STOPA POJAVE NEŽELJENIH DOGAĐAJA NAKON VAKCINACIJE KOD PREDŠKOLSKE DECE U DOMU ZDRAVLJA U INĐIJI

RATE OF THE OCCURRENCE OF ADVERSE EVENTS IN PRESCHOOL CHILDREN AFTER VACCINATION AT THE HEALTH CARE CENTER IN INĐIJA

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ABSTRACT

Introduction: An adverse event following immunization is any undesirable medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. The aim of this study was to determine the rate of occurrence of adverse events in preschool children, after vaccination at the Primary Health Care Center in Indija.

Material and methods: Data were used from the medical and administrative documentation of the Pediatrics Department in Indija. The study covered a period of 11 years and during this period 4,273 children were vaccinated, and 70,558 doses of vaccines were administered.

Results: 13 cases of severe adverse reactions to a vaccine were registered, with a rate of 18.4:100,000 vaccine doses. There were 6 severe adverse reactions to the DTP vaccine per 8,180 administered doses of this vaccine, which was a rate of 73.3:100,000 doses of DTP vaccine. There were 7 cases of severe adverse reactions to the MMR vaccine per 8,505 administered doses of the MMR vaccine, which was a rate of 82.3:100,000 doses of MMR vaccine. The overall rate of adverse reactions in the form of mumps was 47.0:100,000 doses of the MMR vaccine, in the form of rubella rash it was 11.7:100,000 doses of the MMR vaccine and the rate of adverse allergic reactions to the MMR vaccine was 23.5:100,000 doses of the MMR vaccine. According to our results, there were two cases of adverse reactions in the form of allergic reaction, to all vaccines administered, which was the rate of 3:100,000.

Conclusion: This study confirms the very rare occurrence of severe adverse reactions to vaccination and speaks in favor of a far greater benefit from vaccination as compared to the risk of an adverse reaction to vaccination.

Key words: vaccines, adverse reactions after vaccination, allergic reaction

SAŽETAK

Uvod: Neželjeni događaji nakon imunizacije je svaka štetna medicinska pojava koja sledi nakon imunizacije i koja ne mora nužno imati uzročnu vezu sa upotrebo vakcina. Cilj ovog studije je bio da se utvrdi stopa pojavljivanja neželjenih događaja nakon vakcinacije kod dece predškolskog uzrasta u ustanovi primarne zdravstvene zaštite u Indiji.

Materijal i metode: Podaci su korišćeni iz medicinske i administrativne dokumentacije Odeljenja pedijatrije u Domu zdravlja Indija. Istraživanje je obuhvatio period od 11 godina. Tokom navedenog perioda vakcinisano je 4,273 dece i dato 70,558 doza vakcina.

Rezultati: Ovim istraživanjem smo dobili 13 slučajeva težih neželjenih događaja na vakcinaciju što daje stopu od 18.4:100.000 doza vakcine. Neželjene reakcije na DTP vakcinu imalo je 6 slučajeva na 8.180 doza vakcina što iznosi 73.3:100.000 doza DTP vakcine. Neželjenu reakciju na MMR vakcinu imalo je 7 dece na 8.505 datih doza vakcine što daje stopu od 82.3:100.000 doza MMR vakcine. Ukupna stopa postvakcinalnog parotitisa iznosila je 47.0:100.000 datih doza MMR vakcine, postvakcinalne rubele 11.7:100.000 datih doza MMR vakcine i postvakcinalne alergijske reaksije 23.5:100.000 MMR vakcine. Naši rezultati su pokazali dva slučaja neželjene reakcije u vidu alergijskih reakcija, na sve date vakcine, što statistički iznosi 3:100.000 doza vakcina.

Zaključak: Ovo istraživanje potvrđuje veoma retku pojavu težih neželjenih reakcija na vakcinaciju i govori u prilog da su koristi od vakcinacije u odnosu na rizik pojavljivanja neželjene reakcije na vakcinaciju.

Ključne reči: vakcine, neželjene reakcije posle vakcinacije, alergijska reakcija

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UVOD
Smanjenjem morbiditeta i mortaliteta od raznih patogenih vakcina vrše veliki uticaj na javno zdravlje. Redovni i sveobuhvatni programi imunizacije su imali velikog značaja u iskorenjivanju velikih boginja i u eliminaciji dijferencije u većini zemalja sveta. Komplikacije koje se javljaju tokom prirodne infekcije su 1.000 do 10.000 puta češće i praćene su težom kliničkom slikom nego pojava komplikacija nakon vakcinacije protiv iste bolesti [1].

