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COMPARISON OF THE SUCCESS OF IMMUNIZATION AGAINST DIPHTHERIA IN THE ŠUMADIJA DISTRICT BEFORE, DURING, AND AFTER THE COVID-19 PANDEMIC

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Abstract. *Introduction. Diphtheria is an acute respiratory infection caused by the gram-positive bacillus Corynebacterium diphtheria. Diphtheria can manifest with various clinical manifestations ranging from diphtheria of the skin, diphtheria of the eye, nasopharynx, and tonsils to severe respiratory tract infections. Due to the strong exotoxin produced by this bacterium, complications can occur in some organs and organ systems (myocarditis, neuritis, paralysis). It is very important to treat patients with antibiotics and diphtheria antitoxin to reduce the effect of the exotoxin produced by this pathogen. As a preventive measure, the vaccine should be administered in childhood from the age of one. A booster vaccination is given at 2, 7, and 14 years of age. Objective. To determine whether the regular administration of the diphtheria vaccine is carried out according to the mandatory vaccination calendar on the territory of the Šumadija District in Serbia and to compare the results obtained for the period before, during, and after the COVID-19 pandemic. Results and Discussion. Thanks to mandatory vaccination, the morbidity and mortality of children have decreased, and in our country, this serious infection has almost disappeared, i.e. eradicated. In many countries in Asia and Africa, there are cases of occurrence and spread of diphtheria during the year. The study is based on the processing of statistical data for the period 2018 to 2022. During the pandemic caused by the Coronavirus (COVID-19), there was a standstill in health services and interruptions in health care at the primary healthcare level. It was also observed that the percentage of vaccinations administered decreased in the calendar years during the pandemic and immediately after COVID-19. For the period from 01.01.2020 to 31.12.2020, a significant decrease in booster vaccination against diphtheria from 98% to 72% among 7-year-olds and from 96% to 86% among 14-year-olds was observed on the territory of Šumadija District compared to 2018, the period before COVID-19. Conclusion. It is to be feared that the disease, which can assume epidemic proportions due to its easy transmissibility and spread, will re-emerge. Healthcare professionals and the population should continue to be educated about the importance of mandatory vaccination according to the childhood vaccination calendar.*

Keywords: *diphtheria, vaccination, booster vaccination, medical education, COVID-19*

1. INTRODUCTION

Diphtheria is an acute infectious and contagious disease caused by *Corynebacterium diphtheriae*. The exotoxin is an important virulence factor of *Corynebacterium diphtheriae*, as it irreversibly inhibits protein synthesis in many different cells [1]. Also, the diphtheria toxin (DT) has both a local effect and an effect on distant tissues and organs (heart, peripheral nerves), so late effects such as myocarditis, and peripheral motor and sensory neuropathies can occur. There are several clinical forms of diphtheria: the pharyngeal form, the laryngeal form, the diphtheria of the eye, the diphtheria of the nose, and the diphtheria of the skin. The source of infection is only one person, a patient, or a germ carrier [2]. Transmission occurs via respiratory secretions or, more rarely, through direct contact with the patient's skin.

Diphtheria is widespread worldwide, but it is now a rare disease in developed industrialized countries. According to the World Health Organization report for 2016, about 5000 cases of diphtheria are registered annually worldwide [3]. In Serbia, the last case of diphtheria was reported in 1980, which is because high vaccination coverage against this disease was maintained. The last major epidemic of diphtheria was recorded in the countries of the former Soviet Union, where between 1990 and 1998, 157000 people became ill, mostly adults, with 5000 deaths, as a direct consequence of the decline in vaccination coverage and loss of collective immunity [4].

In the past, diphtheria was one of the most important causes of morbidity and mortality in children. Over time, the incidence rate was significantly reduced with the widespread use of diphtheria toxoids and the establishment of a program of systematic immunization of children in the 1940s. [5]. Although respiratory diphtheria is still the most common clinical manifestation of the disease, cutaneous diphtheria is being registered with increasing frequency throughout the world [6]. *Corynebacterium ulcerans* has been identified as the causative agent of cutaneous diphtheria in some European countries such as Belgium, France, Germany, Great Britain, Switzerland, and Sweden. Global vaccination coverage is now estimated at around 86% and the WHO recommends that 95% of the population be vaccinated [3].

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The bacillus *Corynebacterium diphtheriae* was first isolated in 1884 from pseudomembranes, which are the clinical manifestations of diphtheria. Final laboratory confirmation of the clinical diagnosis requires the isolation and identification of *Corynebacterium diphtheriae* from a sample taken from the site of infection, with mandatory verification of the toxigenicity of the isolate. The gold standard for the detection of toxicity is the electro-agar immunoprecipitation test. Enzymatic and immunochromatographic tests are also available for the rapid detection of DT in *Corynebacterium diphtheriae* isolates. In addition, molecular tests have been developed for the detection of gene flow by polymerase chain reaction (PCR) [7].

