Measles Vaccination and Outbreaks in Croatia from 2001 to 2019; A Comparative Study to Other European Countries

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Abstract: Due to the current burden of COVID-19 on public health institutions, increased migration and seasonal touristic traveling, there is an increased risk of epidemic outbreaks of measles, mumps and rubella (MMR). The aim of the present study was to analyze the epidemiological data on MMR immunization coverage and the number of measles cases in 2001–2019 in Croatia and a number of European countries. Results revealed a decreasing trend in vaccination in 2001–2019 throughout Europe. However, Croatia and Hungary still have the highest primary and revaccination coverage, compared to other analyzed countries. The highest number of measles cases was in 2017 in Romania. There was no significant correlation between the percentage of primary vaccination and the number of measles cases (r = −0.0528, p = 0.672), but there was a significant negative correlation between the percentage of revaccination and the number of measles cases (r = −0.445, p < 0.0001). In conclusion, the results of the present study emphasize the necessity to perform a full protocol of vaccination to reach appropriate protection from potential epidemic outbreaks. Furthermore, in the light of present migrations, documenting the migrants’ flow and facilitating vaccination as needed is of utmost importance to prevent future epidemics.

Keywords: measles-rubella-mumps vaccination; Europe; Croatia

1. Introduction

Throughout the world, vaccination with safe, effective, and affordable vaccines for measles, mumps and rubella (MMR) is freely available. The measles vaccination was introduced into the compulsory vaccination program in the Republic of Croatia in 1969. The first vaccination effort vaccinated all children one to six years old. Vaccination against rubella (1975) and mumps (1976) soon followed [1]. MMR vaccination began in 1976. Since the beginning of vaccination against MMR, a vaccine of domestic production (Immunology Institute) has been used. The measles vaccine strain, Edmonston–Zagreb, as well as the rubella vaccine strain, RA 27/3, were produced on human diploid cell culture, while the mumps virus vaccine strain was produced on chicken fibroblast cell culture [2,3]. The use of vaccines against these diseases has led to their almost complete eradication in Croatia, with sporadic cases. The Croatian law prescribes the required minimum coverage for measles vaccination of 95%. In Croatia, outbreaks of measles occurred in 2015 and 2018. In 2018, an outbreak in the southern-Adriatic part of the country was a consequence of the infection of an adult returning from Kosovo, with 15 epidemiologically-linked cases [4]. The median age of infected persons was 33 years, while one case was an 8-month-old infant. Two of these cases had received two doses of a measles-containing vaccine, one
person had taken one dose and three were unvaccinated, while for nine cases, vaccination status was unknown [4]. In regard to neighboring countries, in 2017, there was a small outbreak of measles in Hungary, in close proximity of Osijek-Baranja County, which was not spread wider over the state border due to good epidemiological measures [5]. Measles outbreaks in 2018–2019 in the Croatian cities of Zagreb, Slavonski Brod, Split and Dubrovnik demonstrated possibly suboptimal vaccination coverage in certain cluster(s) of the population [5]. Despite the proximity of Slavonski Brod (tens of kilometers) and frequent commutation between counties, Osijek-Baranja County was not affected.

In the light of flaming waves of the COVID-19 pandemic, other contagious diseases somehow were put aside, partly due to successful vaccination programs, particularly in European countries. In the period between the end of 2019 and the spring of 2022, the COVID-19 pandemic significantly influenced interpersonal contacts, which also have different impacts on measles, mumps and rubella vaccination efforts and burden across the world. For example, Brazil reported a reduction in the number of MMR vaccine doses [6], while interestingly, Japan reported de-creased estimated annual burdens in 2020 for measles (98%), mumps (47%) and rubella (94%) compared with those in 2019 due to social distances in COVID-19 pandemic [7]. However, due to the current burden of COVID-19 on public health institutions, one may expect a decrease in vaccination coverage and potential new outbreaks in near future. We hypothesized that there is a relationship between vaccination coverage and the number of measles cases. The present study aimed to analyze the epidemiological data on population immunization and reflect the number of measles cases in the 2001–2019 period for Croatia and countries of the European region.

2. Materials and Methods

Data collection was performed using European Centre for Disease Prevention and Control (ECDC) reports [8–10] and World Health Organization (WHO) statistics from 2001 to 2019 [11]. For Croatia, data from National Institute of Public Health and Ministry of Health was used (Croatian Health Service Yearbook for years 2001 to 2019 [12–30]).

Statistical analysis: Differences in percentage of vaccination (% vaccination) in observed period among regions/countries were analyzed using Two-way ANOVA, with appropriate post hoc test for multiple comparisons (Sidak’s or Tukey’s multiple comparisons test). Correlation between number of cases per year and vaccination coverage was assessed using Spearman’s correlation. \( p < 0.05 \) was considered statistically significant. GraphPad v6.0 (GraphPad Software, San Diego, CA, USA) and SigmaPlot, version 11.2 (Systat Software, Inc., Chicago, IL, USA) were used for statistical analysis.

