KRETANJE INCIDENCIJE ZAUŠAKA I OBUHVATA PRVOM DOZOM MMR VAKCINE U CRNOJ GORI U PERIODU 2009-2018. GODINE

TRENDS IN MUMPS INCIDENCE AND FIRST DOSAGE OF MMR VACCINE COVERAGE IN MONTENEGRO FROM 2009 TO 2018

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SAŽETAK

Uvod/Cilj: U mnogim evropskim zemljama koje su uvele dve doze MMR vakcine došlo je do posledičnog smanjenja incidencije zaušaka za 97-99%. Ipak, uprkos padu incidencije u svim delovima sveta, dolazi do epidemijskog javljanja zaušaka. Cilj ove deskriptivne studije je bio da se analizira kretanje obolevanja od zaušaka i obuhvata prvom dozom MMR vakcine u Crnoj Gori u periodu 2009-2018. godine.

Metode: Za analizu kretanja obolevanja od zaušaka na teritoriji Crne Gore, u periodu od 2009. do 2018. godine, korišćeni su podaci o broju novoobolelih, preuzeti iz godišnjih izveštaja Instituta za javno zdravlje Crne Gore o kretanju zaraznih bolesti, a za procenu obuhvata prvom dozom MMR vakcine podaci su preuzeti iz godišnjih izveštaja o sprovedenoj imunizaciji u Crnoj Gori i iz elektronskog registra imunizacija.

Rezultati: U Crnoj Gori je, u periodu od 2009. do 2018. godine, ukupno registrovano 256 slučajeva obolevanja od zaušaka, od tog broja 63% činili su muškarci, a smrtnih ishoda nije bilo. Standardizovana stopa incidencije zaušaka (standardizovana prema populaciji sveta) bila je veća za muškarce nego žene i kretala se kod muškaraca od 0 (2018. godine) do 12,4 na 100.000 muškaraca (2012. godine), a kod žena od 0,2 (period 2015-2018. godine) do 7,6 na 100.000 žena (2012. godine). Kod oba pola, i u opštoj populaciji, najniže prosečne vrednosti uzrasno-specifičnih stopa incidencije beležene su u uzrastima do 4 godine starosti i kod starijih od 30 godina. Najveći broj obolelih registrovan je u aprilu i julu mesecu. Najmanji obuhvat prvom dozom MMR vakcine od svega 42,1% zabeležen je 2018. godine.

Zaključak: Neophodno je povećati i održavati nivo obuhvata MMR vakcinom među svim osobama koje treba da dobiju vakcinu. Takođe, neophodno je proširiti zdravstveno-vaspitni rad među opštom populacijom, a naročito među roditeljima, da bi se unapredilo znanje o značaju vakcinacije i opasnosti koju sa sobom nose vakcinama preventabilne bolesti, kako bi se povratio visok stepen poverenja koji je antivakcinalnim lobijem narušen.

Ključne reči: incidencija, zauške, obuhvat, MMR vakcina

SUMMARY

Introduction/Objective: Introducing 2-dose schedules of MMR vaccination in many European countries has reduced the incidence of mumps by 97-99%. However, despite the decline of incidence in all parts of the world, outbreaks of mumps are occurring. The objective of this descriptive study was to analyze the occurrence of mumps and coverage of the first dose of MMR vaccine in Montenegro during the period from 2009 to 2018.

Methods: Data on the number of new patients, taken from the annual reports of the Institute of Public Health of Montenegro on the movement of infectious diseases, were used to analyze the incidence of mumps in the territory of Montenegro from 2009 to 2018, and to estimate the coverage of the first dose of MMR vaccine data were taken from annual immunization reports in Montenegro and from the electronic immunization registry.

Results: In Montenegro, between 2009 and 2018, a total of 256 cases of mumps were registered, of which 63% were males and there were no fatalities. The standardized incidence rate of mumps (standardized by world population) was higher for men than women, and ranged from 0 (2018) to 12.4 per 100,000 men (2012) and from 0.2 (2015-2018) to 7.6 per 100,000 women (2012). In both sexes and in the general population, the lowest average values of age-specific incidence rates were observed in the ages up to 4 years of age and in the over 30s. The largest number of cases of mumps was registered in April and July. The lowest coverage with the first dose of MMR vaccine of only 42.1% was recorded in 2018.

