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Vaccination against COVID-19 – historical foundations

Szczepienie przeciwko COVID-19 – fundamenty historyczne

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Abstract

Vaccinations are a relatively recent development in human history. Variolation, i.e. contacting healthy persons with biological material from mildly ill individuals was the prototype of a vaccine. Although used for centuries, it was only at the end of the 19th century that Louis Pasteur developed the first successful vaccines (including against rabies). Over the years, new preparations against many diseases were developed and improved by modifying, among others, route of administration or antigen vector. The general mechanism of action, i.e. preparing the immune system to fight off a given pathogen, remained unchanged. Vaccination has contributed to the reduced spread of multiple infectious diseases, and even complete elimination of some of them. The discovery of vaccination had a significant impact on reducing mortality, extending lifespan and improving the quality of life. We are again facing the threat of infectious epidemics in this era of advancing globalisation, climate crisis and population migratory movements. These predictions were confirmed by the COVID-19 pandemic. Intensive work of many research centres has led to a rapid development of an innovative mRNA vaccine against this clinical entity. These vaccines act by introducing an mRNA template into the host cell to stimulate antigen synthesis *in vivo*. Once again, science has succeeded in limiting the spread of a disease, which was a historic breakthrough. This paper presents a historical outline of the stages of the development of vaccinology leading to the modern concept and technology of vaccine production.

Keywords: COVID-19, SARS-CoV-2, coronavirus, vaccination, history of medicine

Streszczenie

Szczepienia ochronne pojawiły się na kartach historii ludzkości stosunkowo niedawno. Stosowanym od wieków pierwowzorem szczepionek była wariolizacja, czyli kontaktowanie osób zdrowych z materiałem biologicznym pochodzącym od osób łagodnie chorujących. Metodę tę stosowano przez całe wieki, jednak dopiero pod koniec XIX stulecia Ludwik Pasteur stworzył pierwsze właściwe szczepionki (m.in. przeciwko wściekliźnie). Z biegiem lat opracowywano nowe preparaty przeciwko wielu chorobom i doskonalono je, modyfikując m.in. drogę podania czy wektor antygenu. Ogólny mechanizm działania, polegający na przygotowaniu organizmu na kontakt z patogenem, pozostał ten sam. Dzięki zastosowaniu szczepień ograniczono rozprzestrzenianie wielu chorób zakaźnych, a niektóre z nich nawet wyeliminowano. Odkrycie szczepień miało istotny wpływ na zmniejszenie śmiertelności ludzi, wydłużenie życia oraz poprawę jego jakości. W dobie postępującej globalizacji, kryzysu klimatycznego i migracji ludności problem zagrożenia rozwojem epidemii chorób zakaźnych powrócił. Potwierdzeniem przewidywanych obaw była pandemia COVID-19. Intensywna praca wielu ośrodków badawczych doprowadziła do powstania w krótkim czasie nowatorskiej szczepionki mRNA przeciwko tej chorobie. Preparaty tego rodzaju działają na zasadzie wprowadzenia matrycy mRNA do komórki gospodarza i syntezy antygenu *in vivo*. Po raz kolejny udało się ograniczyć rozprzestrzenianie choroby dzięki nauce, co stanowiło przełom dziejowy. W niniejszej pracy przedstawiono w zarysie historycznym etapy rozwoju wakcynologii prowadzące do powstania nowoczesnej koncepcji i technologii produkcji szczepionek.

Słowa kluczowe: COVID-19, SARS-CoV-2, koronawirus, szczepienia, historia medycyny

