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Measles cases in Split-Dalmatia County (a Croatian tourist region), in May–July 2019: outbreak report and lessons learnt

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Background: Measles elimination was accomplished in Croatia in 2016. Split-Dalmatia County, with population of ca. 425 000 inhabitants, is among the most important Croatian tourist areas with numerous seasonal workers coming during summer months. In both 2018 and 2019, more than 3 million tourists visited this county. In 2000–2018, there were no measles cases in this county, or their number was low (1–3 cases per year). **Methods:** After measles was clinically suspected, all contacts were traced and contacted. Detection of specific IgM/IgG antibodies and real-time reverse transcription–polymerase chain reaction detection of viral RNA were used for laboratory confirmation. Sequencing and genotyping were performed for strains' molecular epidemiology analysis. **Results:** Six epidemiologically unlinked measles virus occurrences happened in Split-Dalmatia County in 15 May–19 July 2019. Causative viral strains belonged to genotypes B3 and D8. Four were single imported cases. Ten patients belonged to two separate clusters within domicile population. Multiple individual and public health measures were implemented. In total, 483 contacts were identified, 64.2% within healthcare system where two persons contracted the disease. **Conclusions:** Besides the importance of timely vaccination of children, the lessons learned from this outbreak point to the need of stricter implementation of other aspects of Croatian measles prevention programme, such as checking of vaccination status in early adulthood. Despite the fact that measles elimination within domicile population in this tourist region has been accomplished and maintained for years, continuous public health workers' efforts are still necessary for identification and diminishment of populational pockets of susceptibility.

Introduction

Measles virus is a highly contagious human infectious agent transmitted via the respiratory route. It causes a systemic disease in humans characterized by fever, cough and skin rash, as well as a transient immune suppression. Despite the availability of safe and efficacious live-attenuated vaccines, measles and its sequelae remain an important cause of global mortality, especially in children in resource-poor settings.[1]

In the period of December 2018–November 2019, over 115 000 cases of measles occurred in World Health Organization (WHO) European region,[2] with more than 13 000 cases reported in the European Union (EU) member states. All EU countries reported cases and over 10 death cases occurred.[3] In Croatia, 52 measles cases were reported in 2019, 14 of which occurred in Split-Dalmatia County, from May to July, and are the subject of this article. These are the last measles cases reported in Split-Dalmatia County.

In the period 2000–2018, less than 12 measles cases have been reported annually in Croatia, with the exception of four import-related outbreaks (2003–2004, 2008, 2014–2015 and 2018).[4] In Split-Dalmatia County, there were no measles cases in majority of these years, or there were only few (figure 1). According to the WHO criteria, interruption of endemic measles transmission was achieved in Croatia in 2015 and since 2016 measles elimination was accomplished.[5,6]

Split-Dalmatia County is the largest county in Croatia with the population of nearly 425 000 residents, which accounts for ca. 11% of the Croatian population. Due to its attractive geographic position on the Adriatic Sea and historical significance, it is among the most important Croatian tourist areas with numerous seasonal workers coming in summer months, especially from neighbouring Bosnia and Herzegovina. In both 2018 and 2019, more than 3 million tourists visited this county, primarily from Western European countries.[7,8]

Measles vaccination was introduced in the Croatian national childhood vaccination schedule in 1968 as a monovalent measles vaccine. In 1976, it was replaced by combined measles-mumps-rubella (MMR) vaccine. Today, MMR vaccination is mandatory and is carried out by primary healthcare paediatricians at the age of 12 months (dose 1) and school medicine specialists for elementary

