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EPIDEMIOLOGICAL SITUATION OF MEASLES IN ROMANIA, ITALY, AND HUNGARY: ON WHAT THREATS SHOULD WE FOCUS NOWADAYS?

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Although the prevalence of wild-type measles virus infection has decreased by >90% in Europe, the disease is still not eliminated and has even reemerged with recurrent outbreaks in different countries, including Romania and Italy. Minor outbreaks of Romanian origin were reported from Hungary as well. In Romania, an outbreak has been ongoing since February 2016. As of October 2017, 9,670 measles cases and 35 deaths were registered in the country. The three most affected counties are located next to the Hungarian border. In Italy, until the end of August 2017, 4,477 cases were reported to the surveillance system. The outbreak affected most of the Italian administrative regions. Until October 2017, three minor measles outbreaks were also detected in Hungary. All of these outbreaks were derived from Romanian cases. Although in these countries, there are vaccination programs running, the spread of the disease raises the possibility of secondary vaccine failure.

Keywords: measles, Romania, Italy, Hungary

Introduction

Measles virus (MeV) is the only member of the genus *Morbillivirus* that causes human disease [1]. Measles is highly contagious, susceptible individuals have a 99% probability of acquiring the virus, if they come in close contact with the infected persons [1]. During the prevaccine era, more than 90% of patients contracted the infection before 10 years of age. In unvaccinated populations, MeV still causes periodic epidemics, with interepidemic period of 2–5 years [1]. The basic reproduction number (R_0 – defined as the average number of secondary cases of an infectious disease arising from a typical case in a totally susceptible

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population) for MeV is 12–18, which is one of the highest known values [2]. R_0 also determines the herd immunity threshold and therefore the vaccination coverage required to achieve elimination. As R_0 increases, higher immunization level is required in the population (Figure 1) [2]. In the case of measles, the critical immunization threshold (q_c) is about 94% based on the following formula: $q_c = 1 - 1/R_0$ (Figure 1) [2, 3].

In 2001, the World Health Organization (WHO) has launched a program to eliminate measles [3]. This is promising, because MeV is a human-specific virus, against which safe and potent vaccines are available [1]. Though the prevalence of wild-type MeV infection has decreased by >90% in Europe, measles is still not eliminated and has even re-emerged with recurrent outbreaks in different countries, including Romania and Italy. Minor outbreaks of Romanian origin were reported from Hungary as well [4, 5]. As EU citizens can travel freely in these countries, the chance of measles import into the neighboring areas increases. The aim of this work is to shed light on the current epidemiologic situation in these countries and on possible consequences for Hungary.

Situation in Romania

A measles outbreak in Romania has been ongoing since February 2016 [5]. As of October 2017, on the website of National Public Health Institute of Romania

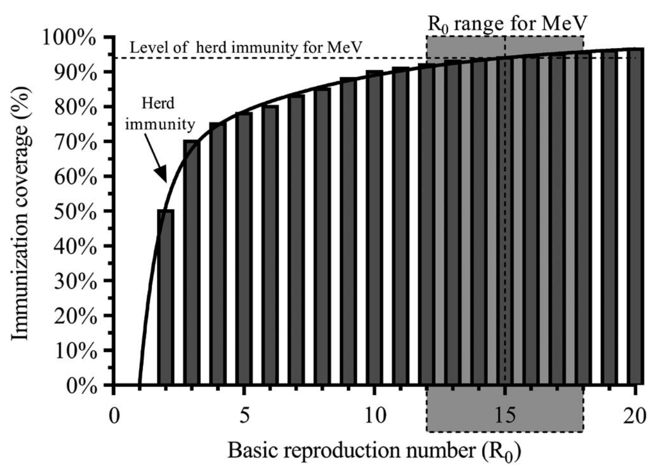

Figure 1. MeV basic reproduction number (R_0), herd immunity, and immunization coverage. As R_0 increases, higher immunization coverage is needed to achieve herd immunity. Gray zone indicates the R_0 estimate of 12–18, the characteristic value of measles [2]

(INSP), 9,670 measles cases and 35 deaths were registered (http://cnscbt.ro/index.php/informari-saptamanale/rujeola-1). Based on the data of this website, the prevalence of laboratory-confirmed cases, the incidence of new occurrences by week, deaths, and mortality of the outbreak were calculated (Figure 2). The mean mortality value is 0.44%, which is higher than usual in the developed countries [6]. Based on the data available on the website of INSP, 46% of deaths occurred between 0 and 1 years of age, 40% between 1 and 10 years of age, and 14% of the deceased were older than 10 years. In 60% of mortality, there were underlying diseases detected. The cause of death was mostly pneumonia (91%). None of the deceased was vaccinated.