INTRODUCTION

Vaccinations are a relatively recent development in human history. Contracting a disease remains the most effective method of developing immunity against many infectious diseases. This observation has led to the concept of variolation, i.e. contacting healthy persons with secretions from mildly ill individuals. Alongside this particular type of immunisation, vaccines in the form of biological preparations that mimic natural infection have been developed[1]. Although the boundary between these two methods may seem blurred (especially in the case of live vaccines), there are some major advantages of vaccines, like low pathogenic potential and high preventive efficacy. The beginnings of variolation trace back to at least the 10th century A.D. First descriptions of variolation as a method for preventing smallpox originate from 16th century China. Variolation was brought to Europe from the Ottoman Empire at the beginning of the 18th century. Until the development of a proper vaccine (*ex definitione*), its "prototype" reduced mortality from 15% to about 2.5%[2]. The breakthrough in the fight against smallpox, caused by the variola virus from the family of poxviruses, is undoubtedly attributed to Edward Jenner, who showed evidence for the protective effect of vaccination with the use of vaccinia virus, another poxvirus species, and later popularised this method of disease prevention (1798). However, it was Louis Pasteur who developed the first proper vaccines containing pathogens with reduced virulence; he developed preparations against fowl cholera (1880), anthrax (1881) and rabies (1882). Subsequent years brought the discovery of vaccines against tetanus (1890), cholera (1892), typhoid (1896), plague (1897), whooping cough (1926), tuberculosis (1927), yellow fever (1932) and influenza (1945). In 1950, Hilary Koprowski, a Polish doctor, made a significant contribution to the history of vaccination as a co-creator of the first effective live vaccine against poliomyelitis, administered orally in the form of drops. This was followed by developing vaccines against measles (1964), mumps (1967), rubella (1970), chickenpox (1974), hepatitis B (1981) and hepatitis A (1992). In 2006, a human papillomavirus vaccine was approved. These vaccines contained live attenuated bacteria or viruses, killed microbes or their particles (proteins, polysaccharides). In 2020, in the face of the coronavirus disease 2019 (COVID-19) pandemic, a new generation mRNA vaccine was developed extremely rapidly. The spike protein of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) induces specific antiviral immunity[3]. With the improvement of vaccine composition, as well as the expansion of disease coverage, the route of administration has also changed; for example, smallpox vaccine was initially administered with a scarifier (by scratching the epidermis). Most preparations are currently administered in the form of intramuscular or intradermal injections. Some vaccines can be administered without a needle, e.g. intranasally (influenza) or orally (poliomyelitis vaccine previously used in Poland). Inhaled[4] and transdermal[5] vaccines are under development. For years, attempts have been made to use edible vaccines contained in vegetables or fruits[6].

THE DEVELOPMENT OF COVID-19 VACCINE

At the end of 2019, the genetic material of SARS-CoV-2[7] was sequenced, with the results published already in January 2020 to accelerate the work on the vaccine[8]. This has triggered unprecedented international collaboration between academic organisations and pharmaceutical corporations. Vaccine parameters, such as the target antigen, the type of carrier, the adjuvant, the route of administration, the immunisation pathway, as well as the methodology of efficacy studies, production capacity, and forecasting the further course of the pandemic, needed to be determined before the vaccine was developed[9].

Some research centres have attempted to create a vaccine using traditional approaches, i.e. with the use of inactivated or attenuated virus. Other centres focused on new generation technologies. The SARS-CoV-2 antigen was to be presented to the patient's immune cells by administering a viral protein subunit, virus-like particle, viral vector, mRNA or DNA vector[10].

On June 24, 2020, China approved Convidecia (CanSino), a vaccine containing an adenoviral vector for emergency use. On August 11, 2020, Russia announced the approval of Sputnik V vaccine (developed by the Gamaleya National Research Center of Epidemiology and Microbiology and containing an adenoviral vector). On December 11, 2020, Comirnaty vaccine (Pfizer–BioNTech, mRNA vector) was authorised for use in the United States of America. One week later, the Spikevax vaccine (Moderna, mRNA vector) received such approval. Five COVID-19 vaccines, including mRNA vaccines: Comirnaty, Spikevax, CVnCoV (CureVac), and adenoviral vaccines: Vaxzevria (AstraZeneca, University of Oxford) and JCOVDEN (Janssen Pharmaceutica NV/Johnson & Johnson), are currently approved for use in Poland.

At the time of writing this paper, the first inhaled COVID-19 vaccine, Convidecia Air (CanSino, adenoviral vector), was developed in China and launched for use as a booster.

mRNA VACCINES

Scientific advances have given rise to more advanced biotechnology methods of antigen presentation, e.g. using an mRNA vector. Such vaccines act by stimulating *in vivo* antigen synthesis in host cells in response to a fragment of genetic material responsible for the production of viral particles (e.g. spike protein)[11]. This technology dates back to the

