

## Vaccine development: A historical perspective

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### Abstract

Prevention from disease is always better than cure. The concept of preventing disease originated during the 17th century when Edward Jenner an English physician contributed to eradicating smallpox. Jenner's work is widely regarded as the foundation of prophylactic measure of disease by the vaccine, the term derived from "Vacca" means cow. The concept of the vaccine is slowly traveling from prophylaxis to therapeutic. However, therapeutic vaccines are under research and development. The first vaccine was developed using virus-infected lesions and in later stages many different types of vaccines such as toxoid vaccines, live attenuated vaccines, inactivated or killed vaccines and subunit vaccines have been formed. Modern advancement in biotechnology research had laid down for the development of the recombinant vaccine. However, the future trend of vaccine development is towards recombinant DNA technology and therapeutic vaccine for targeted diseases. This review article focuses on the historical perspectives of vaccine and the development of the vaccine as it is a core area of research where the life of the human is saved from various possible diseases

**Keywords:** Historical perspectives, Contributions, Prophylactic vaccine, Modern vaccine.

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### Introduction

#### *Edward Jenner and vaccines*

Prevention is better than cure is the common proverb of the public across the world. Preventing infectious diseases by the vaccine is the most successful medical invention in the modern therapeutic era. The miracle of vaccines improved the status of public health across the world. This miracle was invented accidentally by Edward Jenner between 1749-1823 during 1796. Jenner met a dairymaid and heard her saying that "I shall never have an ugly pockmarked face". Jenner then understood that there are some principles due to which dairy maids were protected from this dreadful smallpox disease. This incidence made Jenner follow a path, in May 1796, Jenner observed a young dairymaid who had fresh cowpox lesions on her hand. Jenner inoculated the matter from the lesions of dairymaid's hands to James Phipps, eight year old boy. After 9 days the boy developed mild fever, discomfort, cold and loss of appetite, later he recovered. After two months in July 1796, once again Jenner inoculated the boy with fresh smallpox lesion. But the boy did not develop any disease and confirmed the protection. In the year 1797, Jenner had sent a short communication to the Royal society regarding his findings but it was rejected. In the next year, Jenner studied by experimenting with various cases and published a small booklet called "An Inquiry into the Causes and Effects of the Variolae Vaccinae". Jenner termed his finding as "Vaccine" derived from "Vacca" means cow [1].

Later Jenner tried the same experiment on his baby son and other children, all were protected from smallpox [2]. After these findings, Jenner spent the rest of his professional life by supplying cowpox material to others across the world and explained the scientific background. He himself called him "Vaccine Clerk to the World". On recognizing his work in 1802 the British Government awarded him £10,000 and followed by the year 1807 he received £20,000 [3]. Few days before his death, Jenner stated to a friend: "I am not surprised that men are not grateful to me, but I wonder that they are not grateful to God for the good which he has made me the instrument of conveying to my fellow creatures [4]. Though Jenner's work benefited to the society of human beings, later many controversies against Jenner's concept and anti-vaccination movements were developed in England when Government made vaccination compulsory [5]. By the year 1853 England Government introduced compulsory vaccination, with fines for non-cooperatives and imprisonment for non-payment. Later in 1885, Louis Pasteur developed rabies vaccine, actually, it was rabies antitoxin that was much useful as a post-infection antidote and explained the association between cow and cowpox to include all inoculating agents [6]. This serves as a base for current vaccine production from a suspension of live or inactivated microorganisms. Later many researchers have contributed to the development of vaccines for preventing from various infectious diseases so-called prophylaxis.

### **Golden era of vaccines “Post-Jenner period”**

Louis Pasteur (1822-1895), a chemist was interested in developing various fermented products. His experiments gave a new theory by stopping the old version of spontaneous generations [7]. The contribution of Pasteur in developing vaccine laid as a new branch of medical science termed Immunology [8]. Pasteur discovered a vaccine against fowl cholera and presented his work in French academic des sciences, which can be considered as an origin of Immunology. He coined the phenomenon of vaccination in honor of Edward Jenner [9]. After this contribution, Pasteur was interested in the prevention of anthrax. He demonstrated the efficacy of anthrax in cattle and reduced anthrax mortality in France. Meanwhile

Robert Koch (1843-1910), a physician from Germany interested in microbial science. Koch isolated *Bacillus anthracis* in pure culture [10] and demonstrated the life cycle of Anthrax which demonstrated the causal relationship between specific organism and disease. On another side in France in 1880 Pasteur was informed by the Paris hospital that a young boy was dying from Rabies. He isolated the microbe from the saliva of the boy and tried to induce rabies in rabbit but unfortunately, his effort failed. During the time 1878-1880 Pasteur published various research papers on Anthrax. However, Pasteur and Koch were continuously working on Anthrax independently providing various experimental data about the causative agent of Anthrax. Pasteur was conducting a large scale immunization programme in 1881 at Pouilly-le-Fort by utilizing 70 sheep. He designed the vaccination schedule at 2 steps.