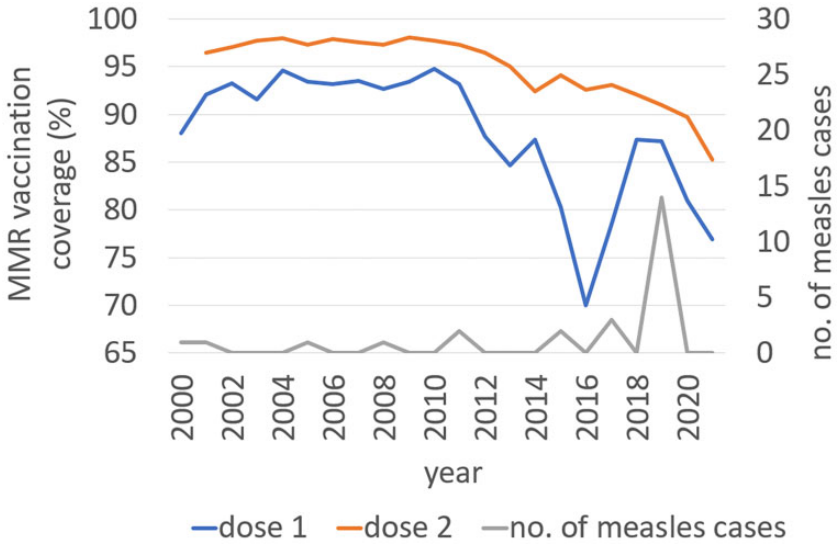

Figure 1 MMR vaccination coverage and the number of measles cases in Split-Dalmatia County, 2000–2021

schools' first graders (dose 2). For Split-Dalmatia County, primary vaccination coverage rates were high until 2011 (figure 1), when parental vaccine hesitancy gained momentum. The coverage rate for the second dose was not as affected, because (i) the parents more readily accept vaccination of older children (the fear of side effects is lessened) and (ii) preventive healthcare measures (including vaccination) for older children are organized differently. Due to strong parental insisting on postponing of primary vaccination, which is particularly common for MMR, paediatricians are sometimes unable to perform primary MMR vaccination as scheduled and the first MMR dose is given later in childhood. Legal consequences for parents who decline or postpone MMR vaccination only for philosophical reasons are minimal, if any.

In this article, we present epidemiological and laboratory investigations during measles outbreak in Split-Dalmatia County, May–July 2019, and describe the individual and public health measures implemented in order to minimize the outbreak. We address the issue of populational pockets of susceptibility to measles and emphasizes the importance of not only timely vaccination of children but also of need of stricter implementation of other aspects of national measles prevention programme, such as checking of vaccination status in adulthood and then receiving missed vaccinations, if still necessary.

Methods

Definition of confirmed cases and contacts

In accordance with the EU measles case definition,[9] confirmed case was a person meeting the clinical criteria (fever and maculopapular rash and one of the following: cough, coryza or conjunctivitis) with laboratory confirmation of measles (detection of IgM antibodies and/or RNA in clinical samples). Any person who was in close contact with a confirmed case during the infectious period of 8 days (4 days before and 4 after the onset of rash) was considered a contact.

Case finding and contact tracing

After the patients contacted primary healthcare physicians, emergency service or infectious disease specialists, County's epidemiologists in charge were informed of suspected measles cases. In accordance with the guidelines set by national Reference Centre for Epidemiology of Infectious Diseases, Croatian Institute of Public Health (CIPH), patients were placed in isolation and were referred to the epidemiologist who conducted interviews, gathered samples for laboratory analysis and conducted outbreak control measures (identified and traced contacts, determined whether contacts are at increased risk, checked vaccination statuses and conducted vaccination of contacts with unknown or incomplete vaccination status).

Laboratory confirmation of measles

Throat or nasopharyngeal swabs, urine and/or blood samples were collected from 14 cases. Detection of measles specific IgM/IgG antibodies and real-time reverse transcription–polymerase chain reaction (RT–PCR) detection of viral RNA were used for laboratory confirmation of measles.

Enzyme-linked immunosorbent assay (ELISA) IgM/IgG (Virotech Diagnostics, Rüsselsheim, Germany) was used for serology. IgM-positive samples were additionally confirmed using indirect immunofluorescence assay (Euroimmun, Lübeck, Germany). According to WHO recommendation, serum samples were also tested for rubella IgM/IgG antibodies using ELISA (NovaTec Immunodiagnostica, Dietzenbach, Germany).

