

Vaccination through time: from the first smallpox vaccine to current vaccination campaigns against the COVID-19 pandemic

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Abstract. The systematic study of the evolution of the concept of vaccination constitutes a fascinating journey through time and the scientific development of effective and safe vaccines against infectious diseases is one of the greatest achievements in the history of medicine. In the western world vaccination dates back to the eighteenth century, a period in which smallpox was a diffused and often lethal disorder, and in many countries attempts at the prevention of such a medical and social threat were conducted. The English surgeon Edward Jenner (1749-1823) is commonly considered the discoverer of the vaccination for smallpox. Moving from remote history to recent periods, the ongoing 2019-2021 coronavirus disease (COVID-19) pandemic has posed a tremendous challenge to the health systems of the countries involved. It has triggered all over the world the rapid development of several effective vaccines, never before prepared in such a brief span of time. It must be acknowledged that modern vaccinology as a science stands at the crossroads of multiple medical specialties and scientific disciplines. In turn, twentieth century explosive progress in the field of vaccination has triggered the development of other important medical areas, from immunopathology to infectious diseases therapy, and from prevention to anti-cancer treatment. Nowadays, effective and diffused control of infectious diseases cannot be done without vaccines, as the COVID-19 pandemic has once again demonstrated, and the role of well structured vaccine programs and of capillary and systematic vaccine campaigns has become central for the health of entire populations all over the world. (www.actabiomedica.it)

Key words: Vaccination, Immunization, History of Medicine, Smallpox, Coronavirus, COVID-19, Epidemics

The systematic study of the evolution of the concept of immunization constitutes a fascinating journey through time and the scientific development of effective and safe vaccines against infectious diseases is one of the greatest achievements in the history of medicine and public health.

In the western world, vaccination dates back to the eighteenth century and involves the administration of an antigenic substance capable of stimulating a human protective immune response against an infectious pathogen (1). In the Enlightenment Europe of the seventeen hundreds smallpox was a diffused and

often lethal disorder, and in many countries attempts at prevention of such a medical and social threat were conducted during the entire century (2).

The English surgeon Edward Jenner (1749-1823) is commonly considered the discoverer of the vaccination for smallpox (3). In his time, in the second half of the eighteenth century, the only intervention deemed useful in contrasting smallpox was the so-called variolation, a technique aimed at infecting healthy people by means of the “matter” obtained from sick persons affected by a mild-moderate form of the infectious disease. Jenner had observed that people suffering from an

attack of cowpox, a not very serious pathology affecting cattle, were protected from contracting the human disease named smallpox. This British physician therefore concluded that, on the one hand, cowpox was an animal disease that generally protected against human smallpox, and on the other, that cowpox, through the application of pathological matter taken from the lesions of sick persons, could be deliberately transmitted from one single individual to another as a protective presidium. In 1796 Jenner obtained matter from cutaneous lesions of a dairymaid, affected by cowpox, and inoculated a healthy boy, who became mildly ill in the week subsequent to the inoculation, recovering by day ten after Jenner's preventive maneuver. Fifty days later Jenner inoculated the same boy with smallpox matter and, since he could not observe any pathological alteration in his small patient, he concluded that protection was complete at that time. After having accurately collected and described many other cases, two years later Jenner published a book entitled "An Inquiry into the Causes and Effects of the Variolae Vaccinae", a milestone in the history of vaccine programs in the United Kingdom.

The clinical application devised by Jenner found many and not rarely important followers all over Europe and, with specific reference to Italy, the physician Luigi Sacco (1769-1836), who today gives his name to a well-known hospital of the city of Milan, propagated the Jennerian method in northern Italy (4). It should be underlined, however, that in the eighteenth century, infectiology as a specific discipline did not exist, and even medical notions relative to infectious diseases were generally confused and often misleading. Not by chance, many scholars believe that, in the course of the nineteenth century, the application of material obtained from lesions of smallpox patients contributed to the diffusion of other infectious pathologies, among them, in particular, syphilis (5). Moreover, the idea that a physician should deliberately determine a disease in healthy people, even if for preventive-protecting purposes, was often refused by many persons who had always seen in physicians, on the contrary, the professionals devoted to cure of sick people (6). In any case, in the course of the eighteenth and nineteenth centuries vaccination spread widely and in this same century it acquired a scientific basis, especially thanks to the work of Louis Pasteur (1822-1895).

