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Analysis of a 3-months measles outbreak in western Liguria, Italy: Are hospital safe and healthcare workers reliable?

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ABSTRACT

Background: From January 2017 to June 2018 more than 7000 measles cases were reported in Italy, of which more than 400 among unvaccinated healthcare workers. We described a measles outbreak occurred in Western Liguria, Italy, characterized by a high involvement of healthcare workers and hospital visitors.
Methods: Suspected measles cases and data regarding vaccination status and clinical management of the patients were collected by reviewing 3 different surveillance systems: the routine mandatory notification system, the National Integrated Surveillance System for Measles and Rubella and the regional reference laboratory for measles diagnosis.
Results: Thirty-six cases were reported, with a median age of 31 years and >95% in unvaccinated subjects. One death occurred, 15 cases were hospitalized. Hospital transmission was confirmed or suspected in 12 cases; amongst this cases, 5 were healthcare workers (a gynaecologist, an obstetric nurse, a radiologist, a physiotherapist and a nurse working in an infectious disease ward), all certified unvaccinated. Phylogenetic analysis revealed the circulation of a single B3 genotype variant.
Conclusions: Our experience highlighted the key role of nosocomial transmission and the need for targeted strategies, in particular (i) to implement a measles catch-up immunization campaign in susceptible groups, especially in healthcare workers, (ii) to intensify the check of immunisation status of healthcare workers and to offer vaccination for those who need it, (iii) to improve timeliness and completeness of surveillance systems. Efforts are needed to guarantee the safety of the hospital and the reliability of the healthcare workers. Only high vaccination coverage among HCWs can prevent the diffusion of measles in the hospital setting.

Background

Between January 2017 and February 2018 the number of notified measles cases in Italy, detected by the Italian National Health Institute and reported to the National Measles and Rubella Integrated Surveillance System, increased considerably compared with previous years. In fact, considering only the first two months of 2018, 805 cases were detected, compared to the 663 cases detected in January–February 2017; most cases were recorded in adolescents and young adults due to the suboptimal vaccination coverage, which has led to large pockets of susceptible subjects; the majority of cases were reported in Sicilia, Lazio, Calabria and Liguria regions.

Overall, in the period January 2017–June 2018, Italy was affected by a large measles outbreak, with more than 7000 notified cases, 3263 hospitalizations and 8 deaths [1]. Four hundred and nine measles cases were reported among HealthCare Workers (HCWs), most of which were unvaccinated [1]. Liguria, a region of 1,556,981 inhabitants located in North-West Italy, reported 105 cases in the same period, with a localized outbreak in Imperia, the west-

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ern province of the region, between November 2017 to January 2018.

The aim of the present study is to analyse the Imperia measles outbreak using data collected by different surveillance systems, focusing on the key role of HCWs and hospital setting in determining chains of transmission and the spread of the disease.

Material and methods

Case definitions

According to the European case definitions [2], a measles "confirmed case" is considered any person not recently vaccinated and meeting specific clinical and laboratory criteria, as follows:

- Clinical criteria: any person with fever AND maculo-papular rash AND at least one of the following three: cough, coryza, conjunctivitis.
- Laboratory criteria: at least one of the following four: isolation of measles virus from a clinical specimen; detection of measles virus nucleic acid in a clinical specimen; measles virus specific antibody response characteristic for acute infection in serum or saliva; detection of measles virus antigen by a direct fluorescent antibody (DFA) in a clinical specimen using measles specific monoclonal antibodies.

A "probable case" is considered any person meeting the above-mentioned clinical criteria and with an epidemiological link by human to human transmission. A "possible case" is considered any person meeting only the clinical criteria. Furthermore, cases that did not meet the above-mentioned criteria were assumed as "non-cases".