Detection of measles virus RNA from throat or nasopharyngeal swab and urine was performed according to the protocol described by Hummel *et al.*[10] For nucleic acid isolation, an automated system QIAxtractor (QIAGEN) was used. Qualitative real-time RT–PCR was performed using a single-tube RT–PCR test kit (Fast One-Step Qualitative Kit). Twenty-five µL reaction mixtures included 5 µL of isolated RNA, 0.2 µM of each primer and 0.1 µM of probe.

Sequencing of N450 (450 nucleotides coding for the 150 carboxyl-terminal amino acids of the nucleoprotein) was done after reverse transcription and nested PCR amplifications using primers N3 (GGATGAGGCGGACCAATACT) and N6.1 (TGACCATGCTGCC ATAGCTT), and N5 (GGAGTAGGAGTGGAACTTG) and N6 (TCTGCCATCGGCTCCAATCG) in the first and second amplification rounds, respectively. Genotyping was performed for samples of seven patients using genotype reference sequences defined by WHO.[11,12] Sequences were deposited in MeaNS2 database (https://who-gmrln.org/means2), with sequence IDs 143155, 143156, 143161, 145334, 145336, 151677 and 151678.

Serological testing of contacts under increased risk of developing measles

A total of 40 contacts with high risk of measles were tested for the presence of measles virus IgG using ELISA (Virotech Diagnostics, Rüsselsheim, Germany or SERION Diagnostics, Würzburg, Germany).

Ethical statement

Ethical approval for this study was not required since all activities were concordant to legal provisions defined by the Croatian Act on the Protection of the Population against Communicable Diseases.[13]

Results

Descriptive epidemiology

During time span of 10 weeks in 2019 (15 May–19 July), six measles virus occurrences happened in Split-Dalmatia County. In total, 14 measles cases were confirmed; 4 were imported individual cases, 10 occurred among domicile population and were grouped in two separate clusters, each comprised of 5 cases.

The first import case, reported on 15 May 2019 on the island of Hvar, was an unvaccinated seasonal worker in tourism from neighbouring Bosnia and Herzegovina. Next two cases occurred among tourists visiting Split and Baška Voda: on 2 June 2019, an incompletely vaccinated primary schoolchild from Eastern Europe fell ill and on 4 July 2019 symptoms occurred in an unvaccinated young adult from Western Europe. For these three patients, the disease started on the first or the second day after arriving to Croatia (high fever, conjunctivitis and coryza). The epidemiological service was informed after the appearance of rash. The fourth individual case was detected on 17 July 2019, it was a Croatian citizen with unknown vaccination status who had been visiting her family in Ireland and fell ill 3 days upon returning home. These four imported measles cases did not cause further disease spread.

On 16 May 2019, an unvaccinated gas station employee from Solin (wider Split area) experienced symptoms of measles; the source of infection remained undetermined. He transmitted the disease to three unvaccinated family members (two children aged 3 and 4 years, and an adult person). One of the children transmitted the disease to a completely vaccinated physician in an infectious disease clinic who developed only mild clinical symptoms (Cluster 1).

The second cluster occurred in July 2019. An unvaccinated Split airport ground flight attendant (resident of Split's neighbouring town Kaštel Novi) became ill, the source of infection remained undetermined. An unvaccinated family member (1.5-year-old child) contracted the disease and an incompletely vaccinated nurse in a primary healthcare infirmary became infected when the patient was examined in the catarrhal phase of the disease. Two other Split airport employees, became ill within 13 days. One was not vaccinated and the other received only one dose of MMR vaccine at 8 months of age.

Schematic presentation of epidemiological data and epicurve are shown in Supplementary figure S1 and figure 2, respectively. Additional data regarding patients' age distribution and vaccination status are presented in Supplementary table S1.

Measles recognition

All patients reported to healthcare facilities during febrile and catarrhal symptoms. Unlike unvaccinated patients, vaccinated adults had a mild form of the disease. In most cases, measles was suspected after the appearance of rash, on average after 3.5 days from the disease onset (median 4 days). The exception was four unvaccinated family contacts, for which the disease appearance was expected. For those cases, the epidemiologists were informed on the same day when the disease was recognized.