Therapy is based on the use of antibiotics and diphtheria antitoxin [8]. Respiratory diphtheria requires respiratory support measures, and cutaneous diphtheria may require surgical treatment of the lesion. Antibiotic therapy is aimed at eliminating the pathogen and stopping the production of exotoxins [9]. Erythromycin is one of the most effective antibiotics. Penicillin can be used as an alternative antibiotic therapy, and *Corynebacterium diphtheriae* is sensitive to a variety of other antimicrobial agents, such as cephalosporins and tetracycline. Macrolides and lincosamides are used in the case of cliques. Antitoxin must be administered immediately because antitoxin only neutralizes circulating toxin molecules that have not yet bound to receptors on the target cells [8].

Diphtheria has been successfully eliminated by the systematic immunization of children. In the future, synthetic monoclonal antibodies could become an adequate substitute for the antitoxin produced in animals [2]. In addition to the applied therapy, immunization with diphtheria toxoid is required (one dose for previously vaccinated individuals, three doses within three months for unvaccinated individuals) to stimulate the synthesis of protective antitoxins, as the natural infection leaves no immunity and there is a possibility of recurrence of the (relapsing) disease [10]. The active immunization of the population with a highly effective vaccine serves to prevent diphtheria. The vaccine contains diphtheria toxoid obtained by the action of formalin on the protein toxin molecule, causing DT to lose its toxicity but retain its immunogenicity [1]. The toxoid induces an immune response and the production of antitoxin. The vaccine prevents the occurrence of symptomatic infection but does not prevent colonization by the bacterium *Corynebacterium diphtheria* and transmission of the disease.

2. Objective

The summary and comparison of results from different years at the level of one district (Šumadija District) in Serbia were conducted to evaluate the success of the performed immunization against diphtheria in a specific period of 2014-2023 (before, during, and after the COVID-19 pandemic).

3. Methods

The methodology of this research work is a descriptive method in which the annual reports on vaccinations conducted for the Šumadija District of the Institute of Public Health Kragujevac and data from the website of the Institute of Public Health of Serbia "Dr. Milan Jovanović Batut" (National Annual Report on Vaccinations Conducted on the Territory of the Republic of Serbia) were used [11, 12, 13, 14, 15]. The scope includes the number of children vaccinated about the number of persons scheduled for vaccination (vaccinated and revaccinated according to the vaccination calendar applied by law in the Republic of Serbia) for the period 2014-2023. Statistical analysis was performed in the Statistical Package for Social Sciences, version 23.0 for Windows (SPSS Inc. Chicago, Illinois, United States). The probability level ($p < 0.05$) was considered significant. The results are presented graphically.

4. Results and discussion

In the active immunization of children, the combined vaccine for the prevention of diphtheria, tetanus, and pertussis (DTP, DiTePer) is most commonly used according to the corresponding vaccination calendar [2]. Diphtheria toxoid can be combined with other vaccines, e.g. against poliomyelitis, hepatitis B and *Haemophilus influenzae* type *b* infections [16]. Since the protective antibody titer gradually decreases with age (in about 30% of 60 to 69-year-olds), a "booster" dose of Toxoid is recommended every 10 years for fully vaccinated adults [17].

The production of vaccines against diphtheria was started at the Torlak Institute in 1930, and compulsory vaccination was introduced in our country in 1937 and again in 1946 [18]. The combined vaccine against diphtheria, tetanus, and pertussis, the DTP vaccine, has been used for decades [19]. After routine use, it has not been used since the beginning of 2015 and has been replaced by a pentavalent vaccine (Pentaxim vaccine) for infants and young children. However, two vaccines against diphtheria and tetanus (DT and Td) are used for booster vaccination at the beginning and end of the eighth school year. Vaccine against diphtheria and tetanus, abbreviated DT (Torlak Ditevaksal-T) for children (DT) and for adults (Td).

The pentavalent DTaP-IPV/Hib vaccine (Pentaxim or Infanrik-IPV/Hib) contains the following active substances: modified toxins (anatoxin or toxoid) of diphtheria and tetanus, a purified, non-cellular (acellular) pertussis component, killed polioviruses and a conjugate vaccine against *Haemophilus influenzae* type *b* [20].

The child receives a pentavalent vaccine, either Pentaxim or Infanrik-IPV/Hib, in three doses, at the end of two months, at the end of three and a half months, and at the end of the sixth month (this is the so-called primary vaccination). The first booster vaccination with the same vaccine is given at the age of 18 months. In environments with a high risk of infection, it is recommended to start vaccination at the end of the sixth week of life. The timing of administration of these vaccines is related to the beginning and end of the eight-year school period [21].

