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# Severe and fatal measles-associated pneumonia during an outbreak in Italy: data from the heart of the epidemic

## Abstract

**Introduction:** Measles is a contagious disease that re-emerged among young adults as a consequence of suboptimal vaccination coverage. Since in the pre-vaccination era measles affected mainly children, little is known about measles-associated respiratory complications in adults. The aim of this study was to describe clinical and radiological findings in adults affected by measles who developed respiratory complications during a recent measles outbreak.

**Material and methods:** In this retrospective chart review-based study we analyzed data from patients admitted for measles from January to June 2018 to a large tertiary care hospital, in one of the main cities in the south of Italy. This city has been the country's heart of the epidemic with a high morbidity and mortality rate.

**Results:** Among 177 patients (mean age 26 ± 9 years), only 2 were vaccinated. Thirty patients (16.9%) had signs of pneumonia on chest radiography. Computed tomography scan showed the following abnormalities: centrilobular nodules (63%), ground-glass attenuation (63%), air-space consolidation (36%), pleural effusion (16%) and pneumothorax (10%). Five patients developed severe lung injury and hypoxemia requiring admission to Intensive Care Unit. Two young unvaccinated women with no past medical history died from acute respiratory failure. The death was sudden and unpredictable.

**Conclusions:** Measles-associated pneumonia in unvaccinated young adults can cause severe respiratory impairment and death. Our findings support the need for a mandatory vaccination policy.

**Key words:** measles, viral pneumonia, acute hypoxemia

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## Introduction

Measles is a highly contagious systemic disease resulting from infection with measles virus. This virus is a member of the genus *Morbillivirus* (*Paramyxoviridae* family), most often transmitted between humans by respiratory droplets over a short distance [1]. The virus causes a systemic illness beginning with fever, cough, coryza, Koplik's spots and conjunctivitis followed by a typical generalized rash. Complications of measles can affect most organ systems. These include pneumonia, encephalitis, chronic neurological conditions, ear infection with permanent hearing loss and blindness [2]. Since the implementation of vaccination strategies, measles morbidity and mortality have decreased worldwide [3]. In 2010, the World Health Assembly declared that measles can and should be eradicated, mainly through vaccination strategies [4]. Subsequently, the vaccination coverage increased, however, in 2015, the global coverage with the first dose of vaccine reached a plateau at 85%, remaining below the target fixed for eradication (90–95%). Since 2016 measles outbreaks have been reported in the European area with a consequent re-emerging of life-threatening complications [5, 6]. In 2017, Italy has been included in the list of European countries with ongoing endemic transmission [7]. Studies have shown that the resurgence of measles in Western countries is due to a suboptimal vaccine coverage

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[8, 9]. This is true particularly in Italy, where the goal of vaccine coverage for measles eradication fixed by the World Health Organization (WHO) in 2010 and 2015 has not been met [7, 10]. In addition, the emergence of anti-vaccination movements, particularly active in this country, has further decreased the coverage [5, 7]. As measles vaccine uptake has been low, particularly in those born in the 1990s and 2000s, this has led to large vaccination gaps among young adults, who have become more vulnerable to the infection [11, 12]. From January to November 2018, 2,427 cases of measles and 8 deaths have been reported in Italy [13]. The highest incidence (50% of all reported cases) was recorded in Sicily, an island of five million inhabitants in the southern part of the country [13]. It is well acquired that pneumonia accounts for most measles-associated morbidity and mortality [2]. However, as in the pre-vaccination era, measles was more common among school-aged children, there are few data on measles-associated respiratory complications in adults. The recent measles outbreak among young adults has provided a unique opportunity to examine the presentation of measles and its respiratory complications in the adult population. The aim of this study was therefore to describe the clinical presentation, the radiological findings and the course of the disease in a group of adults affected by measles who developed respiratory complications (pneumonia and respiratory failure) during a recent measles outbreak.