Until the onset of rash and diagnosis, patients had numerous contacts (483) (table 1), mostly within the healthcare system (64.2%), at work (18.2%) and in families (11.4%). In total, measles patients made 27 visits to healthcare facilities before measles was suspected, making numerous contacts with other patients and healthcare professionals.

Serology and genotyping

For all cases, measles virus infection was confirmed by real-time RT–PCR after viral RNA was isolated from throat or nasopharyngeal swabs and urine. Blood samples were obtained at the beginning of the disease from seven patients (four unvaccinated, two incompletely vaccinated and one with unknown vaccination status), for which IgM/IgG analysis was performed using ELISA: IgM antibodies were found in five subjects, low IgG titre was found in all vaccinated subjects.

Sanger sequencing of N450 region was performed for seven samples. Detected viruses belonged to genotypes B3 and D8 (figure 3, strains indicated with green squares). The two B3 viruses possessed identical N450 sequence, annotated in MeaNS2 database with distinct sequence identifier number (dsID) 5287. Among D8 viruses, two different N450 sequences were obtained, dsID 4683 and dsID 5901, indicated by (a) and (b) in Supplementary figure S1, respectively.

DsID 5287 group of strains (genotype B3) was detected April 2018–November 2020 in 14 different countries (data retrieved form MeaNS2 database, accessed 29 May 2022), including Bosnia and Herzegovina from where one of the patients (a seasonal worker) came to Croatia. DsID 4683 group of strains (genotype D8) was detected in over 60 countries, October 2016–October 2021, including UK and Ukraine from where two patients came to Split-Dalmatian County. DsID 5901 group of strains (also genotype D8) were detected from February till November 2019, in eight countries including Ireland, from where the fourth patient classified as import case came.

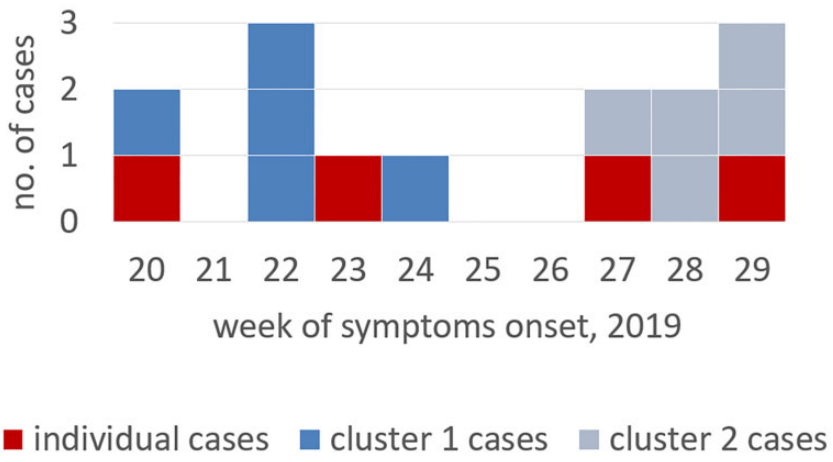

Figure 2 Epicurve of measles cases in Split-Dalmatia County, May–July 2019

Table 1 Classification of contacts of measles patients in Split-Dalmatia County, May–July 2019

Classification	No. of contacts	No. of contacts with increased risk of measles
Family members	55	2
Friends	15	1
Work colleagues	88	9
Persons in healthcare facilities (employees and patients in waiting rooms)	310	28
Other (apartment and ferry boat)	15	0
Total	483	40

Control measures

In accordance with the guidelines defined by the Croatian National Centre for Epidemiology, epidemiologists in charge received information from physicians immediately after measles was suspected. Nineteen unvaccinated or incompletely vaccinated persons that were in contact with infected persons within last 72 h received a measles vaccine (three healthcare workers, eight work colleagues, six patients in waiting rooms and two family members).