The efficacy of the administration of diphtheria toxoid is about 97%. For the DT vaccine, the manufacturer states that three doses given to an infant protect for 3-5 years and that booster vaccinations in the second and seventh year of life provide protection in adolescence. Half of the adult population in the West

still has sufficient antibodies to protect against diphtheria. The WHO recommends that after the last vaccination (usually at 14), the Td vaccine should be administered every ten years [22]. Thank you to the relatively high vaccination coverage rate, estimated at 86% worldwide, diphtheria is considered eliminated in industrialized countries, while it occurs less frequently in developing countries [23]. In 2015, 4530 cases of this dangerous infection were reported worldwide. This is a great success because, despite modern medication, mortality from respiratory diphtheria has not changed for decades [24]. In Serbia, diphtheria has been considered eradicated since 1980. Measures are constantly being taken to keep it that way [18].

A comparison of the results of vaccination with the Pentaxim vaccine in the first year of life in the Šumadija District in 2014 and 2016 is shown in Figure 1.

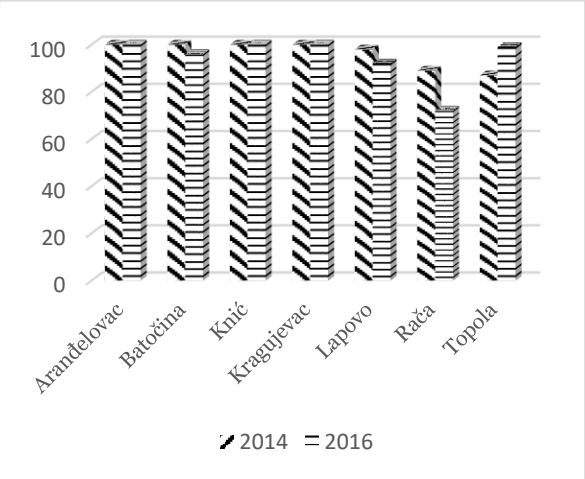

Figure 1. Vaccinations administered with DTP vaccine in the first year of life in 2014 and 2016

The results of DTP vaccination for Šumadija District in the calendar year 2014 show that the largest number of people were vaccinated with the DTP vaccine in the municipalities of Aranđelovac, Batočina, Knić, and Kragujevac, where the percentage of vaccinated people was 100%. The lowest percentage of vaccinated persons was in Topola with 87%, where 146 out of 167 planned persons were vaccinated. Taking into account the total number of planned vaccinations (2508) compared to the number of vaccinated persons (2479) in Šumadija District for the calendar year 2014, it can be concluded that the vaccination was successfully carried out with a coverage of 99%.

Vaccination against diphtheria, tetanus, and pertussis with the DTP vaccine was carried out in the Republic of Serbia in 2014 with a coverage of 95% and an estimated coverage of 92.5%. Based on the estimated total number of live births in the Republic of Serbia in 2013, 4900 children were not vaccinated in 2014. The analysis of the success of DTP vaccination by districts shows that in 2014 the vaccination coverage rate of planned children was below 95% in the following districts: City of Belgrade, Raška, Niš, District of Braničevo, Pomoravlje, and Pčinja. The first booster vaccination against diphtheria, tetanus, and pertussis, i.e. the second against diphtheria and tetanus in the Republic of Serbia, was performed with worse results than in 2013, as was the third in 2014. Half of the districts recorded a vaccination coverage rate below 95% in the second and a quarter in the 7th and 14th districts [11].

A graphical representation of the arithmetic mean and standard deviation of the diphtheria vaccination in the first year of life of infants and the booster vaccination against diphtheria in the 2nd and 7th year of life in 2016 is shown in Figure 2.

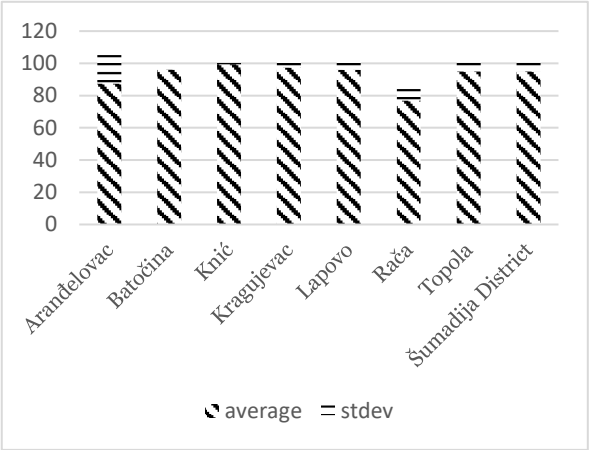

Figure 2. Immunization of children against diphtheria in 2018

Vaccination with the DTP vaccine (Pentaxim) in the first year of life of an infant in the calendar year 2016 in Aranđelovac, the ratio of vaccinated to planned vaccinated is 100%. In Knić, 75 of the planned 75 were also vaccinated, corresponding to 100%. In Kragujevac, 1743 of the planned 1743 were vaccinated, corresponding to 100%. In Topola, the planned number was 172 and the number of vaccinated was 171, corresponding to 99%. In Batočina, 81 of the planned 84 were vaccinated, which is 96%. In Lapovo, 46 of the planned 50 were vaccinated, corresponding to 92%. In Rača, 72 of the planned 100 respondents were vaccinated, which is 72%. The percentage in Šumadija District level in 2016 was 99%, which shows us that the vaccination was successfully carried out.

