Severe Measles Infection

The Spectrum of Disease in 36 Critically Ill Adult Patients

Cédric Rafat, MD, Kada Klouche, MD, Jean-Damien Ricard, MD, PhD, Jonathan Messika, MD, Antoine Roch, MD, PhD, Sonia Machado, MD, Romain Sonneville, MD, Olivier Guisset, MD, Wilfried Pujol, MD, Claude Guérin, MD, PhD, Jean-Louis Teboul, MD, PhD, Natacha Mrozek, MD, Michaël Darmon, MD, PhD, Frank Chemouni, MD, Matthieu Schmidt, MD, Emmanuelle Mercier, MD, Didier Dreyfuss, MD, PhD, and Stéphane Gaudry, MD

Abstract: France has recently witnessed a nationwide outbreak of measles. Data on severe forms of measles in adults are lacking. We sought to describe the epidemiologic, clinical, treatment, and prognostic aspects of the disease in adult patients who required admission to an intensive care unit (ICU). We performed a retrospective analysis of a cohort of 36 adults admitted to a total of 64 ICUs throughout France for complications of measles from January 1, 2009, to December 31, 2011. All cases of measles were confirmed by serologic testing and/or reverse transcription polymerase chain reaction.

The cohort consisted of 21 male and 15 female patients, with a median age of 29.2 years (25th–75th interquartile range [IQR], 27.2–34.2 yr) and a median Simplified Acute Physiology Score (SAPS II) of 13 (IQR, 9–18). Among the 26 patients whose measles vaccination status was documented, none had received 2 injections. One patient had developed measles during childhood. Underlying comorbid conditions included chronic respiratory disease in 9 patients, immunosuppression in 7 patients, and obesity in 3 patients, while measles affected 5 pregnant women.

Respiratory complications induced by measles infection led to ICU admission in 32 cases, and measles-related neurologic complications led to ICU admission in 2 cases. Two patients were admitted due to concurrent respiratory and neurologic complications.

Bacterial superinfection of measles-related airway infection was suspected in 28 patients and was documented in 8. Four cases of community-acquired pneumonia, 6 cases of ventilator-associated pneumonia, 1 case of tracheobronchitis, and 2 cases of sinusitis were microbiologically substantiated.

Of 11 patients who required mechanical ventilation, 9 developed acute respiratory distress syndrome (ARDS). Among the patients with ARDS, extraalveolar air leak complications occurred in 4 cases. Five patients died, all of whom were severely immunocompromised.

On follow-up, 1 patient had severe chronic respiratory failure related to lung fibrosis, and 2 patients had mild lower limb paraparesis along with bladder dysfunction, both of which were ascribable to measles-induced encephalitis and myelitis. Among the 5 pregnant patients, the course of measles infection was uneventful, albeit 1 patient underwent emergent cesarean delivery because of fetal growth restriction.

Measles is a disease with protean and potentially deceptive clinical manifestations, especially in the immunocompromised patient. Measles-associated pneumonitis and its complications, and less commonly postinfectious encephalomyelitis, are the main source of morbidity and mortality. In contrast with the usually benign course of the disease in immunocompetent patients, measles occurring in immunocompromised patients gives rise to lethal complications including ARDS, with or without bacterial superinfection. Other patients potentially at high risk for severe measles are young adults and pregnant women. Measles pneumonitis may predispose to air leak disease in patients using mechanical ventilation. To date, vaccination remains the most potent tool to control measles infection.

