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VACCINATION AGAINST TETANUS OF CHILDREN IN ŠUMADIJA DISTRICT: RETROSPECTIVE ANALYSIS

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Abstract. *Tetanus is a fatal disease that is widespread in underdeveloped countries. Tetanus occurs after injuries, which are the entry point for infection with Clostridium tetani. The bacillus itself secretes a strong and potent exotoxin that causes intoxication of the body, which can be manifested by neuromuscular dysfunction. Tetanospasmin, as a powerful neurotoxin, can lead to a fatal outcome of this disease if adequate protection is not prescribed in time after the injury to prevent further intoxication with this exotoxin. Even greater importance should be attached to neonatal tetanus, which has been more common in rural areas over the last century. The vaccine is one of the safest and most effective measures in the fight against tetanus, as it provides long-term protection in fully immunized individuals. Surgical treatment, appropriate wound care, and the administration of anti-tetanus serum and the vaccine in the first hours after the injury lead to 100% protection against this deadly disease. Objective. To determine whether regular vaccination against tetanus in children in the Šumadija District has been successfully carried out over five years from 2018 to 2022 to achieve satisfactory immunity and protection against this disease for a certain period. Results and discussion. The lowest success rate in immunization against tetanus for the observed five-year period was observed in 2020: 72% for the booster vaccination at the age of seven and 86% for the booster vaccination at the age of fourteen for the area of Šumadija District. Even during the current COVID-19 pandemic in the calendar year 2021, a low tetanus vaccination coverage rate is observed compared to before the pandemic. Based on statistically processed and summarized data, it can be said that the vaccination coverage rate for 2021 is significantly lower for the first vaccination in the first year of life and is 89%, the booster vaccination in the second year of life is 90% and in the fourteenth year of life 87%. It is important to pay attention to immunization status and the completeness and regularity of tetanus vaccination. In some developed countries, special attention is paid to the assessment of tetanus vaccination status by reviewing medical records as part of primary health care. Conclusion. Continuous and improved education of physicians (especially surgeons, anesthesiologists, and emergency physicians) about immunization of the childhood population according to the calendar of mandatory vaccinations against tetanus in the form of panel discussions, lectures, and professional conferences is extremely important. Immunoprophylaxis in children and immunoprophylaxis together with seroprophylaxis and chemoprophylaxis in the elderly is the key to success in the fight against tetanus.*

Keywords: *tetanus, COVID-19, vaccination status, postexposure prophylaxis, education*

1. INTRODUCTION

Tetanus or malignant spasm is a toxic infection that occurs through contamination or infection of a tetanogenic wound [1] with spores or, rarely, vegetative forms of the tetanus bacillus (*Clostridium tetani*). The essential features of a tetanus wound are the presence of anaerobic conditions due to the depth of the injury, a local decrease in oxidation-reduction potential due to tissue necrosis and destruction of muscle mass, a mixed bacterial infection, and circulatory disturbances and vasoconstriction [2]. Damage to the above features creates the conditions for germination of tetanus spores, multiplication of vegetative bacilli, and toxin secretion [3]. In an advanced infection, the tetanus bacilli contribute little to the local inflammation of the wound. However, they produce an exotoxin (tetanospasmin) that increases muscle tone, resulting in an increased response to minimal stimuli and an intermittent muscle spasm. This spasm develops into a generalized muscle spasm [4]. The tetanus toxin, tetanospasmin, is transported from the production site through the motor neurons (retrograde intraaxial and peraxial transport) to the gangliosides in the synaptic membrane.

The transport of toxins into the CNS via endocytosis, blood, and lymphatics is possible but of minor importance. The target site of tetanus toxin activity is the presynaptic terminal endings of the motor neurons in the ventral horns and the postsynaptic spinal neurons [5]. Tetanus toxin prevents the release of acetylcholine and inhibitory neurotransmitters, glycine and γ-aminobutyric acid (GABA) [3]. Therefore, transmission in the neuromuscular synapse and transmission of inhibitory impulses in the CNS is prevented, resulting in spastic paralysis of all muscles, both flexor and extensor groups. [6, 7]. The incubation period is between 3 and 30 days, but can also last three months. In most cases, the disease manifests itself

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clinically in a period of up to two weeks after the injury and infection. The portal of entry for contamination and subsequent development of infection can be burns and chronic ulcers on the lower legs.

