



Whole-Organism Vaccine (Attenuated and Killed Vaccines)

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ABSTRACT

A vaccine is an antigenic substance prepared from the causative agent of a disease, used to provide immunity to a particular disease. The vaccine is often made from attenuated or killed forms of the microbe. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters. We reviewed the recent literature on types of vaccines and older studies were included selectively if historically relevant. Attenuated and killed vaccine have been studied extensively to help eradication the infectious disease development, and thereby decrease the need for drugs.

Keywords: Immunity; Microorganisms; Vaccine; Cell mediated branches

INTRODUCTION

The terms vaccine and vaccination are derived from Variolae vaccinae (smallpox of the cow), the term devised by Edward Jenner to denote cowpox [1]. Vaccine used as a preventive inoculation to confer immunity against a specific disease, usually employing an innocuous form of the disease agent, as killed or weakened bacteria or viruses, to stimulate immune response. The administration of vaccines is called vaccination. Vaccination is the most effective method of preventing infectious diseases; 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 [2]. Several factors must be considered to developing a successful vaccine. The first step is which branch of the immune system is activated, humoral or the cell mediated branches. A second factor is the development of immunologic memory. For example, a vaccine that induces a protective primary response may fail to induce the formation of memory cells, leaving the host unprotected after the primary response to the vaccine subsides [3].

Whole-Organism Vaccines

Vaccine currently in use consists of inactivated (killed) or live but attenuated (avirulent) bacterial cells or viral particles.

Live Attenuated vaccines

An Attenuated Vaccine contain a group of microbes that had been weakened and decreased its virulent under laboratory conditions but it still alive therefore it will be less pathogenic but retain their capacity for transient growth within an inoculated host [4-6]. The most commonly used attenuation system these days is based on a high number of stages or replications of the virus or virulent bacteria in cell lines (viruses) or culture media (bacteria). The microorganisms lose their virulence and do not produce any type of lesion in the animal, but continue to be able to replicate or multiply sufficiently in order to be processed by the immune system but this attenuation system has a small risk of reversion to virulence. For example Bacille Calmette-Guérin is a vaccine against tuberculosis, developed in 1921 by Albert Calmette and Camille Guérin, caused by attenuation of the *Mycobacterium bovis* strain on a medium containing increasing concentration of bile. This strain had adapted after 13 years to growth with increased bile [7].

Other new technique involves the removal of a gene from the virus or bacterial cell, this gene is responsible for a particular disease and virulence (Figure 1). The advantage of this attenuation system the risk reversion to virulence is smaller in vaccines with deletions for example attenuated, gene-deletion mutants of pseudorabies virus (PRV) vaccine

for pigs, in which the thymidine kinase gene and glycoprotein X was removed because thymidine kinase is required for the virus to grow in certain types of cells, so if we removed that gene the virus will be attenuated and can be used as a vaccine [8]. More recently, a vaccine against rotavirus, a major cause of diarrhea in infants and young children, was developed using genetic engineering techniques to modify an animal rotavirus to contain antigens present on the human viruses [9,10]. A major disadvantage is very serious and dangerous because the reversion or the reactivation tendency of the attenuated vaccines that achieved by a mutation in the virus or bacterial cell in result to unfavorable conditions not by genetic engineering techniques So, if a multiple mutation in a virus or bacterial cells is done the "Back-mutation" is less likely to happen, for example: - The influenza vaccine is attenuated by a mutation at 4 genomes of its eight genome segments [11,12]. So this vaccine has never been reactivated to the virulence form [13]. Another example sabin polio vaccine OPV carries only a few (two to six) major attenuating mutations that is given the rapid mutation rates of all viruses leading to subsequent paralytic disease is about one in every 750,000 children receiving the first dose of OPV [14]. The pathology associated with this disease is characterized by severe air sac infection where MG is the primary pathogen followed by secondary infections with *Escherichia coli* and/or viruses such as infectious bronchitis (IBV) virus or Newcastle disease virus (NDV) [15].