Conclusion: It is necessary to increase and maintain the the level of MMR vaccine coverage among all persons who have to be vaccinated. It is also necessary to expand educational work on health-care among the general population, especially among parents, in order to advance the knowledge about the importance of vaccination and the potential dangers that vaccine-preventable diseases carry with them, in order to restore the high level of trust that the anti-vaccine lobby has eroded.

Keywords: incidence, mumps, coverage, MMR vaccine

Introduction

Mumps (*Parotitis epidemica*) is a viral infectious disease that, by its main entry route, belongs to the group of respiratory infectious diseases and, despite being a vaccine-preventable disease for decades, it is still epidemiologically significant. The causative agent of mumps is Mumps virus, which belongs to the family *Paramyxoviridae*, the genus of *Rubulavirus* (1), and it is sensitive in the environment and rapidly inactivated by high temperature, UV radiation, and disinfectants (2-5). Humans are the only known natural hosts of this virus. Mumps is generally a mild disease, with the pathological process primarily localized in the salivary glands. The disease most commonly occurs in children in the atypical, mild form (most of the infections in children under 2 years of age are subclinical), while in adults there may be more severe atypical clinical features present, with possible complications (meningitis, orchitis, etc.) (1,2,5).

Orchitis occurs as the most common and the most significant complication of mumps, with about 20-30% postpubertal males who develop mumps, and in 20% of cases with orchitis, both testicles are affected. Although orchitis is rarely associated with a permanent decrease in the fertility of males, it is recognized as a risk factor for testicular cancer. The next most common complication of mumps is symptomatic aseptic meningitis, which occurs in about 10% of people who develop mumps and usually goes away without consequences. On the other hand, symptomatic oophoritis and mastitis are relatively rare and do not have long-lasting consequences. Mumps infection during the first 12 weeks of gestation is associated with 25% of miscarriages, but its association with congenital malformations has not been proved (2,5). Pancreatitis has been reported as a complication in about 4% of cases, while the association between pancreatitis and diabetes mellitus with this infection has not been explained (3,5).

Before the mumps vaccine became commercially available in the 1960s, mumps was one of the most common communicable diseases in the world, with an incidence rate from 100 to 1,000 per 100,000 population. Until

December 2018, 122 of the 193 (63%) member states of the World Health Organization (WHO) had included the mumps vaccine in their National Immunization Program (the vast majority using the combined MMR vaccine) (2,6). In countries where immunization against mumps is carried out with high vaccine coverage, the incidence of the disease has dropped dramatically (in Montenegro, the mumps vaccine was introduced in the mandatory immunization calendar in 1986). In many European countries introducing 2-dose schedules of MMR vaccine led to the incidence reduction by about 97-99%, and in countries with a single dose calendar the incidence has been reduced by 88-98%. Still, despite this decline in incidence in Europe, but also in other parts of the world, epidemics of mumps are still occurring. However, unlike the pre-vaccination period, in epidemics of mumps adolescents and adults are the most affected groups. It is believed that some of the possible causes of recurrence of epidemics could be: insufficient collective immunity, improper storage of vaccines, failure during the primary or secondary immunization and subsequent inadequate immune response, or loss of vaccine immunity, or reinfection with heterologous strains of Mumps virus (3-6).

An addition to all this is the fact that, in recent years, many countries in the WHO European Region, due to the activity of anti-vaccine movements and the dissemination of false information about the association of the MMR vaccine with autism, have faced with a decline in level of trust in immunization programs and a consequent reduction of the MMR vaccine coverage (6-8). Thus, from 2012 to 2016, there were 11,632 (2014) to 20,936 (2013) reported cases of mumps per year in European Union countries. About 80% of reported cases in the indicated period were from the Czech Republic, Poland, Spain and the United Kingdom. More than half of the mumps cases were vaccinated with 2 doses of the vaccine, and the majority of patients were between 10 and 19 years of age (7,8). In the neighboring countries, certain episodes of mumps epidemics of different proportions were reported, so that in 2011, 8,209 mumps cases were registered in Bosnia and Herzegovina and 7,881 in 2012. In 2012, a total of 584 people with mumps were registered in the Republic of Serbia (9).