3. Results

3.1. MMR Primary Vaccination and Revaccination in Croatia and Osijek-Baranja County 2001–2019

Table 1 presents data on the primary MMR vaccination in Croatia and particularly, Osijek-Baranja County (OBC). There was no significant difference in the percentage of primary vaccination between Croatia and OBC each year from 2001 to 2018. However, there was a significantly higher percentage of primary vaccination in Croatia compared to OBC only in 2019 (\( p < 0.05 \)).
Table 1. Measles-containing vaccine primary vaccination in Osijek-Baranja County and Croatia from 2001 to 2019.

| Year | Osijek-Baranja County | | Croatia | | |
| --- | --- | --- | --- | --- |
| | Primary Vaccination | % | Primary Vaccination | % |
| 2001 | 3312 | 94.7 | 44,989 | 93.6 |
| 2002 | 3217 | 93.3 | 44,467 | 94.7 |
| 2003 | 3019 | 94.7 | 41,388 | 94.5 |
| 2004 | 2914 | 94.5 | 40,985 | 95.7 |
| 2005 | 2849 | 93.8 | 39,783 | 94.8 |
| 2006 | 3128 | 95.4 | 41,721 | 95.4 |
| 2007 | 3032 | 95.3 | 41,437 | 96.1 |
| 2008 | 2964 | 95.3 | 41,714 | 95.5 |
| 2009 | 3030 | 95.3 | 40,484 | 95.0 |
| 2010 | 3188 | 95.3 | 40,484 | 96.0 |
| 2011 | 2992 | 95.3 | 40,492 | 96.0 |
| 2012 | 2902 | 95.3 | 41,606 | 94.8 |
| 2013 | 2928 | 95.3 | 40,885 | 93.8 |
| 2014 | 2783 | 95.3 | 39,862 | 93.7 |
| 2015 | 2300 | 95.3 | 39,446 | 92.8 |
| 2016 | 2547 | 95.3 | 39,476 | 92.8 |
| 2017 | 2520 | 95.3 | 39,430 | 92.8 |
| 2018 | 2579 | 95.3 | 39,970 | 93.2 |
| 2019 | 2259 | 95.3 | 35,491 | 93.0 |

Source for data: Croatian Health Service Yearbooks 2001–2019 [12–30].

Table 2 presents the data on revaccination in Croatia and OBC. In Croatia, the percentage of revaccination compared to primary vaccination significantly increased in 2016 and 2017, with no significant change in other years between 2001 and 2019 (2016, \( p < 0.05 \); in 2017, \( p < 0.05 \)). In OBC, the percentage of revaccination compared to primary vaccination significantly increased in 2009, 2010, 2016, 2017 and 2019 (\( p < 0.05 \)), with no significant change in other years between 2001 and 2019.

Table 2. Measles–rubella–mumps revaccination in Osijek-Baranja County and Croatia in years 2001 to 2019.

| Year | Osijek-Baranja County | | Croatia | | |
| --- | --- | --- | --- | --- |
| | 1. Revaccination | % | 1. Revaccination | % |
| 2001 | 7971 | 99.1 | 101,917 | 99.395 | 97.5 |
| 2002 | 7550 | 99.1 | 99,395 | 97.9 |
| 2003 | 7353 | 99.4 | 92,221 | 90.555 | 98.2 |
| 2004 | 7429 | 99.2 | 86,686 | 84.837 | 97.9 |
| 2005 | 3375 | 98.8 | 46,153 | 45.157 | 97.8 |
| 2006 | 3480 | 98.8 | 46,153 | 45.157 | 97.8 |
| 2007 | 2993 | 98.3 | 42,884 | 42.086 | 98.1 |
| 2008 | 3085 | 99.3 | 40,733 | 39.871 | 97.9 |
| 2009 | 2796 | 99.2 | 39,599 | 39.821 | 98.0 |
| 2010 | 2785 | 99.1 | 39,417 | 38.547 | 97.8 |
| 2011 | 2853 | 98.2 | 40,410 | 39.540 | 97.8 |
| 2012 | 3009 | 95.5 | 41,714 | 40.441 | 96.9 |
| 2013 | 2841 | 98.1 | 41,280 | 40.098 | 97.1 |
| 2014 | 2770 | 97.8 | 41,454 | 40.125 | 96.8 |
| 2015 | 2767 | 96.2 | 41,434 | 39.699 | 95.8 |
| 2016 | 4111 | 96.4 | 43,397 | 41.647 | 96.0 |
| 2017 | 2364 | 94.0 | 39,630 | 37.703 | 95.1 |
| 2018 | 2556 | 95.5 | 38,367 | 36.328 | 94.7 |
| 2019 | 2046 | 93.9 | 36,674 | 34.745 | 94.7 |

