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Evolution of the Development of Typhoid Vaccines in Medical Practice

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Abstract: The article examines the epidemiology of typhoid fever worldwide, as well as in the Russian Federation and in our region, especially in Central Asia. From the moment of receipt of the killed typhoid vaccine to the stage of production of conjugated vaccines, the world experience in the development of vaccine preparations is shown. Typhoid fever is an acute infectious disease caused by the causative agent Salmonella enterica subsp. enterica serotype Typhi (S. Typhi). It is still one of the main causes of morbidity in the economically medium and underdeveloped countries of Asia and Africa. As a result of rapidly developing international tourism, as well as natural disasters, an outbreak of typhoid fever can occur in industrialized countries. Global healthcare is in urgent need of typhoid vaccine prophylaxis due to the growing resistance of S. typhi to antimicrobial drugs, high epidemiological burden, lack of sanitary and hygienic conditions in some regions and the introduction of new protocols for the treatment of the disease. The purpose of the work is to outline the main points in the history of the development of a vaccine against typhoid fever, systematize information about licensed vaccines and discuss possible ways to create new vaccines. Data on vaccines available on the global pharmaceutical market are presented. The main trends in the development of vaccines against S. typhi are outlined. There is a need to improve the effectiveness of existing vaccines and develop new combination vaccines against typhoid fever. Improving the effectiveness of previously developed vaccines and the development of new combined vaccines against typhoid fever remain the main directions of modern vaccinology due to the high epidemiological significance of the disease.

Keywords: Antibiotic resistance, morbidity rate, S. typhi, pathogenesis of typhoid fever, current prospects of vaccine prophylaxis.

Introduction. Typhoid fever is one of the most common infectious diseases of a bacterial nature, exerting a significant socio-economic burden on regions endemic to this disease. Economically medium- and underdeveloped countries with unsatisfactory sanitary and hygienic conditions are most susceptible to typhoid fever. Military conflicts or natural disasters occurring in these territories significantly complicate the situation. However, actively developing international tourism, as well as natural disasters, can cause imported cases of typhoid fever, including in industrial countries [1, 2]. The steadily increasing antibiotic resistance of bacteria, including pathogens of intestinal infections, significantly complicates the fight against intestinal diseases and, according to WHO estimates, is a global problem and the development of vaccines against diseases caused by these pathogens is one of the priorities of modern healthcare. The World Health Organization reports that typhoid fever continues to be a serious problem for health services in many countries. Up to 21 million cases of typhoid fever are registered annually in the world, including more than 160,000 deaths. Typhoid fever is one of the most dangerous infections due to the high incidence rate, long-term hospital treatment, damage to many organs and body systems, the development of severe complications and relapses, and sometimes death. [3, 4]. The incidence of typhoid fever is highest in countries with a hot climate,

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unsatisfactory communal and household arrangements of settlements and a low level of sanitary culture of the population, especially during social and economic disasters and wars [5,6,7].

Many countries in Africa, Asia, Central and South America suffer from typhoid fever (BT). Problems with providing the population with high-quality drinking water are the main cause of the epidemiological crisis in these countries. Given the rapid development of global economic ties, transport communications and tourism in the 21st century, Russia and the CIS will also be at risk of importing typhoid infections. Recently, antibiotic-resistant strains of the pathogen have made the treatment of the disease more difficult. Natural disasters also threaten the spread of typhoid fever as an epidemic [8, 9]. High-quality laboratory diagnosis of typhoid fever is necessary in the absence of a characteristic clinical syndrome in the early days of the disease and subsequent late admission to the hospital, severe complications with etiologically unjustified treatment and high epidemiological danger of unrecognized cases [10,11]. However, the development of measures for the timely treatment or prevention of the disease is also a very important urgent problem. Taking into account this information, it is necessary to more actively vaccinate people at risk, migrant workers and tourists arriving in regions that are disadvantaged by this disease.

The purpose of the work is to outline the main points in the history of the development of a vaccine against typhoid fever, systematize information about licensed vaccines and discuss possible ways to create new vaccines.