## Material and methods

### Study design

Soon after the 2018 measles outbreak, we performed a retrospective study based on chart review. The study consisted in collecting data from the medical records of patients hospitalized for measles in a large city hospital known as "Ospedale Garibaldi". This hospital is located in the city of Catania (300,000 inhabitants), one of the two main cities in Sicily that has been the site of a large measles epidemic where two, out of eighth deaths reported in the country, occurred. This hospital is renowned for providing tertiary care for infectious diseases. Therefore, general practitioners from the city and from the hinterland, refer more severe measles cases to its adults' Emergency Department (ED) in order to access, successively, the Infectious Disease Department.

We therefore reviewed all medical electronic records of patients admitted for measles to this ED from January to June 2018 (no cases were recorded from July to November 2018). All patients were local residents and the infection could be linked to local transmission.

### Data collection and measles case definition

We reviewed electronic records of each patient focusing on demographic data, anamnesis (underlying comorbidities), clinical data (symptoms, signs and presentation of the disease), laboratory and radiological findings. For all patients included in the study, the diagnosis of measles was based on the European Commission case definition [14]. According to this definition, all patients were considered "confirmed cases" when presenting laboratory evidence of infection with measles virus, i.e. detection of viral RNA in a biological sample and/or a positive IgM result in serum.

A "respiratory complication" was defined as the presence of pneumonia on chest X-ray (presence of consolidation and/or diffuse opacities) with or without respiratory failure. As a distinction between secondary bacterial superinfection and primary measles pneumonia could not be made, the term of "measles-associated" pneumonia has been used for this study. All patients who had radiological findings compatible with pneumonia had a computed tomography (CT) scan. For all patients arterial oxygen saturation ($SaO_2$%) was available and for those with $SaO_2 < 90\%$, blood gas analysis was also accessible. Respiratory failure was defined as a partial pressure of oxygen ($PaO_2$) < 60 mm Hg at rest; severe respiratory failure was defined as the percentage of inspired oxygen ($FiO_2$)/$PaO_2$ ratio < 200. Critically ill patients were defined as those who required admission to the Intensive Care Unit. Acute respiratory distress syndrome (ARDS) was diagnosed according to the Berlin criteria [15]. The Local Ethic Committee approved the study and informed consent was obtained by the patients or caregivers.

### Data analysis

Continuous variables were expressed as mean ± standard deviation. Categorical variables were shown as numbers (%). To compare the differences between the groups for continuous variables, t-test was used. To contrast the differences between the groups for categorical variables, a chi-square test was used. Results were considered statistically significant at P value < 0.05. Statistical analyses were performed using SPSS software (IBM, NY).

**Table 1. Demographic and clinical data of patients with or without pneumonia**

| | Pneumonia | Without pneumonia | P value |
|---|---|---|---|
| **N. of patients** | 30 | 147 | |
| **Age (yrs)** | 26 ± 1 | 26 ± 7 | ns |
| **Sex (male)** | 53% | 49% | ns |
| **Previous medical history (n.)** | | | |
| Asthma | 2 | 2 | ns |
| Other | 2 | 0 | ns |
| **Complications** | | | |
| Hepatitis | 72% | 60% | ns |
| Diarrhea | 3% | 8% | ns |
| Thrombocytopenia | 50% | 63% | < 0.05 |
| Leukopenia | 24% | 34% | < 0.05 |

## Results

### Clinical presentation in all study patients

From January to June 2018, a total of 177 patients were referred to the ED for measles (49% males, mean age 26 ± 9 years, range 16–45). Ten patients were rapidly dismissed for mild disease. Out of 177, only two individuals had been previously vaccinated (both with two doses, both dismissed for mild diseases). None reported measles during childhood. Given the young age of the patients, the past medical history was generally unremarkable with some exceptions. Four patients reported mild asthma (2 in the group with pneumonia and 2 in the group without pneumonia), one had Down Syndrome and one had a previous gastric bypass (both in the group with pneumonia) (Table 1). Common clinical manifestations included fever, generally > 38°C (89%), maculopapular rash (93%), cough (43%), Koplik's spots (32%) and conjunctivitis (43%). Common complications included thrombocytopenia, acute hepatitis, leukopenia and diarrhea (Table 1). Two patients presented acute pancreatitis and in one person, seizures occurred.