Source for data: Croatian Health Service Yearbooks 2001–2019 [12–30].
3.2. MMR Primary Vaccination and Revaccination in Croatia and Neighboring Countries in Years 2001–2019

Table 3 presents differences in MMR primary vaccination among Croatia and neighboring countries. There was no significant difference in the percentage of primary vaccination between Croatia and neighboring countries from 2001 until 2015. Afterward, Croatia, Slovenia and Serbia generally had the best primary vaccination success, while Bosnia and Herzegovina (BiH) and North Macedonia had the lowest; e.g., in 2016, the percentage of primary vaccination in BiH was significantly lower compared to Croatia (2016, \( p < 0.05 \)) and Slovenia (2016, \( p < 0.05 \)), while in 2017 and 2018, the percentage of primary vaccination in BiH was significantly lower compared to Croatia (\( p < 0.05 \)), Slovenia (\( p < 0.05 \)), and Serbia (\( p < 0.05 \)). Additionally, in 2018, North Macedonia had significantly lower percentage (75%) of primary vaccination compared to Croatia (2018, \( p < 0.05 \)), Serbia (2018, \( p < 0.05 \)), and Slovenia (2018, \( p < 0.05 \)). Montenegro and the years 2013 and 2019 had to be excluded from the analysis due to missing data.

Table 3. Measles-containing vaccine first dose (%) in Croatia and neighboring countries in the years 2001 to 2019.

| Year | BA | HR | MK | ME | RS | SI |
|------|----|----|----|----|----|----|
| 2001 | 92 | 94 | 92 | *  | 91 | 94 |
| 2002 | 89 | 95 | 98 | *  | 92 | 93 |
| 2003 | 84 | 95 | 96 | *  | 87 | 94 |
| 2004 | 88 | 96 | 96 | *  | 89 | 94 |
| 2005 | 90 | 96 | 96 | *  | 96 | 94 |
| 2006 | 90 | 95 | 94 | 90 | 88 | 96 |
| 2007 | 96 | 96 | 96 | 90 | 95 | 96 |
| 2008 | 84 | 96 | 98 | 89 | 92 | 96 |
| 2009 | 93 | 95 | 96 | 86 | 95 | 95 |
| 2010 | 92 | 96 | 98 | 90 | 95 | 95 |
| 2011 | 89 | 96 | 97 | 91 | 93 | 96 |
| 2012 | 94 | 95 | 96 | 90 | 87 | 95 |
| 2013 | *  | 94 | 96 | 88 | 92 | 94 |
| 2014 | 89 | 94 | 93 | 76 | 86 | 94 |
| 2015 | 83 | 93 | 89 | 64 | 87 | 94 |
| 2016 | 68 | 90 | 82 | 47 | 82 | 92 |
| 2017 | 69 | 89 | 83 | 58 | 86 | 93 |
| 2018 | 68 | 93 | 75 | 42 | 93 | 93 |
| 2019 | *  | 93 | *  | *  | 87 | 94 |

* data not available; BA—Bosnia and Herzegovina; HR—Croatia; ME—Montenegro; MK—North Macedonia; RS—Serbia; SI—Slovenia. Source for data: World Health Organization (WHO) statistics from 2001 to 2019 [11].

Table 4 presents the data on MMR revaccination among Croatia and neighboring countries. In 2001 and 2002, there was a significantly lower percentage of revaccination in Serbia compared to Croatia (\( p < 0.05 \)). There was no significant difference in the percentage of revaccination among Croatia and neighboring countries in 2003–2005 and 2007–2017. In 2006, the percentage of revaccination in BiH was significantly lower compared to Croatia (\( p < 0.05 \)). There was no significant difference in the percentage of revaccination among Croatia and neighboring countries in 2003–2005 and 2007–2017. In 2006, the percentage of revaccination in BiH was significantly lower compared to Croatia (\( p < 0.05 \)). There was no significant difference in the percentage of revaccination among Croatia and neighboring countries in 2003–2005 and 2007–2017. In 2006, the percentage of revaccination in BiH was significantly lower compared to Croatia (\( p < 0.05 \)). There was no significant difference in the percentage of revaccination among Croatia and neighboring countries in 2003–2005 and 2007–2017. In 2006, the percentage of revaccination in BiH was significantly lower compared to Croatia (\( p < 0.05 \)). There was no significant difference in the percentage of revaccination among Croatia and neighboring countries in 2003–2005 and 2007–2017. In 2006, the percentage of revaccination in BiH was significantly lower compared to Croatia (\( p < 0.05 \)).
Table 4. Measles-containing revaccination (%) in Croatia and neighboring countries in the years 2001 to 2019.