(*Medicine* 2013;92: 257–272)

From AP-HP, Service de Réanimation Médico-Chirurgicale, Université Paris Diderot, Sorbonne Paris Cité Hôpital Louis Mourier, Colombes (CR, JDR, JM, DD, SG); Department of Intensive Care Medicine, Lapeyronie University Hospital, Montpellier (KK, SM); Institut National de la Santé et de la Recherche Médicale, INSERM U722, Paris (JDR, JM, DD, SG); Universite Paris Diderot, Sorbonne Paris Cité, UMR 722, Paris (JDR, JM, DD, SG); AP-HP, Service de Pneumologie et Réanimation, Hôpital Tenon, Universite Pierre-et-Marie-Curie, Paris (JM); Aix-Marseille Université, Faculté de Médecine, URMITE UMR CNRS 7278, Marseille, and APHM, Hôpital Nord, Réanimation des Détresses Respiratoires et des Infections Sévères, Marseille (AR); AP-HP, Service de Réanimation Médicale et des Maladies Infectieuses, Université Paris Diderot, Sorbonne Paris Cité, Hôpital Bichat-Claude-Bernard, Paris (RS); Service de Réanimation Médicale, Hôpital Saint-André, CHU Bordeaux, Bordeaux (OG); Service d'Anesthésie et Réanimation, Polyclinique Bordeaux Nord Aquitaine, Bordeaux (WP); Hospices Civils de Lyon, Service de Réanimation Médicale, Hôpital de la Croix Rousse, Lyon (CG); AP-HP, Hôpital de Bicêtre, Service de Réanimation Médicale, Le Kremlin-Bicêtre (JLT); CHU Clermont-Ferrand, Unité de Réanimation Médicale, Pôle REUNNIRH, Clermont-Ferrand (NM); Medical-Surgical Intensive Care Unit, Saint-Etienne University Hospital, and Jean Monnet University, Saint-Etienne (MD); Medico-Surgical Intensive Care Unit, Avicenne Teaching Hospital, Bobigny (FC); AP-HP, Service de Pneumologie et Réanimation Médicale, Groupe Hospitalier Pitié-Salpêtrière, Paris (MS); and Medical Intensive Care Unit, Tours University Hospital, Tours (EM); France.

Abbreviations: ADEM = acute disseminated encephalomyelitis; ARDS = acute respiratory distress syndrome, CAP = community-acquired pneumonia, CDC = Centers for Disease Control and Prevention, CFU = colony-forming units, chest CT = thoracic computed tomography, CK = creatinine kinase, CNS = central nervous system, CSF = cerebral spinal fluid, ECMO = extracorporeal membrane oxygenation, EEG = electroencephalogram, FLAIR = fluid-attenuated inversion recovery, HIV = human immunodeficiency virus, ICU = intensive care unit, IgG = immunoglobulin G, IgM = immunoglobulin M, IQR = interquartile range, IVIG = intravenous immunoglobulin, MIBE = measles inclusion body encephalitis, MRI = magnetic resonance imaging, MSSA = methicillin-sensitive *Staphylococcus aureus*, MV = measles virus, NO = inhaled nitric oxide, NSAID = nonsteroidal antiinflammatory drug, PIE = postinfectious encephalitis and/or myelitis, RT-PCR = reverse transcription polymerase chain reaction, SAPS II = Simplified Acute Physiology Score, VAP = ventilator-associated pneumonia, WHO = World Health Organization.

INTRODUCTION

Measles virus (MV) is a small spherical, enveloped, single-stranded RNA virus belonging to the genus *Morbillivirus* in the family Paramyxoviridae.[15] Despite the availability of an effective vaccine for more than 30 years, measles still represents a major harbinger of death in low income countries, affecting chiefly malnourished infants and claiming about 150,000 lives per year.[44,77] Although it was supposedly on the verge of extinction in France, MV has reemerged spectacularly since 2008 with over 20,000 registered cases of measles.[21,47,60] In the last 3 years, outbreaks have repeatedly been reported elsewhere in Europe, calling into question the assumption that measles is a disease confined to developing countries.[18,24,37,65] Recent works have pointed to insufficient vaccine coverage as the main reason for the resurgence of measles, strengthening claims that this disease is likely to pose unique challenges over the coming years.[37,47,49,77,84] Another major source of concern is the growing proportion of young adults affected by the epidemics, an age group more prone to severe complications such as encephalitis and pneumonia.[49,64]

In comparison to the profuse data available on recent measles epidemics, to our knowledge a study addressing the specificities of severe measles affecting an adult population had yet to be conducted. Herein, we report 36 cases of patients with measles requiring ICU admission.