Isolation and identification of *Clostridium tetani* is aimed at laboratory confirmation of the clinical diagnosis [8], but in most cases does not yield results. *Clostridium tetani* is difficult to culture due to its extreme sensitivity to oxygen, and the percentage of positive cultures is around 30%. When *Clostridium tetani* is isolated on culture media, the ability to produce neurotoxins must be demonstrated with a neutralization test. The bacteriological diagnosis is made based on morphological, cultural, and biochemical characteristics. The toxin production of an isolated strain of *Clostridium tetani* is detected by an *in vitro* agar gel precipitation or a biological test. A rapid detection test (TQS) in the emergency department would be of great importance as it could improve procedures for detecting and confirming tetanus in individuals who have not been previously vaccinated [9].

Tetanus therapy includes surgical treatment of the wound, administration of antibiotics (penicillin or metronidazole) to reduce the number of bacilli in the wound and reduce toxin production [10], passive immunization with human tetanus immunoglobulin to neutralize the toxin that has not bound to the receptors, and vaccination with toxoid as the infection leaves no immunity. The toxin that is already bound to the receptors cannot be neutralized by antibodies. The effects of the toxin must be remedied by non-specific support measures (sedation, maintenance of respiration) until normal regulation of synaptic transmission is restored. Prevention of further intoxication of the diseased organism with bacterial exotoxins is one of the basic measures in treating patients with tetanus [11]. It refers to the treatment of the point of entry of the infection and the application of specific immunotherapy [12].

Vaccination has eliminated childhood tetanus in Western countries [13], and adult tetanus usually occurs later in life when the effect of vaccines administered at a young age wears off. The incidence of disease following minor injuries is becoming more apparent. The likely reason for this is that more severe injuries are treated surgically and active-passive protection is being approached [14]. The latest estimates for 2013 show that coverage with three doses of some vaccines containing tetanus toxoid has reached 86% worldwide, resulting in a sharp decline in the incidence of disease and deaths. When looking only at newborns who died from tetanus, their number in 2013 was less than 50000, and a quarter of a century earlier it was almost 800000 (a decrease of 94%).

The total number of cases of tetanus in the world is estimated at more than one million per year with a mortality rate of 30-50%. Tetanus rarely occurs in developed countries and most often in unvaccinated or incompletely vaccinated elderly people, in whom the protective immunity induced by the vaccine is reduced (decrease in the titer of antitoxic antibodies). In underdeveloped countries, where there is no proper immunization program or health care is poorly organized, tetanus is accompanied by a high mortality rate. Neonatal tetanus is a significant cause of mortality in the countries of Asia and Africa [15], and at least half of the deaths due to tetanus are registered in newborns [16]. Thanks to the high coverage of immunization, which is about 95% in the first year of life, eliminating neonatal tetanus in our country has been made possible [17]. According to WHO data, the last case of neonatal tetanus in Serbia was recorded in 2009.

The aim of this paper is the comparison and interpretation of statistically processed data on the success of vaccination against tetanus in the territory of the Šumadija District in the period from 2018 to 2023. year, as well as comparing the success of vaccination before, during, and after the pandemic of COVID-19.

2. 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. The scope includes the number of children vaccinated and the number of persons scheduled for vaccination (vaccinated and revaccinated according to the vaccination calendar applied by law in the Republic of Serbia) in 2018 and 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) of < 0.05 was considered significant. The results are shown graphically.

3. Results and discussion

Active immunization (vaccination) against tetanus is achieved by using the anti-tetanus vaccine. It contains tetanus anatoxin. Vaccination is carried out according to the legally regulated calendar and includes infants, preschool children, school children, youth, and military conscripts [18]. Once in our country, the combined trivalent DiTePer vaccine (DTP), which contains diphtheria and tetanus toxoid and kills whooping cough (*Bordetella pertussis*) was used in our country for immunization of children. Protection was carried out by administering the tetanus vaccine in the first year of life, in three doses. Revaccination is in the second, seventh, and fourteenth years of life [19]. The vaccine is administered from the third month of life, according to the vaccination calendar. In some countries, pregnant women are immunized, because the transplacental transfer of antibodies enables the prevention of neonatal tetanus [20, 21]. In adults, one "booster" dose of tetanus toxoid is recommended every 10 years, and three "booster" doses after an injury if the person is completely protected by vaccination that has not been more than 10 years ago [22].