Vaccination against diphtheria, tetanus, and pertussis DTP and the combined pentavalent DTaP-IPV-Hib vaccine was administered in the Republic of Serbia in 2016 with a coverage of 94.1% and an estimated coverage of 92.5%. Based on the estimated total number of live births in the Republic of Serbia in 2015, 4850 children were not vaccinated in 2016. Analysis of the success of the first booster vaccination with the DTP vaccine as well as with the combined pentavalent DTaP-IPV-Hib vaccine by districts shows that in 2016 the vaccination coverage rate was above 95 in 36% of districts, with the lowest value in Niš at 67.1%. Coverage of the planned second DT booster vaccination in children aged 7 years was below 95% in 37 municipalities (32%) in Central Serbia and 7 in Vojvodina. The lowest vaccination coverage rate of 50% was recorded in Doljevac, i.e. Apatin 68.9%. The third dT booster vaccination in the 14th year covered less than 95% of the planned children in 60 municipalities (52%) in the central part of Serbia and 16 (36%) in Vojvodina [12].

A comparison of the results of vaccination with the Pentaxim vaccine in the second year of life on the territory of Šumadija District in 2017 (before the COVID-19 pandemic) and 2022 (during and

immediately after the COVID-19 pandemic) is shown in Figure 3.

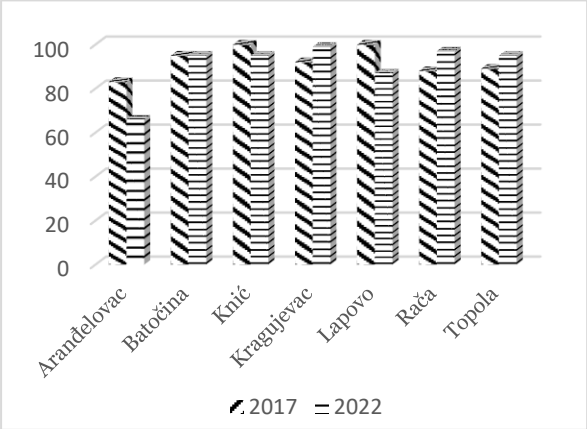

Figure 3. DTP booster vaccination in the second year of life in 2017 and 2022

The highest percentage of people vaccinated with the Pentaxim vaccine in the second year of life for the calendar year 2017 was recorded in the municipality of Knić. Of the planned 72, 72 were vaccinated again, corresponding to 100%. In Lapovo, 53 of the planned 55 were newly vaccinated, i.e. 96%. In Batočina, 80 of the planned 84 were revaccinated, corresponding to 95%. In Kragujevac, 1689 of the scheduled 1840 were vaccinated, corresponding to 92%.

In Topola, 162 of the planned 181 were vaccinated, corresponding to 89%. In the municipality of Rača, 88 of the planned 100 were vaccinated, corresponding to 88%. In 2017, the booster vaccination was also carried out in the 2nd year of life, so the lowest percentage was recorded in Aranđelovac, where 310 of the planned 370 were boostered, corresponding to 83%. Of the total number of planned 2702, 2454 were revaccinated, which means that the estimated revaccination rate in the second year of life at the level of the entire district is 91% and is considered unsatisfactory for this calendar year, as it is below 95%.

Vaccination against diphtheria, tetanus, and pertussis with the combined pentavalent DTaP-IPV-Hib vaccine was carried out in the Republic of Serbia in 2017 with a coverage of 95.1% and an estimated coverage of 95.3%. The first booster vaccination against diphtheria, tetanus, and pertussis in the Republic of Serbia was carried out with almost the same results as in 2016. In 18 out of 25 districts, a vaccination coverage rate of less than 95% is registered in the second year of life. The municipalities where the lowest coverage was achieved in the first booster vaccination are Ub (22.3%) and Surdulica (48%) in central Serbia and Novi Sad (78.5%) in Vojvodina [13].

Booster vaccination with DTaP-IPV-HiB vaccine, Pentaxim vaccine, in the 2nd year of life in Šumadija District in 2022 is not satisfactory, because the overall percentage of booster vaccinations is 93%. The lowest number of re-vaccinated persons was in the municipality of Aranđelovac (253), while the number of planned persons was significantly higher (385), corresponding to 66%, while the highest percentage of re-vaccinated persons was in Kragujevac, namely 99%. In Rača, 63 of the planned 65 people were revaccinated, which is 97%. The same percentage was recorded in Topola. Of the planned 142, 135 were vaccinated, corresponding to 97%.