METHODS

Study Design and Measles Case Definition

In this retrospective study, case detection was conducted through a nationwide survey in France. Eligibility for study inclusion was a confirmed measles infection diagnosed between 2009 and 2011. We contacted 64 ICUs; 1 declined to participate. Nineteen ICUs provided a total of 36 cases.

Measles was deemed confirmed in the presence of the following symptoms which were recorded whenever possible: generalized rash lasting ≥3 days; and temperature ≥38.3°C; and cough, coryza, or conjunctivitis in addition to positive serologic testing or the detection of measles virus-specific nucleic acid by reverse transcription polymerase chain reaction (RT-PCR). Serologic testing was deemed positive in the presence of immunoglobulin M antibody (IgM) or in case of a significant rise in measles antibody level by any standard serologic assay. In the event of positive laboratory testing, a patient did not have to have any of the aforementioned clinical features, in accordance with guidelines from the United States Centers for Disease Control and Prevention (CDC).[14,70]

All cases were indigenously acquired in accordance with the measles classification established by the CDC, which means either that the case could be linked to local transmission or that the rash occurred more than 18 days after entering French territory.[14]

The study was approved by the ethics committee of the Société de Réanimation de Langue Française.

Data Collection

For each patient included we collected data as described below using a standardized data collection form with the help of the patient's attending physician in the ICU.

Demographic and Clinical Characteristics and Vaccination Status

Data included demographic features, measles vaccination status, presence and type of immunodeficiency, underlying cardiovascular and respiratory comorbidities, possible cross-transmission through person-to-person contact, and Simplified Acute Physiology Score (SAPS II).[35] Obesity was defined as a body mass index >30 kg/m^2, in compliance with recommendations set by the World Health Organization (WHO).[54] Cross-transmission was defined as a history of contact with a probable or confirmed case of measles within 7–21 days before rash onset.

Full immunization was considered if a 2-dose vaccine regimen was administered during infancy, in agreement with guidelines from the WHO.[81] On admission symptoms related to measles infection, as defined by the CDC, and including the presence of Köplick's sign, were sought for. Fever was defined as a body temperature ≥38.3°C.

Before admission to the ICU, antimicrobial treatment, steroids, or nonsteroidal antiinflammatory drugs (NSAIDs) administered during the course of the disease were recorded. In patients with respiratory compromise subsequent to measles infection, we noted the time between the onset of measles infection, defined as the presence of the morbillous rash, and the occurrence of dyspnea.

Laboratory Investigations

We reviewed the time course of every clinical event related to measles, including both characteristic features and less common complications. On admission to the ICU, the following laboratory parameters were collected, when available: creatinine kinase (CK) levels, serum creatinine, serum liver enzyme and marker levels (including aminotransferases, alkaline phosphatases, and bilirubin), platelet count, total lymphocyte count, and blood gases. Lymphopenia was defined as a total lymphocyte count <1000/μL. Diagnostic criteria for measles-associated rhabdomyolysis included a CK plasma level rise >2 times the upper limit of normal laboratory range and exclusion of any other potential cause for rhabdomyolysis. Diagnosis of measles-related hepatitis was based on an increase of serum aminotransferases at least >2 times the upper limit of the normal laboratory range in the absence of preexistent liver disease, rhabdomyolysis, or other potential cause of elevated serum aminotransferases. Thrombocytopenia was characterized as a platelet count <150,000 cells/mm^3.

Respiratory Disease Associated With Measles

Whenever possible, thoracic imaging performed within 24 hours of the ICU admission was reviewed by the attending physician and the radiologist. In cases with both a chest X-ray and a thoracic computed tomography (chest CT) scan, higher priority was given to the chest CT in terms of definitive interpretation.

