Spotlight on measles 2010: Excretion of vaccine strain measles virus in urine and pharyngeal secretions of a child with vaccine associated febrile rash illness, Croatia, March 2010

B Kaic (bernard.kaic@hzjz.hr)[1], I Gjenero-Margan[1], B Aleraj[1], T Vilibic-Cavlek[2], M Santak[3], A Cvitković[4], T Nemeth-Blazic[1], I Ivic Hofman[4]

1. Croatian Institute of Public Health, Department of Infectious Disease Epidemiology, Zagreb, Croatia
2. Croatian Institute of Public Health,Virology Department, Zagreb, Croatia
3. Institute of Immunology, Molecular Biomedicine Unit, Zagreb, Croatia
4. Brodsko-posavska County Institute of Public Health, Slavonski Brod, Croatia

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We describe excretion of measles vaccine strain Schwarz in a child who developed a febrile rash illness eight days after primary immunisation against measles, mumps and rubella. Throat swabs and urine specimens were collected on the fifth and sixth day of illness, respectively. Genotyping demonstrated measles vaccine strain Schwarz (genotype A). If measles and rubella were not under enhanced surveillance in Croatia, the case would have been either misreported as rubella or not recognised at all.

Introduction

Vaccination against measles was introduced into the Croatian vaccination schedule in 1968 for all children at the age of 12 months and at first grade of elementary school. The vaccine containing the Edmonston-Zagreb measles virus strain was produced by the Institute of Immunology, Zagreb. In 1976, the monovalent measles vaccine was replaced by a trivalent measles, mumps, rubella (MMR) vaccine, containing the same Edmonston-Zagreb strain of the same producer. In 2008, 18 cases of vaccine-associated mumps were reported that has resulted from transmission of the mumps component (L-Zagreb) to close contacts of children who had received primary vaccination with this trivalent vaccine [3,4,11]. This vaccine was thereafter replaced by Priorix (GSK; containing the RIT 4385 mumps virus strain and the Schwarz measles virus strain) for the first MMR vaccination in January 2009. The MMR vaccine produced by the Croatian Institute of Immunology is still used for the second dose of MMR. Since the MMR vaccine used for primary vaccination was changed in January 2009, vaccine-associated mumps in contacts of vaccinees have no longer been reported [5].

No suspected measles or rubella cases were reported in Croatia during 2010. In the last five-year period, one local outbreak of rubella occurred in Croatia in 2007, affecting 39 adolescents and one outbreak of measles in 2008, affecting 51 people. The illness in the index cases of both outbreaks was imported. Independently of these two outbreaks, only five cases of measles and another five cases of rubella were reported in Croatia from 2005 to 2009, which were eventually discarded by serology or classified as imported. After receiving information on a measles outbreak in Roma children in Bulgaria in 2009 [6,7] and media reports on rubella cases in neighbouring Bosnia and Herzegovina, the Croatian Institute of Public Health sent a circular letter to healthcare workers in Croatia on 15 March 2010 to raise awareness of possible importations of measles and rubella.

Four suspected rubella cases were notified in Croatia in the second half of March 2010. Three cases were discarded based on negative serology for measles and rubella and lack of epidemiological link to a possible source. One case may have had a chance to be exposed to rubella but also had a history of MMR vaccination and is described here.

Case description

A healthy child (14 months-old) was vaccinated on 9 March 2010 with Priorix MMR vaccine according to the Croatian childhood vaccination schedule. The child had facial erythema without fever on 14 March and developed a macular rash and fever on 17 March. It was examined on 21 March at the county hospital and reported as a possible case of rubella to the epidemiology department at the County Institute of Public Health on 23 March.

Since rubella and measles are under enhanced surveillance according to the national action plan for measles and rubella elimination, an epidemiological investigation was initiated, and serum, urine and throat swab specimens for laboratory testing were obtained. The investigation found no similar cases among contacts of the patient. A source of rubella infection was not

identified, however, possible exposure to rubella or measles virus could not be completely excluded, because the child had travelled abroad during the two weeks preceding the illness.

A serum sample and throat swabs were taken on 23 March and a urine specimen on 24 March. On 26 March, the rash was still present. Serum was obtained again from the convalescent child on 11 April. In addition, a serum sample from the asymptomatic pregnant mother was obtained on 24 March.

Laboratory investigation

Serologic tests of the patient and mother were performed at the World Health Organization (WHO) national measles laboratory, Virology Department, Croatian Institute of Public Health. For the detection of specific measles and rubella IgM and IgG antibodies we used commercial ELISA (Rubella IgM/IgG: Dia Sorin; Measles IgM/IgG: Genzyme Virotech GmbH). For detection of specific mumps IgM and IgG antibodies, a commercial immunofluorescence test was used (Euroimmun). Throat swab and urine were initially tested for measles virus at the Department of Molecular Diagnostics, Croatian Institute of Public Health using real-time RT-PCR (Applied Biosystems), using the primer/probe set for the measles virus nucleoprotein (N) gene [2].