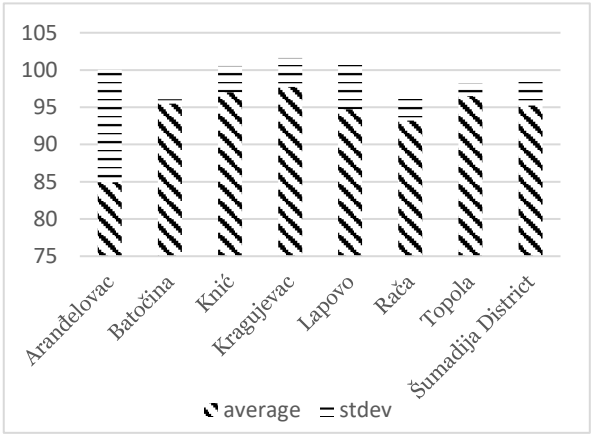

Figure 4. Immunization of children against diphtheria in 2022

In Batočina, the number of planned vaccinations was 75 and the number of revaccinations was 71, which is 95%. In Knić, 70 of the planned 73 were revaccinated, corresponding to 95%. In Lapovo, 46 of the planned 53 people were vaccinated, which is 87%. A graphical representation of the arithmetic mean and standard deviation of the diphtheria vaccination and the booster vaccination against diphtheria in 2022 is shown in Figure 4.

Vaccination of the planned population with the combined pentavalent vaccine was carried out in the Republic of Serbia in 2022 with a vaccination coverage rate of 91.9% (estimated 93%). The analysis of coverage with the combined pentavalent vaccine by district shows that in 2022, coverage in twelve districts reached the target of 95% or more of the planned children, while in two districts coverage of less than 90% was recorded. The lowest vaccination coverage rate of 85.8% is registered in Belgrade [14].

The refusal and postponement of vaccinations, the anti-vaccination lobby, and the resulting accumulation of susceptible unvaccinated, and incompletely vaccinated children, especially during the COVID-19 pandemic due to the restructuring of the work of health facilities, indicate passive surveillance and have called into question the occurrence of other infectious diseases.

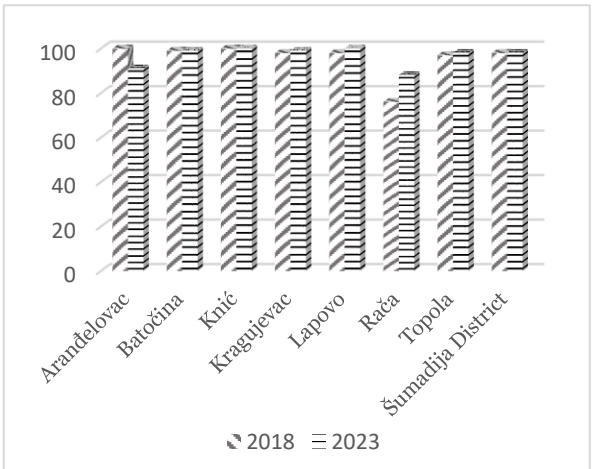

Figure 5. DTP vaccination in 2018 and 2023

A comparison of the results of vaccination with the Pentaxim vaccine in the first year of life in the Šumadija District in 2018 (before the COVID-19 pandemic) and 2023 (during and immediately after the COVID-19 pandemic) is shown in Figure 5.

In 2018, the total number of planned vaccinations in the first year of life was 2575, while the number of vaccinated in Šumadija District was 2525. For 2018, the percentage of vaccinated people was 98%, which tells us that immunization with the Pentaxim vaccine was successfully carried out this year (more than 95% of vaccinated people). We also note that the booster vaccination against diphtheria was carried out in the 2nd and 7th years in Šumadija District. Of the planned total number, more than 95% were always vaccinated, which also shows us that the booster vaccination was successfully carried out in this calendar year in this district. The data analysis showed a statistical significance ($p<0.05$) for 2022 and 2023 for the booster vaccination at the age of 14.

Vaccination against diphtheria, tetanus, and pertussis with the combined pentavalent DTaP-IPV-Hib vaccine was carried out in the Republic of Serbia in 2018 with a coverage of 94.7% and an estimated coverage of 96.5%. The analysis of the success of vaccination with the combined pentavalent DTaP-IPV-Hib vaccine by districts shows that in 2018 the vaccination coverage of planned children in Belgrade, District of Kolubara, Pomoravlje, Raška, Pčinja, Banat, and Srem was below 95%. The lowest coverage was recorded in the Banat District at 90.1%.

