

Increased reports of measles in the Metropolitan City of Milan, northern Italy, September 2023 to March 2024

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Citation style for this article:

Gori Maria, Fappani Clara, Bianchi Silvia, Senatore Sabrina, Colzani Daniela, Pasutto Priscilla, Baggieri Melissa, Gioacchini Silvia, Marchi Antonella, Bucci Paola, D'Ugo Emilio, Faccini Marino, Cereda Danilo, Vezzosi Luigi, Tanzi Elisabetta, Magurano Fabio, Amendola Antonella. Increased reports of measles in the Metropolitan City of Milan, northern Italy, September 2023 to March 2024. *Euro Surveill.* 2024;29(16):pii=2400201. <https://doi.org/10.2807/1560-7917.ES.2024.29.16.2400201>

Article received on 03 Apr 2024 / Accepted on 11 Apr 2024 / Published on 18 Apr 2024

Since late 2023, the Metropolitan City of Milan and surrounding areas (northern Italy) have been experiencing a resurgence of measles, with most cases detected starting from January 2024. During this brief period, we observed measles in travellers from endemic areas, participants in international events, vaccinees and healthcare workers. Indigenous cases have also been identified. Even though we have not yet identified large and disruptive outbreaks, strengthening surveillance and vaccination activities is pivotal to help limit the impact of measles spread.

Since 1 January 2023, the World Health Organization (WHO) European Region countries have documented an alarming resurgence of measles, showing an increase of over 30 times compared with the previous year [1], with large or disruptive outbreaks in Romania, Austria and France [2]. Italy also reported a significant measles resurgence, with 31 confirmed cases between September and December 2023 and 181 between 1 January and 31 March 2024 [3].

As Subnational Reference Laboratory of the Italian measles and rubella surveillance network MoRoNet [4] in the Metropolitan City of Milan and surrounding areas (nearly 4 million inhabitants, Lombardy region, northern Italy), we observed that measles activity began to increase in September 2023 after a period of low activity (August 2019–August 2023). Here we report the latest updates on measles resurgence in the area under surveillance.

Latest updates on measles cases

We investigated 30 suspected measles cases between September 2023 and March 2024, 13 of which were

confirmed through the detection of virus-specific IgM antibodies in serum by enzyme-linked immunosorbent assay, and measles virus (MeV) RNA in paired urine and oropharyngeal swabs samples by real-time retrotranscription (RT) PCR [5]. Notably, nine of the 13 confirmed cases were detected between January and March 2024 (Figure 1).

The median age of the 13 confirmed cases was 33 years (range: 1–49 years), and eight cases were hospitalised. Two cases were fully vaccinated, and one case received one dose of measles-containing vaccine (Table). Eleven of the 13 confirmed cases had a history of travel (to Indonesia, Malaysia, India, Uzbekistan, Thailand and two to other regions in Italy) or were linked to travel-related cases. In detail, Case 2 returned from Malaysia and attended the same business meeting as Case 3, Case 10 was a fully vaccinated healthcare worker, likely infected in the emergency department where Case 9, a returning traveller from Thailand, was admitted.