Today, primary vaccination is carried out with three doses of the combined pentavalent vaccine DTaP-IPV-Hib (Pentaxim) at intervals that must not be shorter than four weeks. Active immunization starts when the child turns two months old. The primary series should be completed in time by six months of age [23]. In incompletely immunized and non-immunized persons older than six months, immunization is carried out with the primary series using the appropriate combined

vaccine following the immunization calendar. The incompletely immunized receive the missing doses, and the non-immunized receive the complete primary series of the combined vaccine. The first revaccination is carried out in the second year of life using one dose of the combined pentavalent vaccine DTaP-IPV-Hib (Pentaxim), i.e. one year after the end of the primary series, and at the earliest after six months. The second revaccination is carried out using one dose of the combined quadrivalent vaccine (DTaP-IPV, Tetraxim) before entering the first grade of primary school or exceptionally during the first grade of primary school [24].

The third revaccination is carried out using one dose of the combined DT vaccine (Ditevaxal-T for adults) in the final grade of elementary school and at the latest by the age of 18. The aforementioned combined vaccines are given intramuscularly in the appropriate dose (0.5 ml). The active substance, whether it is a mono vaccine, i.e. that it is intended only to prevent this disease (Torlakov's Tatavaskal-T or TT), whether combined, constitutes at least 40 IU (international units) of tetanus anatoxin. Auxiliary substances are the same and are found in the same quantities as in the DT vaccine (Ditevaxal-T). According to our by-laws, the mono vaccine against tetanus should be given to adults at ten-year intervals. It is recommended to give four booster doses after reaching 30 years of life [25]. Probably, soon, we will also accept the practice of replacing the monovaccine TT with the combined DT, because it is useful to raise resistance against diphtheria at the same time [26].

In addition to the time criterion, all injured persons are subject to receiving the tetanus vaccine if they do not have proof that less than 10 years have passed since the previous vaccination (with such proof, only the wound is treated surgically). There are two possibilities: fully vaccinated and revaccinated more than 10 years ago receive one dose of TT vaccine in the muscle of the upper arm, at the same time as passive protection with ready-made antibodies (it is human anti-tetanus immunoglobulin (HTIG), but in the opposite hand, i.e. in a different place) [27]. Unvaccinated, incompletely vaccinated, or without proof of vaccination against tetanus undergo complete protection with four doses of TT according to the scheme: 0, 1, 6, and 12 months. The first dose of TT is followed by administration of HTIG.

Contraindications to the use of tetanus toxoid are general for all vaccines. In the event of an injury, only anaphylaxis or a more severe adverse reaction to the previous dose of vaccine containing tetanus toxoid is a contraindication, and only passive immunization using HTIG is applied. In the US, several cases of nerve damage have been reported after vaccination. Similar diseases also occur among unvaccinated people, but it has been concluded that, although extremely rare, tetanus toxoid can be associated with inflammation of the nerves in the shoulder girdle (brachial neuritis) and Guillain-Barre syndrome.

Unfortunately, immunization is not routinely performed in many underdeveloped and developing countries. Tetanus is a preventable disease. The very low frequency of tetanus in countries with a well-organized health service is the result of timely and appropriate treatment of the wound as well as an active immunization program [27, 28]. Protection against tetanus is one of the most effective preventive measures known to medicine. 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 2021 (during and immediately after the COVID-19 pandemic) is shown in Figure 1.

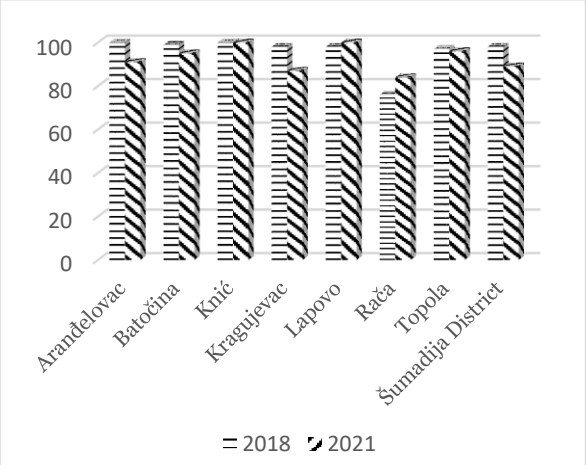

Figure 1. Vaccinations administered with Pentaxim vaccine in the first year of life