The objective of this descriptive study was to analyze the occurrence of mumps and coverage by the first dose of the MMR vaccine in Montenegro during the period from 2009 to 2018.

Methods

In this descriptive study, for the analysis of mumps occurrence in Montenegro from 2009 to 2018 data on the number of reported cases of mumps were taken from Annual reports on occurrence of communicable diseases published by the Institute for Public Health of Montenegro (10), and data about the coverage with the first dose of MMR vaccine were taken from the official Annual reports on immunization in Montenegro (11). Also, additional immunization coverage data were obtained from an electronic immunization registry that allows monitoring of immunization coverage in "real-time" for the entire country, by selecting the desired generation cohort (data from registry for this study were taken on November 13, 2019).

For each year, the incidence rate was calculated by using the number of new cases of mumps for a year as a numerator and population in the middle of the year by the Census of the population, households and apartments in Montenegro as the denominator (Census from 2003 is used for the period 2009-2010 and Census from 2011 for the period 2011-2018).

Age-specific rates were calculated for the following age groups: 0-4, 5-9, 10-14, 15-19, 20-29, 30-39, 40-49, 50-59 and over 60 years of age.

Vaccination coverage is calculated as the percentage of vaccinated children of the number planned to be vaccinated in a calendar year (children who turn one year of age in a calendar year). Vaccination coverage in "real time" was calculated as the percentage of vaccinated persons from a particular generation cohort (on the day when data from the electronic registry immunization were obtained) of the total number of members of that generation.

The analysis of the data collected by the study included descriptive statistics methods. Thus, proportions (ratio of part to whole) were used to calculate the first dose of MMR vaccine coverage, and to calculate the average

values of incidence and the number of diseased, arithmetic means were used with a range from minimal to maximal values. General and age-specific incidence rates were calculated as measures of occurrence of disease. General incidence rates have been standardized by the direct standardization method to allow comparability of results with other reports and studies, using the world population (12,13) as the standard population.

For statistical calculations and charts, Microsoft Excel 2016 and EpiInfo 7.2.3.1 were used.

Results

In Montenegro, between 2009 and 2018, a total of 256 cases of mumps were registered, 63% of which were males (Table 1). In that period there were no fatalities.

In the observed period, crude incidence rates of mumps ranged up to 2 cases per 100,000 persons a year, in males, females and in total, except in the period 2011-2013, when 9.2 (2011), 16.8 (2012) and 7.8 (2013) new cases per 100,000 population were recorded.

The incidence of mumps was higher in males than in females, especially in the years when the highest numbers of new mumps cases were observed – 13.7 diseased males versus 4.8 diseased females per 100,000 (2011) and 21.2 diseased males versus 12.4 diseased females per 100,000 (2012).

The overall standardized incidence rates (by the world population) of mumps ranged from 0.2 (2018) to 20.1 per 100,000 population (2012), in males from 0 (2018) to 12.4 per 100,000 males (2012) and in females from 0.2 (2015-2018) to 7.6 per 100,000 females (2012) (Figure 1).

Average values of age-specific incidence rates of mumps among the total population were highest at the ages 5-9 years (9.6 per 100,000) and 15-19 years (8.8 cases per 100,000), but with wide ranges between the minimal and maximal values (0-41.6 and 0-34.0) (Table 2). Among males, the average age-specific incidence rates were highest at ages 15-19 (11.8 per 100,000) and 5-9 years (10.5 per 100,000), and among females at ages 5-9 (8.7 per 100,000) and 10-14 years (7 per 100,000).

Table 1 Number of new cases of mumps and crude incidence rates (per 100,000) in Montenegro, from 2009 to 2018

Year	Males		Females		Total	
	New cases	Incidence* (per 100,000)	New cases	Incidence* (per 100,000)	New cases	Incidence* (per 100,000)
2009	5	1.6	4	1.3	9	1.3
2010	8	2.6	5	1.6	13	2
2011	42	13.7	15	4.8	57	9.2
2012	65	21.2	39	12.4	104	16.8
2013	24	7.8	24	7.6	48	7.8
2014	4	1.3	4	1.3	8	1.3
2015	5	1.6	1	0.3	6	1
2016	4	1.3	1	0.3	5	0.8
2017	4	1.3	1	0.3	5	0.8
2018	0	0	1	0.3	1	0.2
Average	16	5.2	10	3	26	4.1

* Crude incidence rate

In both sexes and in the general population, the lowest average values of incidence rates were observed in the ages up to 4 years of age and in the over 30s.