A French chemist and microbiologist, Pasteur is retained by many medical historians to be one of the major founders of microbiology, thanks also to his research in methods that could hamper the virulence of pathogenic agents. Pasteur created the first live attenuated bacterial vaccines, such as that against chicken cholera (1870), and developed the first forms of preventive microbiological measures effective against anthrax and rabies (1885), thus paving the way for the development of immune theories in human beings. His studies opened the scientific scenario for the identification of etiologic agents responsible for cholera, typhus and tuberculosis (7).

With regard to this, the French bacteriologist Albert Calmette (1863-1933) a pupil of Louis Pasteur, together with his younger co-worker Camille Guérin (1872-1961), developed the *Bacillus Calmette-Guérin*, or BCG (1909), a vaccine that was soon extensively adopted both in Europe and in America in the fight against the largely diffused disease known as tuberculosis (8).

It is not by chance that the birth of the two medical-scientific disciplines fundamental for the historical development of vaccines, namely infectiology (before) and immunology (after) can be collocated appropriately between the end of the nineteenth century and the beginning of the twentieth century, a period particularly favorable for the discovery of infectious agents and the elaboration of the first structured theories regarding human immune responses, in particular in French speaking and German speaking countries. Already some decades before, in the course of the nineteenth century, the first great vaccination campaigns had been put into action in Europe, starting from English speaking countries and moving to German speaking ones (9).

In 1890 the Danish professor of internal medicine Knud Faber (1862-1956) showed the existence of tetanus toxins and the German bacteriologist Emil von Behring (1854-1917) and the Japanese physician Shibasaburo Kitasato (1853-1931) demonstrated the elaboration, on the part of immunized animals, of antitoxin substances against tetanus toxins (10). These last two scientists also experimentally demonstrated that serotherapy was effective against the so-called "strangling angel", i.e. diphtheria (11). As evidenced in the the first half of the nineteenth century by the

pionieristic research of the French veterinarian of the Pasteur Institute Gaston Ramon (1886-1963), toxoids, which were modified forms of exotoxins, could be used as vaccines given their capability to induce an immune response against the basic toxins (12). To preserve antigenicity and to reduce toxicity, Ramon adopted formaldehyde and heat in the preparation of an anatoxin, a toxoid vaccine effective against diphtheria and tetanus. According to Ramon, the efficacy of this anatoxin could be heightened by adding specific substances boosting antibody responses, including aluminum hydroxide; this consideration led to the conceptual frame of currently used vaccine adjuvants. In the twenties the British immunologist Alexander Glenny together with his co-workers (Wellcome Research Laboratories, London, UK) started to conduct experiments using vaccines prepared from toxoids (deactivated toxins). He demonstrated that whole bacteria were not mandatory in order to generate immunity, and elaborated a toxoid diphtheria vaccine in 1923 followed by a tetanus vaccine in 1926 (13). This research opened the way for the diffused adoption of tetanus toxoid vaccine among the soldiers involved in the second World War, contributing to the saving of the lives of many individuals.

After World War II, in the course of the fifties, further great developments were accomplished in the area of vaccines. The US physician Jonas Salk (1914-1995) elaborated the first effective and safe vaccine to inject in humans against poliomyelitis, composed by dead poliovirus (1952-5). The Polish American microbiologist Albert Bruce Sabin (1906-1993) hypothesized that orally administered, attenuated (meaning weakened live organisms) virus could furnish immunity for a longer time period if compared to dead injected virus, and he developed the first oral polio vaccine (1956-7) (14). Between this date and the early eighties of the twentieth century, when vaccines for hepatitis B became available, a number of other vaccines were introduced in routine vaccine programs, ranging from pertussis to measles, from rubella to epidemic parotitis and spread rapidly (15).