Three unvaccinated family members were home isolated. They were not vaccinated as post-exposure prophylaxis because they were in contact with patients for more than 72 h before measles was recognized. For these three contacts, measles appeared as expected with no further spread due to the timely isolation. One unvaccinated child was also initially home isolated, but parents insisted that it should be examined during the rash phase and this

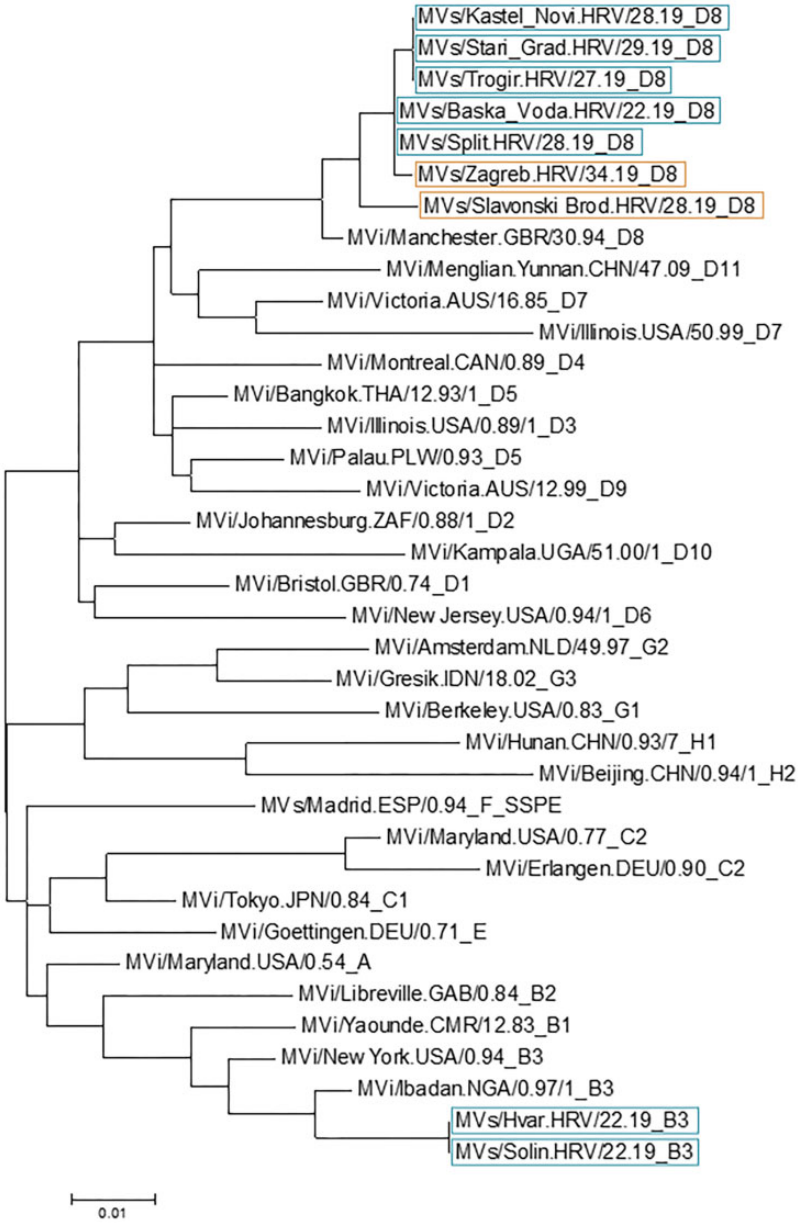

Figure 3 Measles virus phylogenetic tree based on N450 genomic segment. Green squares show viruses detected in Split-Dalmatia County in 2019; orange squares show other measles strains detected in Croatia in 2019. Scale bar indicates number of base differences per site. As genotype references, strains defined by WHO were used (A color version of this figure appears in the online version of this article)

child transmitted measles to the completely vaccinated physician (Supplementary figure S1).

