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MAJOR ARTICLE

A Major Regional Measles Outbreak: Description of Hospitalized Cases in 2017–2018 at Bordeaux University Hospital, France

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Background. Measles remains endemic worldwide, despite current vaccination recommendations, and is associated with high morbidity and mortality rates. We describe all cases hospitalized in Bordeaux University Hospital (BUH), the starting point of a national significant measles outbreak in 2017–2018.

Methods. In this retrospective study, we included all patients hospitalized in BUH from September 1, 2017, to May 31, 2018. Inclusion criteria were age >1 year, clinical symptoms, and biological confirmation by measles immunoglobulin M or measles reverse transcription polymerase chain reaction positivity.

Results. We included 171 patients. Most patients were immunocompetent; only 19% had preexisting medical histories. Most patients had rash and fever (97%), but some cases were atypical and difficult to diagnose. Köplik's spots were reported in 66 cases (38%). The most frequent biological markers were blood inflammation markers (96%) and lymphopenia (81%). Unexpectedly, we found hyponatremia (<135 mmol/L) in 40% of patients. We identified peaks in January and March, corresponding to 76 D8 genotypes and 28 B3 strains. The following complications were reported in 65 patients (38%): pneumonia, hepatitis, and keratitis; 10 had neurological symptoms. One patient had Guillain-Barré syndrome, and a young immunocompromised patient died from measles inclusion-body encephalitis. Most of the patients (80%) had not been correctly vaccinated, including 28 health care workers. Some patients (n = 43, 25%) developed measles despite having plasma IgG. These included 12 possible vaccination failure cases.

Conclusions. During the BUH outbreak, measles was often complicated and sometimes atypical. Vaccination coverage was dramatically insufficient. We also describe vaccination failure cases that must be better investigated.

Keywords. measles inclusion-body encephalitis; measles; outbreak; vaccination failure; vaccination.

Measles infection, one of the most contagious respiratory infections, is transmitted by an airborne route via respiratory droplets. Complications are more frequently reported in young children and adults and can be lethal, especially in immunocompromised patients [1]. Since the introduction and routine use of measles vaccines in the 1960s, measles-attributed deaths dramatically decreased by ~79% from 2000 to 2015 [2].

Despite vaccination campaigns, measles remains endemic in Africa and Asia, but also in Europe. In 2016, the World Health Organization (WHO) estimated that 7 million people had been infected and 89 780 people had died from measles. Mortality ratio estimations vary between <0.01% in industrialized countries and >5% in low-income countries [3].

In France, measles infection is endemic, and there have been 2 recent major outbreaks. According to Santé Publique France, from January 2008 to December 2016, more than 24 000 cases of measles were reported, mainly during the 2010–2011 outbreak and, to a lesser extent, in 2015. More than 1500 infected patients experienced complications, especially pneumonia and neurological complications, and 10 patients died [4]. The last French measles outbreak occurred in 2017–2018 and started in Bordeaux, Nouvelle-Aquitaine, France, where at least 610 cases were reported with a significant hospitalization rate (about 22%) [5].

This retrospective observational cohort study thoroughly describes the cases hospitalized in Bordeaux University Hospital (BUH) during this national outbreak.

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METHODS

Case Definition

All patients with confirmed measles who were hospitalized in BUH between September 1, 2017, and May 31, 2018, were retrospectively reviewed. These patients were hospitalized in the emergency room or conventional hospital units when they had intense or persistent symptoms. Suspected cases were confirmed either by detection of measles-specific immunoglobulin M (IgM) antibody (chemiluminescence immunoassay LIAISON) or by measles RNA in-house real-time qualitative reverse transcriptase polymerase chain reaction (RT-PCR). Positive measles RT-PCR samples were sent for genotyping to the National Reference Centre for Measles, based at Caen University Hospital, Normandy, France.

Patients under one year old were not included because of significant pediatric issues and vaccine timing, and these data have been analyzed separately by pediatricians.

Subgroup Definitions

Complicated cases were defined either by a significant hospital stay (>2 days) or organ dysfunction attributed to measles [1, 6].