### Patients with respiratory complications

Pneumonia was diagnosed in 30 patients (16.9% of those referred to the ED) (mean age 26 ± 1 years, 53% males). No statistical difference was found in the mean age or in the percentage of males between the group with pneumonia and the group without pneumonia (Table 1). All patients had the risk factor of not having been vaccinated. None had an apparent cause of pre-existing immunodepression. Nine patients with pneumonia (30%) developed respiratory failure. Among these, 5 developed severe respiratory failure and critical illness requiring ICU admission, whereas 4 patients had a mild hypoxemia requiring only low flow oxygen administration and were managed in non ICU wards. Excluding the respiratory tract involvement, measles clinical presentation in patients with pneumonia was similar to those without pneumonia. However, in the subjects with pneumonia, leukopenia and thrombocytopenia were significantly less common than in patients without pneumonia (24% *vs* 34% for leukopenia, $P < 0.05$ and 50% *vs* 63 % for thrombocytopenia, $P < 0.05$) (Table 1).

A chest CT scan was performed in all patients who had abnormal X-ray. Bilateral lesions were observed in 89% of the study subjects. The most common radiological findings were as follows: centrilobular nodules (63%), ground-glass attenuation (63%), air-space consolidation (36%), pleural effusion (16%) and pneumothorax (10%) (Table 2). Mild cases had mainly scattered

**Table 2. Radiological findings on CT scan in patients with measles-associated pneumonia**

| | Frequency |
|---|---|
| Centrilobular nodules | +++ |
| Ground-glass attenuation | +++ |
| Air-space consolidation | ++ |
| Pleural effusion | + |
| Pneumothorax | + |

Frequency is reported as ≤ 25% ≥ 75%

**Table 3. Demographic and clinical data of the patients admitted to ICU**

| Pt no. | Age | Sex | Chronic conditions | Hepatitis | CRP | Leukopenia | Thrombocytopenia | CT scan | Survival |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 22 | F | Allergic asthma | No | 31 | No | No | Consolidation<br>Ground glass opacities | Yes |
| 2 | 28 | M | No | Yes | 355 | No | Yes | Consolidation<br>Ground glass opacities<br>Massive sx pneumothorax | Yes |
| 3 | 32 | M | Gastric by-pass | Yes | 73 | Yes | Yes | Extensively diffused centrolobular nodules | Yes |
| 4 | 26 | F | No | Yes | 38 | No | No | Consolidation<br>Minimal ground glass opacities | No |
| 5 | 38 | F | No | No | 354 | No | No | Consolidation<br>Ground glass opacities<br>Nodules | No |

CRP — C-reactive protein; ECMO — extracorporeal membrane oxygenation

centrilobular nodules and ground attenuation, whereas the CT scans of patients with severe respiratory failure varied greatly (see below). Patients presented mainly with dry cough so that sputum could not be collected for microbiological examination. As it was difficult to establish the presence of bacterial superinfection, all patients received a wide spectrum antibiotic treatment with a β-lactam, a macrolide or a fluoroquinolone. Support treatment particularly hydration and electrolytes adjustment, was also given. Oxygen supplementation was used in patients with $PaO_2 < 60$ mm Hg, *via* nasal cannula or mask (if not admitted to ICU).

## Patients with severe hypoxemia and lung injury

Five patients (2.9% of those admitted) developed severe hypoxemia, refractory to oxygen administration ($PaO_2/FiO_2 < 150$) and, being critically ill, were admitted to ICU. Two of these individuals died from acute respiratory failure (1.1%).