A total of 40 contacts at high risk for measles [2 pregnant women, 2 persons receiving chemotherapy, 2 immunocompromised persons, 1 organ transplantation recipient and 33 persons of unknown vaccination status (19 healthcare workers, 6 patients in waiting rooms and 8 work colleagues)] were tested for the presence of IgG antibodies against measles. Seven contacts that were IgG negative and two that were inconclusive were urged to receive measles vaccination. Immunocompromised persons were scheduled for immunoglobulin therapy. None of them developed measles.

The general population was continuously informed by the media (radio, national and local TV and newspapers) regarding the measles occurrence in the community and regarding the importance of vaccination. Frequent appearance of experts in media helped raising public awareness. All parents were invited to vaccinate their children according to the vaccination schedule. People born after 1960 were instructed to determine their vaccination status and in case they had not received full measles vaccination or did not have measles, they were referred to epidemiologists for MMR vaccination.

Although the three children that were among the measles cases described here did not attend kindergartens, all kindergartens in the county were informed to check the vaccination status of the children in care and to instruct the parents regarding the need for regular vaccinations. Kindergarten employees were asked to check their personal vaccination status and to receive missed doses. Information about the disease and its symptoms, along with information about the need for vaccination was continuously displayed on county's National Institute of Public Health website, as well as in waiting rooms. Informative material about measles, including posters and leaflets, were distributed to healthcare facilities and kindergartens.

Discussion

Croatia achieved measles elimination in 2016 and typically only a few cases have been reported yearly for over two decades.[4] Successful elimination led to measles being a very rare disease in Split-Dalmatia County. In 2018, the year before hereby presented cases, an outbreak comprised of 15 measles cases occurred in a neighbouring Dubrovnik-Neretva County,[14] in very similar socio-demographic settings. Its index case had visited few healthcare facilities before clinical recognition of measles, during the period of infectiousness. After this outbreak, CIPH provided several new guidelines and protocols for the prevention of measles, pertaining, among else, to the management of measles cases in healthcare facilities, management of contacts and control measures to childcare facilities. This helped in measles management in Split-Dalmatia County in 2019. Furthermore, due to the 2018 outbreak in Dubrovnik-Neretva County, intensified MMR vaccination campaign was conducted in 2018 also in Split-Dalmatia County, leading to increased vaccination coverage among healthcare workers and children. Despite six independent occurrences of measles in 2019 and numerous visits of patients to healthcare facilities, the virus spread within the healthcare system was minimal. Even though most of the contacts were from the healthcare system, only two patients contracted the disease there: a completely vaccinated physician and an incompletely vaccinated nurse. Both developed mild clinical symptoms. There was no transmission to other patients in waiting rooms.

After the described period, no new cases occurred in Split-Dalmatia County. Because of high media coverage and awareness of healthcare workers regarding circulation of measles virus in the county, we do not think that other measles cases were misdiagnosed or stayed unreported, particularly not among domicile population. Still, we cannot dismiss the possibility that some cases may have remained undetected due to various reasons (mild clinical picture, patients not reporting to the physicians, tourists not seeking medical attention or just being in transit, etc.). Prevention of further spread of the disease during high tourist season was of utmost importance, primarily from perspective of public health, but also for this county's economy. Urgent and frequent informing through all media resulted in a good response to the implementation of outbreak control measures.

Till the end of 2019, 38 other measles cases were identified in Croatia, but they were not geographically nor epidemiologically linked to the cases described in this article. The majority of them occurred during the outbreaks in Zagreb and Slavonski Brod (cities in continental Croatian regions), within different social context and were caused by different measles strains (figure 3, indicated with orange squares). In 2020, 2021 and up till July 2022, no measles cases have been reported in Croatia.

All measles outbreaks that occurred in Croatia in the last 15 years have been less intensive than the outbreaks in other European countries (e.g. North Macedonia, Serbia, Italy, France, Romania or Ukraine) indicating a high level of population immunity in Croatia.[15] However, vaccination coverage achieved in the previous decade is not sufficient to prevent the occurrence of measles in populational pockets of susceptibility, including families with vaccine hesitancy attitudes (i.e. families prone to delaying vaccination for a few years, an attitude sustained by some paediatricians). The two children patients in Cluster 1 and one child in Cluster 2 did not receive MMR vaccine as scheduled by mandatory immunization programme due to parental decision to postpone vaccination (not to refuse it for all time) because of the fear of possible side effects that MMR might cause in infants. In the case of family from Cluster 1, this fear was primarily based on alleged post-vaccinal neurological complications in family members from previous generation.

