**PREGLED LITERATURE – REVIEW ARTICLE**

https://doi.org/10.46793/PP240214004B

# An overview of current vacccines for the prophylaxis of bacterical infections

Pregled aktuelnih vakcina za profilaksu bakterijskih infekcija

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**Summary** Antibacterial vaccines play a central role in modern medicine by providing an effective approach to combating infectious diseases caused by bacteria. The importance of these vaccines lies in their ability to stimulate the immune system to recognise and neutralise bacterial pathogens, or exotoxins produced by them, thereby preventing, or mitigating the severity of bacterial infections. The development and widespread use of antibacterial vaccines have contributed significantly to reducing the global burden of diseases such as pneumonia, meningitis, and sepsis.

Today, the global increase in vaccine-preventable diseases is a worrying trend that is closely linked to the emergence and advocacy of anti-vaccination policies. According to the latest World Health Organisation report, vaccination coverage in Serbia has declined over the past decade, jeopardising the collective immunity and led to recent outbreaks of vaccine-preventable diseases such as whooping cough and measles. Understanding the significance of antibacterial vaccines underscores their importance in promoting individual and community immunity, which ultimately leads to a healthier population and the prevention of antibiotic resistance.

This paper summarises the main characteristics of the different types of antibacterial vaccines, such as whole cell vaccines, subunit vaccines and toxoid vaccines, and provides an overview of the types of bacterial antigens contained in vaccines available for mandatory immunisation (vaccines against tuberculosis, diphtheria, tetanus, pertussis, *Haemophilus influenzae* and pneumoccus) or for non-mandatory immunisation (meningococcal vaccine, typhoid vaccine, cholera vaccine).

**Key words:** antibacterial vaccines, vaccine types, BCG, DTP vaccine, HIB vaccine, pneumococcal vaccine

**Sažetak** Antibakterijske vakcine igraju glavnu ulogu u savremenoj medicini obezbeđujući efikasan pristup u borbi protiv zaraznih bolesti izazvanih bakterijama. Važnost ovih vakcina leži u njihovoj sposobnosti da stimulišu imunski sistem da prepozna i neutrališe bakterijske patogene, ili egzotoksine koje oni proizvode, čime sprečavaju ili ublažavaju ozbiljnost bakterijskih infekcija. Razvoj i široka upotreba antibakterijskih vakcina značajno su doprineli smanjenju globalnog tereta bolesti kao što su pneumonija, meningitis i sepsa.

Danas je globalni porast bolesti koje se mogu sprečiti vakcinama zabrinjavajući trend koji je usko povezan sa pojavom i zagovaranjem politike protiv vakcinacije. Prema poslednjem izveštaju Svetske zdravstvene organizacije, pokrivenost vakcinacijom u Srbiji je opala tokom protekle decenije, što je ugrozilo kolektivni imunitet i dovelo do nedavnih izbijanja bolesti koje se mogu sprečiti vakcinom, poput velikog kašlja i malih boginja. Razumevanje značaja antibakterijskih vakcina naglašava njihov značaj u promovisanju imuniteta pojedinca i zajednice, što na kraju dovodi do zdravije populacije i prevencije rezistencije na antibiotike.

Ovaj rad sumira glavne karakteristike različitih tipova antibakterijskih vakcina, kao što su celo ćelijske vakcine, podjedinične vakcine i toksoidne vakcine, i daje pregled tipova bakterijskih antigena sadržanih u vakcinama dostupnim za obaveznu imunizaciju (vakcine protiv tuberkuloze, difterije, tetanusa, pertusisa, *Haemophilus influenzae* i pneumoka) ili za neobaveznu imunizaciju (vakcina protiv meningokoka, tifusa i kolere).

**Ključne reči:** antibakterijske vakcine, tipovi vakcina, BCG, DTP, HIB, pneumokokna vakcina

## INTRODUCTION

The history of vaccines begins with the ancient practice of variolation in China and the Middle East and extends to the late 18th century when Edward Jenner's groundbreaking work on cowpox laid the foundation for the first vaccine to protect against smallpox. In the 20th century, vaccines were developed against diseases such as polio, measles, mumps, and rubella, leading to significant advances in public health. In recent decades, the global community has

faced new challenges, including the fight against emerging infectious diseases such as HIV/AIDS and Ebola, as well as the ongoing fight against influenza. The recent COVID-19 pandemic has led to the global acceptance of new technologies for vaccine development, as a result of scientific innovation and the collaborative efforts of researchers, medical professionals, and policy makers to protect public health.