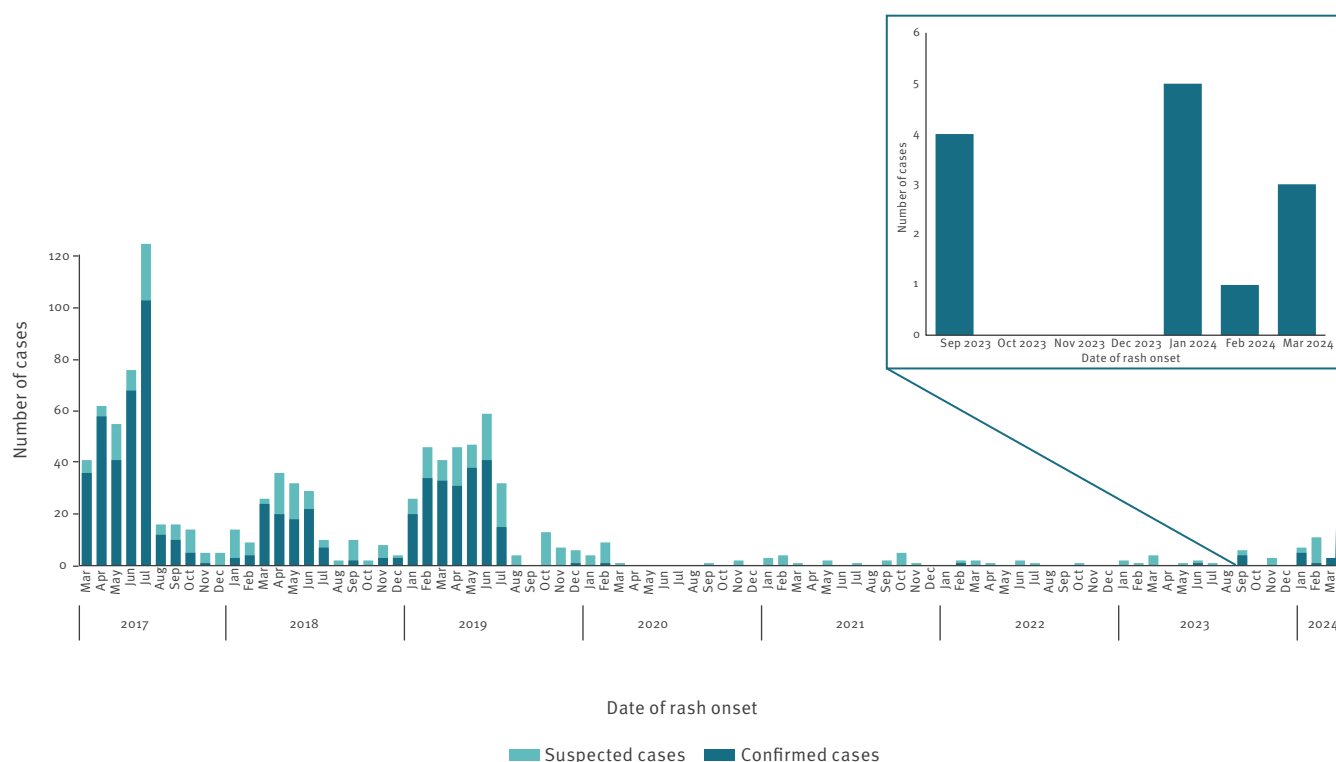
At the time of writing, we have confirmed three cases (Cases 11, 12 and 13) returning from the same international exhibition held in northern Italy in week 9 2024.

Genotyping and phylogenetic analysis

Isolates from the confirmed cases were successfully genotyped by amplifying and sequencing the highly variable 450 nucleotide (nt) region in the C-terminal of the nucleoprotein (N-450) according to the WHO manual [5]. All sequences were classified as genotype D8 (Figure 2).

FIGURE 1

Suspected (n = 1,010) and confirmed (n = 669) measles cases in the Metropolitan City of Milan and surrounding areas, Italy, March 2017–March 2024