| Year | BA | HR | MK | ME | RS | SI |
|------|----|----|----|----|----|----|
| 2001 | 86 | 98 | 94 | *  | 74 | 98 |
| 2002 | 90 | 98 | 95 | *  | 75 | *  |
| 2003 | 85 | 98 | 97 | *  | 96 | *  |
| 2004 | 88 | 98 | 95 | *  | 96 | *  |
| 2005 | 90 | 98 | 95 | *  | 98 | *  |
| 2006 | 61 | 98 | 96 | *  | 90 | 99 |
| 2007 | 95 | 98 | 95 | 95 | 96 | 98 |
| 2008 | 92 | 98 | 95 | 96 | 97 | 99 |
| 2009 | 88 | 97 | 97 | 87 | 98 | 98 |
| 2010 | 91 | 98 | 99 | *  | 91 | 96 |
| 2011 | 88 | 98 | 98 | 97 | 90 | 96 |
| 2012 | 94 | 97 | 96 | 97 | 90 | 96 |
| 2013 | *  | 97 | 96 | 97 | 82 | 95 |
| 2014 | 92 | 97 | 96 | 95 | 91 | 94 |
| 2015 | 88 | 96 | 93 | 94 | 87 | 96 |
| 2016 | 78 | 96 | 93 | 86 | 90 | 93 |
| 2017 | 80 | 95 | 97 | 83 | 91 | 94 |
| 2018 | 68 | 95 | 94 | 86 | 90 | 94 |
| 2019 | *  | 95 | *  | 91 | 94 | 94 |

* data not available; BA—Bosnia and Herzegovina; HR—Croatia; ME—Montenegro; MK—North Macedonia; RS—Serbia; SI—Slovenia; Source for data: World Health Organization (WHO) statistics from 2001 to 2019 [11].

3.3. MMR Primary Vaccination and Revaccination in European Countries 2001–2019

Data for Tables 5 and 6 cover Austria, Hungary, Croatia, Czech Republic, Denmark, Germany, Italy, Poland, France, Belgium and Ukraine.

Table 5 presents data on MMR primary vaccination in European countries. Austria and the Czech Republic and the years 2008, 2013, 2018 and 2019 had to be excluded for analysis because of partly missing data. In 2001, the percentage of primary vaccination in Italy was significantly lower compared to Hungary (p < 0.05), Croatia (p < 0.05), Denmark (p < 0.05) and Poland (p < 0.05). Furthermore, in 2001, Belgium had a significantly lower percentage of primary vaccination compared to Hungary (p < 0.05). In 2002, the percentage of primary vaccination in Italy was significantly lower compared to Hungary (p < 0.05), Denmark (p < 0.05) and Poland (p < 0.05). Moreover, in 2002, Belgium had a significantly lower percentage of primary vaccination compared to Hungary (p < 0.05). In 2003 and 2004, Belgium had a significantly lower percentage of primary vaccination compared to Hungary (p < 0.05). In 2009, the percentage of primary vaccination in Italy was significantly lower compared to Hungary (p < 0.05), Denmark (p < 0.05) and Poland (p < 0.05). Moreover, in 2002, Belgium had a significantly lower percentage of primary vaccination compared to Hungary (p < 0.05), Denmark (p < 0.05) and Poland (p < 0.05). In 2003 and 2004, Belgium had a significantly lower percentage of primary vaccination compared to Hungary (p < 0.05). In 2009, the percentage of primary vaccination in France was significantly lower compared to Hungary (p < 0.05), Croatia (p < 0.05), Germany (p < 0.05), Italy (p < 0.05), Poland (p < 0.05) and Belgium (p < 0.05). There was no significant difference in the percentage of primary vaccination between EU countries from 2005 until 2007 and from 2010 until 2017. According to available data, differences in the percentage of primary vaccination between Ukraine and other European countries were analyzed for the period between 2013 and 2017. In 2014, 2015 and 2016, Ukraine had a significantly lower percentage of primary vaccination compared to Hungary (p < 0.05), Croatia (p < 0.05), Denmark (p < 0.05), Germany (p < 0.05), Italy (p < 0.05), Poland (p < 0.05), France (p < 0.05) and Belgium (p < 0.05). There was no significant difference in the percentage of primary vaccination between Ukraine and Italy in 2013, and 2017, Austria and the Czech Republic were excluded from the analysis because of partly missing data.
Table 5. Measles-containing vaccine 1st dose (%) in European countries from 2001 to 2019.