In 2018, the CIPH recommended checking immunization status of healthcare workers from specific departments (infectious disease units, haematology, paediatrics, neonatal care and emergency units) regarding measles by evaluating medical documentation (which is often unavailable for individuals over 30 years of age) or by serological testing.[16] It also recommended vaccination of healthcare workers without evidence of immunity at the beginning or during employment. In 2020, the CIPH extended this recommendation to all healthcare workers in primary healthcare units and hospitals as well as for employees in preschool children facilities.[17] In the two measles clusters described here, the virus spread to pockets of susceptibility within residential population started with unvaccinated individuals working at positions with very high frequency of contacts with different clients, many of which came from abroad. It may be useful to recommend to check vaccination status of all workers in frequent contact with tourists, especially now after few seasons in which the incidence of respiratory viral diseases and transmission of respiratory viruses has been reduced due to measures set in place because of the COVID-19 pandemic.[18,19] All 6 WHO Regions have reported disrupted immunization activities during COVID-19 pandemics and measles outbreaks and epidemics are already becoming more frequent in some world regions.[20] The ongoing war in Ukraine and rising numbers of refugees pose additional risk for new measles outbreaks in Europe. In tourist areas with both tourists and seasonal workers coming from all over the world (as it is the case with Split-Dalmatia County), recognition of populational pockets of susceptibility and implementation of catch-up vaccination may become crucial again.

Despite the abundance of information available on the internet and social networks, studies have shown that in Croatia healthcare workers are still the major source of information and have the greatest influence on the attitudes of parents towards childhood vaccinations.[15] Therefore, besides persistent education of parents regarding relevance of vaccination and participating in public health vaccination campaigns, it is important that physicians do not sustain vaccine hesitancy without medical reasons. As stated in documents legislated by Croatian Ministry of Health,[21] parents that refuse to vaccinate their children only for philosophical argumentation should be referred by primary physicians to epidemiologists for further

counselling. After they are given comprehensive explanations, many of them agree to vaccinate their children, especially if, by that time, the children are no longer infants or toddlers. If they are still refusing to vaccinate the children, physicians have an option but not a legal obligation to report such parents to sanitary inspectorate. As most of medical professionals hold the opinion that thorough informing of parents (sometimes for several times and by different specialists, if needed), leads to much better results than any of repressive approaches, usually there are no legal consequences for parental vaccination refusal.

Besides timely vaccination of children, stricter implementation of other aspects of mandatory vaccination programme, such as checking of MMR vaccination status at the end of high school education or at 24 years of age and then receiving all missed vaccinations, if still necessary,[21] would also reduce existence of pockets of susceptibility within residential population, not only in counties characterized by heavy seasonal populational fluctuations but also in Croatia in general.

Supplementary data

Supplementary data are available at *EURPUB* online.

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Conflicts of interest: None declared.

Data availability

The data underlying this article are available in MeaNS2 database at https://who-gmrln.org/means2, and can be accessed with sequence IDs 143155, 143156, 143161, 145334, 145336, 151677 and 151678.

Key points

- Despite the fact that measles elimination in Croatia has been accomplished and successfully maintained for years, vaccination coverage achieved in previous decades is not sufficient to prevent the occurrence of measles in populational pockets of susceptibility, especially in regions characterized by heavy populational fluctuations due to tourism.
- The study emphasizes the importance of timely vaccination of children, but also of the need of stricter implementation of other aspects of Croatian measles prevention programme, such as checking of vaccination status later in life (e.g. at the end of high school education or at 24 years of age, as advised by Croatian Institute of Public Health) and then receiving missed vaccinations, if still necessary.
- Besides persistent education of parents regarding relevance of measles vaccination, it is important that physicians do not support measles vaccine hesitancy without medical reasons.

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