TABLE

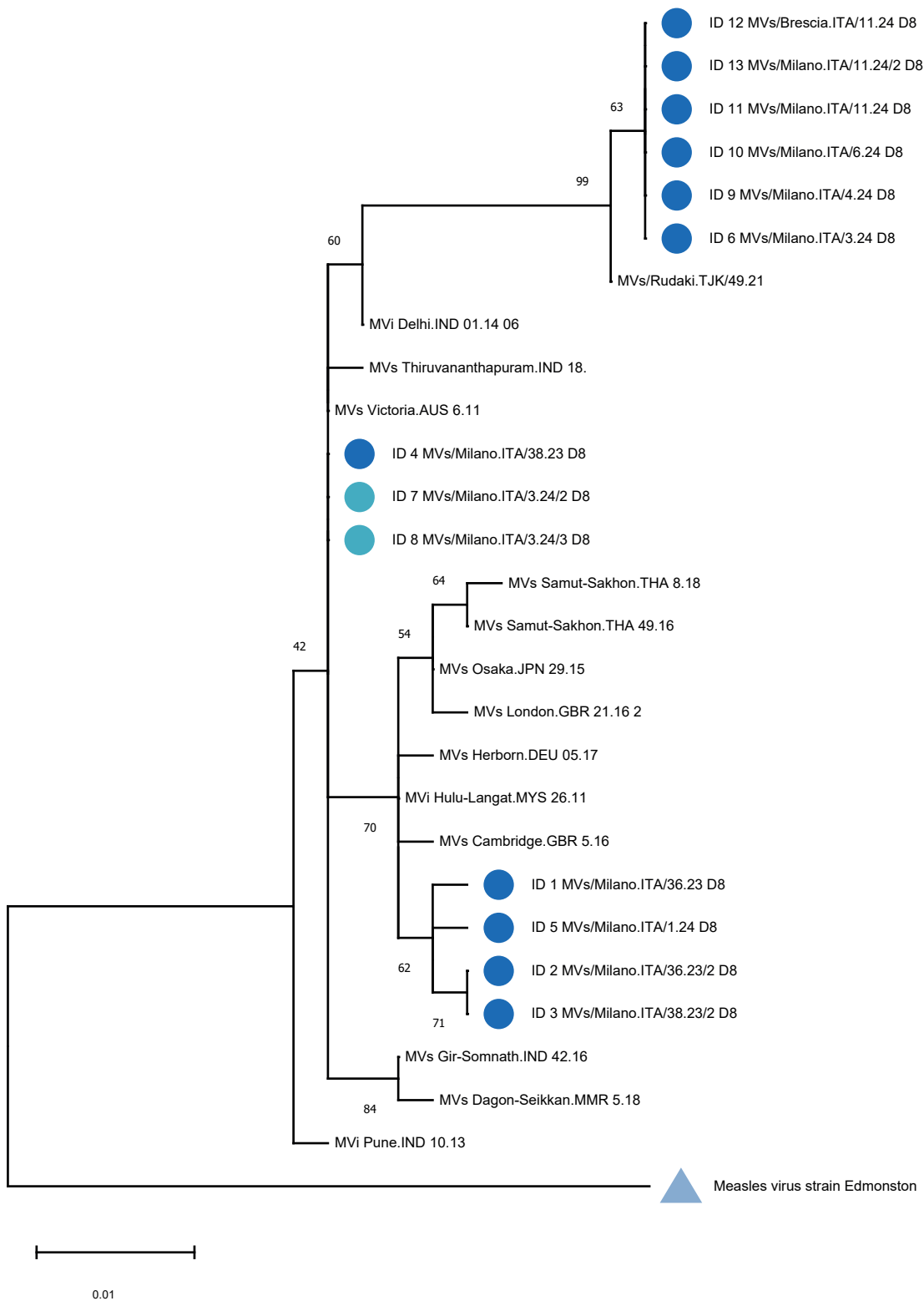
Confirmed measles cases in the Metropolitan City of Milan and surrounding areas, Italy, September 2023–March 2024 (n = 13)