Despite the positive impact of vaccination on reducing neonatal and infant morbidity and mortality in recent decades (1), the alarming increase in vaccine-preventable diseases is a worrying trend that is closely linked to the emergence and advocacy of anti-vaccination policies. It is estimated that vaccinations against 14 different pathogens administered between the years 2021 and 2030 will prevent approximately 51.5 million deaths (2). Today, vaccines continue to play a critical role in the prevention and control of infectious diseases and offer hope for a healthier and more resilient future (3).

The protection conferred by vaccination is influenced by many genetic and environmental factors, including age, maternal antibody levels, previous antigen exposure, vaccination schedule and vaccine dose. Pathogenic microorganisms that are candidates for vaccine development have several common characteristics that affect the effectiveness of the vaccines themselves, such as the course of the disease they cause, the degree of antigenic variation and stage of the life cycle, the host species, and the presence of reservoirs in nature. The best vaccine candidates are microorganisms that cause acute diseases, as they usually induce a strong immune response with long-term or lifelong immunity in affected individuals. A vaccine derived from such a pathogen would therefore be expected to induce a similar level of protective immunity in the vaccinated individual. Microorganisms that cause chronic diseases often lead to an inadequate immune response and the inability to eliminate the pathogens, which is one of the reasons for the chronic course and progression of the disease. Therefore, vaccines against these pathogens less effectively induce protective immunity in vaccinated individuals (4).

Vaccines against microorganisms with low antigenic variations have good efficacy because postvaccinal memory cells and effector mechanisms of immunity successfully recognize the pathogen at each subsequent exposure. In contrast, microorganisms with high levels of antigenic variations (such as HIV or influenza viruses) successfully evade postvaccinal immunity, making the development of vaccines against these pathogens quite complex, or requiring the production of seasonal vaccines, as is the case with influenza viruses (4). Microorganisms that have a large number of developmental stages or morphological forms during their developmental cycle have a high antigenic diversity in each individual stage/form (such as the malaria pathogen, *Plasmodium* spp.). The vaccine against such pathogens should contain a wide range of antigens expressed in the different developmental stages, which is very difficult to achieve in the development of the vaccine (5).

To completely eliminate a microorganism from the population and eradicate the disease, it is necessary that this microorganism only causes disease in the human population and that it has no reservoir in animals or in the environment. The only disease that has been eradicated today is smallpox, as it only affects humans, there is no reservoir in nature, the virus is antigenically stable and a related virus from the same family, was used to develop the vaccine, which is a weak pathogen for humans (6).

In terms of the number of antigenic epitopes, vaccines can be monovalent or polyvalent. Monovalent vaccines are designed to immunize against one antigen or microorganism, while multivalent or polyvalent vaccines are designed to immunize against two or more strains of the same microorganism, or against two or more different microorganisms (combined vaccines). Vaccines can also be heterotypic if they are produced using microorganisms that are pathogenic to animals and cause no or a mild form of the disease in humans. These vaccines include the BCG vaccine against tuberculosis and the smallpox vaccine.

Vaccines can be administered prophylactically, i.e. before contact with the pathogen, or post-exposure, i.e. after contact with the pathogen (e.g. tetanus or rabies vaccines). Most prophylactic vaccines are administered in childhood, early enough to prevent possible exposure to the pathogen, and usually require one or more boosters at intervals of weeks or months apart. Vaccinations may also be required by law or recommended based on certain epidemiologic indications.

In most cases, infectious agents enter our bodies via the mucous membranes, but vaccines are most often administered parenterally (subcutaneously, intradermally, or intramuscularly), which is not the natural route of infection. Exceptions are the oral and nasal vaccines, which follow the route of entry of the infectious agent and thus induce local mucosal immunity (oral live vaccine against poliomyelitis, typhoid or cholera or nasal live vaccine against influenza). The immune response to vaccines can be enhanced by the addition of adjuvants. The most commonly used adjuvants are aluminum (aluminum phosphate, potassium aluminum sulfate, aluminum hydroxide), monophosphoryl lipid A (MPL), cytosine phosphoguanine (CpG), saponins, and squalene.

Today, different types of antimicrobial vaccines are used for the prophylaxis of infectious diseases: whole-cell vaccines (inactivated or live attenuated vaccines); subunit vaccines (recombinant, conjugated polysaccharide, polysaccharide, and VLP vaccines); toxoid vaccines; nucleic acid vaccines (mRNA and DNA vaccines) and viral vector vaccines (Table 1) (7, 8).