The continuous outbreak is driven presumably by poor surveillance quality and suboptimal population immunity [4]. The vaccination coverage in Romania is below 90% [4].

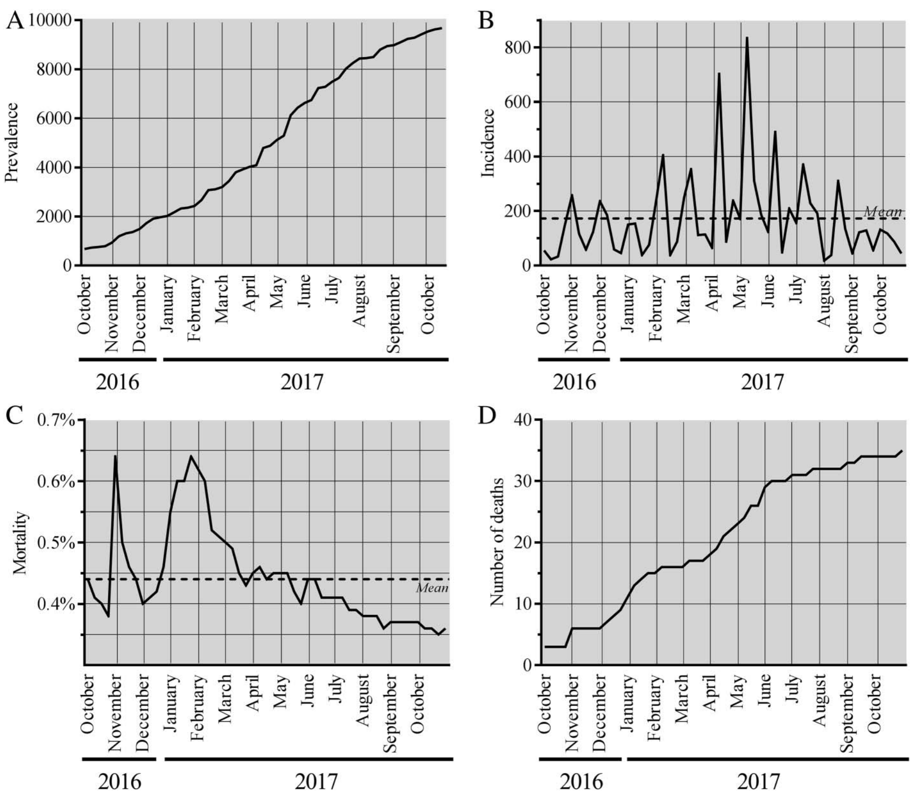

Figure 2. (A) Prevalence, (B) incidence, (C) value of calculated mortality, and (D) number of death cases of the ongoing measles outbreak in Romania

Thirty-eight out of the 41 Romanian counties are affected with the disease and in six of these, the morbidity rate per 100,000 people is higher than 99.01 (Figure 3). Among these six counties, three (Timiş, Arad, and Satu Mare) are located next to the Hungarian border (Figure 3).

Situation in Italy

In January 2017, the Italian National Health Institute (ISS) detected an increase in the number of measles cases. ISS immediately started to intensify surveillance and investigate the outbreak. Until the end of August 2017, 4,477 cases were reported to the surveillance system, of which 76.3% were laboratory-confirmed [7]. The current outbreak affected most of the Italian administrative regions (Figure 4) [7]. Based on the data of ISS, 88% of the cases were unvaccinated and 6.6% occurred among healthcare workers. Three deaths due to respiratory insufficiency were detected among children aged 16 months, 6 years, and 9 years, respectively. All of them were unvaccinated. Measles was laboratory-confirmed in all of the deceased children [7]. Based on the data of the WHO Measles Nucleotide Surveillance Database (MeaNS; www.who-measles.org), the strains turned from D8 to B3 genotype at the beginning of 2017. Vaccination coverage