Discordant cases were defined as patients with measles-specific immunoglobulin G (IgG) antibody at measles diagnosis. These patients either had a history of prior measles infection, and the current measles episode was then identified as reinfection [7], or they had previously received at least 1 measles vaccine injection, and the current measles was then identified as a vaccine failure [8].

Laboratory Tests

We reported the main biological parameters. Lymphocytes and platelet counts were expressed in billions per liter (G/L); normal values were between 1.24–3.56 and 150–445 G/L, respectively. Sodium and potassium were expressed in mmol/L; normal values were 135–145 and 3.5–5 mmol/L, respectively. C-reactive protein (CRP) was expressed in mg/L and was considered increased if >5 mg/L.

We reported liver function through the values of alanine aminotransferase (ALT; normal value <55 UI/L) and aspartate aminotransferase (AST; normal value <34 UI/L). We reported acute renal dysfunction (creatinine >90 µmol/L in patients with prior normal renal function). Oxygen partial pressure (pO_2) was expressed in millimeters of mercury (mmHg), and hypoxemia was defined as a pO_2 <80 mmHg.

Measles serology was performed by chemiluminescence immunoassay (CLIA) analysis with the LIAISON system (DiaSorin, Saluggia, Italy) for IgM and IgG, with qualitative and semiquantitative detection (IgG threshold value of 15 UA/mL). Nucleic acids were extracted using the MagNA Pure Compact Kit (Roche, Penzberg, Upper Bavaria, Germany). RNA amplification was performed with a LightCycler thermocycler (Roche).

Statistical Analysis

We performed descriptive analyses using Microsoft Excel. The patient characteristics, clinical symptoms, and laboratory results are presented as percentages and means with ranges.

Patient Consent Statement

The design of the work was approved by the Research Ethics Committee of Bordeaux University Hospital. Written informed consent was waived, as it was an observational and retrospective analysis of our usual clinical practice. All patient data were anonymized for the purpose of analysis, and confidential data were protected in accordance with appropriate national standards.

RESULTS

Patient Characteristics

During the study period, 171 patients were hospitalized and included in our study: 46 children and 125 adults. The median age (range) was 22.5 (1–63) years, with 33% of the patients between 20 and 30 years old, and the sex ratio was 1.03 (87 men and 84 women).

Of these patients, 77 (45%) were hospitalized in the emergency department, and 94 (55%) were hospitalized in different units, including the pediatric, dermatology, and infectious disease departments. For these 94 patients, the mean hospitalization length (range) was 5.5 (1–60) days.

Most patients were immunocompetent children or young adults; only 19% had a preexisting medical history, and 6 women were pregnant. Thus, only 7 patients had immunosuppressive treatment (Table 1).

Clinical Findings

The main clinical findings are listed in Table 1. One patient did not have a rash, while 6 patients had atypical rashes: 2 patients reported intense pruritus, 1 had vesicular lesions, 1 had an eczematiform rash, 1 had edematous lesions, and 1 had abnormal pruritic lesions due to associated scabies. The mean rash duration (range) was 6.5 (2–12) days (data available for 46 patients).

Only 4 patients did not report fever. Conversely, 3 patients reported prolonged fever lasting at least 7 (range, 7–13) days, justifying prolonged hospital stay. Unexpectedly, 7 patients complained about urinary tract symptoms (dysuria, pain, or incontinence). The characteristics of the patients presenting with these atypical symptoms and signs are detailed in Supplementary Table 1.

Laboratory Tests

Only 131 patients underwent blood analysis. The main biological abnormalities are listed in Table 2.

The most frequent biological markers were elevated CRP levels (n = 126, 96%) and lymphopenia (n = 106, 81%).