Neželjeni događaji težeg stepena nakon vakcinacije javljaju se veoma retko. Malo je verovatno da će neki neželjeni događaji biti otkriveni u kliničkim ispitivanjima pre izdavanja dozvola za korišćenje vakcina, zbog njihove niske učestalosti, ograničenog broja upisanih ispitanika i drugih ograničenja u studiji. Sta-ga je praćenje neželjenih događaja nakon vakcinacije neophodno. Osnova praćenja bezbednosti vakcina su pregled i analiza spontano prijavljenih neželjenih događaja [2].

Neželjeni događaji nakon imunizacije je svaka štetna medicinska pojava koja sledi nakon imunizacije i koja ne mora nužno imati uzročnu vezu sa upotrebm vakcina [3]. Radna grupa za sigurnost vakcina je svrstala neželjene događaje nakon vakcinacije u 5 grupa: 1) reakcije povezane sa proizvodima vakcine; 2) reakcije povezane s nedostacima u kvalitetu vakcine; 3) reakcije povezane sa greškom imunizacije; 4) reakcije povezane sa anksioznosću; 5) slučajni događaji - uzrokovani nečim drugim osim proizvodom vakcine [3].

Klasifikacija postvakcinalnih reakcija prema vremenu pojavljivanja je takođe izuzetno važna za bolje razumevanje njihove prirode: 1) neposredni tip - javlja se u roku od nekoliko minuta do najkasnije 4 sata nakon davanja vakcine; 2) odgođeni tip - javlja se satima do nekoliko dana kasnije (i do 2 – 3 nedelje) nakon vakcinacije [4].

Lokalne reakcije na mestu davanja vakcine javljaju se kod 25 – 50% vakcinisanih, a blage sistemske reakcije viđaju se kod oko 50% vakcinisanih [5].

Zakonom je predviđeno obavezno prijavljivanje neželjenih reakcija posle imunizacije nadležnom stručnom timu za trajne kontraindikacije u Zavodu za javno zdravlje i Agenciji za lekove i medicinska sredstva, a stručni tim odlučuje o trajnoj kontraindikaciji za datu vakcinu [6].

Cilj ove studije je bio da se utvrdi stopa pojava neželjenih događaja nakon vakcinacije kod dece predškolskog uzrasta u ustanovi primarne zdravstvene zaštite u Indiji.

INTRODUCTION
By decreasing morbidity and mortality from different pathogens, vaccines have a great influence on public health. Regular and comprehensive immunization programs have had great significance in the eradication of smallpox and the elimination of diphtheria in most countries of the world. Complications occurring during natural infection are 1,000 to 10,000 times more frequent and are accompanied by a more severe clinical presentation than the occurrence of complications after vaccination against the same disease [1].

Severe adverse events upon vaccination occur very rarely. Due to their low frequency, the limited number of registered test subjects and other limitations of studies, for certain adverse events, it is highly unlikely that they will be discovered during clinical testing before the issuance of permits for vaccine application. This is why monitoring adverse events after vaccination is necessary. The basis of monitoring the safety of vaccines is the review and analysis of spontaneously reported adverse events [2].

An adverse event following immunization is any undesirable medical occurrence which follows immunization, and which does not necessarily have a causal relationship with the usage of the vaccine. [3]. The Working Group on Vaccine Safety has categorized adverse events after immunization into 5 groups: 1) vaccine product-related reactions; 2) vaccine quality defect-related reactions; 3) immunization error-related reactions; 4) immunization anxiety-related reactions; 5) coincidental events – caused by something other than vaccine components [3].

The classification of postvaccine reactions by the time of occurrence is also of great significance for the understanding of their nature: 1) immediate type – occurs within several minutes to a maximum of 4 hours after vaccine administration; 2) delayed type – occurs a number of hours to several days (up to 2 – 3 weeks) after vaccination [4].

Localized reactions at the vaccine injection site occur in 20 – 50% of vaccinated individuals and mild systemic reactions are registered in around 50% of the vaccinated individuals [5].