1. The primary immunization was performed with low virulence culture.
2. After 12 days the secondary immunization was performed with less attenuated culture.

Then after a period of two weeks, the sheep were challenged by inoculating with virulent anthrax strain in vaccinated and unvaccinated sheep. After a few days, the unvaccinated sheep have died but vaccinated sheep were healthy. This finding made Pasteur more successful in vaccinology. Moreover, the concept of booster vaccine also originated later which helped to understand the immune mechanism. Meanwhile in 1881 Joseph Lister, a surgeon organized seventh International Medical Conference at London. Lister also invited Koch to the conference. Pasteur's finding influenced Lister to develop the use of antiseptics principles in surgery. During the conference, Koch demonstrated a laboratory technique for isolating, staining the bacteria and their importance. Pasteur 20 year's senior to Koch also attended the demonstration of Koch and appreciated him on admiration that became a great achievement for Koch. However, there was a basic controversy between Koch and Pasteur as by profession Koch was a physician but Pasteur was a chemist. Moreover, the controversy was enhanced due to France and German war in 1870. Soon after this conference, Pasteur and Koch openly conflicted with each other. Robert Koch and his students Gaffky, Löffler published many articles commenting on Pasteur's work on the attenuation of anthrax vaccine. They

accused that Pasteur's finding on attenuated anthrax vaccine was done using impure culture and errors were made during inoculation.

In 1882 Pasteur elucidated to Koch's comment during the fourth International Congress of Hygiene and Demography held in Geneva, Switzerland. By that time Koch became very famous due to the discovery of tubercle bacillus. Koch attended as an audience in Pasteur's presentation on attenuation and vaccination. Koch refused to recognize Pasteur's findings of attenuation techniques as he believed that biological and chemical characteristics of microbes are specific and permanent. In contrast to Koch's theory, Pasteur understands that microbial constituent can be lost and can be recovered. Pasteur stated that the existence of these variations was of great importance on understanding the epidemiology of various infectious diseases to which Koch did not agree and stated that Pasteur is not a physician and may not be having knowledge on the pathological process and symptoms of diseases. In 1882, Koch presented and demonstrated his findings at a meeting in Berlin Physiological society. The demonstration included 200 microscopic preparation which was the most regarded and significant presentation to date in Medical history [11]. Later, in 1885 Pasteur developed a vaccine against Rabies, which was the last discovery of Pasteur. Behring Kitasato in 1902 developed tubercle vaccine prepared from human tubercle bacilli by attenuation process. Behring termed the vaccine “Bovo vaccine” which was the first vaccine against tuberculosis. However, the vaccine was inducing a good immune response but offered the risk of human infection from immunized animals. Meanwhile, Koch was developing tuberculosis vaccine called “Tauruman” which was probably the second vaccine attempt against tuberculosis. However, the effects more or less similar to bovo vaccine became a failure. [12]. Albert Calmette and Camille Guérin discovered a vaccine against tuberculosis prepared from a strain of the attenuated live bovine tuberculosis bacillus, *Mycobacterium bovis*, and termed it as *Bacillus Calmette-Guérin*. Till date, worldwide BCG remains as the most widely used vaccine with proved safety profile [13,14].

There are various manufacturers of BCG vaccine available across the world and producing different qualities based on the proportionate of viable cells per dose [14]. For long being it was misunderstood that TB could be conquered by antibiotics but BCG vaccination led to contentment for several decades. In early 1990 this situation radically changed when the World Health Organization (WHO) declared TB a global emergency [15,16]. Worldwide BCG vaccine is procured more by UNICEF (The United Nations Children's Fund) on behalf of the Global Alliance for Vaccines and Immunization. Even though, the efficacy of the BCG vaccine still remains to be notorious, live attenuated BCG vaccine is still the only vaccine in use for the prevention of TB in humans.

