before distribution is fill and finish, which is the process of filling vials with vaccines and packaging them for distribution. Although this is a conceptually simple

part of the vaccine manufacture process, it is often a bottleneck in the process of distributing and administering vaccines.[93][94][95]

Vaccine production techniques are evolving. Cultured mammalian cells are expected to become increasingly important, compared to conventional options such as chicken eggs, due to greater productivity and low incidence of problems with contamination. Recombination technology that produces genetically detoxified vaccine is expected to grow in popularity for the production of bacterial vaccines that use toxoids. Combination vaccines are expected to reduce the quantities of antigens they contain, and thereby decrease undesirable interactions, by using pathogen-associated molecular patterns.[92]

Vaccine manufacturers

In 2012 the increasing role of Indian and Chinese vaccine manufacturers in meeting the global demand for vaccine doses was noted.[96] The Serum Institute of India was at that point the world's largest manufacturer of vaccines against measles and rubella, as well as combination DTP vaccines. The Serum Institute of India made a name for itself as developer of vaccines when it brought into production its measles vaccine using a MRC-5 cell culture instead of chicken eggs, allowing for a productivity increase at 10% to 20% compared to Merck Group and GlaxoSmithKline. In 2012 it was estimated that two out of three vaccinated children globally had been immunized using a vaccine manufactured by the Serum Institute of India. In 2012 China ranked as the largest vaccine manufacturing country in the world, with 46 registered vaccine manufacturers focusing on meeting China's domestic need for vaccine doses. 90% of doses for the Chinese National Immunization Program were supplied by the state-owned China National Pharmaceutical Group.[97]

Delivery systems

The development of new delivery systems raises the hope of vaccines that are safer and more efficient to deliver and administer. Lines of research include liposomes and *ISCOM* (immune stimulating complex).[98]

Notable developments in vaccine delivery technologies have included oral vaccines. Early attempts to apply oral vaccines showed varying degrees of promise, beginning early in the 20th century, at a time when the very possibility of an effective oral antibacterial vaccine was controversial.[99] By the 1930s there was increasing interest in the prophylactic value of an oral typhoid fever vaccine for example.[100]

An oral polio vaccine turned out to be effective when vaccinations were administered by volunteer staff without formal training; the results also demonstrated increased ease and efficiency of administering the vaccines. Effective oral vaccines have many advantages; for example, there is no risk of blood contamination. Vaccines intended for oral administration need not be liquid, and as solids, they commonly are more stable and less prone to damage or to spoilage by freezing in transport and storage.[101] Such stability reduces the need for a "cold chain": the resources required to keep vaccines within a restricted temperature range from the manufacturing stage to the point of administration, which, in turn, may decrease costs of vaccines.

A microneedle approach, which is still in stages of development, uses "pointed projections fabricated into arrays that can create vaccine delivery pathways through the skin".[102]

An experimental needle-free[103] vaccine delivery system is undergoing animal testing.[104][105] A stamp-size patch similar to an adhesive bandage contains about 20,000 microscopic projections per square cm.[106] This dermal administration potentially increases the effectiveness of vaccination, while requiring less vaccine than injection.[107]

Veterinary medicine

See also: Influenza vaccine § Flu vaccine for nonhumans, and Vaccination of dogs

Goat vaccination against sheep pox and pleural pneumonia

Vaccinations of animals are used both to prevent their contracting diseases and to prevent transmission of disease to humans.[108] Both animals kept as pets and animals raised as livestock are routinely vaccinated. In some instances, wild populations may be vaccinated. This is sometimes accomplished with vaccine-laced food spread in a disease-prone area and has been used to attempt to control rabies in raccoons.

Where rabies occurs, rabies vaccination of dogs may be required by law. Other canine vaccines include canine distemper, canine parvovirus, infectious canine hepatitis, adenovirus-2, leptospirosis, bordatella, canine parainfluenza virus, and Lyme disease, among others.

Cases of veterinary vaccines used in humans have been documented, whether intentional or accidental, with some cases of resultant illness, most notably with brucellosis.[109] However, the reporting of such cases is rare and very little has been studied about the safety and results of such practices. With the advent of aerosol vaccination in veterinary clinics, human exposure to pathogens that are not naturally carried in humans, such as Bordetella bronchiseptica, has likely increased in recent years.[109] In some cases, most notably rabies, the parallel veterinary vaccine against a pathogen may be as much as orders of magnitude more economical than the human one.

DIVA vaccines

DIVA (Differentiation of Infected from Vaccinated Animals), also known as SIVA (Segregation of Infected from Vaccinated Animals) vaccines, make it possible to differentiate between infected and vaccinated animals.

DIVA vaccines carry at least one epitope less than the equivalent wild microorganism. An accompanying diagnostic test that detects the antibody against that epitope assists in identifying whether the animal has been vaccinated or not.

The first DIVA vaccines (formerly termed marker vaccines and since 1999 coined as DIVA vaccines) and companion diagnostic tests have been developed by J.T. van Oirschot and colleagues at the Central Veterinary Institute in Lelystad, The Netherlands.[110][111] They found that some existing vaccines against pseudorabies (also termed Aujeszky's disease) had deletions in their viral genome (among which was the gE gene). Monoclonal antibodies were produced against that deletion and selected to develop an ELISA that demonstrated antibodies against gE. In addition, novel genetically engineered gE-negative vaccines were constructed.[112] Along the same lines, DIVA vaccines and companion diagnostic tests against bovine herpesvirus 1 infections have been developed.[111][113]

The DIVA strategy has been applied in various countries and successfully eradicated pseudorabies virus. Swine populations were intensively vaccinated and monitored by the companion diagnostic test and, subsequently, the infected pigs were removed from the population. Bovine herpesvirus 1 DIVA vaccines are also widely used in practice.