| Year | AT  | HU  | HR  | CZ  | DK  | DE  | IT  | PL  | FR  | BE  | UA |
|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| 2001 | 79  | 99  | 94  | *  | 94  | 91  | 77  | 97  | 85  | 82  | *  |
| 2002 | 78  | 99  | 95  | *  | 99  | 91  | 81  | 98  | 86  | 82  | *  |
| 2003 | 79  | 99  | 95  | 99  | 96  | 92  | 84  | 97  | 87  | 82  | *  |
| 2004 | 74  | 99  | 96  | 97  | 96  | 92  | 86  | 97  | 88  | 82  | *  |
| 2005 | 75  | 99  | 96  | 97  | 95  | 93  | 87  | 98  | 87  | 88  | *  |
| 2006 | 80  | 99  | 95  | *  | 90  | 94  | 88  | 99  | 89  | 92  | *  |
| 2007 | 79  | 99  | 96  | 98  | 95  | 90  | 98  | 90  | 92  | *  |   |
| 2008 | 83  | 99  | 96  | 97  | *  | 95  | 90  | 98  | 93  | 88  | *  |
| 2009 | 76  | 99  | 95  | *  | 84  | 96  | 90  | 98  | 70  | 95  | *  |
| 2010 | *  | 99  | 96  | *  | 85  | 96  | 91  | 98  | 89  | 95  | *  |
| 2011 | *  | 99  | 96  | *  | 87  | 96  | 90  | 98  | 91  | 95  | *  |
| 2012 | *  | 99  | 95  | *  | 90  | 97  | 90  | 98  | 90  | 96  | *  |
| 2013 | *  | 99  | 94  | *  | 89  | 97  | 90  | 98  | 91  | 79  |   |
| 2014 | 96  | 99  | 94  | 99  | 90  | 97  | 87  | 97  | 91  | 96  | 56 |
| 2015 | *  | 99  | 93  | *  | 91  | 97  | 85  | 96  | 90  | 96  | 56 |
| 2016 | 95  | 99  | 90  | 98  | 94  | 97  | 87  | 96  | 90  | 96  | 42 |
| 2017 | 97  | 99  | 89  | 97  | 97  | 92  | 94  | 90  | 96  | 86  |   |
| 2018 | 94  | 99  | 93  | 96  | 95  | 97  | 93  | 93  | 96  | 96  | *  |
| 2019 | *  | 99  | 93  | 92  | 96  | 97  | 94  | *  | 96  | *  |   |

* data not available; AT—Austria; HU—Hungary; HR—Croatia; CZ—Czech Republic; DK—Denmark; DE—Germany; IT—Italy; PL—Poland; FR—France; BE—Belgium; UA—Ukraine; Source for data: World Health Organization (WHO) statistics from 2001 to 2019 [11].

Table 6. Measles-containing revaccination (%) in selected European countries from 2001 to 2019.

| Year | AT  | HU  | HR  | CZ  | DK  | DE  | IT  | PL  | FR  | BE  | UA |
|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| 2001 | 34  | 99  | 98  | 97  | 87  | *  | *  | 96  | *  | *  | *  |
| 2002 | 39  | 99  | 98  | 98  | 92  | 27  | *  | 97  | *  | *  | *  |
| 2003 | 46  | 99  | 98  | 97  | 88  | 53  | *  | 97  | *  | *  | *  |
| 2004 | 47  | 99  | 98  | 97  | 88  | 51  | *  | 96  | *  | *  | *  |
| 2005 | 91  | 99  | 98  | 97  | 91  | 66  | *  | 90  | *  | *  | *  |
| 2006 | 61  | 99  | 98  | 98  | 91  | 77  | *  | 99  | *  | 78  | *  |
| 2007 | 56  | 100 | 98  | 98  | 88  | 83  | *  | 98  | *  | 78  | *  |
| 2008 | 62  | 100 | 98  | 98  | 98  | *  | 88  | *  | 97  | *  | 81  |   |
| 2009 | 64  | 99  | *  | 98  | 85  | 89  | *  | 95  | *  | 83  | *  |
| 2010 | *  | 100 | 98  | 98  | 85  | 90  | *  | 94  | *  | 61  | 83  | *  |
| 2011 | *  | 100 | 98  | 98  | 86  | 92  | *  | 95  | 67  | 83  | *  |
| 2012 | *  | 99  | 97  | 99  | 87  | 92  | *  | 95  | 72  | 85  | *  |
| 2013 | *  | 99  | 97  | 99  | 86  | 92  | 84  | 93  | 75  | 85  | 54 |
| 2014 | 87  | 100 | 97  | 96  | 84  | 93  | 83  | 95  | 77  | 85  | 57 |
| 2015 | *  | 99  | 96  | 99  | 80  | 93  | 83  | 94  | 79  | 85  | 57 |
| 2016 | 89  | 99  | 96  | 93  | 85  | 93  | 82  | 93  | 80  | 85  | 31 |
| 2017 | 84  | 99  | 95  | 90  | 88  | 93  | 86  | 93  | 80  | 85  | 84 |
| 2018 | 84  | 99  | 95  | 94  | 90  | 93  | 89  | 92  | 83  | 85  | *  |
| 2019 | *  | 99  | 95  | *  | 90  | 93  | 88  | *  | 85  | *  |   |

* data not available; AT—Austria; HU—Hungary; HR—Croatia; CZ—Czech Republic; DK—Denmark; DE—Germany; IT—Italy; PL—Poland; FR—France; BE—Belgium; UA—Ukraine; Source for data: World Health Organization (WHO) statistics from 2001 to 2019 [11].