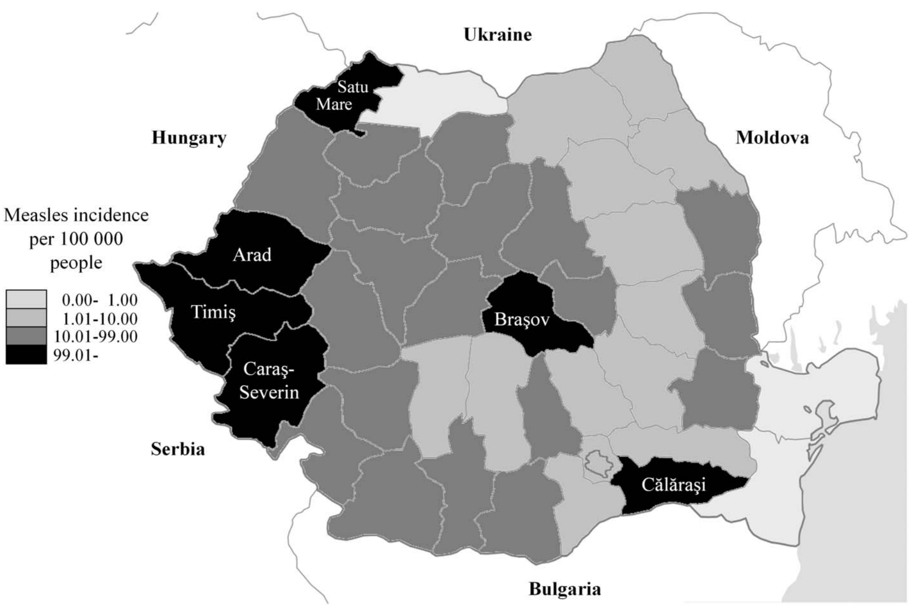

Figure 3. Measles incidence per 100,000 people in Romanian counties in 2017

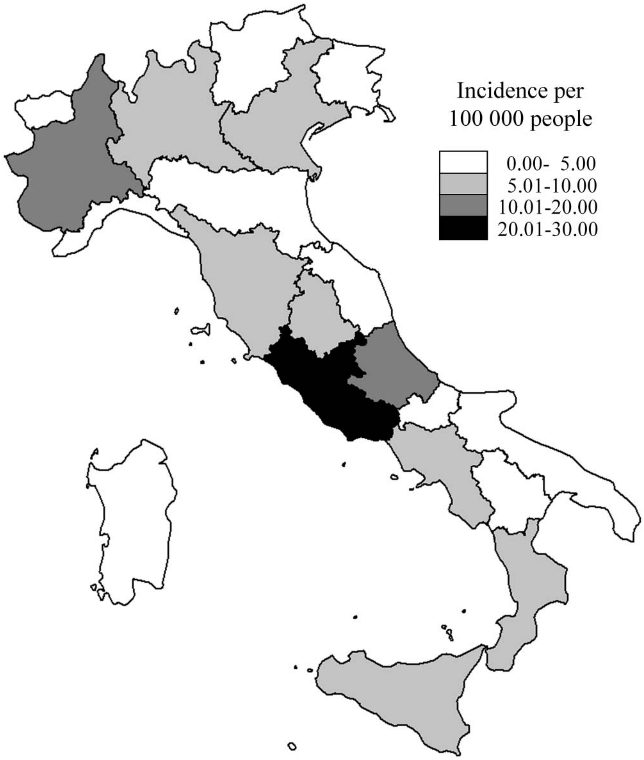

Figure 4. Measles incidence per 100,000 people in Italian provinces in 2017

is below 90% in Italy nowadays [7]. Decreased uptake of measles vaccine in the country in recent years is the result of vaccine hesitancy.

The size of the described outbreak highlights that there are wide measles immunity gaps in the Italian population, which is challenging to elimination [7]. The connection between the Romanian and Italian epidemics cannot be ruled out, since in the MeaNS database, the same genotype (B3) was registered during 2017.

Consequences for Hungary

The measles vaccination program is very effective in Hungary, since the introduction of the mandatory vaccination in 1969 [8]. In 1984, the administration of the vaccine was postponed from 12 to 15 months of age, to provide more permanent immunity. To further strengthen the immunological reaction, revaccination was also first organized in 1990 to decrease the number of persons without appropriate immune response [8, 9]. As a result of the vaccination program, more than 99.5% of the population has been vaccinated, which eliminated the regular circulation of MeV in Hungary [8, 9]. However, lifelong immunity after active immunization is disputable due to primary or secondary vaccine failure [3, 10].