By interpreting the statistical data, it was noted that in the territory of the municipality of Aranđelovac, out of the total number of children planned for vaccination in the first year of life, which is 394 infants in 2018, 394 were vaccinated, which is 100%. In the city of Knić, out of 76 planned, the same number was vaccinated, which is 100%. In the city of Batočina, out of 79 planned, 78 were vaccinated, which is 99%. In the city of Kragujevac, out of 1750 planned, 1726 infants were vaccinated, which is 98%. In the city of Lapovo, out of the planned 42, 41, or 98%, were vaccinated. In the city of Topola, out of 149 planned, 145 were vaccinated, which is 97%. In the city of Rača, out of 85 planned, 65 infants were vaccinated, which is 76%. Taking into account the total number planned for vaccination in the first year of life (2575) compared to the number of vaccinated (2525), in the territory of Šumadija District for 2018, the percentage of vaccinated is 98%, which tells us that immunization with the Pentaxim vaccine for this year successfully implemented (more than 95% of those vaccinated).

In the territory of the municipality of Aranđelovac, of the total number planned, which is 385 infants for the year 2021, 352 were vaccinated, which is 91%, which is the lowest percentage for this municipality so far compared to the previously observed period. In the city of Kragujevac, out of 1760 planned, 1541 infants were vaccinated, which is 87%, so it is considered that in 2021, the vaccination of infants in the first year of life with three doses of the pentavalent vaccine at the level of the city of Kragujevac was not successfully implemented. In the city of Rača, out of 70 planned, 59 infants were vaccinated, which is 84%. In the city of Batočina, out of 75 planned, 71 were vaccinated, which is 95%. In the city of Topola, out of 125 planned, 120 were vaccinated, which is 96.00%. In the city of Knić, out of 75 planned, the same number of infants were vaccinated, which is 100%. In the city of Lapovo, out of the planned 58, 58, i.e. 100%, were vaccinated. The total percentage of those vaccinated in the first year of life in

all municipalities in the Šumadija District for the year 2021 was 89%, which tells us that immunization was not successfully implemented because the percentage of those vaccinated is less than 95%.

A graphical representation of the arithmetic mean and standard deviation of the tetanus vaccination in the first year of life of an infant and the booster vaccination against tetanus in the 2nd, 7th, and 14th year of life of children in 2018 is shown in Figure 2.

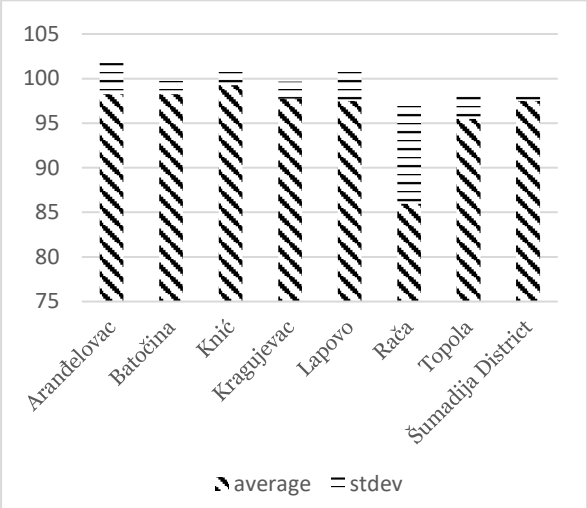

Figure 2. Immunization of children against tetanus in 2018

In the territory of the Šumadija District in 2018. revaccination against tetanus was carried out at 2, 7, and 14 years of age. Of the total planned number, there were always more than 95% vaccinated, which also tells us that the revaccination in this calendar year was successfully implemented in this district. When looking at revaccination in the 2nd, 7th, and 14th year of life in the calendar year 2021, the situation has changed significantly compared to 2018, the percentage of those revaccinated in the 2nd, 7th, and 14th year of life is below 95% which means that the revaccination was not successfully carried out. The reason for this is the postponement of vaccination due to contact with positive persons, quarantine, fear and ignorance of parents, as well as due to the restructuring of the work of the health facilities themselves, which carried out the vaccination themselves during the COVID-19 pandemic.