The analysis of the success of the first booster vaccination with the combined pentavalent DTaP-IPV-Hib vaccine by district shows that in 2018 the vaccination coverage rate was above 95% in 40 of the districts, the lowest in Banat District at 82.2%. The lowest vaccination coverage rate for the second and third booster vaccination against diphtheria and tetanus is registered in the Kolubara District [15].

The percentage of vaccinated people at the level of the entire Šumadija District for 2023 is 98%, which tells us that the vaccination was successful. The percentage of vaccinated is still below 95%, except in the seventh year of life before enrollment and entry into the first grade of elementary school, which every child, i.e. parents, is legally obliged to do. The evaluation and the greatest possible success of the vaccination carried out (≥95%) leads to a reduction in morbidity and mortality from the infectious diseases mentioned and to the possibility of complete eradication or elimination of the infectious disease.

The reinforcement of the vaccination program due to possible unforeseen future events in the world is also becoming increasingly important, all to build collective immunity against vaccine-preventable diseases [25, 26]. Summarizing this statistical data, we emphasize that it is essential to constantly educate undecided, distrustful, and uncertain parents and health workers, which is an effective strategy for vaccinating the target population at the country level. Limiting the available evidence through the media and means of public information about the occurrence of an infectious disease with the possibility of its epidemic occurrence with low vaccination coverage leads to and emphasizes the risk of morbidity and mortality from various infectious diseases [27, 28]. Therefore, all healthcare efforts, as far as primary healthcare activities are concerned, should focus on improving the quality of routine immunization, especially after the COVID-19 pandemic as well as during many wars that together have led to the collapse of the healthcare system in many countries.

There is data on a prolonged epidemic of diphtheria in several West African countries as well as on the sporadic occurrence of the disease in all WHO regions [29]. Maintaining high immunization coverage through vaccination and booster vaccination, which is a legal requirement in our country, allows careful monitoring of mandatory vaccination and is an excellent key to preventing diphtheria outbreaks and controlling the disease itself.

The data analysis showed a statistical significance ($p<0.05$) for 2018 and 2023 for the booster vaccination at the age of 14. The largest decline in the last 20 years in the target groups of certain vaccines during the COVID-19 pandemic, the accumulation of a vulnerable population, a part of the population outside the health system, makes collective immunity insufficient [30] with the risk of sporadic cases of disease, but also of epidemic outbreaks due to vaccine-preventable diseases with complications and the need for hospitalization. However, urgent action can bear fruit and lead to good results if incompletely immunized children are provided with vaccinations that were missed during the COVID-19 pandemic. Strengthening the immunization program due to possible unforeseen future events in the world is also gaining importance [31]. Immunization coverage is one of the indicators of the availability of primary health care and the assessment of the capacity of the health system.

5. Conclusion

The epidemiological situation of COVID-19, the control measures applied to the affected population and contact persons, as well as the enormous commitment of health personnel in terms of testing and vaccination against COVID-19 contributed to a drastic reduction in vaccination coverage according to the vaccination calendar with all vaccines on the planned target dates groups and thus collective immunity with the risk of epidemic disease. Two years after the pandemic, immunization against diphtheria in the entire district is 99% in 2022, indicating that immunization has been successful. A well-functioning immunization system is one of the key elements for a strong health system and preparing the country for future public health challenges.

Reference

1. N. C. Sharma et al., "Diphtheria," *Nat. Rev. Dis. Primers*, vol. 5, no. 1, 81, Dec. 2019. DOI: 10.1038/s41572-019-0131-y PMid: 31804499
2. A. Lamichhane, S. Radhakrishnan, "Diphtheria," in *StatPearls [Internet]*, Treasure Island, FL, USA: StatPearls Publishing, Jan. 2024. PMid: 32809746
3. M. Muscat, B. Gebrie, A. Efstratiou, S. S. Datta, D. Daniels, "Diphtheria in the WHO European Region, 2010 to 2019," *Eurosurveillance*, vol. 27, no. 8, 2100058, Feb. 2022. DOI: 10.2807/1560-7917.ES.2022.27.8.2100058 PMid: 35209973