Data collection

Between November 2017 and January 2018, 38 suspected measles cases were collected by surveillance systems in the western district of the Liguria Region, province of Imperia, 13 of which (34.2%) were reported in the city of Sanremo. Information about laboratory analysis, vaccination status, age, occupational status, contacts and clinical management was obtained by blending data from three surveillance systems: the routine mandatory notification system; the National Integrated Surveillance System for Measles and Rubella; molecular sequencing and genotyping of virus by the regional reference laboratory [1,3,4]. Clinical complications of measles cases reported in our results referred to those reported by the National Integrated Surveillance System for Measles and Rubella and mentioned in the Monthly Measles and Rubella Report of the Italian National Health Institute [1].

Laboratory analysis

Laboratory analysis consisted of two different levels of investigation. The first-level analysis is performed by the peripheral laboratory; it provides measles virus-specific antibodies assessment. Second-level analysis is performed by the Regional Reference laboratory for Measles and Rubella diagnosis, located in the San Martino Policlinic Hospital, Genoa. In accordance with international standards established by the global laboratory network, the second-level laboratory provides rapid detection by real-time and block RT-PCR and genetic characterization by entire sequence analysis of Haemagglutinin-coding region (H) and 450 nucleotides encoding the COOH-terminal 150 aminoacids of the Nucleoprotein (N) in line with the international standards established by the global laboratory network [5,6].

Vaccination status assessment

Vaccination status was assessed for all cases and defined as certified if it was checked by administrative databases, reported if a certified status was not present, but the patient self-declared his or her vaccination status. Due to the lack of availability of computerized databases, a checked vaccination status was not accessible in some older cases.

Transmission setting assessment

A deep investigation about contacts and transmission setting was performed. A case was considered hospital-related if the contact occurred during a hospitalization or a visit to a hospitalized subject; community-related if the nosocomial exposure was excluded. HCWs with measles were considered as hospital -related.

Results

Data were obtained by blending three data sets: the routine mandatory notification system (sample size: 38 cases), the database of the National Integrated Surveillance System for Measles and Rubella (sample size: 38 cases) and the database of the regional reference laboratory (sample size: 36 cases). Data contained in routine mandatory notification system include laboratory, demographic, clinical and transmission setting information. The database of the National Integrated Surveillance System for Measles and Rubella contains laboratory, demographic, clinical, vaccination status, transmission setting and public health measures data. Confirmation of measles cases, including genotyping data, derived from the database of the regional reference laboratory. For 2 cases data from the regional reference laboratory are missing.

Laboratory data

Out of 36 cases registered by regional reference laboratory, measles confirmation was obtained in 34 cases (89.5%), 30 of which had molecular analysis; genotypic analysis was performed in 19 cases and identified one single B3 genotype variant with a >99% homology with other B3 viruses isolated in Italy in 2016–2017 (Fig. 1). Two were non-cases because of negative laboratory results (5.3%). For the 2 cases for whom laboratory data were missing, 1 case was classified as probable (2.6%) and the other one (2.6%) as possible.

Demographic data

Fig. 2 shows the distribution of measles cases. The epidemic peak was reached in January 2018, with 19 cases reported (52.8%). Overall, twenty cases were female (55.6%) and the median age was 31 years (IQR = 6.5–39). As reported in Table 1, the highest number of cases was seen in the age group 15–39 years, while the highest incidence was seen in children aged under 1 year.

Clinical data

Fifteen cases were hospitalized (41.6%). Complications, as defined by the National Integrated Measles–Rubella Surveillance System, were reported in 11 cases (30.6%): transaminase elevation (n = 8; 22.2%), conjunctivitis (n = 4; 11.1%), thrombocytopenia (n = 3; 8.3%), respiratory failure (n = 3; 8.3%), stomatitis (n = 2; 5.6%), laryngotracheobronchitis (n = 2; 5.4%), diarrhea (n = 2; 5.4%), pneumonia (n = 2; 5.4%). One case died (2.7%) due to measles complications (pneumonia and respiratory failure).