With special reference, immunization against diphtheria, tetanus, and whooping cough 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%. Based on the assessment of the total number of live births in the Republic of Serbia in 2017, 2200 children were not vaccinated with the combined pentavalent DTaP-IPV-Hib vaccine in 2018. There were no reported cases of tetanus in the territory of the Republic of Serbia (without data for Kosovo and Metohija) in 2018. In the previous reporting year, two cases of this disease were reported. There were no registered cases of tetanus in newborns in 2018. The last case of this disease with a fatal outcome was registered in 2009 in Pčinja District [29].

Vaccination of the intended population with the combined pentavalent vaccine was carried out in the Republic of Serbia in 2021 with a vaccination coverage rate of 90.8% (estimated 91.5%). Analysis of vaccination coverage with the combined pentavalent vaccine by district shows that in 2021, vaccination coverage reached the target of 95% or more of the planned children in only four districts (Pirot, Kolubara, Jablanica and Nišava) while in nine districts (Raška, Zaječar, Pčinja, Šumadija, City of Belgrade, and Bačka) a vaccination coverage of less than 90 was registered. The first booster vaccination against diphtheria, tetanus, and whooping cough with the combined pentavalent vaccine (DTaP-IPV-Hib) in the 2nd year of life was carried out in the Republic of Serbia with a coverage of 82.3%. At the age of 14, it was 90%, i.e. 75.4% [29].

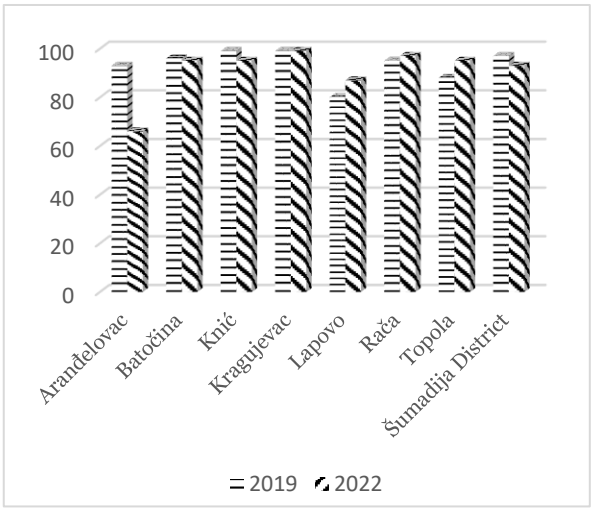

Figure 3. Repeat vaccinations carried out with the Pentaxim vaccine in the second year of life in 2019 and 2022

The percentage of those vaccinated at the level of the entire Šumadija District for the calendar year 2019 is 97%, which indicates that the immunization of children in the first year of life was successfully implemented. Based on statistically processed data on the revaccination of children in their 2nd year of life, we can see that in the city of Aranđelovac, out of the total number planned, which is 389 inhabitants for 2019, 363 were revaccinated, which is 93%. In Rača, out of 65 planned, 62 were revaccinated, which is 95%. In Batočina, out of 74 planned, 71 were revaccinated, which is 96%. In Topola, out of 153 planned, 134 were revaccinated, which is 97%. In Knić, out of 83 planned, 82 small children were revaccinated, which is 99%. In Kragujevac, out of 1730 planned, 1714 children were revaccinated, which is 99%. A graphical representation of comparative revaccination with Pentaxim vaccine in the 2nd year of life in the Šumadija District in 2019 and 2022 is showen in Figure 3.

The lowest success rate for booster vaccinations in the second year of life was achieved in the municipality of Lapovo. Of the planned 45 booster vaccinations, 36 were carried out, i.e. 80%. The percentage at the level of the Šumadija District in 2019 was 97%, which tells us that the revaccination of children in the second year of life with the Pentaxim vaccine was successfully carried out. Regarding revaccination, the lowest percentage of those vaccinated in the seventh year of life was in the municipality of Rača and amounted to 92.7%. The lowest percentage of those revaccinated at the age of 14

was in Aranđelovac which amounted to 87.4%. Vaccination of the planned population with the combined pentavalent vaccine was carried out in the Republic of Serbia in 2019 with coverage of 95.1% [29]. Based on the assessment of the total number of live births in the Republic of Serbia in 2018, 2205 children were not vaccinated with the combined pentavalent vaccine in 2019. In 2019, there were no reported cases of tetanus.