Scientists have put and still, are putting much effort in applying the DIVA principle to a wide range of infectious diseases, such as, for example, classical swine fever,[114] avian influenza,[115] Actinobacillus pleuropneumonia[116] and Salmonella infections in pigs.[117]

History

Prior to the introduction of vaccination with material from cases of cowpox (heterotypic immunisation), smallpox could be prevented by deliberate Variolation with smallpox virus. The earliest hints of the practice of variolation for smallpox in China come during the 10th century.[118] The Chinese also practiced the oldest documented use of variolation, dating back to the fifteenth century. They implemented a method of "nasal insufflation" administered by blowing powdered smallpox material, usually scabs, up the nostrils. Various insufflation techniques have been recorded throughout the sixteenth and seventeenth centuries within China.[119]:60 Two reports on the Chinese practice of inoculation were received by the Royal Society in London in 1700; one by Martin Lister who received a report by an employee of the East India Company stationed in China and another by Clopton Havers.[120]

Mary Wortley Montagu, who had witnessed variolation in Turkey, had her four-year-old daughter variolated in the presence of physicians of the Royal Court in 1721 upon her return to England.[119] Later on that year Charles Maitland conducted an experimental variolation of six prisoners in Newgate Prison in London.[121] The experiment was a success, and soon variolation was drawing attention from the royal family, who helped promote the procedure. However, several days after Prince Octavius of Great Britain was inoculated he died in 1783.[122] In 1796 the physician Edward Jenner took pus from the hand of a milkmaid with cowpox, scratched it into the arm of an 8-year-old boy, James Phipps, and six weeks later variolated the boy with smallpox, afterwards observing that he did not catch smallpox.[123][124] Jenner extended his studies and in 1798 reported that his vaccine was safe in children and adults and could be transferred from arm-to-arm reducing reliance on uncertain supplies from infected cows.[125] Since vaccination with cowpox was much safer than smallpox inoculation,[126] the latter, though still widely practiced in England, was banned in 1840.[127]

Following on from Jenner's work, the second generation of vaccines was introduced in the 1880s by Louis Pasteur who developed vaccines for chicken cholera and anthrax,[13] and from the late nineteenth century vaccines were considered a matter of national prestige. National vaccination policies were adopted and compulsory vaccination laws were passed.[123] In 1931 Alice Miles Woodruff and Ernest Goodpasture documented that the fowlpox virus could be grown in embryonated chicken egg. Soon scientist cultivated other viruses in eggs. Eggs were used for virus propagation in the development of a yellow fever vaccine in 1935 and a influenza vaccine in 1945. In 1959 growth media and cell culture replaced eggs as the standard method of virus propagation for vaccines.[128]

The twentieth century saw the introduction of several successful vaccines, including those against diphtheria, measles, mumps, and rubella. Major achievements included the development of the polio vaccine in the 1950s and the eradication of smallpox during the 1960s and 1970s. Maurice Hilleman was the most prolific of the developers of the vaccines in the twentieth century. As vaccines became more common, many people began taking them for granted. However, vaccines remain elusive for many important diseases, including herpes simplex, malaria, gonorrhea, and HIV.[123][129]

Generations of vaccines

First generation vaccines are whole-organism

vaccines – either live and weakened, or killed forms.[130] Live, attenuated vaccines, such as smallpox and polio vaccines, are able to induce killer T-cell (T_C or CTL) responses, helper T-cell (T_H) responses and antibody immunity. However, attenuated forms of a pathogen can convert to a dangerous form and may cause disease in immunocompromised vaccine recipients (such as those with AIDS). While killed vaccines do not have this risk, they cannot generate specific killer T cell responses and may not work at all for some diseases.[130]

Second generation vaccines were developed to reduce the risks from live vaccines. These are subunit vaccines, consisting of specific protein antigens (such as tetanus or diphtheria toxoid) or recombinant protein components (such as the hepatitis B surface antigen). They can generate T_H and antibody responses, but not killer T cell responses.

DNA vaccines are examples of third generation vaccines.[130][131] In 2016 a DNA vaccine for the Zika virus began testing at the National Institutes of Health. Separately, Inovio Pharmaceuticals and GeneOne Life Science began tests of a different DNA vaccine against Zika in Miami. Manufacturing the vaccines in volume remains unsolved.[132] Clinical trials for DNA vaccines to prevent HIV are underway.[133]

Trends

Scientists are now trying to develop synthetic vaccines by reconstructing the outside structure of a virus; this will help prevent vaccine resistance.[134]

Principles that govern the immune response can now be used in tailor-made vaccines against many noninfectious human diseases, such as cancers and autoimmune disorders.[135] For example, the experimental vaccine CYT006-AngQb has been investigated as a possible treatment for high blood pressure.[136] Factors that affect the trends of vaccine development include progress in translatory medicine, demographics, regulatory science, political, cultural, and social responses.[137]

Plants as bioreactors for vaccine production

Transgenic plants have been identified as promising expression systems for vaccine production. Complex plants such as tobacco, potato, tomato, and banana can have genes inserted that cause them to produce vaccines usable for humans.[138] Bananas have been developed that produce a human vaccine against hepatitis B.[139] Another example is the expression of a fusion protein in alfalfa transgenic plants for the selective directioning to antigen presenting cells, therefore increasing vaccine potency against Bovine Viral Diarrhea Virus (BVDV).[140][141]

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