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1970s (Fig. 1), when both the structure of mRNA and the possibility of creating synthetic liposomes were discovered. When encapsulated in liposomes as a carrier, mRNA easily penetrates into cells. This made it possible to use the technology in practice[12]. Katalin Karikó and Drew Weissman were the pioneers of using mRNA in vaccines. At the end of the 20th century, they published papers on the development of a vaccine against the human immunodeficiency virus (HIV), a drug for the treatment of the acquired immunodeficiency syndrome (AIDS), as well as on the treatment of cystic fibrosis and strokes. Subsequent reports described attempts to develop mRNA vaccines against influenza. However, the high seasonal variability of the virus was a barrier in this case. The manufacture of mRNA vaccines against influenza is still unprofitable. In 1993, it was confirmed that the administration of synthetic mRNA encoding the influenza virus nucleoprotein in mice can induce cytotoxic T cells to show increased activity against infected cells. It was already at that time when the antigen-encoding mRNA vector was stabilised by adding two untranslated regions at the 5' and 3' ends: a polyadenylated (polyA) tail and a 5' cap structure. This change increased its half-life, stability and translation efficiency. The method is still used today. Since the 1990s, attempts have been made to use this approach in both infectious and neoplastic diseases, with positive, though still unsatisfactory outcomes[13]. It was not until COVID-19 vaccinations were developed that the full potential of the mRNA vector was shown. Strong induction of cellular response, which was also confirmed during work on the prevention of respiratory syncytial virus (RSV) infections, is the greatest advantage of mRNA vaccines. The mRNA-based technology is therefore preferred for vaccines intended to induce this type of immune response for full efficacy[14]. The lack of efficacy of convalescent plasma in the treatment of COVID-19[15] and the favourable outcomes of vaccination indicate the key role of cellular response in the fight against SARS-CoV-2 infection.

FEAR OF VACCINATION

Fear of immunisation has accompanied people since the beginning of variolation[1,16]. People vaccinated by Jenner were afraid of turning into a cow[17]. Later preparations also gave rise to many doubts. Louis Pasteur received the first vaccination against rabies himself to alleviate the fear among patients[6]. Each subsequent vaccine raised concerns. Science is sometimes distorted and used for political or economic agendas. This may limit the positive impact of discoveries and novel solutions. It has also undoubtedly contributed to the reduced vaccination coverage against various diseases[18]. The currently registered mRNA vaccines against COVID-19 raise concerns due to the new mechanism of action of some preparations, which has not been used on a large scale so far. These concerns relate to two issues in particular: antibody dependent enhancement (ADE) and antigenic mimicry. A virion (viral particle) enters cells by attaching to their surface receptors. The host's immune system produces antibodies against the surface antigens of the virus as a result of humoral response, leading to its neutralisation. In some cases, the host may generate less specific antibodies, which helps the virus enter the cell. This is most likely to occur in patients after repeated contact with the antigen due to vaccination or re-infection. Patients with severe COVID-19 presented higher total antibody titres, which could contribute to ADE induction. Therefore, one of the challenges in developing COVID-19 vaccines is to generate a pool of antibodies in the patient's body that will neutralise the virus without generating an excessive response after contact with the pathogen[19].

Since the beginning of the pandemic, SARS-CoV-2 infection has been associated with an increased risk of stroke and other thromboembolic complications. With the progress of mass vaccination, rare yet catastrophic cases of thrombosis associated with thrombocytopenia and antibodies against