The percentage of vaccinated is higher only in the 14th year of life and is 98%, while the percentage in the 2nd and 7th year of life is still below 95% and is 93% and 91% respectively. 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%. In 2022, one case of tetanus was reported in a person over 60 years of age [29].

It is important to pay attention to immunization status and the completeness and regularity of post-injury tetanus vaccination. In some developed countries, special attention is paid to the assessment of the status of immunization against tetanus by checking medical records within the framework of primary health care. Great focus is given to supplementary vaccination due to the weakening of immunity after 10 years, especially in the elderly population. Rapid diagnosis using a rapid tetanus test and timely treatment are also necessary to reduce mortality from this disease. Future vaccination strategies should be oriented to better and more effective raising of health culture and the level of health awareness about infectious and deadly diseases that can occur after injuries. A comparison of the results of vaccinations with the Pentaxim vaccine in the first year of life on the territory of Šumadija District in 2020 (during the COVID-19 pandemic) and 2023 (after the COVID-19 pandemic) is shown in Figure 4.

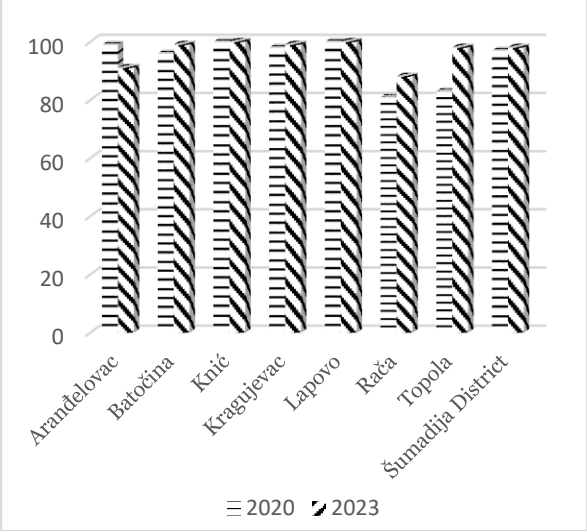

Figure 4. Regarding vaccinations administered with Pentaxim vaccine in the first year of life

It was noted that in the territory of the municipality of Aranđelovac, out of the total number planned, which is 388 infants for 2020, 386 were vaccinated, which is 99%. In Knić, out of 78 planned, the same number of infants were vaccinated, which is 100%. In Lapovo, out of the planned 52, 52 were vaccinated, i.e. 100%. In Kragujevac, out of 1750 planned, 1722 infants were vaccinated, which is 98%. In Batočina, out of 82 planned, 79 were vaccinated, which is 96%. In Rača, out of 70 planned, 57 infants were vaccinated, which is 81%, so it can be concluded that the percentage of vaccinated in this municipality was not satisfactory. The same situation can be observed in the city of Topola, out of 154 planned, 128 were vaccinated, which is 83%.

In the territory of the municipality of Aranđelovac, out of the total number planned, which is 373 infants for the year 2023, 340 were vaccinated, which is 91%. In Topola, out of 146 planned, 144 were vaccinated, which is 98%. In the city of Batočina, out of 80 planned, 79 were vaccinated, which is 99%. In Kragujevac, out of 1630 planned, 1629 children were vaccinated, which is 99%. In Knić, out of 73 planned, the same number were vaccinated, so that it amounts to 100%. In Lapovo, out of the planned 55, 55, i.e. 100%, were vaccinated, which tells us that in 2023, immunization was successfully carried out on the territory of this municipality. In Rača, out of 80 planned, 70 infants were vaccinated, which is 88%. The percentage of those vaccinated at the level of the entire Šumadija District is 98%, which indicates that the immunization was successfully carried out. The percentage of those revaccinated is still below 95%, except in the seventh year of life before enrollment and starting the first grade of primary school, which is the legal obligation of every child, that is, parents. The data analysis showed a statistical significance ($p<0.05$) for 2018 and 2023 for the booster vaccination at the age of 14.