Case ID	Date of rash onset	Vaccination status	Hospitalisation	Genotype	MeanS2 DSId	Source	Sequence name
1	7 Sept 2023	Yes, 1 dose	Yes	D8	8383	Travel (Indonesia or Singapore)	MVs/Milano.ITA/36.23
2	8 Sep 2023	No	Yes	D8	8477	Travel (Malaysia)	MVs/Milano.ITA/36.23/2
3	20 Sep 2023	No	Yes	D8	8477	Travel-spread (linked to Case 2)	MVs/Milano.ITA/38.23/2
4	21 Sep 2023	Yes, 2 doses	No	D8	2279	Travel (India)	MVs/Milano.ITA/38.23
5	6 Jan 2024	No	No	D8	8581	Travel (Uzbekistan)	MVs/Milano.ITA/1.24
6	15 Jan 2024	No	Yes	D8	8491	Travel (Italy)	MVs/Milano.ITA/3.24
7	19 Jan 2024	No	Yes	D8	2279	Indigenous	MVs/Milano.ITA/3.24/2
8	19 Jan 2024	No	Yes	D8	2279	Indigenous	MVs/Milano.ITA/3.24/3
9	23 Jan 2024	No	Yes	D8	8491	Travel (Thailand)	MVs/Milano.ITA/4.24
10	6 Feb 2024	Yes, 2 doses	No	D8	8491	Travel-spread (linked to Case 9)	MVs/Milano.ITA/6.24
11	12 Mar 2024	No	Yes	D8	8491	Travel (Italy)	MVs/Milano.ITA/11.24
12	12 Mar 2024	No	No	D8	8491	Travel (Italy)	MVs/Brescia.ITA/11.24
13	12 Mar 2024	No	No	D8	8491	Travel (Italy)	MVs/Milano.ITA/11.24/2

MeanS2: World Health Organization Measles Virus Nucleotide Surveillance; DSId: distinct sequence identifier.

FIGURE 2

Phylogenetic analysis of measles isolates identified in the Metropolitan city of Milan and surrounding areas, Italy, September 2023–March 2024 (n = 13)



The tree was constructed using genotype A strain MVs/Vaccine/Edmonston as outgroup (grey triangle).

Evolutionary analyses were conducted in MEGA11 [13]. The evolutionary history was inferred by using the Maximum Likelihood method based on the Kimura 2-parameter model [14]. Branch support (1,000 bootstrap iterations [15]) is provided next to the nodes. The tree with the highest log likelihood (-918.56) is shown. The percentage of trees in which the associated taxa clustered together is shown next to the branches. Initial tree(s) for the heuristic search were obtained automatically by applying Neighbour-Join and BioNJ algorithms to a matrix of pairwise distances estimated using the Maximum Composite Likelihood (MCL) approach, and then selecting the topology with superior log likelihood value. The phylogenetic tree includes sequences from travel-related cases and linked to travel-related cases (blue circles) and indigenous cases (light blue circles).

All isolates were submitted to the GenBank sequence database (<https://www.ncbi.nlm.nih.gov/genbank/>) [6] (accession numbers: PP334141–PP334142 and PP556752–PP556762) and deposited in the WHO Measles Virus Nt Surveillance database (MeaNS2, <https://who-gmrln.org/means2>) [7]. Five different Distinct Sequence Identifiers (DSId) were assigned (8383, 8477, 2279, 8581, 8491). Notably, six sequences were identical and belonged to a previously described variant, namely DSId 8491 [8,9].

Discussion

Prior to the COVID-19 pandemic period, we observed three epidemic peaks in the Metropolitan City of Milan and surrounding areas: March–June 2017, April–June 2018 and January–July 2019 [10]. Since August 2019, we noticed a significant drop in measles cases with only four confirmed cases of 86 suspected as of August 2023, none of which was autochthonous.

Those affected between September 2023 and March 2024 were mostly adults and young adults; two cases were fully vaccinated and one case received one dose of measles-containing vaccine.

To note, we noticed an increase in the number of measles cases after the holiday seasons, in September 2023 and January 2024. However, since January 2024, we have continued to observe measles cases. Almost all confirmed cases had a history of travel or were linked to travel-related cases. We have also observed two non-travel-related cases (Cases 7 and 8, referred to as indigenous), which had not been detected since 2019. Although these two cases were affected by the same DSId 2279 and lived north-west of Milan, no epidemiological correlation was found, suggesting the presence of underreported cases in mid-January 2024. In the aftermath, a provision of the Italian regional health authorities raised the attention on measles surveillance, investigating all cases with fever and rash (Regional regulation n. G1.2024.0004194, 6 February 2024).