Causes and pathogenesis of typhoid fever. According to modern concepts, this infection is severe, but completely curable. Reports of outbreaks of chloramphenicol-resistant BT appeared only in the 70s of the last century. However, S. typhi strains isolated from patients remained sensitive to ampicillin and co-trimoxazole. Since the late 80s of the last century, epidemic outbreaks of tuberculosis caused by strains resistant to ampicillin, co-trimoxazole and chloramphenicol have been reported. Fluoroquinolones and third-generation cephalosporins are currently the main drugs for the treatment of BT, but, unfortunately, there is a decrease in sensitivity to them [12, 13, 14].

Currently, the causative agent of BT has been studied at the molecular biological level. There is evidence that S. typhi can penetrate into the deep layers of the intestinal wall through the epithelium through both active adhesion and penetration and passive transfer of bacteria inside CD18+ leukocytes. Despite the fact that structural changes in Peyer's plaques in modern BT remain fundamentally consistent, there is a noticeable polymorphism, which is manifested by the simultaneous manifestation of various variants of pathomorphological changes, such as brain swelling, necrosis of Peyer's plaques, "clean" ulcers and pigmentation. Generally accepted concepts correspond to the sequence of structural changes observed in Peyer's plaques. But the simultaneous detection of Peyer's plaques at different stages of morphogenesis at the beginning of the disease can be considered natural. However, this does not allow us to talk about a strict "stage-by-stage" disease [14, 15, 16]. The phase theory of typhoid pathogenesis, developed by several authors, is still in use. On its basis, the following links of pathogenesis are distinguished: penetration of the pathogen into the body, development of lymphadenitis, bacteremia, intoxication, parenchymal diffusion, removal of the pathogen from the body, creation of immunity and restoration of homeostasis. The above scheme is conditional, because studies have shown that the penetration of pathogens into the blood occurs already in the first two phases. Thus, it is more correct to talk about interrelated and often coincident stages of typhoid fever development. [17 - 20].

The main diagnostic measures of typhoid fever. Thanks to the success in the 1870s and 1880s, inactivated vaccines against plague, cholera and typhoid fever were developed. The killed typhoid vaccines were developed by R. Pfeiffer and W. Kolle in Germany and A. Wright in the UK. The creation of inactivated parenteral whole cell vaccines was inspired by early efforts to create a killed

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typhoid vaccine. Vysokovich successfully applied a "warmed" typhoid vaccine in one of the regiments of the Russian army in 1898, which contained bacterial cells inactivated by heating. Since 1915, vaccination with typhoid fever has become mandatory for many units of the Russian army and military institutions. The combined typhoid-paratyphoid vaccine A and B (TAB) was introduced into the antiepidemic protection system of the Russian army in 1916. In the 1930s, adults in the USSR were vaccinated against tetanus, paratyphoid A and B, and typhoid fever. The chemical multivaccine was developed to combat typhoid fever, paratyphoid A and B, Flexner and Sonne dysentery, cholera and tetanus as part of research aimed at theoretical and experimental substantiation of complex and associated immunization [22-25].

Between 1954 and 1967, two different vaccines were field tested in Yugoslavia, Guyana, Poland and the USSR: vaccine K, which was inactivated with acetone, and vaccine L, which was created by heating and phenoling S. Typhi cells. These studies have shown that inactivated whole cell typhoid vaccines provide a high level of protection; vaccine K provides more protection than vaccine L. Many attempts have been made to find protective antigens of typhoid vaccines. In studies of vaccines K and L, it was shown that only antibodies to the H antigen demonstrated to some extent the effectiveness of the vaccines that were studied. On the other hand, responses to antigens O and Vi did not indicate how effective these vaccines were for humans. Thus, none of the components of the vaccine preparations has been identified as protective. Inactivated parenteral whole cell vaccines were extremely reactogenic, so they were not widely used and were excluded from traditional immunization programs. Having received the attenuated S. strain. Typhi Gal E Ty21a, R. Germanier and E. Fiirer made a significant breakthrough in the development of vaccines against typhoid fever [18]. Subsequently, this strain has been successfully used to produce safe and effective live vaccines. The vaccine against typhoid fever obtained on the basis of this strain was tested in the city of Alexandria (Egypt) in 1978-1981 in a controlled field [26-31].