Details regarding the supportive care and oxygenation in case of acute respiratory failure were collected upon admission and monitored throughout the ICU stay.

Acute respiratory distress syndrome (ARDS) was defined in compliance with the Berlin conference on ARDS.[69] Adjunctive therapies of ARDS including prone positioning, inhaled nitric oxide (NO), and extracorporeal circulation membrane oxygenation (ECMO) were recorded.

Airway Bacterial Superinfection and Coinfection Case Definition

For any given episode of suspected airway bacterial superinfection, the following data were collected: time to occurrence after ICU admission, site of infection (tracheobronchitis, sinusitis, otitis, and pneumonia), pneumonia type (community-acquired pneumonia [CAP], ventilator-associated pneumonia [VAP]), bacterial diagnosis, microbiologic sampling procedure,

antibiotic resistance profile, the prescribed antibiotic, and the duration of the treatment.

Samples deemed valid for microbiologic assessment included sputum culture, blood culture, and detection of urine antigens of *Streptococcus pneumoniae* and *Legionella pneumophila*. VAP referred to ventilator-associated infection of the lower airway tract arising 72 hours after intubation for mechanical ventilation. In the setting of VAP, bacterial superinfection was defined by the presence of a new infiltrate, at least 2 of the following criteria: temperature >38.3°C, purulent tracheal secretions or purulent sputum, an elevated leukocyte count >10,000/µL, and a positive quantitative culture of distal secretions obtained from tracheal aspirations (threshold $\geq 10^6$ colony-forming units [CFU]/mL), bronchoalveolar lavage (threshold $\geq 10^4$ CFU/mL), or protected specimen catheter (threshold $\geq 10^3$ CFU/mL), according to prior data and guidelines.[12]

CAP was defined in the case of microbiologically documented coinfection of the lower airway tract before hospitalization or within 72 hours of hospital admission. If the patient required mechanical ventilation upon admission, microbiologic sampling and interpretation were conducted in a fashion similar to that for VAP. Otherwise, if spontaneous breathing was maintained, bacterial superinfection was based on the yield of sputum culture (threshold $\geq 10^7$ CFU/mL) and *S. pneumoniae* and *L. pneumophila* urinary antigen testing.

Measles-Directed Antiviral Treatment

We collected data related to antiviral therapies directed against measles. This category comprises therapies aimed directly at measles, ribavirin and polyvalent immunoglobulin (IVIG), therapies directed against measles-induced inflammation and cross-immunization, steroids and plasma exchange, and vitamin A. Variables of interest were time between measles onset and initiation of the first measles-directed treatment, duration, and dose of treatment.

Follow-Up

In patients who survived ARDS or neurologic complications following measles infection, details regarding the clinical examination on follow-up were collected when readily available.

Outcome and Statistical Analysis

Data are reported as median (25th–75th interquartile range [IQR]) or proportions as appropriate. Statistical analysis was performed using GraphPad Prism (GraphPad Software, v. 5.0).

RESULTS

Temporal Distribution of Measles Infection in 35 Cases

The yearly and monthly distribution of 35 cases of measles infection is displayed on Figure 1. One patient whose final diagnosis was measles inclusion body encephalitis (MIBE) was not included in the analysis given the undetermined time of infection and the highly variable delay between the onset of the disease and the inaugural neurologic symptoms. In all but 1 case, measles infection occurred during winter or spring. The vast majority of cases occurred during the year 2011 (74.3%). Three epidemic waves of gradually increasing magnitude throughout the 3-year survey could be observed with an epidemic peak culminating in February 2011.
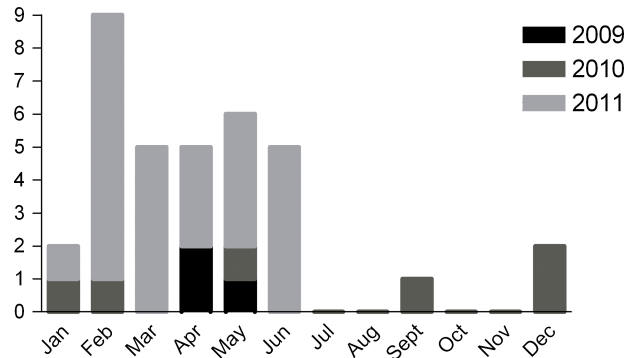