In recent decades vaccine technology has made great strides, and this is particularly important since SARS-CoV-2 vaccines technologies are based on discoveries made after polio vaccines. The last fifty years have seen the identification of genes of pathogenic

microorganisms that are able to determine clinical diseases and that encode the proteins stimulating human immune responses against the pathogens themselves. As a consequence, medical laboratories of the third millennium have been able to prepare antigens adopted in the generation of modern vaccines. Even more recently, pathogenic microorganisms have been genetically modified in order to elaborate virus strains which are weakened to provide an effective and safe basis for attenuated vaccines (16). With reference to viruses difficult to cultivate in the laboratory, and also with regard to particularly hazardous pathogenic microorganisms, the technology based on recombinant DNA has been demonstrated to be of great use. DNA vaccination appears as a potentially effective means of inoculating a host with genes. The latter encode immunogenic proteins from pathogens, and when the genes are inserted into the host cells, they access transcriptional and translational machinery. The elaboration of proteins within the cells allows the processing into epitopes and the subsequent presentation on the part of MHC-I and MHC-II. Once the host cells have been used to produce elevated levels of target proteins, the result is a strong cell mediated immune response. While DNA vaccination by means of plasmids has usually involved vectors targeted to transient antigen expression in injected tissues, future-generation plasmids are designed for site-directed integration of transgenes into safe sites in host genomes, so furnishing an original method for a sustained and stable expression of antigens for vaccination (17). In synthesis, nowadays vaccines are complex preparations not only containing antigens, but also all the substances useful for maintaining the vaccines themselves effective and safe, including preservatives, stabilizers, surfactants and sometimes adjuvants. Moreover, therapeutic vaccines today represent a stimulating tool for the active immunotherapy of malignancies and aim at managing late-stage diseases by utilizing the immune system of the patients themselves (18).

In the last two years, the ongoing coronavirus disease (COVID-19) pandemic has posed a tremendous challenge to the health systems of the countries involved (4). It has triggered all over the world the rapid development of several effective vaccines, that have never before been prepared in such a brief span of time. Once again, in this specific scenario

too, knowledge of medical history is fundamental for understanding how such extremely rapid achievements have been possible. In effect, as has been recently clearly and authoritatively noted on scientific-technical grounds, the initial stage of the design and evolution of SARS-CoV-2 vaccines is not to be ascribed to the year 2020, but dates back to years before, in which the use of extremely adaptable vaccine platforms (among others in particular RNA) and the tailoring of structural biology instruments for the production of immunogens strongly stimulating human immune systems were being elaborated and redefined in research laboratories (19). At the level of communication, the rapid preparation of SARS-CoV-2 vaccines has posed additional, new challenges to correct information regarding the benefits and risks of vaccination. It was only about forty years ago, in 1976, that the first vaccine patient information sheets elaborated by the US Centers for Disease Control and Prevention were released, but since then ethical, scientific and legal issues have led to a profound reconsideration and improvement in vaccine information statements, as they are called today (20). Last but not least, the recent history of the COVID-19 pandemic and of the development of SARS-CoV-2 vaccines poses challenges on economic grounds too, considering the unprecedented need for worldwide supplies and for timely and quantitatively adequate availability of targeted vaccines (21). Consequently, the theme of the appropriate equality in access to these vaccines, on a planetary scale, constitutes a further ethical-economical issue in the complex and evolving scenario of vaccination campaigns against COVID-19.

In conclusion and at the end of this journey through “medical” time, it must be acknowledged that modern vaccinology as a science stands at the crossroads of multiple medical specialties and scientific disciplines, being in particular debtor both to health care branches born and developed at the end of the nineteenth century (infectiology) and those at the beginning of the twentieth (immunology). In turn, the explosive progress in the field of vaccination during the twentieth century has per se triggered the development of other important medical areas, ranging from immunopathology to infectious diseases therapy, and from prevention to anti-cancer treatment, as the

universal program of vaccination against human papillomavirus has clearly shown in more recent times.