Another concern with Attenuated live vaccines is also carry a potential risk of contamination with adventitious viruses introduced during the attenuation process, from the cell lines used, and/or from the animal sera or other biologics often used in cell cultures. Very early Theiler's yellow fever attenuated virus was once "stabilized" with human plasma thought to contain hepatitis B virus, resulting in many cases of hepatitis [16]. In 1960 it was discovered that the sabin vaccine was contaminated with oncogenic virus SV40 from the monkey cells used to amplify polioviruses [17]. Live Attenuated Vaccines can cause severe complications in immunocompromised patients due to HIV or from chemotherapy treatment [18]. The main advantage of attenuated vaccine is provide prolonged immune system exposure to the individual epitopes on attenuated organisms resulting produced the memory T Lymphocytes, activated all phases of the immune system (for instance IgA local antibodies are produced), inducing a cell-mediated response because it is ability of many attenuated vaccine to replicate within host cells, and also Provides more durable immunity therefore, boosters are required less frequently [19]. These properties are important in third world countries due to a round 20% of individuals fail to return for each subsequent booster.

Attenuated Vaccines should be store in cold temp, this reason make live attenuated vaccines an excluded choice to transport to countries with lack of refractions [12]. In addition to their low coast and fast immunity.

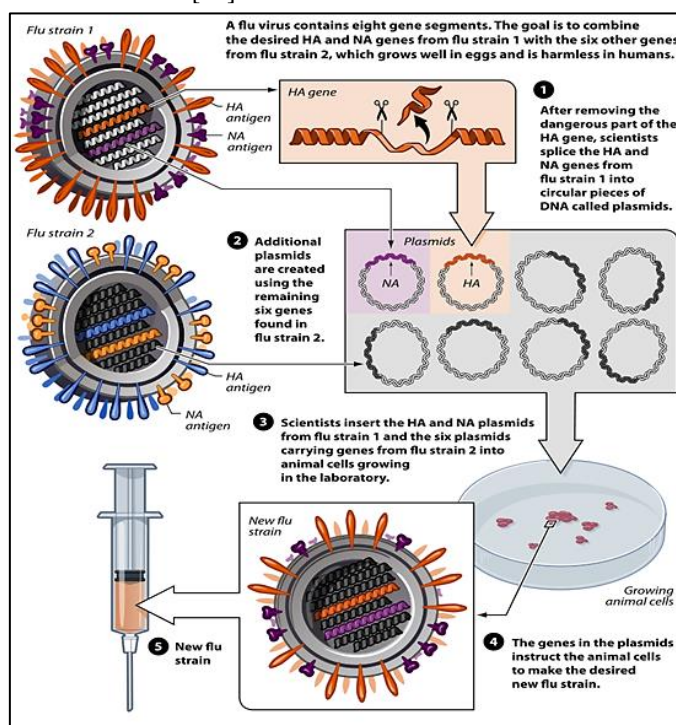


Figure 1: Avian flu vaccine development by reverse genetic engineering technique. (national institutes of health, part of the united state department of health and human services)

Inactivated viral or bacterial vaccines:

An Inactivated vaccines or killed vaccines is a vaccine consist from virus, bacterial or other pathogens that have been grown in a specialized culture and then completely killed by heat, radiation or chemicals so it is no longer capable of replication in the host and to be effective must contain much more antigen than live vaccines (Figure 2) [20]. Inactivated process is critically important to maintain the structure of epitopes on surface antigens during inactivation.