FIGURE 1. Temporal distribution of 35 measles infection cases. Y axis: number of cases per corresponding month. Note: The patient admitted for MIBE was not included in the analysis given the undetermined time of infection and the highly variable delay between the onset of the disease and the inaugural neurologic symptoms.

Baseline Characteristics, Demographic Variables, and General Symptoms Associated With Measles

Baseline characteristics, demographic and ICU-related variables, and general symptoms of patients with measles-associated pneumonitis—the prevailing clinical pattern—are depicted in Table 1. The total patient cohort consisted of 21 men and 15 women with a median age of 29.2 years (IQR, 27.2–34.2 yr). Median SAPS II score on admission was 13 (IQR, 9–18). The patient's vaccination status with respect to measles was readily available in 26 cases: 7 patients received a single dose of the vaccine, and 19 patients had never been vaccinated. One patient reported that he had previously contracted measles during childhood. With the potential exception of this patient, none of the patients was fully immunized against measles.

Measles infection developed as a result of possible cross-transmission in 10 cases (27.8%). Underlying comorbid conditions were chronic respiratory disease in 9 patients, immunosuppression in 6 patients, and obesity in 3 cases. Measles affected pregnant women in 5 instances; 2 of these patients contracted measles before the 24th week of pregnancy. Causes of chronic respiratory disease in this group of patients included intermittent asthma (n = 6), bronchiectasis (n = 1), chronic obstructive pulmonary disease (n = 1), and restrictive lung disease (n = 1). Reasons for immunosuppression were human immunodeficiency virus (HIV) infection (CD4+ lymphocyte count: 10 cell/mm³, 3 month prior hospital admission) (n = 1), maintenance immunosuppressive regimen for kidney transplantation (n = 3), common variable immunodeficiency (n = 1), and stage IV non-Hodgkin lymphoma (n = 1). Twenty-five patients (71.4%) were deemed healthy before measles infection.

Three patients received corticosteroids, 4 patients received NSAIDs, and 3 patients received both. None of these patients had any other cause of immunosuppression. In all cases these treatments either were administered as part of over-the-counter self-medication or were prescribed by the general practitioner before hospital admission.

The following characteristic signs of the illness were found upon hospital admission: fever (n = 24, 66.7%), cough (n = 18, 50%), coryza (n = 15, 41.7%), pharyngitis (n = 20, 55.6%), and conjunctivitis (n = 15, 41.7%). The presence of Köplick's sign was noted in 12 cases (33.3%). The presence of a rash suggestive of measles either was present during the course of the hospital stay (n = 30, 83.3%) or had been experienced by the

TABLE 1. Clinical, Laboratory, and Imaging Features and Outcome in 34 Patients With Measles Pneumonitis

Characteristic	No. (%)
No. of patients	34
Median age, yr (IQR)	27.8 (24.9–30.9)
Male sex	19 (55.9)
Obesity*	3 (8.8)
Underlying immunosuppression	5 (14.7)
Pregnancy	5 (11.8)
Chronic respiratory disease	9 (26.5)
Antiinflammatory treatment†	10 (29.4)
Measles-related features	
Time between first measles-related symptoms and ICU admission, d‡ (IQR)	6 (3–7)
Presence of morbillous rash§	32 (94.1)
Vaccination status¶	0
Laboratory results on admission	
Creatinine levels** (IQR)	56 (54–80)
ALAT levels†† (IQR)	144 (33–118)
CK levels‡‡ (IQR)	144 (62–569)
LDH levels‡‡ (IQR)	760 (466–1016)
Platelet count§§ (IQR)	188,000 (140,750–241,750)
Total leukocyte count§§ (IQR)	5165 (4275–8575)
Lymphocyte count§§ (IQR)	505 (323–377)
Respiratory-related features	
Pulmonary bacterial coinfection/superinfections¶¶	10
Presence of lobar consolidation at initial thoracic imaging***	8 (23.5)
Mechanical ventilation	11 (32.4)
Air leak complications	4 (11.8)
Measles-related specific treatments	
Ribavirin	1 (2.9)
Vitamin A	2 (5.9)
IVIG	3 (8.8)
Measles-related specific treatments (total)	6 (17.6)
ICU management-associated variables	
SAPS II	13 (9–18)
Vasopressor support	4 (11.8)
ARDS	9 (26.5)
ICU LOS†††	3 (2–11.8)
Mortality in the ICU	5 (14.7)