Overall, we observed five different genotype D8 DSIds from Asia and from two other Italian regions, suggesting multiple introductions of MeV; however, in contrast to outbreaks that occurred between 2017 and 2019 [10,11], no onward transmission was observed so far. This could be due to the major effort of the competent authorities to improve vaccination coverage and recommend vaccination in fragile populations, travellers and healthcare workers (Regional regulation n. G1.2024.0004194, 6 February 2024). Indeed, the Lombardy Region currently has achieved 96% vaccination coverage of the first dose of measles-containing vaccine and 93% for the second dose (unpublished data).

Particular attention should be paid to DSId 8491 that was the most frequent variant, being detected in six cases. The first case affected with this variant was

identified in Italy in mid-January [9] and was also responsible for an outbreak in the Federation of Bosnia and Herzegovina between December 2023 and February 2024 [12]. At the time of writing (March 2024) we have observed three cases (Cases 11, 12 and 13) who had attended the same international exhibition, which may represent a potential superspreading event. The Italian national health authorities were promptly alerted. These cases were affected by the DSId 8491 variant. Importantly, it has been demonstrated that this D8 variant can be detected with reduced sensitivity by some currently used diagnostic tests [8].

The probability of exposure to MeV is expected to rise in the coming weeks due to the typical seasonal pattern of the virus [2].

Of note, the area under surveillance represents the most important Italian connection to central and northern Europe, with tourist, migratory and business mobility of people, which increases the risk of importation as well as exportation of measles between countries.

Conclusion

Measles is on the rise in the Metropolitan City of Milan and surrounding areas, mainly among adults and also involving vaccinated individuals and healthcare workers. Even though we have not yet identified large and disruptive outbreaks, strengthening fever and rash surveillance and catch-up vaccination activities is pivotal to help limit the impact of cross-border transmission following travels to endemic countries, and facilitate control of new clusters.

Ethical statement

Ethical review and approval and patient consent were waived for this study as it was carried out as part of the Integrated Measles-Rubella Surveillance, performed by law in accordance with the Prime Minister's Decree of 3 March 2017 (<https://www.gazzettaufficiale.it/eli/id/2017/05/12/17A03142/sg>).

Funding statement

This research was funded by the Lombardy Region (Regional Surveillance and Control Plan for measles and rubella, Decree n. 2131, 1 March 2017, approved by DGR XI/3450, 28 July 2020).

Use of artificial intelligence tools

None declared.

Data availability

Sequence data associated with this study have been deposited in the MeaNS2 database, and in GenBank under identification numbers PP334141–PP334142 and PP556752–PP556762.

Acknowledgements

The authors wish to thank Marco Mentasti and the staff of the General Directorate of Welfare of the Lombardy Region for the help in retrieving the epidemiological data.

Conflict of interest

None declared.

Authors' contributions

Conceptualisation: SB and AA; investigation: MG, CF, SB, DCo, SS, MF, DCe and LV; data curation: MG, CF, and SB; writing—original draft preparation: MG, CF, SB and AA; contributed analysis: MG, CF, SB, DCo, PP, MB, SG, AM, PB, and ED; project administration: FM and AA; supervision: ET, FM, and AA; resources: DCe; funding acquisition: AA; writing—review and editing: SS, ET, FM and AA.