Most cases of mumps were registered in April and July, especially in July 2011 (30 cases) and April 2012 (27 cases) (Figure 2). In May and June 2012, more than 10 cases per month were registered, while in all other months, regardless of the year, up to 10 cases of mumps were registered.

Data from the official annual immunization reports indicate a fall in vaccination coverage for the first dose of MMR vaccine (MMR 1st dose vaccine) (Figure 3). As of 2014, coverage values

were less than 80%, with the lowest MMR 1st dose vaccine coverage of 42.1% recorded in 2018.

The drop in vaccination coverage for the first dose of MMR vaccine is also evident from the real-time coverage monitoring data for individual cohorts. The lowest real-time MMR 1st dose vaccine coverage of 51.9% was also recorded for the 2018 generation cohort.

The highest incidence rates of mumps were registered from 2011 to 2013, while a progressive decline in vaccination coverage for the first dose of MMR vaccine below the satisfactory level (<80%) has been recorded since 2014, with the lowest values in 2018 (42.1%) (Figure 4).

Table 2 Average values of age-specific incidence rates (per 100,000) of mumps in Montenegro, from 2009 to 2018

Age groups	Average value of incidence rate* per 100,000 (minimum-maximum values)		
	Males	Females	Total
0-4	1.1 (0-3.9)	0.8 (0-2.7)	0.9 (0-3.3)
5-9	10.5 (0-40)	8.7 (0-43.4)	9.6 (0-41.6)
10-14	7.9 (0-37.4)	7.0 (0-20)	7.5 (0-29)
15-19	11.8 (0-43.8)	5.6 (0-23.5)	8.8 (0-34)
20-29	9.3 (0-39.7)	5.8 (0-23.1)	7.6 (0-31.6)
30-39	4.4 (0-23.4)	1.1 (0-6.9)	2.8 (0-12.7)
40-49	1.2 (0-4.8)	1.2 (0-7.1)	1.2 (0-4.8)
50-59	1.9 (0-11.8)	0.5 (0-2.4)	1.2 (0-7.1)
60+	0	0.2 (0-1.6)	0.1 (0-0.9)

* Age specific incidence rate

Figure 1 Standardized* incidence rates (per 100,000) of mumps in Montenegro, from 2009 to 2018

* World standard population WHO 2000-2025 used as the standard population.

Figure 2 Distribution of new cases of mumps by months in Montenegro, from 2009 to 2018

Figure 3 Vaccination coverage for the first dose of MMR vaccine in Montenegro from 2009 to 2018

Discussion

The results of our study show that epidemic parotitis in Montenegro occurred mostly sporadically from 2009 to 2018, and epidemically from 2011 to 2013.

In the same period, the situation in the neighboring countries was diverse, so in the Federation of Bosnia and Herzegovina, the crude incidence rate (per 100,000) of mumps was highest in 2011 (252.9) and 2012 (242.8). The highest overall standardized incidence

rate in Serbia (by population of Europe) was recorded during 2012 and it was 7.9 per 100,000 inhabitants, while in Italy and Croatia, only sporadic occurrence of mumps was recorded in the period covered by this study (total standardized incidence rate according to the population of Europe, was less than 2 per 100,000). Because of the geographical proximity of Montenegro to these two countries (Federation of Bosnia and Herzegovina and Serbia), which also recorded epidemic occurrence of mumps, and due to the fact that

Figure 4. Comparative view of crude incidence (per 100,000) of mumps and vaccination coverage (%) for the first dose of MMR vaccine in Montenegro, from 2009 to 2018

there is intensive daily population movement among these countries, it can be said with great certainty that these epidemics are related, but adequate epidemiological research should be conducted to confirm this (8,14-16).

If we look at the region of Europe, mumps epidemics were recorded in the Czech Republic, Poland, Spain, Slovakia and the UK with the highest total standardized incidence rates, by population of Europe, for the period covered by our study, registered in the Czech Republic in 2016 (62.1 per 100,000), and then in Slovakia in 2015 (33.7 per 100,000) (8).