Abbreviations: ALAT = alanine aminotransferase, LDH = lactate dehydrogenase, LOS ICU = length of stay in the intensive care unit.

*Defined by a body mass index $\geq$30 kg/m^2.

†Prior to ICU admission, includes steroids and nonsteroid antiinflammatory therapies other than usual medication.

‡Measles onset being defined by the onset of rash or initial respiratory symptoms in the absence of rash.

§At any time.

¶Number of patients with full immunization, defined by completion of a 2-injection regimen.

**Median levels in μmol/L.

††Median levels in IU/L.

‡‡Median count of total platelet count, expressed as cells per mm^3.

§§Median count, expressed as cells per mm^3.

¶¶Number of bronchopulmonary coinfection and superinfection during the entire hospital stay.

***At least 1 area of consolidation on the thoracic imaging performed within 24 hours of the ICU admission.

†††Length of stay in the ICU, in days.

patient before hospitalization and had since receded (n = 2, 5.6%). In 4 cases (11.1%), there was no evidence of the morbillous rash during or before hospitalization; all 4 of these patients were immunodepressed (kidney transplantation, n = 3; HIV, n = 1).

Spectrum of Measles-Associated Complications Precipitating ICU Admission

Measles pneumonitis, with or without bacterial superinfection, was the sole complication requiring hospitalization in an ICU unit (n = 32). The median time between the onset of

measles and the development of dyspnea was 6 days (IQR, 3–7 d). One patient developed histologically ascertained Hecht (giant cell) pneumonia following measles infection and after a first course of chemotherapy for non-Hodgkin lymphoma. Neurologic complications prompting ICU admission were observed in 2 cases, including 1 case of postinfectious encephalitis and/or myelitis (PIE) and 1 case of MIBE. Two patients developed both respiratory and neurologic complications, both of which were affected by PIE. Eleven patients required mechanical ventilation. Indications for mechanical ventilation were acute respiratory failure due to measles pneumonitis-related complications (n = 8) and measles-induced neurologic complications (n = 3).