In the 1980s, placebo-controlled trials of an oral live typhoid vaccine based on the Ty21a strain in capsules with an intestinal soluble coating were conducted in Santiago, Chile. The study covered 109,000 school students. The administration of three doses of the vaccine within one week showed its effectiveness at 67%. This efficiency was maintained for three years. The vaccine based on the Tu21a strain provided the same protection as the parenteral vaccine from cells inactivated by heating and phenol. At the same time, the vaccine, taken orally, caused practically no side effects. The Ty21a strain was used to create the next generation of improved oral live vaccines. In particular, the vaccine packaged in two-chamber sachets containing lyophilized vaccine and bicarbonate-ascorbate buffer proved to be more convenient for large-scale use. Immediately before use, both sachets were mixed with 100 ml of water. A field trial in Santiago showed that three doses, taken one dose each day, provided better protection than the encapsulated form. Within three years, the vaccine provided 77% protection. The search for new carriers and methods of antigen-carrier binding to create conjugates have had a significant impact on the development of vaccines [31, 32, 33].

Thus, one of the methods of assessing the quality of polysaccharide vaccines, in addition to laboratory pharmaceutical expertise, is the study of data in registration dossiers. The complete characterization of intermediates, including purified proteins, polysaccharides and conjugates, depends on the assessment of the initial structures by various high-tech methods such as nuclear magnetic resonance imaging (NMR), exclusive multi-angle light scattering chromatography SEC-MALLS, etc., structural units inherent in a particular polysaccharide, the authenticity of the protein component and the assessment of the conjugate quality by molecular weight the masses.

Current trends and prospects of typhoid vaccine prophylaxis in the present time. There are three types of typhoid vaccine that are licensed in the world: conjugate vaccine (typhoid conjugate vaccine,

TCV), unconjugated Vi-polysaccharide vaccine (VIPs) and live attenuated vaccine. Since 2008, WHO has been recommending live, attenuated and non-conjugated vaccines.

Vianvac, a liquid vaccine against typhoid fever with Vi-polysaccharides, has been registered and successfully used in Russia. This vaccine consists of a solution of chromatographically pure capsule polysaccharide, which contains Vi-antigen obtained from the culture of S. typhi supernatant. Over the twenty years of VIANVAC vaccination in Russia, the incidence of typhoid fever has decreased by about 24 times. From 475 cases per year for five years before the start of vaccination in 1998 to 24 cases in 2017 In Russia from 2009 to 2018, 303,063 people who were at risk and lived in areas of natural disasters with flooding of territories received the VIANVAK vaccine. In 2012, 5,950 people were vaccinated against flooding in the city of Krymsk in the Krasnodar Territory, and 8,651 people were vaccinated against floods in the Khabarovsk Territory. Rospotrebnadzor reports that none of the vaccinated individuals contracted typhoid fever [34-37].