Table 6 presents data on MMR revaccination in EU countries. Austria, Italy, France and Belgium and the years 2001, 2008, 2009 and 2019 had to be excluded from analysis due to missing data. In 2002, the percentage of revaccination in Germany was significantly lower compared to Hungary (2002, \( p < 0.05 \)), Croatia (2002, \( p < 0.05 \)), Czech Republic (2002, \( p < 0.05 \)), Denmark (2002, \( p < 0.05 \)) and Poland (2002, \( p < 0.05 \)). In 2003 and 2004, the percentage of revaccination in Germany was significantly lower compared to Hungary (2003, \( p < 0.05 \); 2004, \( p < 0.05 \)), Croatia (2003, \( p < 0.05 \); 2004, \( p < 0.05 \)), the Czech Republic (2003, \( p < 0.05 \); 2004, \( p < 0.05 \)) and Poland (2003, \( p < 0.05 \); 2004, \( p < 0.05 \)). There was no
significant difference in percentage of revaccination between EU countries from 2005 until 2007 and from 2010 until 2018. Again, according to available data, differences in the percentage of revaccination between Ukraine and other European countries were analyzed for the period between 2013 and 2017. In 2013, 2014, 2015 and 2016, Ukraine had a significantly lower percentage of revaccination compared to Hungary—a particularly low percentage revaccination in 2016, only 31% \( p < 0.05 \)—Croatia \( p < 0.05 \), Czech Republic \( p < 0.05 \), Denmark \( p < 0.05 \), Germany \( p < 0.05 \), Italy \( p < 0.05 \), Poland \( p < 0.05 \), France \( p < 0.05 \) and Belgium \( p < 0.05 \). There was no significant difference in the percentage of revaccination between Ukraine and other EU countries in 2017. Austria was excluded from analysis because of partly missing data.

Table 7 presents the number of measles cases in European countries, from 2001 to 2019. In 2006, 2018 and 2019, Ukraine had a significantly higher number of measles cases compared to all other European countries listed in Table 7. There was no significant difference in the number of measles cases among European countries in the periods between 2002 and 2005, 2007 and 2009, 2011 and 2017.

Analysis of the association between the percentage of primary vaccination and number of measles cases, just as between the percentage of revaccination and the number of measles cases between 2001 and 2019 included available data from the following countries: Austria, Hungary, Croatia, Czech Republic, Denmark, Germany, Italy, Poland, France, Belgium, Ukraine, Bosnia and Herzegovina, North Macedonia, Montenegro and Serbia. There was no significant correlation between the percentage of primary vaccination and the number of measles cases \( r = -0.0671 \ p = 0.298 \) but there was a significant moderate negative correlation between the percentage of revaccination and the number of measles cases \( r = -0.357 \ p < 0.0001 \).
### Table 7. Cont.

|    | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 |
|----|------|------|------|------|------|------|------|------|------|
| FR | 15,206 | 234 | 859 | 13.2 | 272 | 4.2 | 267 | 4.1 | 364 | 5.5 |
| DE | 1609 | 20 | 167 | 2 | 1772 | 21.7 | 446 | 5.4 | 2646 | 30.4 |
| GR | 40 | 4 | 3 | 0.3 | 3 | 0.3 | 1 | 0.1 | 1 | 0.1 |
| HU | 5 | 0.5 | 2 | 0.2 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| IT | 5181 | 85 | 682 | 11.2 | 2216 | 36.4 | 116 | 2 | 2646 | 30.4 |
| ME | 38 | 1 | 61 | 1.6 | 86 | 2.2 | 110 | 2.9 | 48 | 1.3 |
| PL | 4015 | 187 | 3843 | 179.5 | 1074 | 50.3 | 53 | 2.6 | 2435 | 123.3 |
| RO | 5 | 0.5 | 2 | 0.2 | 1 | 0.1 | 0 | 0 | 0 | 0 |
| RS | 370 | 51.5 | 0 | 0 | 1 | 0.1 | 37 | 5.1 | 383 | 53.3 |
| SK | 2 | 0.4 | 1 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 |
| SI | 22 | 11 | 2 | 1 | 1 | 0.5 | 52 | 25.3 | 18 | 8.7 |
| UA | 1333 | 29.2 | 12,746 | 279.5 | 0 | 0 | 0 | 0 | 105 | 2.3 |
| UK | 1083 | 17 | 1902 | 30.4 | 1900 | 30.7 | 133 | 2.1 | 92 | 1.4 |