In many European countries, a decline in the coverage for the first dose of MMR vaccine has led to an increased fear of epidemic occurrence of all diseases covered by this vaccine (3,5).

It is interesting to follow the vaccination coverage for the first dose of MMR vaccine in countries where outbreaks of mumps occurred in the aforementioned period. Thus, in the Federation of Bosnia and Herzegovina, vaccination coverage was at a satisfactory level until 2016 (> 80%, but has since been less than 70%). In Montenegro, the first drop in vaccination coverage below the desirable values was recorded in 2014 and has been constantly declining since that year (even less than 50% in recent years). In both the Federation of Bosnia and Herzegovina and Montenegro, the fall in vaccination coverage occurred only after the years in which the largest number of patients was registered (9,16).

In all the other years covered by the study, as well as in the several years preceding this period (important period for monitoring, since the first dose is predominantly received after children turn one year of life, and mumps most commonly occurred in the age group of 5-9 years), vaccination coverage for the first dose of MMR vaccine in countries where outbreaks of epidemic parotitis were reported was above satisfactory levels at all times (8,9). An identical situation with vaccine coverage was observed in Montenegro as well.

The results of our study, as well as the reports on mumps outbreaks from other countries in Europe, indicate that there has been a partial shift to the right when it comes to the age at which the disease is predominant so that in the aforementioned period mumps occurred

most commonly in people aged 5-29 years (children, adolescents, young adults) (8,14-16).

This study did not indicate a higher incidence of mumps in any period of the year, a similar loss in the seasonal pattern of Mumps virus infections was observed in other European countries where mumps outbreaks were reported in the period covered by this study (8,14-16).

The somewhat higher incidence of the disease reported in males is more likely because of the fact that, due to the possible relatively frequent complications, epidemic parotitis is easier to recognize in males and that its incidence in females is underestimated. The same situation was observed in the pre-vaccine, and during the vaccine era, the number of reported cases of mumps infection in males was almost always higher than the number of reported cases in females (17).

The broad interquartile ranges of the MMR vaccine effectiveness in the prevention of epidemic parotitis (the interquartile range of effectiveness for 2 doses is 31-95% and for 1 dose 49-92%) make this component of the MMR vaccine the least protective, even at times of satisfactory coverage (> 80%). Because of the above, epidemic occurs of mumps is a reality, especially in environments suitable for the spread of epidemics (schools, colleges, garrisons) (2,3,5).

There are some studies that indicate that in many mumps outbreaks in Europe, during the period covered by this study, a large number of cases was diagnosed among those vaccinated with 2 doses of MMR vaccine (up to 90%). Also, the risk was significantly higher for those who received the last dose of MMR vaccine 5 or more years ago. This has actualized the issue of the MMR vaccine effectiveness in protecting against mumps and considering changing the vaccine calendar (18-24).

Some studies have suggested the possibility (and some have proven) that there is a difference between the genotype of the circulating Mumps virus and that in MMR vaccines, and a potential cold chain disruption was previously recognized as a potential cause for the lack of protective effect of the MMR vaccine and which is essential for this vaccine to be maintained (stored at +2 to +8° C, in a dark

place for up to one hour before administration). It should be noted that genotyping of the circulating Mumps virus is not done routinely, and cold chain surveillance is an obligation of the services that are in charge of implementing national immunization programs (18-24).

Our study had several limitations. Firstly, we did not estimate the second dose of vaccine effectiveness since we did not have data available for that. Secondly, there might have been under-ascertainment of reported cases as several cases may have not visited a clinician.

Conclusion

In order to maintain a stable epidemiological situation and avoid mumps outbreaks, it is necessary to increase and maintain the immunization coverage among all persons who have to be vaccinated to a minimum of 80%. This means the implementation of all measures and activities, including continuous revision of vaccination records, inviting non-vaccinated persons to be vaccinated, conducting organized emergency immunization activities in areas where it is otherwise impossible to provide a high percentage of coverage ("Catch-up" vaccination of generation cohorts with lower vaccination coverage). It is also necessary to expand health-care work among the general population, especially among parents, then to improve knowledge of the importance of vaccination and the potential dangers that vaccine-preventable diseases are carrying with them, all in order to restore the high level of trust in immunization that has been present for years.

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