PMCid: PMC8874865
4. C. Jarrett et al., "Strategies for addressing vaccine hesitancy - A systematic review," *Vaccine*, vol. 33, no. 34, pp. 4180 – 4190, Aug. 2015.
DOI: 10.1016/j.vaccine.2015.04.040
PMid: 25896377
5. P. Aaby, H. Ravn, C. S. Benn, "The WHO Review of the Possible Nonspecific Effects of Diphtheria-Tetanus-Pertussis Vaccine," *Pediatr. Infect. Dis. J.*, vol. 35, no. 11, pp. 1247 – 1257, Nov. 2016.
DOI: 10.1097/INF.0000000000001269
PMid: 27753772
6. J. P. Mangion, S. Mancini, C. Bachy, A. de Weggheleire, F. Zamatto, "Diphtheria in Europe," *Public Health Action*, vol. 13, no. 2, pp. 31 – 33, Jun. 2023.
DOI: 10.5588/pha.23.0011
PMid: 37359068
PMCid: PMC10290257
7. M. Prygiel et al., "Challenges of Diphtheria Toxin Detection," *Toxins*, vol. 16, no. 6, 245, May 2024.
DOI: 10.3390/toxins16060245
PMid: 38922140
PMCid: PMC11209151
8. S. A. Truelove et al., "Clinical and Epidemiological Aspects of Diphtheria: A Systematic Review and Pooled Analysis," *Clin. Infect. Dis.*, vol. 71, no. 1, pp. 89 – 97, Jun. 2020.
DOI: 10.1093/cid/ciz808
PMid: 31425581
PMCid: PMC7312233
9. L. F. Hewitt, "Use of antibiotics in the treatment of experimental diphtheria infections," *Br. J. Exp. Pathol.*, vol. 31, no. 5, pp. 597 – 602, Oct. 1950.
PMid: 14791911
PMCid: PMC2073362
10. A. J. Leidner et al., "Cost-effectiveness of adult vaccinations: A systematic review," *Vaccine*, vol. 37, no. 2, pp. 226 – 234, Jan. 2019.
DOI: 10.1016/j.vaccine.2018.11.056
PMid: 30527660
PMCid: PMC6545890
11. *Izveštaji o sprovedenoj imunizaciji na teritoriji Republike Srbije u 2014. godini*, Institut za javno zdravlje Srbije "Dr Milan Jovanović Batut", Beograd, Srbija, 2015.
(Reports on immunization carried out on the territory of the Republic of Serbia in 2014, Institute for Public Health of Serbia "Dr Milan Jovanović Batut", Belgrade, Serbia, 2015.)
Retrieved from:
https://www.batut.org.rs/index.php?category%20id=140
Retrieved on: Jan. 20, 2024
12. *Izveštaji o sprovedenoj imunizaciji na teritoriji Republike Srbije u 2016. godini*, Institut za javno zdravlje Srbije "Dr Milan Jovanović Batut", Beograd, Srbija, 2017.
(Reports on immunization carried out on the territory of the Republic of Serbia in 2016, Institute for Public Health of Serbia "Dr Milan Jovanović Batut", Belgrade, Serbia, 2017.)
Retrieved from:
https://www.batut.org.rs/index.php?category%20id=140
Retrieved on: Jan. 20, 2024
13. *Izveštaji o sprovedenoj imunizaciji na teritoriji Republike Srbije u 2017. godini*, Institut za javno zdravlje Srbije "Dr Milan Jovanović Batut", Beograd, Srbija, 2018.
(Reports on immunization carried out on the territory of the Republic of Serbia in 2017, Institute for Public Health of Serbia "Dr Milan Jovanović Batut", Belgrade, Serbia, 2018.)
Retrieved from:
https://www.batut.org.rs/index.php?category%20id=140
Retrieved on: Jan. 20, 2024
14. *Izveštaji o sprovedenoj imunizaciji na teritoriji Republike Srbije u 2022. godini*, Institut za javno zdravlje Srbije "Dr Milan Jovanović Batut", Beograd, Srbija, 2023.
(Reports on immunization carried out on the territory of the Republic of Serbia in 2022, Institute for Public Health of Serbia "Dr Milan Jovanović Batut", Belgrade, Serbia, 2023.)
Retrieved from:
https://www.batut.org.rs/index.php?category%20id=140
Retrieved on: Jan. 20, 2024
15. *Izveštaji o sprovedenoj imunizaciji na teritoriji Republike Srbije u 2018. godini*, Institut za javno zdravlje Srbije "Dr Milan Jovanović Batut", Beograd, Srbija, 2019.
(Reports on immunization carried out on the territory of the Republic of Serbia in 2018, Institute for Public Health of Serbia "Dr Milan Jovanović Batut", Belgrade, Serbia, 2019.)
Retrieved from:
https://www.batut.org.rs/index.php?category%20id=140
Retrieved on: Jan. 20, 2024
16. S. M. Aljunid et al., "Economic impact of switching from partially combined vaccine 'Pentaxim® and hepatitis B' to fully combined vaccine 'Hexaxim®' in the Malaysian National Immunization Program," *BMC Health Serv. Res.*, vol. 22, no. 1, 34, Jan. 2022.
DOI: 10.1186/s12913-021-07428-7
PMid: 34986870
PMCid: PMC8734051
17. I. Rengganis, "Adult Diphtheria Vaccination," *Acta Med. Indones.*, vol. 50, no. 3, pp. 268 – 272, Jul. 2018.
PMid: 30333279
18. Z. Radovanović, *Istina o vakcinama: Priručnik za savesne roditelje,* 2. dopunjeno i prošireno izdanje, Smederevo, Srbija: Heliks, 2017.
(Z. Radovanović, *The truth about vaccines: Manual for conscientious parents*, 2nd amended and expanded ed., Smederevo, Serbia: Helix, 2017.)
19. M. Prygiel, E. Mosiej, P. Górska, A. A. Zasada, "Diphtheria-tetanus-pertussis vaccine: past, current & future," *Future Microbiol.*, vol. 17, no. 3, pp. 185 – 197, Feb. 2022.
DOI: 10.2217/fmb-2021-0167
PMid: 34856810
20. K. Yang, H. Kim, E. Ortiz, C. Huoi, J. Kang, "Post-Marketing Safety Surveillance of a Childhood Pentavalent Diphtheria-Tetanus-Acellular Pertussis-Polio and Haemophilus influenzae Type B (DTaP-IPV//Hib) Vaccine in South Korea," *Infect. Dis. Ther.*, vol. 12, no. 2, pp. 499 – 511, Feb. 2023.
DOI: 10.1007/s40121-022-00724-7
PMid: 36520326
PMCid: PMC9925623
21. R. Petrović, *Imunizacije*, Beograd, Srbija: Velarta, 1996.
(R. Petrović, *Immunizations*, Belgrade, Serbia: Velarta, 1996.)
22. F. Kahn, T. Lepp, J. Storsaeter, "Primary diphtheria immunization of adolescents and adults with low-dose vaccine, a survey of historic evidence from the literature," *Acta Paediatr.*, vol. 112, no. 2, pp. 242 – 245, Feb. 2023.
DOI: 10.1111/apa.16589
PMid: 36333877
PMCid: PMC10099547
23. Z. Garib, M. C. Danovaro-Holliday, Y. Tavarez, I. Leal, C. Pedreira, "Diphtheria in the Dominican Republic: reduction of cases following a large outbreak," *Rev. Panam. Salud Publica*, vol. 38, no. 4, pp. 292 – 229, Oct. 2015.
PMid: 26758220