Table 1. Population Characteristics and Clinical Symptoms (n = 171)

Patient Characteristics (n = 171)	Patients, No. (%)
Median age (range), y	22.53 (1–63)
Sex M/F	87 (51)/84 (49)
Immunocompetent	138 (81)
Pregnant women	6 (3.5)
Medical history	32 (19)
Chronic untreated infectious disease	4 (2)
Hepatitis B	2
Hepatitis C	1
Pulmonary tuberculosis	1
Autoimmune disorders	7 (4)
Idiopathic thrombocytopenic purpura	1
Nephrotic syndrome	1
Crohn's disease	1
Antiphospholipid syndrome	1
Ankylosing spondylitis	1
Suspected[a]	2
Immune deficiency	3 (1)
Lymphocyte T deficiency with RHOH deficit	1
Di George syndrome	1
Suspected[b]	1
Solid organ transplant recipients	2 (1)
Heart transplant	1
Lung transplant	1
Neoplasia or hematologic malignancy	3 (1)
Malformative syndrome	1
Alcohol abuse	4 (2)
Immunosuppressive therapy	7 (4)
Antirejection drugs (tacrolimus, MMF, corticosteroids)	2
MMF	1
Anti-TNF	1
Chemotherapy	2
Immunotherapy	1
Symptoms and signs (n = 171)	
Fever	167 (97)
Rash	170 (99)
Atypical rash	6 (3.5)
Köplik's spots	66 (38)
Cough	151 (88)
Rhinitis	127 (74)
Conjunctivitis	105 (61)
Dyspnea	29 (17)
Diarrhea	44 (26)
Vomiting	36 (21)
Urinary tract symptoms	7 (4)

Abbreviations: MMF, mycophenolate mofetil; RHOH, Ras homolog gene family H; TNF, tumor necrosis factor.

[a]Suspected with no definitive diagnosis: 1 patient with chronic diarrhea and another with acrosyndrome.

[b]Suspected with no definitive diagnosis: disseminated bacillus Calmette-Guerin during childhood then recurrent infections.

Interestingly, some patients (n = 53, 40%) presented with hyponatremia (mean 131 mmol/L), with hypokalemia in approximately half (n = 31). They were mainly adult women, with digestive signs in 24 (45%) (Supplementary Table 1).

Table 2. Description of Abnormal Biological Results (n = 131)

Biological Parameter	Absolute Number of Abnormal Biological Results/Number of Tested Samples, No.[a] (%[b])	Mean of Abnormal Biological Results (Range)
Blood inflammation (CRP), mg/L	126/131 (96)	62 (5.4–215)
Lymphopenia, G/L	106/131 (81)	0.5 (0.09–1.15)
Thrombocytopenia, G/L	55/131 (42)	120 (54–149)
Hyponatremia, mmol/L	56/131 (43)	131.4 (125–134)
Hypokalemia, mmol/L	31/131 (23)	3.2 (2.6–3.47)
Renal failure, µmol/L	6/131 (4,5)	98 (91–110)
Biological hepatitis, IU/L	73/103 (70)	ALT 289 (60–975), AST 192 (39–864)
Hypoxemia, mmHg	13/13 blood gas tested	60.5 (45–73.5)

Abbreviations: ALT, alanine aminotransferase, AST, aspartate aminotransferase; CRP, C-reactive protein; PCR, polymerase chain reaction.

[a]Number of tested samples (n = 131), except for biological hepatitis (n = 103), and hypoxemia (n = 13).

[b]Percentage of abnormal values following blood analysis.

Biological Diagnosis

Measles serology and RT-PCR were performed in 153 and 121 patients, respectively. PCR was examined in mostly oral fluid samples (n = 119), but was also positive in 7 extrasalivary samples (5 blood samples, 1 urine sample, and 1 conjunctival swab).

Measles-specific IgM antibodies were positive in 134 patients (134/153, 87%), and all 121 patients tested had a positive RT-PCR (119 in the saliva and 2 in the blood samples) (Figure 1).

Among the 121 positive RT-PCR samples, 104 (86%) were successfully genotyped. The D8 genotype was dominant (62%) compared with the B3 genotype (23%). These 2 genotypes were responsible for 2 successive measles outbreak peaks in January and March, respectively (Supplementary Figure 1). Six samples were not amplifiable (NA), and the other genotyping data were missing (n = 11).