Today, effective and diffused infectious diseases control and containment cannot be done without vaccines, as the last two years of COVID-19 pandemic has once again demonstrated, and the role of well structured vaccine programs and of capillary and systematic vaccine campaigns have become central for the health of entire populations all over the world.

Acknowledgements: The Author would like to thank Professor Luisa Camaiera, B.A., M.Phil., for her correction of the English.

Conflict of interest: The author declares that he has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

References

1. Lombard M, Pastoret PP, Moulin AM. A brief history of vaccines and vaccination. *Rev Sci Tech Off Int Epiz* 2007; 26: 29-48.
2. Conti AA. Historical evolution of the concept of health in Western medicine. *Acta Biomed* 2018; 89: 352-354.
3. Riedel S. Edward Jenner and the history of smallpox and vaccination. *Proc (Bayl Univ Med Cent)* 2005; 18: 21-25.
4. Conti AA. Historical and methodological highlights of quarantine measures: from ancient plague epidemics to current Coronavirus disease (COVID-19) pandemic. *Acta Biomed* 2020; 91: 226-9.
5. Zakir F, Islam F, Jabeen A, Moni SS. Vaccine development: a historical perspective. *Biomedical Research* 2019; 30: 452-5.
6. Conti AA. Protective face masks through centuries, from XVII century plague doctors to current health care professionals managing the COVID-19 pandemic. *Acta Biomed* 2020; 91(4):e2020124.
7. Berche P. Louis Pasteur, from crystals of life to vaccination. *Clin Microbiol Infect* 2012; 18 Suppl 5: 1-6.
8. Bettencourt PJG. The 100th anniversary of bacille Calmette-Guerin (BCG) and the latest vaccines against COVID-19. *Int J Tuberc Lung Dis* 2021; 25: 611-613.
9. Cavaillon JM. Historical links between toxinology and immunology. *Pathog Dis* 2018; 76: 1-12.
10. Faber K. Die Pathogenie des Tetanus. *Berl Klin Woch* 1890; 27: 717-20.
11. Behring E, Kitasato S. Ueber das Zustandekommen der Diphtherie-Immunität und der Tetanus-Immunität bei Thieren. *Dtsch Med Wochenschrift* 1890; 49: 1113-4.

12. Ramon G. Sur la toxine et l'anatoxine diphtériques. Pouvoir flocculant et propriétés immunisantes. *Ann Inst Pasteur* 1924; 38: 1-10.
13. Glenny AT, Hopkins BE. Diphtheria toxoid as an immunizing agent. *Brit J Exp Pathol* 1923; 4: 283-8.
14. Baicus A. History of polio vaccination. *World J Virol* 2012; 1: 108-14.
15. Helfert SM. Historical aspects of immunization and vaccine safety communication. *Current Drug Safety* 2015; 10: 5-8.
16. Hilleman MR. Vaccines in historic evolution and perspective: a narrative of vaccine discoveries. *Vaccine* 2000; 18): 1436-1447.
17. Bertino P, Urschitz J, Hoffmann FW, et al. Vaccination with a piggyBac plasmid with transgene integration potential leads to sustained antigen expression and CD8(+) T cell responses. *Vaccine* 2014; 32: 1670-7.
18. Guo C, Manjili MH, Subjeck JR, Sarkar D, Fisher PB, Wang XY. Therapeutic cancer vaccines: past, present, and future. *Adv Cancer Res* 2013; 119: 421-475.
19. Fauci S. The story behind COVID-19 vaccines. *Science* 2021; 372: 109.
20. Orenstein WA, Douglas RG, Rodewald LE, Hinman AR. Immunizations in the United States: success, structure and stress. *Health Affairs* 2005; 24: 599-610.
21. Zhang R. Economic impact payment, human mobility and COVID-19 mitigation in the USA. *Empir Econ* 2021; 20: 1-20.

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Received: 29 August 2021

Accepted: 10 September 2021

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