**Table 1**. Types of antimicrobial vaccines
**Tabela 1.** Tipovi antimikrobnih vakcina

| **VACCINE TYPE** | |
|---|---|
| **WHOLE-CELL VACCINES** | |
| Live attenuated vaccines | BCG<br>Typhoid fever (oral vaccine)<br>Cholera (oral vaccine) |
| Inactivated vaccines | Pertussis<br>Cholera (oral vaccine)<br>Plague |
| **SUBUNIT VACCINES** | |
| Recombinant protein vaccines | *Neisseria meningitidis* type B (MenB) |
| Conjugated polysaccharide vaccines | *Haemophilus influenzae* type b (Hib)<br>*N. meningitidis* type C (MenC)<br>*S. pneumoniae* PCV 10, 13, 15, 20<br>*N. meningitidis* type A,C,W,Y (MenACWY) |
| Polysaccharide vaccines | *S. pneumoniae* 23 serotypes (PPV23) |
| **TOXOID VACCINES** | |
| | Diphtheria<br>Tetanus<br>Pertussis (acellular pertussis vaccine DTaP) |
| **NUCLEIC ACID AND VIRAL VECTOR VACCINES** | |
| Messenger RNA (mRNA) for COVID-19 and DNA vaccines (so-called "naked" DNA vaccines) | |
| Replicating vector (Ebola virus vaccine) and non-replicating vector vaccines (Covid-19 vaccine) | |

## WHOLE-CELL VACCINES

Whole-cell vaccines contain a whole microorganism (bacterium or virus), which may be alive but attenuated or inactivated (dead). These vaccines are derived from the microorganisms that cause the disease, or they may be heterotypic, i.e. derived from related bacteria or viruses.

Live attenuated and inactivated vaccines differ not only in the viability of the microorganism, but also in numerous characteristics such as the route of administration, the type and duration of immunity they induce, the number of doses and the amount of antigens administered, and the need for the addition of adjuvants.

### Live attenuated vaccines

These vaccines consist of whole bacteria or viruses that are capable of replicating in the human body, but whose pathogenicity has been reduced or lost by previous treatments, while their immunogenicity remains intact. Because a large amount of antigen is released during replication, these vaccines elicit a strong immune response by simultaneously triggering innate and adaptive defense mechanisms and stimulating both humoral and cellular immune responses. They are generally very effective, but a single dose is usually not sufficient to generate lasting immunity, so one or more booster doses are required (9).

The technology of multiple passaging of microorganisms under unfavorable, nutrient-poor conditions (in an incompatible host or by subculturing *in vitro*) was previously used to obtain these vaccines, resulting in mutations associated with a reduction in the pathogenic potential of the vaccine strain. New attenuation methods include the use of recombinant DNA technology to achieve direct mutations or elimination of genes encoding important virulence factors. Compared to other types of vaccines, the distribution and storage of live attenuated vaccines requires a "*cold chain*" to maintain their viability (7, 8).

The use of live attenuated vaccines is contraindicated in persons with congenital or acquired immunodeficiencies, in persons receiving immunosuppressive therapy, and in pregnant women, as they may experience complications due to over-proliferation of the vaccine strain and disease outbreak. It is also possible for the vaccine strain to regain its virulence, but this is extremely rare (9).

### Inactivated vaccines

Inactivated vaccines consist of the entire microorganism, which has previously been killed by heat, γ-irradiation, or chemicals (formaldehyde, beta-propiolactone). In this way, the structure of the immunogenic epitopes is preserved, but the pathogen's ability to multiply is switched off, which reduces the possibility of renewed virulence. Since the pathogen cannot replicate in the host organism, inactivated vaccines cause a weaker immune response. Furthermore, the immune response is mainly based on humoral immunity and the production of circulating antibodies, as the microorganisms are unable to migrate intracellularly and activate cellular immunity. For this reason, these vaccines are administered in several doses. They are more stable than live vaccines and less demanding to handle in terms of the cold chain (7, 8).

## SUBUNIT VACCINES

Subunit vaccines contain antigenic epitopes of microorganisms in the form of proteins or polysaccharides, which are obtained by purification or recombinant DNA technology. The epitopes obtained in this way can be administered individually or in combination with other components of the vaccine to increase their immunogenicity. The use of subunit vaccines has the advantage over live attenuated vaccines in that they do not carry the risk of complications due to the multiplication of the vaccine strain or the return of its virulence, but the immune response is weaker compared to live vaccines (8).