A graphical representation of the arithmetic mean and standard deviation of the tetanus vaccination in the first year of an infant's life and the booster vaccination against tetanus in children aged 2, 7, and 14 in 2020 is shown in Figure 5.

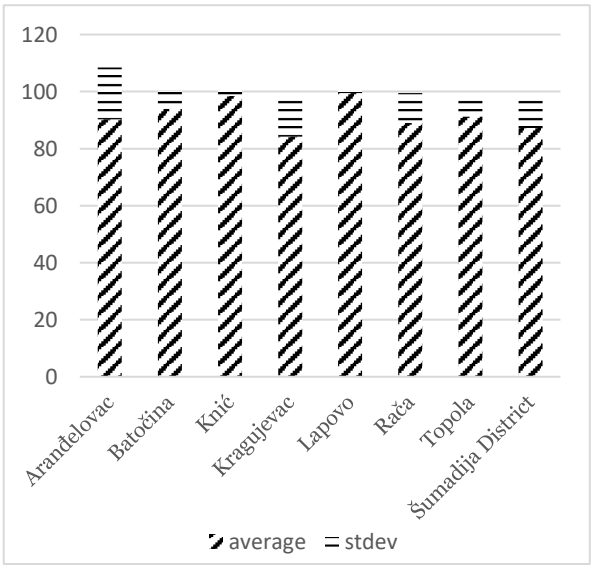

Figure 5. Immunization of children against tetanus in 2020

The percentage of those revaccinated in the Šumadija District for 2020 was not satisfactory and always amounted to less than 95%, which we can relate to the COVID-19 virus, which appeared for the first time in Serbia this year. Although we know that this is tetanus, which belongs to the group of preventable diseases, the diagnosis of which is established solely based on the anamnesis and clinical picture, we should emphasize the importance of quick and urgent prescribing of adequate therapy and immunization

(seroprophylaxis and continuous vaccine prophylaxis) in specialized health institutions with the consultation of a doctor if there are injuries that may be the result of the penetration of *Clostridium tetani* and the production of neurotoxins. Also, it should be emphasized the importance of checking the immunization rate in Serbia, especially during the COVID-19 pandemic, given that the decrease in the immunization rate during the said pandemic is observed even immediately after the same [30].

Vaccination of the planned population with the combined pentavalent vaccine was carried out in the Republic of Serbia in 2020 with coverage of 91.7%. Tetanus is registered in individual cases, mostly in people over 60 years old. In the period from 2010 to 2020, a total of 23 patients were registered. In 2020, there were no reported cases of tetanus [29].

As already mentioned, the COVID-19 pandemic started in Serbia this year. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of COVID-19, first emerged in Wuhan, China in December 2019 and was declared a global pandemic by the WHO by March 2020 [31]. The transmission of SARS-CoV-2 usually takes place through the droplet route. The average incubation period is 6 days and symptoms usually include fever, cough, dyspnoea, myalgia, or fatigue.

While most patients tend to have mild disease, fewer patients develop severe hypoxia requiring hospitalization and mechanical ventilation. Several direct antiviral agents, immunomodulatory steroid therapy, and various cytokine blockers appear promising in the early stages of the disease [32, 33]. However, an effective vaccine was developed that helped contain the pandemic. Further progress in the development of combined and new vaccines and the improvement of the immunization process has been made possible [34]. The COVID-19 pandemic has overwhelmed health systems in most countries and led to huge economic losses.

4. Conclusion

We can see the difference in the total percentage of those vaccinated in the period from 2018 to 2023. Immunization is considered successful for one calendar year if the percentage of vaccination is greater than 95%. By observing and comparing data from 2018 and the period from 2019 to 2022, we notice that the total number of people vaccinated with the Pentaxim vaccine in the Šumadija District, in the period during and after COVID-19, was significantly lower. The consequence of the lower number of vaccinated people due to the COVID-19 pandemic may result in a decrease in collective immunity as well as a greater possibility for the occurrence of some sporadic cases of this disease. The lower number of vaccinated people due to the COVID-19 pandemic may lead to a decrease in collective immunity and a greater likelihood of the occurrence of some sporadic cases of this deadly disease.

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