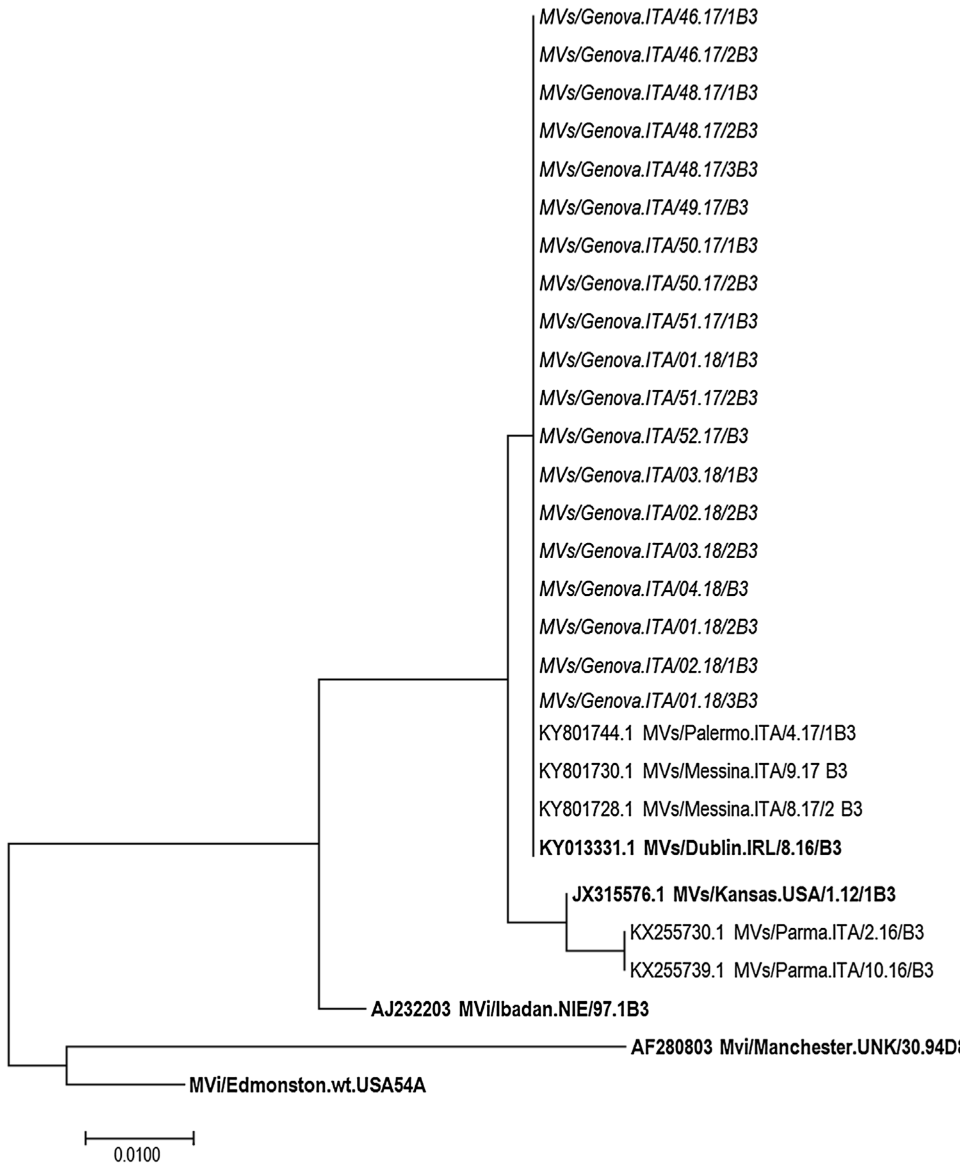

Fig. 1. Neighbour-joining tree for measles nucleotide sequences, based on COOH-terminal N gene, including WHO reference strains (bold), selected B3 viruses isolated in Italy in 2016–2017 and measles strains (italics, n = 19) detected in Liguria, November 2017.