The law stipulates mandatory reporting of adverse reactions upon immunization to the relevant expert team for permanent contraindications at the Institute of Public Health and to the Medicines and Medical Devices Agency, while the expert team is the one deciding on permanent contraindications of the given vaccine [6].

The aim of this study was to determine the rate of occurrence of adverse events after vaccination in preschool children immunized at the primary health care center in India.
**MATERIJALI I METODE**

Istraživanje je sprovedeno kao studija preseka, korišćenjem podataka iz medicinske dokumentacije Odeljenja pedijatrije u Domu zdravlja Indija. Na Odeljenju se uredno vodi vakcinalni karton za svakog pacijenta. Analizirani su podaci iz posebnih protokola evidencije o neželjenim efektima vakcinacije, redovan protokol vakcinacije i izveštaji vakcinacije za period od januara 2009. do decembra 2019. godine.

Na odeljenju pedijatrije Doma zdravlja u Indiji sprovodi se aktivna imunizacije lica određenog uzrasta prema Pravilniku o Programu obavezne i prepoređene imunizacije stanovništva protiv određenih zaražnih bolesti, osim kod onih lica kod kojih su utvrđene trajne kontraindikacije. Zarazne bolesti protiv kojih se sprovodi obavezna aktivna imunizacija lica određenog uzrasta su: tuberkuloza, difterija, tetanus, dečja paraliza, veliki kašalj, male boginje, rubela, zauške, hepatitis B, oboljenja izazvana hemofilusom influenzetip B, i oboljenja izazvana streptokokom pneumonije [6].

Ovo istraživanje je uključilo pojavu težih neželjenih reakcija na vakcine, bez uključivanja postvakcinalne povišene temperature, otoka i hiperemije na mestu ubrizgavanja, razdražljivosti i sl., koji spadaju u lakše neželjene reakcije koje su evidentirane našim protokolima. Teže neželjene reakcije na neodređenim dana vakcinacije i nakon revakcine DT, OPV i MMR vakcinom (Tabela 2). Ostale obavezne vakcine nisu dale teže neželjene reakcije koje su evidentirane ovim protokolima.

**MATERIALS AND METHODS**

Research was carried out in the form of a cross-sectional study, through the use of data from the medical documentation of the Pediatrics Department of the Health Care Center in Indija. A record of vaccination is regularly kept at the Department for each patient. Data from special record protocols on adverse effects of vaccination were analyzed, as were the regular vaccination protocol and the vaccination reports for the period January 2009 – December 2019.

Active immunization of persons of a particular age is carried out at the Department of Pediatrics of the Health Care Center in Indija, in keeping with the Rulebook on the Program of mandatory and recommended immunization of the population against certain infectious diseases, with the exception of those persons for whom permanent contraindications have been determined. Infectious diseases against which mandatory active immunization is carried out, in persons of a particular age, are the following: tuberculosis, diptheria, tetanus, polio, whooping cough, measles, rubella, mumps, hepatitis B, diseases caused by *Haemophilus influenzae* bacterium type B, and diseases caused by *Streptococcus pneumoniae* [6].

This research encompassed the occurrence of severe adverse reactions to vaccines, without including postvaccine elevated temperature, swelling and/or hyperemia at the injection site, irritability, etc., which are categorized as mild postvaccine reactions and occur in more than 1 in 10 children receiving the vaccine.

Data were entered and grouped in Microsoft Word tables, while statistical processing was performed in the form of absolute and relative frequencies.

**REZULTATI**

Naše istraživanje je obuhvatio period od januara 2009. do decembra 2019. godine, a tokom navedenog perioda vakcinisano je ukupno 4.273 dece predškolskog uzrasta. Ukonan broj datih doza vakcina je iznosio 70.558. Obuhvat vakcinacije u Opštini Inđija iznosio 70.558. Obuhvat vakcinacije u Opštini Inđija u ovom periodu, svake godine obuhvata je 96%. U Tabeli 1 prikazan je broj dece koja su vakcinisana određenom vakcinom i broj datih doza po određenoj vakcini u istraživanom periodu.

**RESULTS**

Our research covered the period from January 2009 to December 2019, and during that period a total of 4,273 preschool children were vaccinated. The total number of administered vaccine doses was 70,558. The scope of vaccination in the Municipality of Indija fulfills the goals of the national immunization program, i.e., every year during this period the coverage was over 96%. Table 1 shows the number of children vaccinated with particular vaccines and the number of administered doses per type of vaccine in the period covered.