None of these patients was vaccinated and none smoked. One of them suffered from mild asthma and another one had previous gastric bypass. The remaining three patients had no significant medical history. All reported 2- to 7-day fever and maculopapular rash before arriving at the ED. Microbiological assessment, in order to exclude bacterial superinfection, included broncoaspirate and blood culture (aerobic and anaerobic bacteria). All these cultures were negative in three patients (n. 1, 2, 3). Rhinovirus was detected in the nasal swab of patient n. 3. No microbiological data were available for the two women who died suddenly. The clinical course and the radiological findings varied greatly among these five patients (Table 3).

The patient n. 1 (a girl with mild asthma, no inhaled steroids use reported) had severe hypoxemia and bilateral extensive areas of ground glass with little consolidation on CT scan, however, she rapidly recovered and within 10 days CT scan was normal. The patient n. 3 also had rapid recovery although CT scan showed a massively diffused centrilobular nodules.

The patient n. 2 had a complicated, long clinical course that is worth mentioning. This 32-year-old man (gastric bypass one year earlier, but normal body mass index) after 4 days of symptoms (fever and vomiting) was transported to the ED in severe respiratory distress ($PaO_2/FiO_2 < 150$) and transferred immediately to the ICU where he was treated with extracorporeal membrane oxygenation (ECMO). The CT scan at admission showed diffuse ground glass areas and consolidation, and successively, he developed left massive pneumothorax, pneumomediastinum and subcutaneous emphysema (Figure 1). A chest tube was positioned and removed after 5 days. The patient was recovering very slowly and areas of consolidation were still present after 20 days. At 2 months of follow-up, the chest X-ray was normal.

The patient n. 4 was a 26- year-old woman with no past medical history. After 7 days of fever (amoxicillin was prescribed at home) she was admitted to the ED perfectly conscious with $SaO_2$ 90% at room air and diffuse bronchospasm. Laboratory data showed an increase in AST (234/UL) and a mild increase in CRP (38 mg/L), normal leucocytes and platelets. The chest X-ray showed a right basal opacity. The patient, whose