### Recombinant protein vaccines

Protein vaccines used to be obtained by conventional protein purification techniques, which have been almost completely replaced by recombinant DNA technology techniques due to their difficulty, low efficiency, and high cost. In the production of protein vaccines using DNA technology, the DNA containing the gene for the target antigen is inserted into the genome of a microorganism that

produces an antigenic protein when it multiplies. The most commonly used microorganisms are *Escherichia coli* or yeasts, as they are easy to cultivate in the laboratory and synthesize antigenic proteins of pathogens in large quantities together with other proteins. The antigenic target polypeptide is then isolated from the mixture of newly synthesized proteins and further purified before being used for immunization.

The advantage of recombinant DNA technology is that it is used to obtain only the antigenic target protein without the risk of potentially harmful pathogen components being present in the vaccine, as is the case with conventional methods. The main disadvantage of these vaccines is the weak activation of the cellular immune response.

**Conjugated polysaccharide vaccines and polysaccharide vaccines**

Subunit vaccines can also be produced from polysaccharides of microorganisms and are important vaccines for immunity against encapsulated bacteria. Encapsulated polysaccharides are present in large quantities on the bacterial surface, making their isolation and purification much easier than that of proteins. Polysaccharide antigens only trigger a T-independent immune response in children under two years of age. Therefore, the efficacy of these vaccines is usually improved by conjugation with protein carriers, which then elicit a T-dependent immune response. A conjugated vaccine is a combination of a protein carrier and a polysaccharide, with diphtheria and tetanus anatoxins or their modifications (e.g. diphtheria toxoid CRM197) most commonly used as carriers (7, 8).

## TOXOID VACCINES

Anatoxins or toxoids are used as vaccines to prevent diseases mediated by exotoxins, such as diphtheria and tetanus. These vaccines contain exotoxin molecules that have been chemically modified, usually after treatment with formaldehyde, so that they have lost their toxicity and retained their immunogenicity. Vaccination with anatoxins activates the humoral immune response and the production of neutralizing antibodies against the toxin, thus preventing the occurrence of severe forms of disease mediated by toxins (7, 8).

## NUCLEIC ACIDS VACCINES AND VIRAL VECTOR VACCINES

These are two novel types of vaccines that were primarily developed for the prophylaxis of severe viral infections, such as Ebola and COVID-19. To date, none of these vaccines have been developed and approved for the prophylaxis of bacterial infections.

Nucleic acid vaccines consist of nucleic acid that is extracted from pathogens and enables the direct synthesis of the target antigen in the organism of the vaccinated person. So far, vaccines based on messenger RNA (mRNA) have proven effective in preventing severe forms of the disease COVID-19 caused by the SARS-CoV-2 virus, while vaccines made from pure DNA molecules (so-called "naked" DNA vaccines) are still in the experimental phase.

Viral vector vaccines are based on the incorporation of DNA with the gene for the target antigen of the pathogen into a viral vector which is a carrier for this gene of the microorganism. After vaccination, the viral vector enters the host's cells and the DNA with the inserted pathogen gene begins to be transcribed into mRNA, from which the target antigens are formed. Depending on whether the vector replicates in the host cells or not, a distinction is made between replicating vector vaccines (Ebola virus vaccine) and non-replicating vector vaccines (Covid-19 vaccine) (8, 10).

## ANTIBACTERIAL VACCINES USED FOR MANDATORY ACTIVE IMMUNIZATION IN SERBIA

Mandatory active immunization includes the immunization of children from birth to the age of 14 against diseases that cause serious and potentially fatal complications. It is carried out according to the vaccination schedule with single vaccines against one pathogen and with combination vaccines against several different bacterial and/or viral pathogens. Antibacterial vaccines mandatory in Serbia includes vaccines against tuberculosis, diphtheria, tetanus, whooping cough, diseases caused by *Haemophilus influenzae* type b and *Streptococcus pneumoniae*. Vaccine coverage with mandatory antibacterial vaccines in Serbia in past decade is shown presented in Table 2 (11). The main data source for immunization coverage in Serbia is the most recent WHO/UNICEF Electronic Joint Reporting Form (eJRF) on Immunization, the “WHO/UNICEF Estimates of National Immunization Coverage (WUENIC)”, which are the official estimates produced annually by WHO and UNICEF on the basis of immunization coverage data reported by Member States, and which can be accessed via the “Interactive WHO and UNICEF coverage estimates country profiles” (https://worldhealthorg.shinyapps.io/wuenic-trends-2023/), and the latest data published in the “WHO Immunization Data Portal” (https://immunizationdata.who.int/listing.html?topic=coverage&location=SRB) and in the “Immunization Country Profiles – UNICEF DATA” (https://data.unicef.org/resources/immunization-country-profiles/).