To support this, we examined the data about imported measles cases in the literature in 2017. To our knowledge, until October, three minor measles outbreaks were detected in the country. All of these outbreaks were derived from Romanian cases.

The first occurrences were detected from January 29, 2017 until March 10, 2017 in Makó and Szeged. During this period, 54 cases with measles-specific clinical symptoms were reported [5]. About 15 cases were confirmed and the remaining 39 could be excluded by laboratory methods. Based on sequencing of viral RNA genome, five cases revealed genotype B3 (data were kindly provided by Dr. Zita Rigó, National Reference Laboratory for Measles and Rubella, National Public Health Institute, Budapest, Hungary), which were identical with the Romanian and Italian genotypes based on the data of the MeaNS. Thus, the connection with the Romanian epidemic seems to be supported. In consequence of efforts and interventions, including active measles surveillance, quarantine, isolation, aspecific preventive measures (medical examination, education, and usage of protective equipment), observing in-patients, epidemiological monitoring of healthcare workers, immunological screening, and post-exposure vaccination, the public health office could successfully terminate the occurrence of further measles cases in Csongrád County. Of note, the high vaccination coverage (>99%) of the Hungarian population also played an important role in this success [8]. However, the spread of the disease among vaccinated healthcare workers raises the possibility of secondary vaccine failure.

The second group of imported cases was detected at the end of July in Nyíregyháza, Szabolcs-Szatmár-Bereg County. Six unvaccinated Romanian children were admitted to hospital because of typical signs of measles. These cases were also confirmed by the National Reference Laboratory for Measles and Rubella [11]. The disease could spread among the Hungarian population, since the MeV infection of two healthcare workers (who were in close contact with the Romanian children) was also confirmed [11, 12].

The third group was consisted of four Romanian children, temporarily staying in Bács-Kiskun County. The patients were 9, 11, and 13 months and 2 years of age, none of them were vaccinated. These cases were also confirmed by the National Reference Laboratory for Measles and Rubella [13, 14]. There was no spreading detected among the Hungarian population [13, 14].

These data, in line with a recent study, raise the possibility of gaps in population-level immunity against measles in Hungary [15]. Several reports describe a significant proportion of secondary vaccine failure in populations with sustained high vaccination coverage after long absence of MeV transmission with the resultant lack of natural boosting, and waning of both the concentration as well as the avidity of anti-measles IgG antibodies [10, 16–19]. Although avidity of antibodies may slightly decrease with time, majority of the population with secondary vaccine failure are characterized by antibodies of high-avidity index. Such outbreaks were registered in Russia, Belarus, Germany, and Slovenia [10, 17, 18].

The finding that high proportions of secondary vaccine failure were detected in countries with well working vaccination programs emphasizes the necessity of studies assessing population immunity against MeV [10].

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Bellini, W. J., Icenogle, J. P.: Measles and rubella viruses. In Versalovic, J., Carroll, K. C., Funke, G., Jorgensen, J. H. (eds): Manual of Clinical Microbiology, 10^{th} Edition. ASM Press, Washington, 2011, pp. 1372–1387.
2. Guerra, F. M., Bolotin, S., Lim, G., Heffernan, J., Deeks, S. L., Li, Y., Crowcroft, N. S.: The basic reproduction number (R_0) of measles: A systematic review. Lancet Infect Dis **17**, e420–e428 (2017).
3. Holzmann, H., Hengel, H., Tenbusch, M., Doerr, H. W.: Eradication of measles: Remaining challenges. Med Microbiol Immunol **205**, 201–208 (2016).
4. Kriss, J. L., Stanescu, A., Pistol, A., Butu, C., Goodson, J. L.: The World Health Organization Measles Programmatic Risk Assessment Tool – Romania, 2015. Risk Anal **37**, 1096–1107 (2017).
5. European Centre for Disease Prevention and Control: Epidemiological Update: Measles – Monitoring European Outbreaks, 7 July 2017. ECDC, Solna, Sweden, 2017.
6. Rota, P. A., Moss, W. J., Takeda, M., de Swart, R. L., Thompson, K. M., Goodson, J. L.: Measles. Nat Rev Dis Primers **2**, 16049 (2016).
7. Filia, A., Bella, A., Del Manso, M., Baggieri, M., Magurano, F., Rota, M. C.: Ongoing outbreak with well over 4,000 measles cases in Italy from January to end August 2017 – What is making elimination so difficult? Euro Surveill **22**, 30614 (2017).