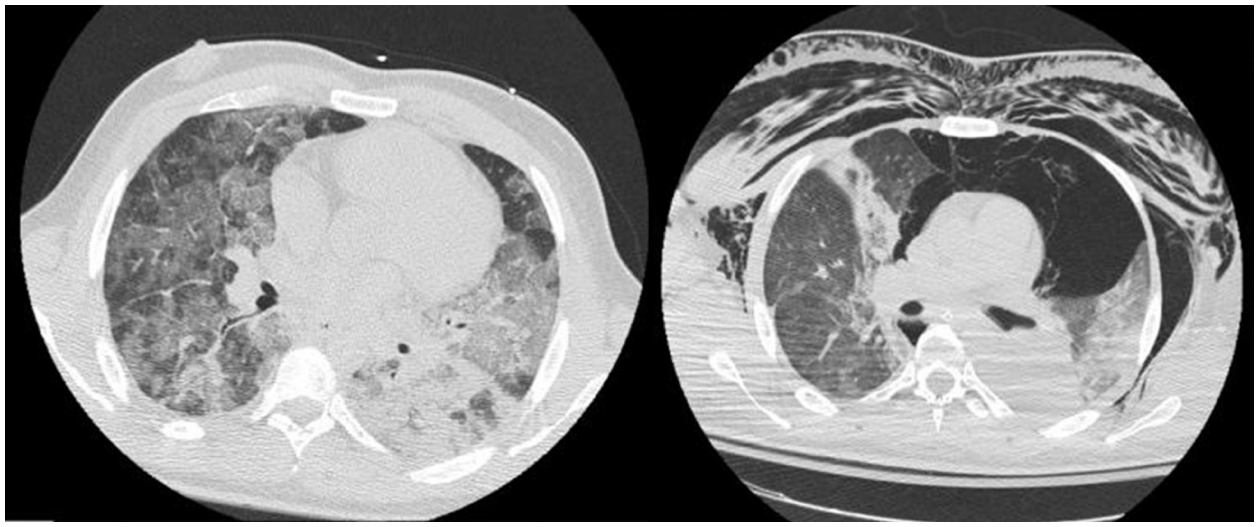

**Figure 1.** CT scan of patient n. 2 at admission (left) and after 3 days (right)

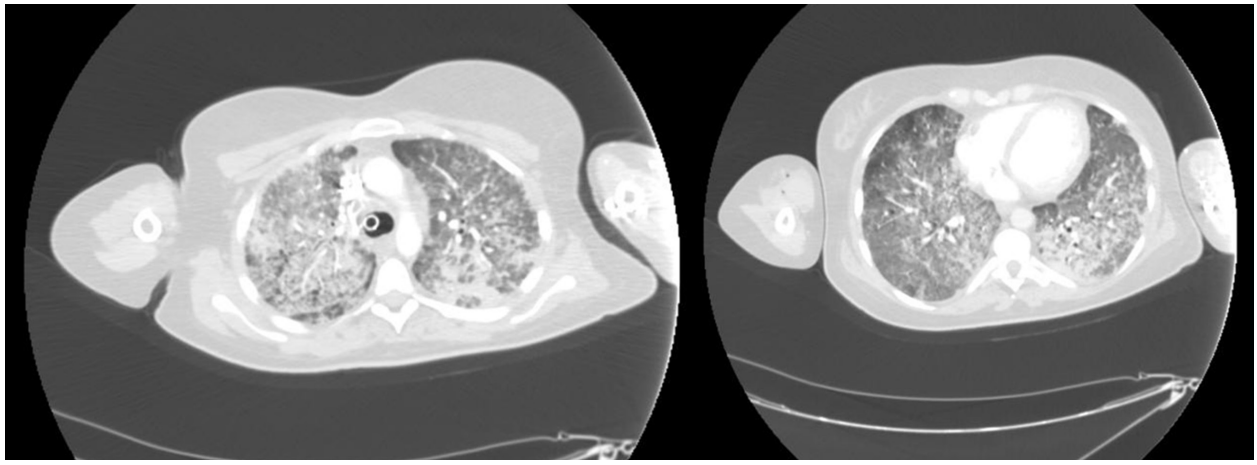

**Figure 2.** CT scan of patient n. 5 at admission before intubation. She died soon after

condition did not appear so severe in the first evaluation, received support treatment with hydration and a wide spectrum β-lactam. Within 48 hours, the respiratory conditions suddenly deteriorated, respiratory distress increased and $PaO_2/FiO_2$ was below 100. The patient died soon after admission to ICU and intubation. It is peculiar that the CT scan showed two areas of consolidation in the right lung while the left lung was substantially spared with only a minimal amount of ground glass in the left lower lobe. The extension of the lung damage on CT scan did not reflect the severity of hypoxemia.

The patient n. 5 was a 38-year-old woman with no past medical history. After two days of fever and rash she was admitted with $SaO_2$ 83% at room air, $PaO_2/FiO_2$ 150, leukocytes 10700/mcL, CRP 354 mg/L, AST 136 UI/L. Differently from the previous patient, her CT scan showed a massive involvement of both lungs with diffuse consolidation, ground glass and nodules (Figure 2). The woman was intubated but soon after she died from ARDS.