**Table 2.** Antibacterial vaccine coverage in Serbia in past decade (11)

**Tabela 2.** Obuhvat vakcinacijom sa antibakterijskim vakcinama u Srbiji u protekloj deceniji (11)

| | Vaccine coverage in Serbia in past decade (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Vaccine | 2022 | 2021 | 2020 | 2019 | 2018 | 2017 | 2016 | 2015 | 2014 | 2013 |
| BCG | 96 | 98 | 98 | 98 | 98 | 97 | 98 | 98 | 98 | 97 |
| DTP1 | 97 | 96 | 97 | 99 | 98 | 98 | 97 | 98 | 97 | 98 |
| DTP3 | 92 | 91 | 92 | 97 | 96 | 95 | 92 | 95 | 93 | 95 |
| HIB3 | 92 | 91 | 92 | 97 | 96 | 95 | 92 | 95 | 94 | 92 |
| PCV3 | 89 | 88 | 87 | 92 | 67 | - | - | - | - | - |

*BCG-vaccine against tuberculosis (https://immunizationdata.who.int/pages/coverage/bcg.html?CODE=SRB&YEAR=); DTP-vaccine coverage with diphtheria, tetanus, and pertussis vaccine: DTP1-first dose, DTP3-third dose (https://immunizationdata.who.int/pages/coverage/dtp.html?CODE=SRB&ANTIGEN=&YEAR=); HIB3-vaccine coverage with all three doses of vaccine against H. influenzae (https://immunizationdata.who.int/pages/coverage/hib3.html?CODE=SRB&YEAR=); PCV3-vaccine coverage with all three doses of conjugate antipneumococcal vaccine (https://immunizationdata.who.int/pages/coverage/pcv.html?CODE=SRB&ANTIGEN=&YEAR= ).*

*BCG-vakcina protiv tuberkuloze (https://immunizationdata.who.int/pages/coverage/bcg.html?CODE=SRB&YEAR=); DTP-pokrivenost vakcinom protiv difterije, tetanusa i pertusisa: DTP1-prva doza, DTP3-treća doza (https://immunizationdata.who.int/pages/coverage/dtp.html?CODE=SRB&ANTIGEN=&YEAR=); HIB3-pokrivenost sa sve tri doze vakcine protiv H. influenzae (https://immunizationdata.who.int/pages/coverage/hib3.html?CODE=SRB&YEAR=); Pokrivenost PCV3 vakcinom sa sve tri doze konjugovane antipneumokokne vakcine (https://immunizationdata.who.int/pages/coverage/pcv.html?CODE=SRB&ANTIGEN=&YEAR= ).*

In addition to mandatory active immunization, various antibacterial vaccines such as vaccines against *Neisseria meningitidis*, *Salmonella typhi*, and *Vibrio cholerae,* which are not included in the current vaccination calendar in Serbia may be recommended as mandatory for specific indications. The administration of antibacterial vaccines also reduces the risk of misuse and overuse of antibiotics and has a direct impact on the global burden of antimicrobial resistance (12, 13).

Before administering the vaccine, it should be determined whether the person has any of the general or specific contraindications to active immunization. According to the Rulebook on Immunization and Methods of Protection with medicines (i.e. „*Pravilnik o imunizaciji i načinu zaštite lekovima*“, Official Gazette of the RS No. 88/2017, 11/2018, 14/2018, 45/2018, 48/2018, 58/2018, 104/2018, 6/2021, 52/2021 and 66/2022), general contraindications for active immunization are the presence of acute diseases, febrile conditions, anaphylaxis to vaccine components and serious adverse reaction to the previous dose of the vaccine. General contraindications for the use of live attenuated vaccines include various immunologic disorders (congenital and acquired immunodeficiency, malignancies, and use of immunosuppressive therapy) and pregnancy.

It is important to note that certain vaccines have specific contraindications, which means that there are certain situations in which they should not be used. The tuberculosis vaccine (BCG) is contraindicated in persons with weakened cellular immunity due to HIV infection or other diseases with impaired immune response, and the pertussis vaccine is contraindicated in persons with developing central nervous system disorders (epilepsy, infantile spasms, progressive encephalopathy).

## ACTIVE IMMUNIZATION AGAINST TUBERCULOSIS

*Mycobacterium tuberculosis* resides most of its life cycle as an intracellular bacterium in alveolar and tissue macrophages and triggers a cellular immune response. Since this form of immunity is not transferred transplacentally from mother to fetus (as is the case with IgG antibodies), newborns are particularly at risk of developing severe infections.