Reported severe adverse reactions to vaccines, recorded in our protocols, were the following: inconstant crying lasting more than three hours, the occurrence of mumps symptoms, the occurrence of rubella, swelling, rash, and other.

Adverse reactions to immunization were reported after the application of the DTP and MMR vaccines and after booster shots of DT, OPV and MMR vaccines.
DISCUSSION

Vaccination represents the most effective method of preventing infectious diseases. The adverse events that may occur after vaccination administration represent a potential risk to a child's health. Routine vaccination must offer significant protection against infectious diseases, and the risk of severe postvaccine adverse reactions must be minimal.

Through this research we identified 13 cases of adverse reactions to vaccination over a period of 11 years, in a sample of 4,273 children, i.e., in 70,558 administered vaccine doses, which in percentages amounts to 0.018%, i.e., 18.4 per 100,000 doses (1:5,555).

According to our research, the greatest number of children with an adverse reaction to vaccination was recorded in 2013, when children aged 2 – 4 months were immunized with the first or second dose of DTP. This is a combined vaccine which consists of the concentrated and purified diphtheria toxoid, the concentrated and purified tetanus toxoid, and dead whole cells of the bacterium Bordetella pertussis, the causative agent of pertussis, adsorbed on a mineral carrier (aluminum phosphate); (Table 2). Severe adverse reactions to other mandatory vaccines were not recorded in these protocols.

TABLE 1. Number of administered vaccine doses

| Vaccine          | Number of children vaccinated with the specified vaccine (n) | Number of vaccine doses received (n) |
|------------------|-------------------------------------------------------------|-------------------------------------|
| BCG              | 4263                                                        | 4263                                |
| Hep B            | 4269                                                        | 12807                               |
| DTP              | 2045                                                        | 8180                                |
| OPV              | 3892                                                        | 12051                               |
| Hib              | 2045                                                        | 8180                                |
| DtaP-IPV-Hib     | 2203                                                        | 8812                                |
| DT               | 3883                                                        | 3883                                |
| IPV              | 12                                                          | 56                                  |
| DT/IPV           | 356                                                         | 356                                 |
| pneumococcus     | 860                                                         | 3440                                |
| MMR              | 4257                                                        | 8505                                |
| influenza        | 21                                                          | 25                                  |
| **TOTAL**        | **70558**                                                   |                                     |

BCG – vaccine against tuberculosis; DTP – vaccine against diphtheria, tetanus and pertussis; OPV – oral polio vaccine; Hib – vaccine against infections caused by the Haemophilus influenzae B bacteria; Hep B – vaccine against hepatitis B; DT – vaccine against diphtheria and tetanus; IPV – inactivated vaccine against pertussis; DT/IPV – vaccine against diphtheria, tetanus and pertussis; IPV – inactivated vaccine against poliomyelitis; MMR – vaccine against measles, rubella and mumps; DtaP-IPV-Hib – combined vaccine against diphtheria, tetanus, acellular pertussis, poliomyelitis and infections caused by the Haemophilus influenzae B bacterium.
Najveći broj dece je imao kliničku sliku poštivakalendarskim godinama u kojima smo sproveli istražive i mumpsa (Tabela 2) približno jednako u svim prvu dozu žive atenuisane vakcine protiv morbila, ružica, rubeli i zauški; kasnije dobijali su revakcine; DT – vakcina protiv difterije i tetanusa (yesterday an acellular vaccine against pertussis is administered). The reported adverse reaction was inconsolable crying lasting for more than three hours (Table 2). There were 6 cases of adverse reactions to the DTP vaccine per 8,180 administered doses of the vaccine, which amounts to 73.3:100,000. The team for determining adverse events after vaccination recommended that each one of these children should continue their immunization by receiving the acellular booster shot of the vaccine against pertussis.

According to the data from literature, severe adverse events after DTP vaccination, such as inconsolable crying lasting more than three hours, occur in 1:100 of immunized children, while elevated body temperature > 40.5°C and febrile convulsions occur in 0.3 – 1% of vaccinated children [5,7].