## Discussion

In this study, we describe the clinical and radiological presentation of measles-associated pneumonia during a recent measles outbreak in a group of patients admitted to the emergency room of a large tertiary care city hospital. Few previous researches have evaluated measles-associated respiratory complications in adults [16, 17]. The low availability of data is due to the fact that in pre-vaccine time measles occurred, at least in Western countries, mainly in school-aged children. Therefore, data on respiratory

complications in selected adult groups are rare, although it is generally accepted that the burden of complications in adults is heavier than in children [2]. Pneumonia is one of the most common life-threatening complications [18]. The main finding of our study is that, during this latest outbreak, measles-associated pneumonia has been common, severe and fatal among unvaccinated otherwise healthy young adults. Making a comparison with other studies on the incidence of measles-associated pneumonia during the latest outbreaks is difficult, due to differences among methodologies. In the city of Messina (not far from Catania) in 2017, in a group of 59 patients with measles, only 4% developed pneumonia [19]. We found a definitely higher incidence; however, we assessed patients who were referred to the ED for a severe clinical presentation. It is noteworthy that, in the same time frame evaluated in our study (January to July 2018), the incidence of measles-associated pneumonia in Italy has been around 10%, with 7% of the patients presenting respiratory failure [13]. This percentage includes children (probably lowering the incidence), but it is relevant that the highest frequency of complications and mortality has been reported in adults > 20 years [7, 13]. In addition, six out of eight deaths in Italy were adults. An observation that can be inferred from our data is that, although the lack of vaccination was a major risk factor for all patients, the respiratory morbidity and mortality from measles was unpredictable. In a previous report on patients admitted to ICU for measles, a number of patients had immunodepression (organ transplantation of HIV infection) and important respiratory morbidity [17]. In our patients, there was no known cause of immunodepression. It is true that two out of 5 patients admitted to ICU had a comorbidity (mild asthma and gastric bypass), but the two patients who died, apparently, had no previous or chronic disease. Perhaps, a difference in infecting genotypes can be evoked, however, we were not able to differentiate the genotypes and so far, no correlation between the genotype and the severity of the disease has been suggested [2]. In addition, we were not able to discern a putative bacterial superinfection, as there was no time for collecting bronchial aspirate. Perhaps, in one of the two patients (n. 5), a bacterial infection could be suspected as CRP was high. However, this is only a speculation as no post-mortem was available.

One of the aims of this study was to define radiological features of measles-associated pneumonia. It is well acquired that the main feature of viral pneumonia is a radiological interstitial pattern [20, 21, 22]. A typical measles pneumonia is characterized by peribronchial nodular infiltration and reticulonodular infiltration with thickened interlobular septa [20]. Hilar lymphadenopathy and pleural effusion have also been described [21]. Sometimes fibrosis has been observed on follow-up images 20]. In a previous report describing critically ill adults, the CT scan showed an exclusive pattern of interstitial pneumonitis in 61 % of the patients, whereas only in a minority of cases, alveolar consolidation was found [17]. We observed that 4 out of 5 patients had consolidation and this can be due to the severity of the disease. Usually, as the viral disease progresses, consolidation areas can overlap ground-glass. In addition, bacterial coinfection cannot be excluded as the cause of consolidation, particularly if associated with increased inflammation markers [23]. One remark is that in critically ill patients, we did not find a clear correlation between radiological findings and the severity of hypoxemia. Kakoullis *et al*. recently reported in 11 cases of pneumonia that occurred in Greece, an inverse correlation between $PaO_2/FiO_2$ and the presence of reticular pattern [16]. We found that patients with mild respiratory impairment had predominately a ground glass pattern and the presence of reticular patterns was uncommon. Also, the two patients who died had different radiological features. One had a massive extension of centrilobular nodules and consolidation in both lungs, whereas the other one only had well defined consolidations in one lung, yet she was severely hypoxemic.

We conclude that during the latest measles epidemic the respiratory impairment has been frequent, severe, fatal and unpredictable. The paradigm that complications from viral infections occur only in fragile or immunodeficient patients should now be revisited. The non-vaccinated status is a major risk factor for measles-associated complications even in healthy young subjects. These data strongly support the concept that implementation of vaccination policies should be mandatory.

## Conflict of interest

None declared.

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