Complications

Complications were frequent in our cohort (n = 65, 38%); 8 patients were admitted to intensive care units (ICUs), and 1 died. Complications mainly occurred in patients with no prior medical history (n = 132, 77%).

Pneumonia was the most frequent complication (n = 46, 27%). Some patients were particularly at risk; for example, half of the asthmatic patients had pneumonia. It was often not possible to differentiate viral from bacterial pneumonia in the medical records, and almost all patients were treated with antibiotics. Regarding the documented bacterial superinfections, the most frequently isolated bacteria were *Haemophilus influenzae* and *Staphylococcus aureus* (methicillin-susceptible). One young patient who was immunosuppressed after a lung transplantation developed

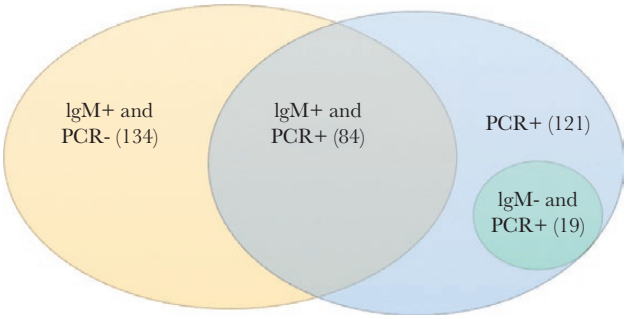

Figure 1. Venn diagram representation showing biological confirmation of measles, detailing patients with positive serology (positive immunoglobulin M = IgM+), negative serology (negative IgM = IgM-), and/or polymerase chain reaction positivity (PCR+).

pulmonary aspergillosis and may have developed an inclusion pneumonia.

Other complications were less frequent; hepatitis occurred in 28 patients (16%), and neurological complications in 10 (6%) (Table 3). Of the 10 patients, 7 had neurological signs requiring lumbar puncture and 2 had lymphocytic meningitis with a negative cerebrospinal fluid PCR. Interestingly, 1 patient with no medical history developed Guillain-Barré syndrome and was hospitalized for 7 days in the ICU before long-term rehabilitation. A young heart transplant patient suffered from measles inclusion-body encephalitis (MIBE). Transmission probably occurred 3 months earlier. This patient had no rash or fever, only neurological symptoms that worsened despite specific treatment. After hospitalization in the neurological unit and then in the ICU for 60 days, this patient died. We noted seroconversion during hospitalization and repeated positive PCR results in saliva and urine, but negative PCR results in 2 successive lumbar punctures with no intrathecal synthesis.

Finally, concerning complications in the 6 pregnant women, only 1 went on to develop pneumonia that required antibiotics. Conversely, 5 out of 7 patients treated with immunosuppressive therapy developed complications such as pneumonia (n = 3) and MIBE.

There was no clear association between a particular symptom or complication and genotype. However, a correlation trend was observed between genotype D8 and neurological complications (7 of 10 patients had genotype D8).

Table 3. Description of Measles Complications in 66 Patients

Complication	Patients, No. (%)
Pneumonia	46 (27)
Upper lower tract infections	9 (5)
Pharyngitis	5
Media otitis	3
Bacterial tonsillar abcess[a]	1
Bilateral keratitis	7 (4)
Digestive complications	28 (16)
Severe biological hepatitis[b]	28 (16)
Liver failure	0
Pancreatitis	0
Neurological complications	10 (6)
Requiring lumbar puncture	7
Guillain-Barré syndrome	1
MIBE	1
Febrile seizure[c]	2
Intense headache	1
Headache associated with paresthesia	2
Confusion[d]	1
Encephalopathy due to hypercapnia[d]	1

Abbreviations: ALT, aspartate aminotransferase; AST, alanine aminotransferase; ICU, intensive care unit; MIBE, measles inclusion body encephalitis.

[a]Documented abscess, due to *Fusobacterium nucleatum* and *Streptococcus anginosus*.

[b]ALT and/or AST up to 10-fold the upper limit.