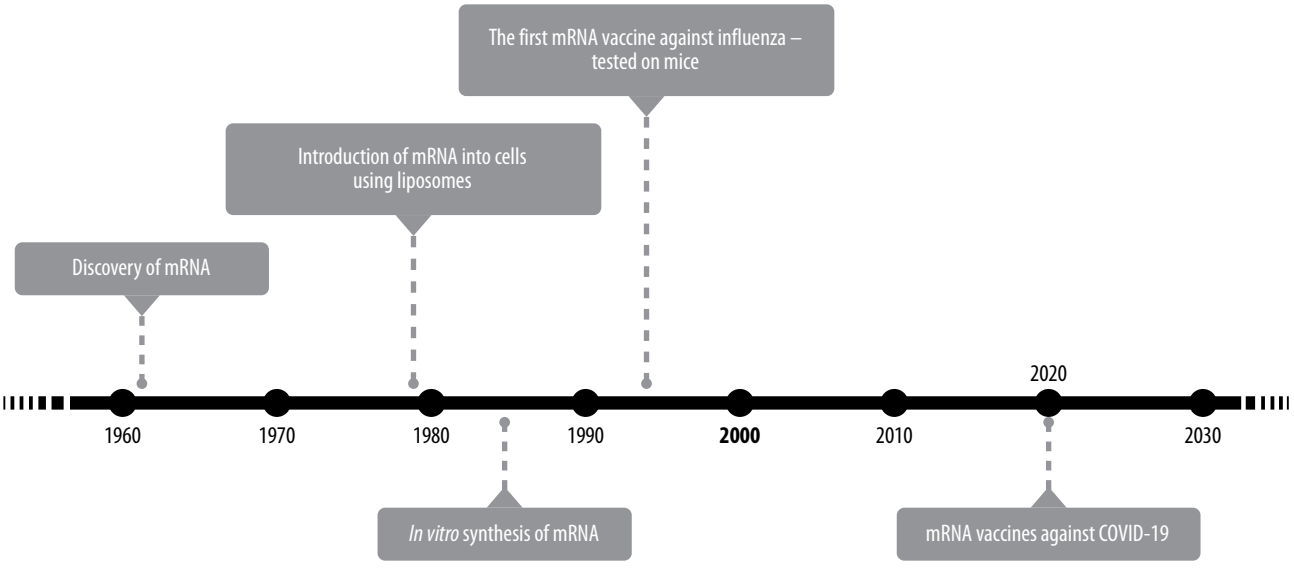

Fig. 1. A timeline of mRNA discoveries[12]

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platelet factor 4 (PF4) began to be reported. Although novel vaccines offer great flexibility in terms of antigen selection and limiting it to single molecules, it may happen that the host organism will produce antibodies with affinity for its own proteins (antigenic mimicry)[20]. Single cases of myocarditis associated with this mechanism have also been reported[21]. Considering the scale of vaccination, the above cases are extremely rare, and the safety of COVID-19 vaccines has also been confirmed among children aged 6–11 years[22] and pregnant women[23].

EFFICACY OF VACCINATIONS

Vaccinations have had an enormous impact on human mortality rates. While the development of the first vaccines and the elimination of extremely dangerous diseases such as smallpox from the population was a milestone for civilization, the introduction of mass vaccination programmes against diseases that were statistically less deadly, but also posed a challenge due to the extent of their spread, was a great breakthrough in the second half of the 20th century. After 1980, diphtheria, mumps, pertussis, and tetanus showed more than 92% decline in morbidity and at least 99% decline in mortality. Endemic transmission of poliovirus, as well as measles and rubella viruses has been eliminated in the United States. The incidence of hepatitis A, acute hepatitis B, *Haemophilus influenzae* type b infections and chickenpox dropped by more than 80%. The decrease in morbidity and mortality due to invasive pneumococcal disease (*Streptococcus pneumoniae*) was 34% and 25%, respectively[24]. Easy production, low cost, safety profile and efficacy make mRNA vaccines ideal candidates for the prevention and treatment of infectious diseases. The efficacy of COVID-19 vaccines is also promising. In fully vaccinated populations, vaccine efficacy is 89.1% for SARS-CoV-2 infection, 97.2% for COVID-19-related hospitalisation, 97.4% for admission to the intensive care unit, and 99.0% for death[25]. To date, nearly 63.2% of the global population has received at least one dose of the COVID-19 vaccine[26]. By August 2022, over 22 million people in Poland had been fully vaccinated[27].

CHALLENGES

Although more than 12 billion doses of COVID-19 vaccines have been administered worldwide[28], there are still approximately 2.7 billion unvaccinated people. In developing countries, active prevention of COVID-19 was implemented in less than 15% of the population, which is in stark contrast to data from highly developed countries. There are currently several clinical trials underway to assess the efficacy of fewer doses of the COVID-19 vaccine to make it available to a wider population[29]. Some sources indicate that vaccination against the Omicron variant is less effective[30]. However, this variant causes milder disease, and additionally, the infection can act like "Jenner's cowpox", immunising the population for some time.

Considering its structure and properties (tendency to mutate), as well as the scale of the pandemic favouring its unprecedented ability to multiply, SARS-CoV-2 has an enormous potential to generate new, more virulent or more infectious variants.

CONCLUSIONS

Vaccinations have reduced the spread of diseases and the resulting mortality for hundreds of years. Despite many concerns about immunisation, the benefits to society are disproportionately greater. Further development of vaccinology may lead to the eradication of some diseases. It is important to remember, however, that some pathogens have the potential to escape herd immunity and give rise to new deadly threats. As shown on the example of the COVID-19 pandemic, we are able to quickly develop a vaccine against new, unknown diseases. This is of particular importance in the era of progressive globalisation, climate changes and large migratory movements.

Conflict of interest

The authors report no financial or personal relationships with other individuals or organisations that could adversely affect the content of the publication and claim ownership of this publication.

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