Toxoids are a modified form of exotoxins produced by bacteria in order to reduce toxicity and improve antigenicity. The modification of toxin can be achieved by the addition of formalin. Toxoids are used as vaccines because they induce an

immune response to the original toxin. In 1890 Knud Faber has demonstrated the existence of tetanus toxins [17]. In the same year, Behring and Kitasato demonstrated the production of antitoxins against tetanus antitoxin after immunizing the rabbits [18]. The concept of toxoid vaccine was found out by Ramon and Descombey in 1920. They made a major contribution to the development of an effective vaccine for both tetanus and diphtheria using formaldehyde for reducing the toxic property. In 1923 Glenny and Hopkins showed that diphtheria toxin could be converted into toxoid by the action of formalin which reduces its toxicity and maintained antigenicity [19,20]. The tetanus toxoid vaccine was proven to be successful when it was used to prevent tetanus in the military during World War II [21]. Albert Sabin in 1961 developed oral polio vaccine and thus termed as Sabin vaccine. It is also called trivalent oral polio vaccine.

Measles is a contagious disease that is caused by a virus belonging to Paramyxoviridae. A vaccine against measles was first introduced in 1963 and improved in 1968. Vaccination against measles was introduced by Maurice Hilleman and colleagues [22]. Measles vaccine is usually administered in combination with other live attenuated vaccines of mumps and rubella. The combined MMR vaccine was introduced to induce immunity less painfully than three separate individual injections at the same time, on different schedules.

Baruch Blumberg in 1965 won the Nobel Prize for the discovery of hepatitis B virus called Australian antigen termed because blood sample was Australian aborigine's that reacted with an antibody in the serum of an American haemophilia patient. During 1975 Blumberg and Millman developed the first hepatitis B vaccine by the heat-treated form of the virus. Later, the first hepatitis B vaccine was approved by FDA in 1981 which was plasma-derived for hepatitis B vaccine for human use prepared from hepatitis B virus-infected donors by pasteurization and treatment with formaldehyde [23]. Recombinant DNA technology has an enormous impact on developing a new vaccine for the benefit of human society by making vaccines safe and economical. Effective recombinant hepatitis B vaccines have been available since the 1980s and included in National vaccination programme in all the countries. The vaccination was highly successful in reducing the disease burden by eliciting a good immune response for lifelong protection against hepatitis B [24].

The World Health Assembly a forum of the World Health Organization (WHO) in 1988 determined to eradicate poliomyelitis by the year 2000 and since then there has been a remarkable decline in the incidence of poliomyelitis [25]. OPV produces humoral immunity to all three types of poliovirus, and in the event of infection, protects the individual from polio paralysis by preventing the spread of poliovirus to the nervous system. In 2012, the World Health Assembly declared the completion of polio eradication as a programmatic emergency for global public health. The Global Polio Eradication Initiative (GPEI) in discussion with national health authorities, global health initiatives, scientific experts, donors, and other stakeholders and, in response to a directive of the World Health

Assembly, proposed polio eradication plan 2013-2018, for establishing a polio-free world [26]. Recently, there are many vaccines developed against various vaccine-preventable diseases with the application of modern biotechnological principles.

### **Modern vaccines**

The concept of vaccine development progressing from the prophylaxis to therapeutic by immunizing with a sequence of DNA or specific peptides, and are used for the treatment of infectious and non-infectious diseases is called therapeutic vaccine [27]. Therapeutic vaccines are focused as a viable option by using a patient's own immune system for active immunotherapy of cancers, tuberculosis, and HIV [27-29]. U.S. FDA approved the first therapeutic vaccine in the year 2010, Provenge manufactured by the Dendron Corporation, a novel method for treating prostate cancer [30]. On the other hand, peptide-based vaccines an emerging as novel therapeutics targets to elicit robust immune responses through antigenic determinants for several cancers including urological cancers and prostate cancer [31].

### **Conclusion**

Vaccines are the most successful medical invention to prevent many infectious diseases. Although many vaccines have been developed against various infectious disease unlike smallpox still there is an existence of bio burden on vaccine-preventable diseases. However, modern research discovering has a greater contribution by finding new vaccines to protect society from infectious diseases. Although vaccines and vaccination programme are more successful, there was a lot of struggle behind the discovery of vaccines. The present modern era of vaccinology has to focus the vaccine efficacy to transit from prophylaxis to therapeutic to combat many infectious and non-infectious diseases, which is highly challenging and spurring with promising results against new disease targets.

### **Conflicts of Interest**

The authors declare no conflict of interest.

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