[c]Febrile seizures occurred only in children.

[d]Patient hospitalization in the ICU.

Hospital-Acquired Cases

We reported 28 measles cases in health care workers (HCWs), 14 of whom had hospital-acquired measles. Most were incompletely vaccinated (≥80%). Moreover, 5 patients were probably contaminated during their hospital stay by HCWs or other patients.

Immunization Status and Incongruous Cases

Most of the patients (n = 127, 74%) were not appropriately vaccinated (Figure 2). However, vaccination data were difficult to obtain as the patients and general practitioners often ignored the vaccine status, and these data were rarely mentioned in the medical records.

Among the 153 patients who had available serology, 43 (28%) had positive measles-specific IgG antibodies at the time of measles diagnosis; 29 (67%) of the 43 also had a positive saliva PCR. Of these 29 patients, 13 (45%) were not vaccinated and 2 (7%) reported a history of past measles in childhood with IgM positivity, suggesting reinfection.

The other 14 cases were possible vaccination failure cases. Among them, 2 patients had IgG levels between 15 and 30 UI/mL, which could correspond to the onset of seroconversion, and these were therefore excluded. The characteristics of the 12 possible vaccination failure cases are detailed in Supplementary Table 2. However, significant data were still missing regarding their vaccinations (doubtful status, number, and date of injections). Out of these 12 patients, only 2 (16%) developed complications associated with their measles infection.

Measles-Specific Therapy

Only 4 patients were treated by intravenous immunoglobulin (IVIG) infusions. All had immune deficiency (heart and lung transplantations, 1 DiGeorge syndrome, and 1 nephrotic syndrome). The patient with MIBE had emergency treatment with ribavirin and vitamin A, in addition to IVIG infusions.

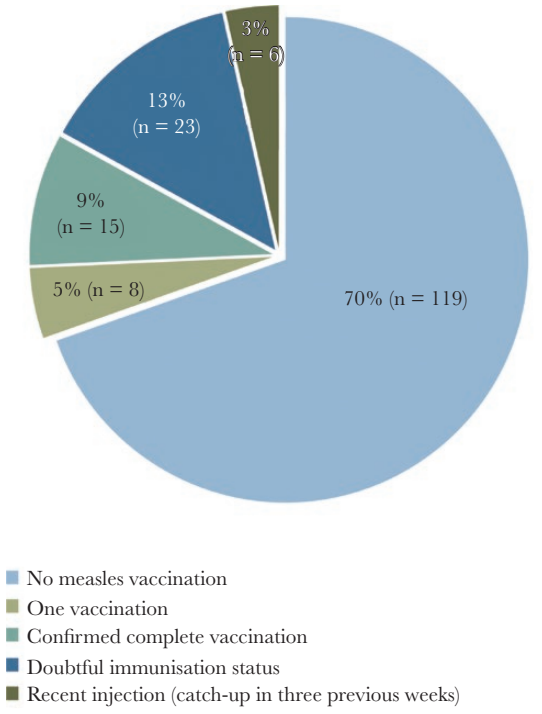

Figure 2. Immunization status of the study population, shown as percentages (n = 171).

DISCUSSION

This measles epidemic in Bordeaux Metropole (area of ~780 000 inhabitants) marked the onset of the last French outbreak in 2017–2018. The 171 patients included in our study represented ~17% of all the cases reported nationally during this period [5].

This large epidemic population allowed us to identify several significant factors in relation to other studies [9]. First, we noticed a significant number of complicated cases (38%), especially pneumonia, hepatitis, and neurological complications, sometimes revealing measles infection and often requiring prolonged hospitalization. Complication rates are usually slightly lower in the literature, at ~30% [10]. We can explain this trend in complications by the fact that our population had a median age higher than in other outbreaks; indeed, older people develop more measles complications [11, 12]. However, complications mainly occurred in patients with no prior medical history (77%). Still, immunocompromised patients are particularly at risk, as 1 young heart-transplanted patient died from MIBE and 1 lung-transplanted patient had a possible inclusion pneumonia. The absence of a rash and a higher frequency of neurological signs make the diagnosis even more difficult in this vulnerable population.