Excessive heat inactivation cause denaturation of protein therefore the epitope depend on structure of protein are altered or damaged. So the most successful methods to kill the pathogen depend on chemicals such as Formaldehyde, phenol, and binary ethylenimine (BEI) [21]. In the preparation of an inactivated viral vaccine the inactivation process is a very important step. The traditional agent for inactivation of the virus is formaldehyde. Excessive treatment can destroy immunogenicity whereas insufficient treatment can leave infectious virus capable of causing disease. Soon after the introduction of inactivated polio vaccine during the period of 1956 to 1958, there was an outbreak of paralytic poliomyelitis in the USA use to the distribution of inadequately inactivated polio vaccine and demonstrated that the inactivation of this virus with formaldehyde was not a linear or first-order reaction. This incident led to a review of the formaldehyde inactivation procedure and other inactivating agents are now available, such as binary ethylenimine (BEI) [22]. The Foot-and-Mouth Disease virus (FMD) inactivation was relatively slow, about 0.2-0.3 log 10 per hour. Because formaldehyde not only reacts with the virus produced but with many other components in the medium, such as proteins and amino acids, its concentration can become rate-limiting and inactivation plots may show tailing-off, resulting in residual infectivity that cause post-vaccination outbreaks. Much faster and safer inactivation with linear inactivation kinetics was obtained with aziridines and BIE. Under optimal conditions, inactivation rates of BIE are in the range of 0.5-1.0 log 10 per hour. In general, the inactivation takes 40-48 hours, which will guarantee complete inactivation of all virus particles in a batch. On other study formaldehyde added during the BEI-inactivation process strongly augments inactivation rates with a hundred to thousand-times (to 2.5-3.5 logs per hour). This will enable inactivation during a working day or just overnight with even higher safety levels of the vaccines. Also, it is known that formaldehyde cross-links viral proteins which will stabilize the antigen. The short inactivation times will limit proteolytic destruction of 146S antigen and increase antigen yields [23]. The mechanism of 'synergistic effect' of BEI+ formaldehyde is not understood well. However, formaldehyde is known for its cross-linking property of capsid proteins thereby stabilizing the 146S particle of FMD virus, increase antigen yields and enabling the BEI to attack on nucleic acid more easily therefore the endurance of the immune response will be favorably influenced. Likewise, the glutaraldehyde also fixes the antigen leading to alterations in the arrangement of the RNA and protein subunits of 146S [24]. Sodium thiosulfate 20% was added to the virus after the inactivation in a final concentration of 2% (up to 24 h) to neutralize the effect of BEI, also sodium bisulfite 20% was added after inactivation to neutralize the rest of formaldehyde [25].

All of these inactivated ways lead to destroy the pathogen's ability to replicate and causing diseases but still keeps its antigenicity and because of this, the immune system will recognized it and produce protective antibody against them [21], they are less effective than attenuated vaccine in inducing cell-mediated immunity and eliciting a secretory IgA, therefore the killed vaccine requires more than one dose or multiple boosters to induce the immune response and the people with immunodeficiency are advised to use inactivated vaccine instead of attenuated vaccine [26]. Inactivated viral or bacterial vaccines can transport to developing countries; because it doesn't require a cold temperature to still in the active form vaccine, as attenuated type [20]. The risks of inactivated whole-organism vaccine appear when the formaldehyde failed to kill the entire virus in vaccines. The encephalitis-type reactions occurred in small percentage of infants receiving the whole-organism pertussis vaccine these vaccines have led to development of a new a cellular vaccine for pertussis [27].

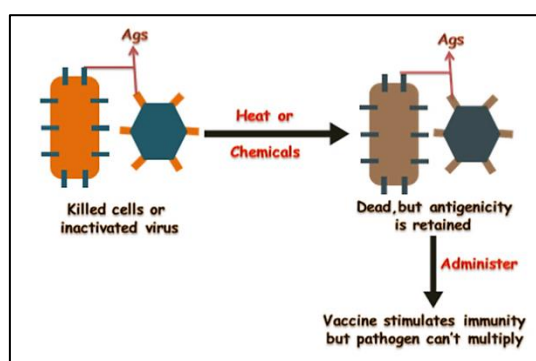


Figure 2: Virulent bacteria or virus killed by heat or by chemicals such as formalin to prepared inactivated vaccine

CONCLUSION

The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters. We reviewed the recent literature on types of vaccines and older studies were included selectively if historically relevant. Attenuated and killed vaccine have been studied extensively to help eradication the infectious disease development, and thereby decrease the need for drugs.

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