Vaccination status

Vaccination status was known for all cases (n = 36), 94.4% (n = 34) of which were unvaccinated and 5.6% (n = 2) had received only one dose of measles-containing vaccine. A certified vaccination status, checked by administrative databases, was available for 23 cases (63.9%), 22 of which were unvaccinated (95.7%), while one case received one dose of measles-containing vaccine (4.3%) ten months before the outbreak. An anamnestic reported vaccination status was available for 13 cases (36.1%), 12 of which were unvaccinated (92.3%), while one case received one dose of measles-containing vaccine (7.7%). No vaccinated cases with 2 doses were reported.

Transmission setting

For 18 out of 36 measles cases an epidemiological link was confirmed or suspected (Fig. 3). A hospital transmission setting was confirmed or suspected for 12 cases (33.3%); amongst these cases, 5 were HCWs (13.8%) (a gynaecologist, an obstetric nurse, a radiologist, a physiotherapist and a nurse working in an infectious disease ward), all certified unvaccinated. As explained in Fig. 3 the main epidemiological route involved 10 cases and was represented by a hospitalized paediatric case (Case 3) that, after being infected at school, spread the disease in Sanremo Hospital to other 4 individuals, 2 of which were HCWs. Other epidemiological links started from 2 community-related cases, one hospitalized in Intensive Care Unit involving 2 HCWs and one attended the emergency department involving another patient. Following a further in-depth analysis, 3 more cases (aside from the 38 cases monitored by surveillance systems) were identified: all of them were secondary contacts of laboratory-confirmed cases, however no information about their laboratory analysis, vaccination status or clinical data was available, and therefore they were excluded from the present analysis.

Public health measures

In response to the outbreak, the following measures were promptly put in place: isolation of suspected cases with limitation of the contacts with susceptible people; hospitalization only for those cases presenting symptoms or signs of measles

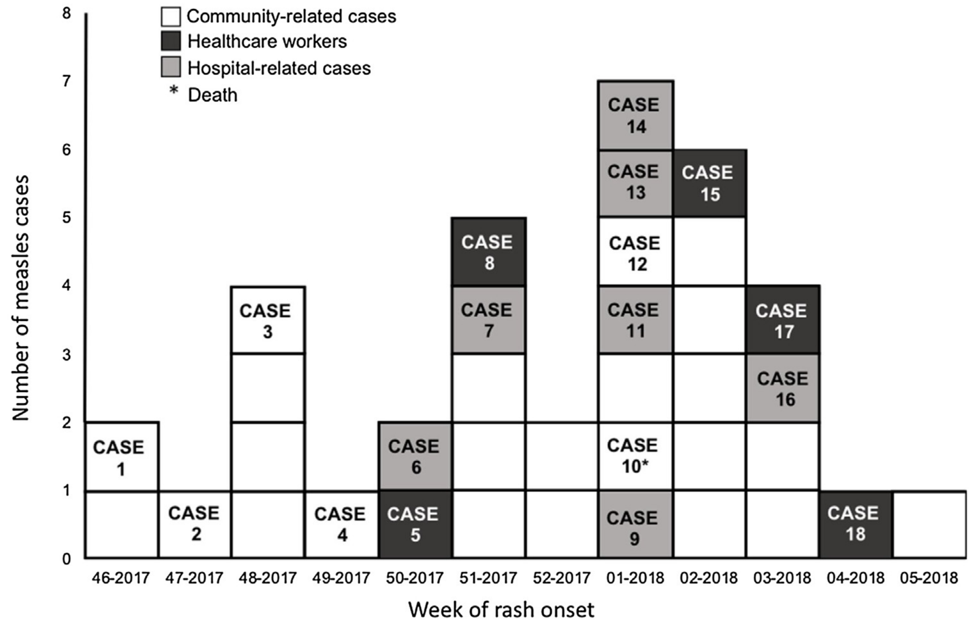

Fig. 2. Temporal distribution by week of rash onset of measles cases, Imperia, Liguria, Italy, November 2017–January 2018 (n = 36). Every single block corresponds to one single case. Blocks identified with the label "case 1, case 2, . . ." represent measles cases for which an epidemiological link was confirmed or suspected, as shown in Fig. 3.