Active immunization is carried out with BCG vaccine, which belongs to the heterotypic vaccines, as it contains lyophilized, live attenuated bacilli of the *Mycobacterium bovis* strain Bacillus Calmette-Guerin. Attenuated BCG strains lack the Region of Difference 1 (RD1) domain, which is associated with the loss of the major virulence factor - the secretory antigen ESAT-6 of 6 kDa. There are currently six types of BCG strains used for vaccination: BCG Pasteur 1173 P2, BCG Danish1331, BCG Glaxo 107, BCG Tokyo 172-1, BCG Russia-I and BCG Brazil. They differ in their attenuation properties, phenotypic variations, the number of viable microorganisms, the formulation and the degree of protective immunity induced (14).

After intradermal application, vaccine triggers a cellular immune response that provides variable protection against tuberculosis (40-70%). In our country, it is administered to newborns, and at the latest at the age of 12 months if there are contraindications to its use in newborns (premature babies, neonatal jaundice, intracranial bleeding, etc). In addition to neonates, the BCG vaccine is also used for active immunization of children and adults who have not received this vaccine and who are at high risk of tuberculosis (family members with tuberculosis, residence in a country with a high prevalence of tuberculosis), or at the request of the parents if they come from countries where BCG vaccination is not mandatory (15).

Studies on the efficacy of BCG vaccination have shown that this vaccine does not prevent infection with *M. tuberculosis* but provides significant protection against severe clinical forms of tuberculosis (tuberculous meningitis and disseminated forms of tuberculosis) in infants and young children when administered immediately after birth. It also does not prevent the reactivation of latent pulmonary tuberculosis in persons who already have tuberculosis. To increase the effectiveness of antimycobacterial vaccines novel research are focused on different vaccine schedule with additional doses of BCG vaccine in adults, intravenous route of administration, and development of subunit adjuvanted vaccine like M72, that is a recombinant fusion protein consisting of antigens Mtb32A and Mtb39A and novel combination of adjuvant AS01E that combines monophosphoryl lipid (MPL) with QS-21 (a purified saponin fraction) (16).

In addition to the general contraindications, specific contraindications for BCG vaccination include congenital or acquired immunodeficiencies, hematological malignancies, HIV infection, the use of immunosuppressive therapy and pregnancy, as a generalized BCG infection may develop.

## ACTIVE IMMUNIZATION AGAINST DIPHTHERIA, TETANUS AND PERTUSSIS (WHOOPING COUGH)

Diphtheria and tetanus are diseases mediated by exotoxins produced by *Corynebacterium diphtheriae* or *Clostridium tetani* after infection, while numerous virulence factors of *Bordetella pertussis* are involved in the pathogenesis of whooping cough. Neutralizing antitoxic antibodies are important for immunity against diphtheria and tetanus, while immunity against *B. pertussis* is mediated by a combination of humoral and cellular immunity. Active immunization

against these diseases is achieved with combined vaccines, which always contain concentrated and purified anatoxins of diphtheria and tetanus, while the components of the vaccine that protects against whooping cough may be:
- Inactivated whole cells of the causative agent of whooping cough, *B. pertussis* (DTP vaccine, ALDIPETE-T®). The administration of vaccines containing the entire pertussis component is contraindicated in children with progressive diseases of the central nervous system (uncontrolled epilepsy, infantile spasms, progressive encephalopathy) (17).
- Acellular pertussis vaccine containing single *B. pertussis* antigens or a combination thereof (DTaP). The *B. pertussis* antigens contained in this vaccine may be pertussis toxoid (PT), filamentous hemagglutinin (FHA), pertactin outer membrane protein (PRN) and fimbrial antigens 2 and 3 (FIM 2 and 3).

The DTP and DTap vaccine were previously used as a single combination vaccine. Today it is used as part of the combined pentavalent vaccine against diphtheria, tetanus, pertussis, polio and *Haemophilus influenzae* type b diseases DTaP-IPV-Hib (Pentaxim®).

The latest WHO data shows that approximately 14.3 million children did not receive any dose of the DTP vaccine in 2022. In the same year, the DTP vaccination coverage in Serbia was 97%, with 2,000 children not receiving any dose of DTP. The global DTP vaccine coverage has fallen from 86% in 2019 to 81% in 2021, which represent the lowest level since 2008 (11).