References

1. World Health Organization Regional Office for Europe (WHO/Europe). A 30-fold rise of measles cases in 2023 in the WHO European Region warrants urgent action. Copenhagen: WHO/Europe; 14 Dec 2023. Available from: <https://www.who.int/europe/news/item/14-12-2023-a-30-fold-rise-of-measles-cases-in-2023-in-the-who-european-region-warrants-urgent-action>
2. European Centre for Disease Prevention and Control (ECDC). Measles on the rise in the EU/EEA: considerations for public health response. Stockholm: ECDC; 16 Feb 2024. Available from: <https://www.ecdc.europa.eu/en/publications-data/threat-assessment-brief-measles-rise-eueea-considerations-public-health-response>
3. Istituto Superiore di Sanità (ISS). Il bollettino della sorveglianza integrata morbillo-rosolia. [Integrated surveillance for measles and rubella bulletin]. Rome: ISS; 5 Apr 2024. Italian. Available from: https://www.epicentro.iss.it/morbillo/bollettino/RM_News_2024_71.pdf
4. Istituto Superiore di Sanità (ISS). MoRoNet Lab | liberi dal morbillo e dalla rosolia. [MoRoNet; free from measles and rubella]. Rome: ISS. [Accessed: 3 Apr 2024]. Italian. Available from: <https://moronetlab.it/>
5. World Health Organization (WHO). Manual for the laboratory diagnosis of measles and rubella virus infection, 2nd edition. Geneva: WHO; 1 Jan 2007. Available at: <https://www.who.int/publications-detail-redirect/WHO-IVB-07.01>
6. Benson DA, Cavanaugh M, Clark K, Karsch-Mizrachi I, Lipman DJ, Ostell J, et al. GenBank. *Nucleic Acids Res.* 2013;41(Database issue) D1:D36-42. PMID: 23193287
7. Genetic diversity of wild-type measles viruses and the global measles nucleotide surveillance database (MeaNS). *Wkly Epidemiol Rec.* 2015;90(30):373-80. PMID: 26211016
8. Pérez-Rodríguez FJ, Cherpillod P, Thomasson V, Vetter P, Schibler M. Identification of a measles variant displaying mutations impacting molecular diagnostics, Geneva, Switzerland, 2023. *Euro Surveill.* 2024;29(5):2400034. <https://doi.org/10.2807/1560-7917.ES.2024.29.5.2400034> PMID: 38304951
9. Fappani C, Gori M, Bianchi S, Canuti M, Colzani D, Baggieri M, et al. Letter to the editor: Further identification of a measles variant displaying mutations impacting molecular diagnostics, Northern Italy, 2024. *Euro Surveill.* 2024;29(7):2400079. <https://doi.org/10.2807/1560-7917.ES.2023.29.7.2400079> PMID: 38362623
10. Fappani C, Gori M, Bianchi S, Terraneo M, Bilardi E, Colzani D, et al. Differential diagnosis of fever and rash cases negative for measles and rubella to complement surveillance activities. *J Med Virol.* 2023;95(10):e29141. <https://doi.org/10.1002/jmv.29141> PMID: 37796084
11. Bianchi S, Faccini M, Lamberti A, Senatore S, Ciceri G, Frati ER, et al. Measles surveillance activities in the Metropolitan Area of Milan during 2017-2018. *J Prev Med Hyg.* 2019;60(4):E286-92. PMID: 31967085
12. Musa S, Salimović-Bešić I, Džambić JB, Tihčić N, Bajramović A, Arapčić S, et al. Ongoing measles outbreak, the Federation of Bosnia and Herzegovina, December 2023 to February 2024. *Euro Surveill.* 2024;29(9):2400107. <https://doi.org/10.2807/1560-7917.ES.2024.29.9.2400107> PMID: 38426241
13. Tamura K, Stecher G, Kumar S. MEGA11: Molecular Evolutionary Genetics Analysis Version 11. *Mol Biol Evol.* 2021;38(7):3022-7. <https://doi.org/10.1093/molbev/msab120> PMID: 33892491
14. Kimura M. A simple method for estimating evolutionary rates of base substitutions through comparative studies of nucleotide sequences. *J Mol Evol.* 1980;16(2):111-20. <https://doi.org/10.1007/BF01731581> PMID: 7463489
15. Felsenstein J. Confidence limits on phylogenies: an approach using the bootstrap. *Evolution.* 1985;39(4):783-91. <https://doi.org/10.2307/2408678> PMID: 28561359

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