complications; contacts investigation and information collection including immunization, health and pregnancy status and risk factors for severe illness; post-exposure vaccinations to all susceptible contacts (subjects aged >6 months) and administration of immunoglobulins to susceptible contacts at high risk of complications, such as pregnant women, immunocompromised subjects and infants below 6 months of age. The undertaken measures have ensured the confinement of the outbreak, since only one measles case was reported after January 2018 in Imperia province.

Table 1
Number, percentage and incidence of reported measles cases stratified by age group, Imperia, Liguria, Italy, November 2017–January 2018.

Age group (years)	Number	Percentage	Incidence (per 100,000 inhabitants)
<1	4	11.1	296.95
1–4	4	11.1	69.2
5–14	5	13.9	29.69
15–39	14	38.9	27.65
>39	9	25.0	6.44
Total	36	100.0	16.82

Discussion

In the described outbreak, hospital and HCWs had a key role for the transmission of the measles disease, as reported in previous outbreaks in Italy [7–9]. One third of cases were infected in hospital, despite the implemented infection control measures within the facilities and the limitation of hospitalization only for cases with complications.

Several studies were conducted to identify affected groups and public settings in which measles transmission occurred and reported the probable risk of measles transmission both in community and in healthcare settings. Public settings for transmission included mostly educational and healthcare facilities. Other public transmission settings were identified among particular communities, as antivaccination groups with philosophies and religious beliefs that oppose vaccination [10].

In a review published in 2012, that included several studies reporting general measles outbreaks, Authors stated that the nosocomial measles cases represented the 22.1% on the total of measles cases occurred during outbreaks worldwide, with an increasing

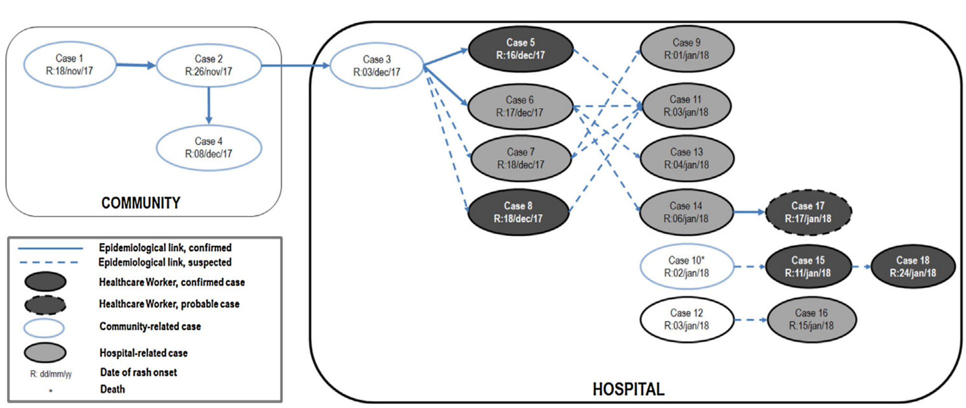

Fig. 3. Network diagram representing measles transmission routes by settings, Imperia, Liguria, Italy, November 2017–January 2018.

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trend in recent years compared with data from previous studies on this topic. This increase may be linked to a better report of cases, but more probably reveals a true increase in this mode of transmission [11].

In the described outbreak HCWs were highly involved, representing 13.8% of all cases: this rate is higher compared to the percentage of HCWs among measles cases reported in Italy from January 2017 to June 2018 [1]. The mandatory vaccine law, approved in July 2017 by the Italian government, increased the number of obligatory vaccinations in the age group 0–16 years, including measles-containing vaccines [12]. However, this intervention does not solve the problem of low vaccine coverage in adults and especially in HCWs, who instead should be the first promoters of the good vaccination practices.