## ACTIVE IMMUNIZATION AGAINST *HAEMOPHILUS INFLUENZAE* TYPE B

The most important virulence factor of *H. influenzae* is the polysaccharide capsule, which enables the invasiveness of this bacterium. *H. influenzae* with type b capsules (Hib) is highly pathogenic to humans and often causes fatal meningitis in immunocompromised individuals. Neutralizing anticapsular antibodies provide good protection against this pathogen. The vaccine against *H. influenzae* type b contains the capsular polysaccharide polyribosyl ribitol phosphate (PRP), which can be administered alone or conjugated with a protein component such as tetanus toxoid or the outer membrane protein complex (OMPC) of the bacterium *Neisseria meningitidis* to increase immunogenicity. In our country, it is administered as part of the pentavalent vaccine DTaP-IPV-Hib (Pentaxim®), which contains the capsular PRP polysaccharide *H. influenzae* type b conjugated with tetanus toxoid (16).

## ACTIVE IMMUNIZATION WITH DTaP-IPV-Hib PENTAVALENT COMBINED VACCINE

DTaP-IPV-Hib (Pentaxim®) contains diphtheria and tetanus toxoid adsorbed on aluminum hydroxide, pertussis toxoid and filamentous hemagglutinin adsorbed on aluminum hydroxide, *H. influenzae* type b capsular polysaccharides conjugated with tetanus toxoid and inactivated poliovirus types 1, 2 and 3 (17).

The first vaccination is administered with three doses of DTaP-IPV-Hib from the child's second month of life and should be completed by the sixth month of life. The interval between the individual doses should not be less than four weeks.

The booster vaccination is administered three times:
- first booster vaccination in the second year of life with one dose of the pentavalent vaccine DTaP-IPV-Hib
- second booster vaccination at the age of seven (before entering the first grade of elementary school) with one dose of the quadrivalent vaccine DTaP-IPV (Tetraxim®)
- third booster vaccination in the last year of primary school with one dose of the bivalent DT vaccine (Ditevaxal-T® for adults)

The vaccine is administered intramuscularly into the thigh muscles in infants and young children and into the deltoid muscle of the upper arm in older children. If the basic immunization has not been carried out or is incomplete, the corresponding vaccines can be administered to persons older than six months to carry out the basic immunization of the unvaccinated (according to the schedule for regular vaccination) or to catch up on the doses not received in time.

## ACTIVE IMMUNIZATION AGAINST *STREPTOCOCCUS PNEUMONIAE*

*Streptococcus pneumoniae* lives on the mucosa of the upper part of the respiratory tract, from where it spreads to the surrounding tissue thanks to a polysaccharide capsule. It causes upper respiratory tract infections (sinusitis, otitis media), which are associated with the risk of serious complications such as pneumonia, bacteremia, sepsis, and meningitis. Two types of vaccines against this bacterium have been developed, based on capsular polysaccharides (PPV polysaccharide vaccine) or a conjugate of capsular polysaccharides with a protein carrier (PCV conjugate vaccines).

### Polysaccharide vaccine (PPV) Pneumovax® 23

Polysaccharide vaccine is a polyvalent vaccine containing the capsular polysaccharides of 23 different strains of *S. pneumoniae* (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F), which account for 80-90% of the strains that cause the disease. It is used for the active immunization of children from 2 years of age, adolescents, and adults against pneumococcal disease. As it triggers a T-independent immune response which is not effective in young children due to insufficient production of anticapsular antibodies, it is not recommended for immunization of children under two years of age (17).

The polysaccharide vaccine is not routinely administered to healthy individuals, but to individuals at increased risk of severe pneumococcal infection due to chronic disease, diabetes, asymptomatic or symptomatic HIV infection, asplenia or splenectomy, malignancies, or immunosuppressive therapy. Vaccination and booster vaccination is carried out with one dose of vaccine administered intramuscularly or subcutaneously. The vaccine can be combined with one of the conjugated vaccines PCV15 or PCV20 for active immunization of persons at particular risk (18, 19).

**Conjugate vaccines (PCVs)**

The conjugated vaccines PCV10 - Synflorix® or PCV13 - Prevenar 13® are administered to children from the age of two months according to the vaccination calendar. These vaccines contain the most common pneumococcal serotypes that cause disease in children. After intramuscular administration, they lead to a T-dependent immune response which provides effective protection in over 90% of vaccinated children. Children who are particularly susceptible to pneumococcal infections can be revaccinated with the polysaccharide vaccine later in life (20).