8. Rigo, Z., Szomor, K. N., Nagy, O., Takacs, M.: Are we protected? Imported measles – On the way to eradication. Acta Microbiol Immunol Hung **59**, 119–129 (2012).
9. Vegh, M., Hari-Kovacs, A., Roth, H. W., Facsko, A.: Ophthalmological symptoms of measles and their treatment. Orv Hetil **158**, 1523–1527 (2017).
10. Santibanez, S., Prosenc, K., Lohr, D., Pfaff, G., Jordan Markocic, O., Mankertz, A.: Measles virus spread initiated at international mass gatherings in Europe, 2011. Euro Surveill **19**, 20891 (2014).
11. Emberi Erőforrások Minisztériuma [Ministry of Human Capacities]: Kórházhigiénés és Járványügyi Felügyeleti Főosztály: Heti tájékoztató a hazai járványügyi helyzetről 2017. 31. hét [Deputy State Secretariat for Chief Medical Officer's Affairs of the Ministry of Human Capacities of Hungary: Weekly information on the epidemiological situation, 31st week, 2017]. 2017. Available at https://www.antsz.hu/data/cms83263/2017_31_heti.pdf
12. Emberi Erőforrások Minisztériuma [Ministry of Human Capacities]: Kórházhigiénés és Járványügyi Felügyeleti Főosztály: Heti tájékoztató a hazai járványügyi helyzetről 2017. 33. hét [Deputy State Secretariat for Chief Medical Officer's Affairs of the Ministry of Human Capacities of Hungary: Weekly information on the epidemiological situation, 33rd week, 2017]. 2017. Available at https://www.antsz.hu/data/cms83265/2017_33_heti.pdf
13. Emberi Erőforrások Minisztériuma [Ministry of Human Capacities]: Kórházhigiénés és Járványügyi Felügyeleti Főosztály: Heti tájékoztató a hazai járványügyi helyzetről 2017. 35. hét [Deputy State Secretariat for Chief Medical Officer's Affairs of the Ministry of Human Capacities of Hungary: Weekly information on the epidemiological situation, 35th week, 2017]. 2017. Available at https://www.antsz.hu/data/cms83267/2017_35__honlapheti.pdf
14. Emberi Erőforrások Minisztériuma [Ministry of Human Capacities]: Kórházhigiénés és Járványügyi Felügyeleti Főosztály: Heti tájékoztató a hazai járványügyi helyzetről 2017. 34. hét [Deputy State Secretariat for Chief Medical Officer's Affairs of the Ministry of Human Capacities of Hungary: Weekly information on the epidemiological situation, 34th week, 2017]. 2017. Available at https://www.antsz.hu/data/cms83266/2017_34_heti.pdf
15. Böröcz, K., Csizmadia, Z., Mészáros, V., Varga, V., Telek, V., Farkas, K., Balogh, P., Berki, T., Németh, P.: A measles vaccine efficacy study – Identifying potentially susceptible cohorts in Hungary. Immunol Q **9**, 8–9 (2017).
16. Kontio, M., Jokinen, S., Paunio, M., Peltola, H., Davidkin, I.: Waning antibody levels and avidity: Implications for MMR vaccine-induced protection. J Infect Dis **206**, 1542–1548 (2012).
17. Atrasheuskaya, A. V., Kulak, M. V., Neverov, A. A., Rubin, S., Ignatyev, G. M.: Measles cases in highly vaccinated population of Novosibirsk, Russia, 2000–2005. Vaccine **26**, 2111–2118 (2008).
18. Atrasheuskaya, A. V., Blatun, E. M., Neverov, A. A., Kameneva, S. N., Maksimov, N. L., Karpov, I. A., Ignatyev, G. M.: Measles in Minsk, Belarus, 2001–2003: Clinical, virological and serological parameters. J Clin Virol **34**, 179–185 (2005).
19. Pannuti, C. S., Morello, R. J., Moraes, J. C., Curti, S. P., Afonso, A. M., Camargo, M. C., Souza, V. A.: Identification of primary and secondary measles vaccine failures by measurement of immunoglobulin G avidity in measles cases during the 1997 Sao Paulo epidemic. Clin Diagn Lab Immunol **11**, 119–122 (2004).