Interestingly, the clinical presentation was often atypical, especially the rash characteristics. Moreover, Köplik's spots and, to a lesser extent, fever were missing. In the literature, Köplik's spots are described in ~70% of measles cases [13]. However, a recent Japanese study found low sensitivity (48%) and specificity rates (80%) for Köplik's spots as a diagnostic marker for measles [14]. In our study, we suspected that Köplik's spots were underdiagnosed because of incorrect diagnosis, or they were sought too late. Unexpectedly, many patients had hyponatremia, sometimes requiring hospitalization and intravenous supplementation. An association between measles and hyponatremia has recently been described [15], but a physiopathological link remains unclear.

These atypical forms seem to be more frequent in adults with no prior medical condition, but more studies are needed. Finally, this reminds us that measles still present a challenge to diagnose, leading to delayed diagnosis and perhaps to increased infectivity.

Another strength of our study concerns the virological diagnosis. The combination of serology and PCR improved measles diagnosis and helped us to understand reinfection and vaccination failure better. Moreover, genotyping allowed us to find 2 circulating strains that were responsible for 2 consecutive epidemic peaks. To date, 24 genotypes have been described. The B3, D4, D8, D9, G3, and H1 genotypes are currently circulating [16]. In our study, there was no association between symptoms or complications and virus genotype. So far, the literature does not describe any link between the symptoms or severity and the genotype, but more studies are needed.

Our study has some limitations. The literature does not provide a clear definition of complicated cases due to measles. Therefore, a comparison with other outbreaks is difficult. Due to the retrospective nature of our study, some patients had no blood analysis, and important data were missing (such as viral pneumonia and, especially, vaccination data), making it difficult to analyze vaccination failure cases correctly. In the literature, vaccination failure appears to be frequently associated with mild disease, known as modified measles, which is less contagious [17, 18]. This association with milder disease may agree with our data, as 10 patients had uncomplicated measles among the 12 possible cases of vaccination failures in our study population. Importantly, patients with modified measles remain contagious, even though this is slightly reduced [18]. Many hypotheses exist that can explain vaccination failures, especially waning immunity [8, 18]; children's vaccination schedules are also a factor, as vaccination before the age of 9 or 12 months has been reported to be less efficient [19, 20]. Interestingly, 2 patients reported measles infection during childhood, suggesting reinfection, probably also due to waning immunity; alternatively, these 2 patients might have been misdiagnosed with measles at that time.

Finally, our study sheds light on possible improvements in measles care. First, the population in France remains undervaccinated, and this includes HCWs, which explains the successive outbreaks in recent years. According to the WHO, vaccination coverage should aim to reach 95% of the world population to eradicate

the measles virus. However, no French department has reached this target. Vaccination coverage is at 85%–90% in only 7 departments [21]. Thus, vaccination status must be carefully checked, especially in HCWs and people born after 1980, the date when measles vaccination was introduced in France.

We also found that immunization status was often ignored by the patients or their general practitioner. Some devices might help to improve the situation in the future, such as an online platform or shared medical records. Measles serology is not recommended after contact with an infected patient. Indeed, IgG positivity is a poor indicator of immunity [22]. An avidity test might function better to identify protective antibody rates, but it is not routinely available [23].

Measles treatment remains controversial. In our study, only 1 patient received antiviral therapy associated with vitamin A treatment. There is no specific antiviral treatment for measles [24]. However, complications could be prevented with vitamin A supplementation [25], as recommended by the WHO and the American Academy of Pediatrics [26], and this treatment is particularly well tolerated. Ribavirin may also be helpful in critical cases [27], but more studies are required to clarify its role.

In conclusion, several improvements must be made in the treatment of measles and to prevent future outbreaks that could lead to complicated and sometimes lethal cases. Insufficient vaccination coverage remains a major public health concern. More studies are required, especially concerning the specific treatment of severe infection and vaccination failure.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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