The child's paired sera were tested in parallel. The first serum tested negative for IgM and IgG antibodies against rubella virus and mumps virus, while measles antibodies were equivocal for IgM and negative for IgG. The child's second serum obtained on 11 April also tested negative for both IgM and IgG rubella antibodies, while measles antibodies were negative for IgM, but IgG-positive, and mumps antibodies were postitive for IgM as well as for IgG. The mother was negative for IgM and positive for IgG antibodies against both measles and rubella virus (the mother's vaccination status could not be determined with certainty). The child's throat swab was negative in RT-PCR for measles RNA, while the urine tested positive.

An additional RT-PCR was performed, targeting the 3'-end of the N gene [1]. PCR products were obtained from throat swab and urine, sequenced and compared using the BLAST algorithm, and finally identified as Schwarz vaccine strain (genotype A).

Discussion

We demonstrated excretion of the Schwarz measles vaccine virus in a child with a vaccine-associated febrile rash illness in urine and in pharyngeal excretions.

Virus excretion in vaccinees has been reported before [8-10], but to our knowledge, this is documented for the first time for the Schwarz vaccine strain. Interestingly, although the blood for serology testing was obtained 14 and 32 days after vaccination, the child still had no antibodies to rubella virus in either serum sample. It is unclear why there was no seroconversion to rubella 32 days after vaccination, although this is not an unusual finding. The dynamics of measles and mumps antibodies were as expected for someone who had either been vaccinated or had natural infection, indicating that the child did not have impaired antibody production kinetics in general.

According to WHO guidelines for measles and rubella elimination, routine discrimination between aetiologies of febrile rash disease is done by antibody assays, not necessarily by virus detection [12]. However, in a patient recently MMR-vaccinated, only molecular techniques can differentiate between wildtype measles or rubella infection or vaccine-associated disease.

This case report demonstrates that excretion of Schwarz measles virus occurs in vaccinees. Also, it demonstrates a need to strengthen surveillance of measles and rubella cases continuously, also in countries that are currently approaching elimination of measles and rubella.

Competing interests:
Maja Santak is an employee of the Institute of Immunology, Zagreb, the national vaccine producer.

References

1. Forcić D, Baricević M, Zgorelec R, Kruzić V, Kaić B, Marina BM, et al. Detection and characterization of measles virus strains in cases of subacute sclerosing panencephalitis in Croatia. Virus Res. 2004;99(1):51-6.
2. Hummel KB, Lowe L, Bellini WJ, Rota PA. Development of quantitative gene-specific real-time RT-PCR assays for the detection of measles virus in clinical specimens. J Virol Methods. 2006;132(1-2):166-73.
3. Kaic B, Aleraj B, Ljubicic M, Gjenero-Margan I, Nemeth-Blazic T, Simunovic A et al. Adverse events following immunization in Croatia in 2005. [Croatian]. Report. Zagreb: Croatian Institute of Public Health, 2006.
4. Kaic B, Gjenero-Margan I, Aleraj B, Ljubin-Sternak S, Vilibic-Cavlek T, Kilvain S, et al. Transmission of the L-Zagreb mumps vaccine virus, Croatia, 2005-2008. Euro Surveill. 2008;13(16):pii=18843. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=18843
5. Kaic B, Gjenero-Margan I, Aleraj B, Ljubicic M, Nemeth-Blazic T, Simunovic A, et al. Adverse events following immunization in Croatia in 2007-2008. [Croatian]. Report. Zagreb: Croatian Institute of Public Health, 2008. [Accessed 10 May 2010]. Available from: http://www.hzjz.hr/epidemiologija/nuspojave2008.pdf
6. Marinova L, Kojouharova M, Mihneva Z. An ongoing measles outbreak in Bulgaria, 2009. Euro Surveill. 2009;14(26):pii=19259. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19259
7. Marinova L, Muscat M, Mihneva Z, Kojouharova M. An update on an ongoing measles outbreak in Bulgaria, April-November 2009. Euro Surveill. 2009;14(50):pii=19442. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19442
8. Morfin F, Beguin A, Lina B, Thouvenot D. Detection of measles vaccine in the throat of a vaccinated child. Vaccine. 2002;20(11-12):1541-3.
9. Rota PA, Khan AS, Durigon E, Yuran T, Villamarzo YS, Bellini WJ.. Detection of measles virus RNA in urine specimens from vaccine recipients. J Clin Microbiol. 1995;33(9):2485-8.
10. Strebel PM, Papania MJ, Dayan GH, Halsey NA. Measles vaccine. In: Plotkin S, Orenstein W, Offit P, editors. Vaccines. 5th ed. Philadelphia: Elsevier; 2009.
11. Tesović G, Poljak M, Lunar MM, Kocjan BJ, Seme K, Vukić BT, et al. Horizontal transmission of the Leningrad-Zagreb mumps vaccine strain: a report of three cases. Vaccine. 2008;26(16):1922-5.
12. World Health Organization. Surveillance Guidelines for Measles, Rubella and Congenital Rubella Syndrome in the WHO European Region. Copenhagen: WHO; 2009. p.6-14. Available from: http://www.euro.who.int/__data/assets/pdf_file/0018/79020/E93035.pdf