Synflorix® contains capsular polysaccharides of 10 pneumococcal serotypes (11, 41, 51, 6B1, 7F1, 9V1, 141, 18C1, 19F1, 21F1) conjugated with protein carriers: Protein D (obtained from non-typeable *H. influenzae*), tetanus toxoid and diphtheria toxoid (17).

Prevenar 13® contains capsular polysaccharides of 13 pneumococcal serotypes (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) conjugated to a genetically modified diphtheria toxin (CRM197), which serves as a protein carrier. The previously used vaccine Prevnar 7®, which contained seven serotypes, has been replaced by a thirteen-valent vaccine that contains these seven serotypes and is supplemented by six new serotypes (17).

Basic immunization is carried out in children from the age of two months with three vaccine doses at least four weeks apart until the age of six months. If the basic immunization begins after the age of six months, it can be carried out with one or two doses of conjugated vaccines with a mandatory booster vaccination.

The booster vaccination is carried out with one dose of PCV10 or PCV13 in the second year of life, at the earliest six months after completion of the first vaccination series.

Vaccination and booster vaccination can be carried out at the same time with the pentavalent vaccine DTaP-IPV-Hib (Pentaxim®).

## NON-MANDATORY ANTIBACTERIAL VACCINES

### MENINGOCOCCAL VACCINE

The diseases caused by *Neisseria meningitidis*, meningococcal sepsis and meningitis, are potentially fatal diseases with severe neurological consequences in survivors. Meningococcal disease is most common in children and adolescents, and persons with weakened immune systems are particularly susceptible. The most important virulence factor is the polysaccharide capsule, and 13 serogroups have been identified based on the capsular antigens, of which A, B, C, X, Y and W135 cause endemic and epidemic infections.

Meningococcal vaccines are based on encapsulated polysaccharides that are administered alone (MPSV4 vaccine) or conjugated with a protein carrier (MCV4 vaccine). Both vaccines can be administered to children from the age of two. The most commonly used vaccines are MenACWY conjugate vaccine (Menactra®, Menveo® and MenQuadfi®), which is given to children aged 11 to 12 years and to children and adults at increased risk of meningococcal disease (individuals with splenectomy, sickle cell anemia, complement deficiency of the C5-C9 component, bone marrow transplant and persons who have contact with patients) (17, 21).

MenB vaccine with meningococcal serogroup B (Bexsero® and Trumenba®), which is administered to persons over 10 years of age who are at risk of developing meningococcal disease. According to its composition, this vaccine consists of two components, it belongs to the recombinant vaccines, as it contains the recombinant proteins NHBA (Neisserial Heparin Binding Antigen), NadA (Neisseria adhesin A) and fHbp (factor H binding protein) of *N. meningitidis* serogroup B, and it also contains outer membrane vesicles OMV (eng. outer membrane vesicles) of *N. meningitidis* serogroup B (17, 22).

### TYPHOID VACCINE

Typhoid fever is caused by *Salmonella typhi*, an intracellular bacterium whose only natural host is humans. The disease has a severe course with the risk of serious complications with a fatal outcome but can also develop into a chronic form in a small number of persons affected. Active immunization can be carried out with various types of vaccines, such as

- Typhim Vi® - an inactivated polysaccharide vaccine administered intramuscularly in a single dose to children over 2 years of age and adults.
- Vivotif® - a live attenuated vaccine administered orally in four doses to children over 6 years of age and adults.

These vaccines are administered as mandatory active immunization of persons exposed to certain infectious diseases (persons living in a common household with carriers, employees of municipal companies for wastewaste disposal, sanitation, cemeteries, etc.), or travelers to endemic areas (17, 23).

### CHOLERA VACCINE

Cholera is a disease caused by the bacterium *Vibrio cholerae*, which is endemic in many areas of the world. It is transmitted through the consumption of contaminated water and causes a diarrhea syndrome. Of great importance for immunity are mucosal immunity (secretory IgA), which blocks the attachment of the bacteria to the intestinal epithelial cells, and antitoxic neutralizing antibodies, which bind to the cholera toxin and limit but do not completely eliminate the disease. For this reason, orally administered vaccines have the best efficacy (17, 24):

- Dukoral® - inactivated monovalent oral vaccine containing inactivated *V. cholerae* O1 and the recombinant B subunit of cholera toxin
- ShanChol® and Euvichol-Plus/Euvichol - bivalent vaccines containing inactivated *V. cholerae* O1 and *V. cholerae* O139.

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**Primljen/Received:** 14.2.2024.
**Prihvaćen/Accepted:** 28.2.2024.