As of 2015, the pentavalent vaccine containing the acellular component against whooping cough, the inactivated component against polio, the conjugated vaccine against Haemophilus influenzae bacterium type B, and the anatoxic component against diphtheria and tetanus, is within the national program of mandatory immunization. According to the results of our research, this vaccine did not result in severe adverse reactions (Figure 1). Insight into the annual report of the Institute of Public Health of Vojvodina showed an almost twofold decrease in the number of reported adverse reactions to the DTP vaccine during 2016 and 2017 as compared to 2015 [8].

The group with the second highest number of post-vaccine adverse events was the group of children who had been receiving their first dose of the live attenuated.
The rate of adverse events in preschool children after vaccination at the health care center in Inđija is approximately uniformly in all the calendar years for which the research was carried out. The greatest number of children had the clinical presentation of postvaccine parotitis; there was one case of postvaccine rubella; and there was one case of acute allergic reaction within half an hour of vaccine administration. Seven cases of adverse reactions after the administration of 8,505 doses of the MMR vaccine were noted, which was a rate of 82.3 per 100,000 doses of the vaccine. The total rate of postvaccine parotitis in our study was 47.0:100,000 doses of the vaccine; the total rate of postvaccine rubella was 11.7:100,000 doses of the vaccine; and the total rate of postvaccine mild allergic reaction was 23.5:100,000 doses of the vaccine, in the application of the trivalent MMR vaccine (one allergic reaction occurred in the application of the RV MMR, OPV and DT vaccines).

A study carried out in the Zhejiang Chinese province showed that the total rate of adverse events upon MMR vaccine administration was 34.3 per 100,000 doses, and the rate of severe adverse reactions was 5.6 per 100,000 doses [9].

National active monitoring in the United Kingdom determined a rate of 12 cases per 100,000 doses noted after the administration of a single-component vaccine against morbilli amongst children under 16 years old [10].

In their study, Patja et al. discovered three cases of severe adverse postvaccine reactions occurring after MMR vaccine administration, which was equal to an incidence of 0.1 – 0.5 per 100,000 vaccine doses for all of the three viral components together [11].
izveštaji Svetске alergološке organizacije daju podatak o procenjenoj stopi alergijskih reakcija od 1:50.000 do 1:1.000.000 i anafilaksije od 1:100.000 do 1:1.000.000 datih doza vakcine [12]. Anafilaksija nakon imunizacije je veoma retka i noviji izveštaji Su a saradnika daju podatak stope od 1,3 slučaja na 1 milion primljenih doza u SAD-u [13].

U našem istraživanju nismo uočili polnu predominaciju za pojavu neželjenih reakcija na vakcinu (Tabela 2). U analizama Mek Nila i saradnika uočena je prevaga muškog pola kod mlađih od 19 godina i ženskog pola kod starih od 19 godina [14].

ZAKLJUČAK

Neželjene reakcije nakon vakcinacije, uključujući i alergijske reakcije, veoma su retke. Obzirom da postoje postvakcinalne reakcije široke kliničke prezentacije veoma je važno izdiferencirati prave teške postvakcinalne reakcije. Kod pojave neželjenih reakcija, uključujući i alergijske reakcije na vakcinu, potrebna je klinička i alergološka obrada kako se ne bi odlagala ili prekunula redovna vakcinacija. Ovo istraživanje, kao i mnoga druga istraživanja na ovu temu, potvrđuje veoma retku ratu pojave neželjenih reakcija na vakcinaciju. Rizici od neželjenih reakcija od imunizacije su daleko manji u odnosu na koristi dobijene što obuhvatnijom vakcinacijom, kako pojedinca tako i celog kolektiva.

SKRAĆENICE

BCG – vakcina protiv tuberkuloze
DTP – vakcina protiv difterije, tetanusa i pertusisa
OPV – oralna polio vakcina
Hib – vakcina protiv infekcija izazvanih hemofilusom influence B
Hep B – vakcina protiv hepatitisa B
RV – revakcina
DT – vakcina protiv difterije i tetanusa
IPV – inaktivisana vakcina protiv poliomijelitisa
DT/IPV – vakcina protiv difterije, tetanusa i poliomijelitisa, inaktivisana
MMR – vakcina protiv malih boginja, rubele i zauški
DtaP-IPV-Hib – kombinovana vakcina protiv diferije, tetanusa, acelularnog pertusisa, poliomijelitisa i infekcija izazvanih hemofilusom influence B

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Rate of the occurrence of adverse events in preschool children after vaccination at the Health Care Center in INĐIJA

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