24. L. W. Rümke, H. C. Rümke, "Diphtheria: a 'forgotten' disease?," *Ned. Tijdschr. Geneeskd.*, vol. 163, no. 42, D4036, Oct. 2019.
PMid: 31609562
25. G. Kaur et al., "Routine Vaccination Coverage - Worldwide, 2022," *MMWR Morb. Mortal. Wkly Rep.*, vol. 72, no. 43, pp. 1155 – 1161, Oct. 2023.
DOI: 10.15585/mmwr.mm7243a1
PMid: 37883326
PMCid: PMC10602616
26. Q. Hasan, Y. F. Hutin, R. Hajjeh, "Immunization in the Eastern Mediterranean Region: some signs of post-COVID-19 recovery, but more work ahead," *East. Mediterr. Health J.*, vol. 29, no. 9, pp. 681 – 683, Sep. 2023.
DOI: 10.26719/2023.29.9.681
PMid: 37776128
27. V. Petrović, *Imunizacija protiv zaraznih bolesti*, Novi Sad, Srbija: Medicinski fakultet, 2015.
(V. Petrović, *Immunization against infectious diseases*, Novi Sad, Serbia: Faculty of Medicine, 2015.)
Retrieved from:
https://izjzv.org.rs/uploads/52458a10-bf00-7942-ce12-/Imunizacija_protiv_zaraznih_bolesti.pdf
Retrieved on: Jan. 20, 2024
28. V. Turkulov i sar., *Infektivne bolesti za studente medicine,* 2. izdanje, Novi Sad, Srbija: Medicinski fakultet, 2015.
(V. Turkulov et al., *Infectious diseases for medical students,* 2nd ed., Novi Sad, Serbia: Faculty of Medicine, 2015.)
29. *Clinical management of diphtheria: guideline*, WHO/DIPH/Clinical/2024.1, WHO, Geneva, Switzerland, 2024.
Retrieved from:
https://iris.who.int/bitstream/handle/10665/375887/WHO-DIPH-Clinical-2024.1-eng.pdf?sequence=1
Retrieved on: Feb. 20, 2024
30. E. Sifuentes-Rodríguez, D. Palacios-Reyes, "COVID-19: The outbreak caused by a new coronavirus," *Bol. Med. Hosp. Infant. Mex.*, vol. 77, no. 2, pp. 47 – 53, 2020.
DOI: 10.24875/BMHIM.20000039
PMid: 32226003
31. A. A. Al-Dar et al., "Diphtheria resurgence in Sada'a-Yemen, 2017-2020," *BMC Infect. Dis.*, vol. 22, no. 1, 46, Jan. 2022.
DOI: 10.1186/s12879-022-07033-x
PMid: 35016630
PMCid: PMC8751122