N—number of measles cases; AL—Albania; AT—Austria; BE—Belgium; BA—Bosnia and Herzegovina; BG—Bulgaria; HR—Croatia; CZ—Czech Republic; FR—France; DE—Germany; GR—Greece; HU—Hungary; IT—Italy; ME—Montenegro; PL—Poland; PT—Portugal; MK—North Macedonia; RO—Romania; RS—Serbia; SK—Slovakia; SI—Slovenia; UA—Ukraine; UK—United Kingdom of Great Britain and Northern Ireland; *

*p < 0.005 2006, 2018 and 2019 Ukraine vs. all other countries; Source for data: World Health Organization Regional Office for Europe [31].

### 4. Discussion

After the introduction of the measles vaccination, the number of affected patients decreased significantly. Before 1968 (when compulsory vaccination against measles was introduced in Croatia), the average annual number of patients in Croatia was around 15,000, while in the last ten years, this number has stayed below 20, with the exception of 2015, when we had an epidemic with 206 patients, and in 2018, with the measles epidemic in Dubrovnik-Neretva County [4]. Interestingly, our results show that in Croatia, the percentage of revaccination compared to primary vaccination significantly increased in 2016 and 2017. Analysis of neighboring countries of Croatia revealed that Croatia, Slovenia, and Serbia generally had the best primary vaccination success, while Bosnia and Herzegovina (BiH) and North Macedonia had the lowest primary vaccination percentage and BiH also had the lowest percentage of revaccination compared to neighboring countries (Tables 3 and 4). Interestingly, in the first decade of the 21st century, Italy, Belgium and France had the lowest MMR primo-vaccination coverage of analyzed European countries. There was no significant difference in the percentage of primary vaccination between EU countries from 2005 until 2007 and from 2010 until 2017. However, in the period 2013–2017, Ukraine had the lowest primary vaccination and revaccination coverage compared to other European countries (e.g., in 2016 Ukraine had 47% primary vaccination and 31% revaccination). The highest percentages of coverage are seen in Hungary and Croatia (Tables 5 and 6). This is in agreement with the notification rate per million population for measles. In Croatia from November 2020–October 2021 [8] and February 2021–January 2022, there were zero cases, and in Slovenia, Hungary, Slovakia, Czech Republic, Bulgaria, Greece, and Portugal, there were no cases of measles. Other EU countries reported 0.001–0.099 cases [9]. In contrast, in the period February 2020–January 2021, only Croatia, Hungary and Slovakia reported a notification rate per million of zero, while the majority of other EU countries had from 0.001–0.999 [10]. This could be attributed to suboptimal vaccine coverage in Europe, which led to a major resurgence of measles in recent years [32]. Several reasons may underline that situation, including increasing trends of vaccine hesitancy or refusal due to perception of measles risk and burden, mistrust in experts, concerns about vaccine safety, effectiveness, and accessibility [32]. Furthermore, migrations and consequences of wars or economical migrations from the countries with disturbed health care systems also influence vaccination coverage of the population. Importantly, one may hypothesize that the decrease in vaccination in the EU and neighboring countries increases the risk of an epidemic surge in the near future.
The biggest problem is the continuous decline in vaccination coverage of preschool children, which is below the minimum 95% and can lead to an epidemic [33]. Recently, in the study conducted in the frame of the CABCOS3 project, it was reported that the Hungarian serum samples and Croatian serum samples were largely overlapping in seropositivity ratios, which might be attributed to the intrinsic biological dynamics of vaccination-based humoral immunity to measles. Individuals 34–43 years old had the lowest seropositivity ratios (78%) [34]. A prospective study conducted in Prague, Czechia, on a total of 2782 participants aged 19–89 years, analyzed the level of measles-specific antibodies in serum samples and showed that the seropositivity rate in naturally immunized participants (before 54 years) was significantly higher than in fully vaccinated persons aged 19–48 (98.0% (95% CI: 96.5–99.0%) vs. 93.7% (95% CI: 92.4–94.9%)). Lower seropositivity persistence (86.6%) was found in a cohort of those born in 1971–1975, vaccinated mostly with one dose, compared to naturally immunized persons or compared to participants fully vaccinated with two doses [35]. Furthermore, in 2019, 59 measles cases were reported between 1 January and 11 March in Austria; 47 of them fulfilled the cluster case definition. Forty out of 47 patients (85.1%) were unvaccinated, while the age distribution of cases suggested measles immunity gaps in adults [36]. In Zagreb, Croatia, in the period from December 2014 to April 2015, 122 measles cases were notified, 93% of which were unvaccinated persons, age younger or equal to four years, and older than 20 [37]. The outbreak was successfully resolved, and Croatia has an excellent measles elimination profile [38]. Interestingly, in Korea, 2019, there were 26 measles case-patients, aged 18–28 years. Twenty-five of them had previously received the MMR vaccine (12/26, 46% (two doses); 13/26, 50% (one dose)), and 16 (62%) had positive results of measles IgG prior to measles diagnosis [39]. Altogether, these are important information in the light of the previously mentioned outbreak among adults in Dubrovnik-Neretva County [4], suggesting that the lack of previous immunization, together with a decrease in seropositivity, present a risk for future epidemic outbreaks.