Critical points in the different operating surveillance systems were also observed: a limited completeness of data about laboratory confirmation, hospital admission, symptoms, complications (that are not always correctly recorded as required by the European Case definition of measles [2]), vaccination status and source of infection. Furthermore, classification of cases can be erroneous or not updated (after new information was collected), together with a lack of integration with rubella data infection (approximately 20% of cases satisfying the clinical definition of measles can be represented by cases of rubella) [13].

Conclusions

An integration of all efforts to rapidly detect new measles cases and interrupt the spread of the disease is necessary, particularly in nosocomial settings, together with supplementary immunization activities, as measles catch-up vaccination campaigns targeting susceptible individuals, especially HCWs.

In particular, it is necessary to identify susceptible groups and to conduct supplementary immunisation actions, such as an intensified activity by Hospital Occupational Health Unit, not only by checking immunisation status of HCWs and offering vaccination for those who need it, but also promoting and encouraging immunization, for example by developing educational material to increase HCWs awareness about vaccine preventable diseases [14].

Strengthening surveillance system is also one of the strategies to be implemented for the elimination of measles, in particular by increasing notification rates via a prompt reporting to the local health authority, enhancing completeness and comprehensiveness of notifications and improving completeness and timeliness of the National Integrated Surveillance System for Measles and Rubella. HCWs play a pivotal role in achieving the target of measles elimination, both as professionals who promote vaccines and subjects who gets vaccinated.

To conclude, and to answer to the question "Are hospital safe and healthcare workers reliable?", our study demonstrates that when HCWs are not immunized against measles, they are not reliable against the spreading of this disease and the hospital setting itself could enhance the diffusion of the pathogen, putting at risk patient, visitors and HCWs themselves.

Efforts are needed to guarantee the safety of the hospital and the reliability of the HCWs. Only high vaccination coverage among HCWs can prevent the diffusion of measles in the hospital setting. Other experiences have already shown that nosocomial measles transmission represents a major public health threat, contributing to the spread of the disease and facilitating its reintroduction in regions where it had been previously eliminated. Future studies will comprehensively monitor this type of transmission and the effectiveness of targeted prevention strategies, with the main goal of global measles eradication.

Conflict of interest

None declared.

Funding statement

Not applicable.

Authors' contributions

AO coordinated virological/epidemiological investigation, designed the study, analysed data, drafted and revised the manuscript. FB, MFP and SS advised on analysis, wrote, drafted and revised the manuscript. PC, PC and CA confirmed measles cases, performed the genotyping of biological samples and revised the manuscript. BB and FA coordinated laboratory activities. DZ and MM performed the epidemiological investigation, collected data and coordinated surveillance and control activities in ASL1 Imperiese local health authority. LS and GI supervised virological/epidemiological investigation and laboratory activities and revised the manuscript. All the authors reviewed and approved the final manuscript.

CRediT authorship contribution statement

Andrea Orsi: Conceptualization, Formal analysis, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Francesca Butera:** Formal analysis, Writing - original draft, Writing - review & editing. **Maria F. Piazza:** Formal analysis, Writing - original draft, Writing - review & editing. **Sara Schenone:** Formal analysis, Writing - original draft, Writing - review & editing. **Paola Canepa:** Data curation, Writing - review & editing. **Patrizia Caligiuri:** Data curation, Writing - review & editing. **Claudia Arcuri:** Data curation, Writing - review & editing. **Bianca Bruzzone:** Data curation, Methodology. **Daniela Zoli:** Data curation, Investigation. **Marco Mela:** Data curation, Investigation. **Laura Sticchi:** Data curation, Supervision, Writing - review & editing. **Filippo Ansaldi:** Data curation, Methodology. **Giancarlo Icardi:** Data curation, Supervision, Writing - review & editing.

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