In October 2017, the WHO Strategic Advisory Group of Experts on Conjugated Vaccines (TCV) made similar recommendations on the use of routine immunization in endemic regions. At the end of December 2017 WHO has prequalified the first typhoid vaccine with Vi-conjugated tetanus toxoid Typbar-TCV® (Bharat Biotech, India). Typbar-TCV® is registered in India, Cambodia, Nepal and Nigeria. In December 2020, WHO approved the second typhoid vaccine, which is Vi-conjugated. TYPHIBEV® is manufactured by Biological E. Limited (BE), India, and consists of a Vi-polysaccharide combined with a non-toxic derivative of the diphtheria toxin CRM19715. This medicine was developed in collaboration with GlaxoSmithKline. India is engaged in manufacturing. According to WHO recommendations, the conjugated vaccine should be administered once intramuscularly to children aged six months and adults aged forty-five and over in a volume of 0.5 ml containing 25 micrograms of Vi-capsule polysaccharide. For children aged two years and older, an unconjugated Vi-polysaccharide vaccine is administered subcutaneously or intramuscularly in a volume of 0.5 ml with a Vi-capsule polysaccharide content of 25 micrograms. People over the age of six are recommended to administer the live attenuated vaccine orally in capsule form, starting with three doses, and in the USA and Canada — four doses. Studies by several authors have shown that the Typbar-TCV® vaccine is more effective and immunogenic than the unconjugated vaccine. In addition, Vi-antibodies produced during immunization with this vaccine have a higher avidity than antibodies produced when using an unconjugated vaccine. Six weeks after primary immunization, IgG class antibodies to Vi-polysaccharide (GMT anti-Vi IgG) with Typbar-TCV® were 1,292.5 U/ml, and with an unconjugated vaccine — 411.1 U/ml. These results were obtained in double immunization of people aged 2 to 45 years. Two years after the start of the study, secondary immunization was performed. After six weeks of GMT, the anti-Vi IgG of the conjugated vaccine was 1685.3 U/ml, and the unconjugated vaccine was 445.6 U/ml [38, 39, 40].

Three years after a single vaccination of persons aged 2 to 45 years, the GMT of anti-Vi IgG was 282.3 U/ml for the Typbar-TCV® vaccine and 228.8 U/ml for the unconjugated vaccine. After 5 years, the GMT of anti-Vi IgG was 190.1 and 153.7 units/ml, respectively. Six weeks after a single immunization, Typbar-TCV® GMT anti-Vi IgG was 1,937.4 units/ml in children aged 6 to 23 months. In 84% of children who received immunization, the antibody titer was high before they reached the age of 5. The effectiveness of the conjugated Typbar-TCV® vaccine and the unconjugated Typhim Vi® vaccine (Sanofi Pasteur, Inc., France) was evaluated 28 days after the initial vaccination of people aged 18 to 60 years. It has been shown that the use of Typbar-TCV® promotes the induction of a significantly higher titer of IgG Vi antibodies (GMT anti-Vi IgG - 562.9 U/ml, seroconversion level 100%) than trials of the Typbar—TCV® vaccine were conducted on two groups of people aged 6 to 23 months and from 2 to 45 years old. The results showed that seroprotection for both groups was about

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85% two years after a single vaccination, which is significantly higher than seroprotection of Vi-polysaccharide vaccines (59%) [41, 42, 43].

An economic assessment of various approaches to immunization with conjugated typhoid vaccines has shown that routine vaccination of children under the age of 1 year under the expanded program is most effective in areas where the incidence is more than 50 cases per 100,000 people per year. It is recommended to carry out immunization followed by a single vaccination of children aged 5 to 14 years, if this figure increases to 130 cases per 100,000 people [31]. Vi-polysaccharide vaccines such as Typbar®, Typhim Vi®, Typherix®, Bio TyphTM, Shantyph® and Vivotif® live attenuated vaccine, as well as combined vaccines containing Vi-capsule polysaccharide S. Typhi and antigenic particles of inactivated hepatitis A pathogen such as Hepatyrix® and ViVAXIM®, are widely used in medical institutions [44, 45, 46, 47].

Conclusions. Thus, the etiology of typhoid fever was known more than a hundred years ago, but the disease, which is usually moderate or severe and sometimes recurrent, still poses a serious threat to global health.In cases where non-specific prevention, such as compliance with sanitary and hygienic standards and control of drinking water quality, is not available and antimicrobial therapy is ineffective due to the growing antibiotic resistance of the pathogen, vaccination may be the most effective method of preventing infectious diseases.

A study of the current state and trends in the development of typhoid vaccine prophylaxis has shown significant progress in vaccinating various population groups, including children under two years of age. Many of the developed vaccines have passed all licensing stages and are now available for purchase worldwide. improving the effectiveness of previously developed vaccines due to the high epidemiological significance of the disease.

Improving the effectiveness of previously developed vaccines and the development of new combined vaccines against typhoid fever remain the main directions of modern vaccinology due to the high epidemiological significance of the disease.

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