It has been shown that several factors may influence the parental decision to choose MMR vaccination, such as confidence in experts and vaccine, measles severity, responsibility toward child and community health and peer judgment [32]. Through educational activities foreseen within CABCOS, our goal is to increase public awareness of the importance of vaccination and increase the share of vaccinated children. Trends of a decrease in immunization coverage are followed in other countries in the region. For example, in the years 2018 to 2020, in Kosovo, >90% (N = 430) of children 12–24 months old had fully completed immunization personal plans. There were delays in immunizations, from 1 to 3 months, mainly due to the COVID-19 pandemic, lack of time for parents to take the child for vaccination or the child being sick at the scheduled time of vaccination. The difference between non-vaccination and full vaccination was only related to the age of children (p < 0.001) [40].

In contrast to the situation in Croatia (Tables 3 and 4), in Serbia, over the period 2000–2017, there was a significant decline in coverage of primary vaccination against measles, mumps, rubella (MMR) (p ≤ 0.01). In the same period, coverage of all subsequent revaccinations significantly decreased, e.g., in the second dose against MMR before enrollment in elementary school (p < 0.05) [41]. In Western Europe, the situation with vaccination coverage varies. 2018–2019 data in the UK, London area, showed that the coverage of children with dose two of MMR vaccine at their fifth birthday has been consistently low (76.3%) [42]. Results of the present study showed that Germany (Tables 5 and 6) had also significantly lower primary vaccination and revaccination percentages compared to other countries in 2003 and 2004. Importantly, there was no significant difference in the percentage of revaccination between EU countries from 2005 until 2007 and from 2010 until 2018. It is not clear what was the cause of differences in immunization coverage in the period 2007 until 2010.

A recent systematic review (PROSPERO CRD42019157473; 1 January 2000 to 22 May 2020) identified studies on vaccine-preventable disease outbreaks involving migrants resid-
ing in the EU/EEA and Switzerland (including measles, mumps and rubella). 47 different vaccine-preventable disease outbreaks in 13 countries were reported in 45 studies. 40% of outbreaks (mostly varicella and measles) occurred in shelters or temporary refugee camps. Measles were the most reported outbreaks involving migrants (n = 24; 6496 cases) and 11 of them were associated with migrants from eastern European countries. There were only three reported rubella outbreaks (487 cases) and two reported mumps outbreaks (293 cases) [43]. As a study in 2017 demonstrated, the most important factor that prevented the resurgence of measles was vaccine coverage rates, regardless of the economic status of the country or the number of incoming travelers or migrants. In 2017, the incidence of measles was the highest in Romania (46.1/100,000), which has the lowest coverage rate (75%), followed by Ukraine (10.8/100,000) and Greece (8.7/100,000). Overall vaccination coverage with two doses in these countries was less than 84% [44]. Data from a 2017 survey on national immunization strategies to provide vaccinations for migrants show that Portugal, Italy, Croatia and Slovenia offer migrant children and adolescents all vaccinations included in the National Immunization Plan, and Greece and Malta provide only certain vaccinations, including those against measles–mumps–rubella and diphtheria–tetanus–pertussis and poliomyelitis. Portugal, Malta, Italy and Croatia also offer vaccination to adults. Vaccinations are delivered in holding centers and/or community health services in all countries. No country delivers vaccinations at the entry site to the country [45]. Thus, the finding of the present study, that there is a significant moderate negative correlation between the percentage of revaccination and the number of measles cases, provides additional support for the importance of the completion of vaccination protocols, since this correlation was not found in primo-vaccination.

5. Conclusions

In conclusion, the present study demonstrates that there is a negative correlation between the second vaccination (revaccination) and the number of measles cases, which emphasizes the necessity to perform a full protocol of vaccination to reach appropriate protection from potential epidemic outbreaks. Thus, it is important to have a strategy to document migrants’ flow and facilitate vaccination as needed; this is of utmost importance to prevent future epidemics. Additionally, follow-ups on seropositivity upon vaccination in the adult population should be monitored to highlight potential regions or sub-population at greater risk to be points of epidemic outbreaks.

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