Respiratory Complications Associated With Measles

Measles Pneumonitis and Imaging Characteristics

All patients except 2 underwent thoracic imaging within 24 hours of ICU admission. Chest CT scan results were readily available for 10 patients. Typical aspects of measles pneumonitis are displayed in Figure 2. Thoracic imaging among patients admitted for measles disclosed an exclusive pattern of interstitial pneumonitis in 21 (61.7%) cases. In all but 1 patient, chest CT scans, when performed, disclosed evidence of interstitial lesions. Of 9 patients, the pattern of interstitial pneumonitis consisted of micronodular opacities (n = 4), ground-glass opacities (n = 4), and reticulonodular lesions (n = 3). Mixed alveolar and interstitial lesions were seen in 4 (11.7%) cases. Lesions, when present, were predominantly bilateral (89.5%). In this same group of patients, thoracic imaging upon admission did not display any abnormality in 3 cases (21.2%). In all cases, imaging was chest X-Ray exam. In 1 case, a bilateral interstitial lesion pattern was substantiated on follow-up exam, and in the 2 remaining patients, the prevailing diagnosis was measles pneumonitis because of biologically ascertained measles infection, significant hypoxemia, and lack of alternative diagnosis. In the group of patients with CAP along with measles pneumonitis (n = 4), areas of consolidation were noticed in 2 instances. Two patients using mechanical ventilation had repeated CT scans during their stays in the ICU because of persistent and severe hypoxemia. In both cases, in addition to the interstitial lesion pattern initially substantiated, the CT scans demonstrated lobar consolidation of the lower lobes and evidence of fibrosis (thickened septa and retractile bronchiectasis in 1 case, bronchiectasis and disseminated cystic lesions in the other). Neither of these 2 patients had microbiologic evidence of pulmonary superinfection at the time the control chest CT scan was performed.
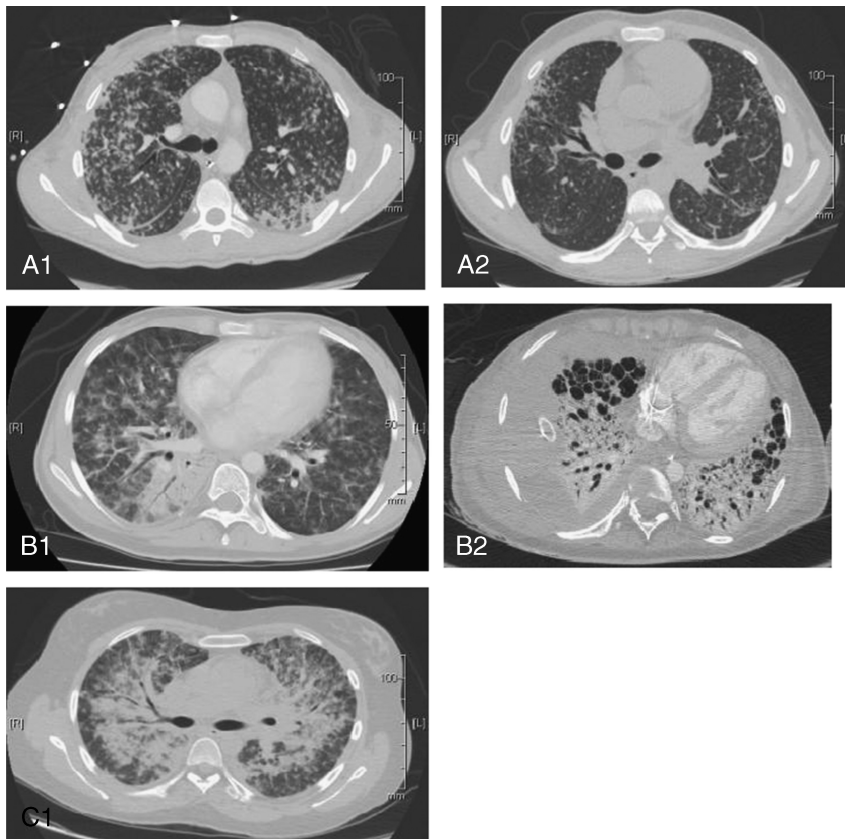

FIGURE 2. Typical aspects of measles pneumonitis on CT scan. A1. Scan from a 27-year-old kidney transplant patient, on admission to the ICU: interstitial pneumonitis with disseminated micronodular distribution. A2. Follow-up chest CT scan 3 months after ICU admission: fibrosing interstitial pneumonia with micronodules, thickened interlobular septa, and focal areas of retraction. B1. Scan from an 18-year-old patient with common variable immunodeficiency, on admission to the ICU: interstitial pneumonitis with bilateral reticulonodular infiltrates and ground-glass opacities and lung consolidation of the lower right lung. B2. Scan from Day 21 after admission to the ICU: right hemothorax with chest tube, bilateral bronchiectasis, and cystic lesions of the lungs. C1. Scan from 30-year-old kidney transplant patient, on admission to the ICU: bilateral, alveolar, and interstitial opacities with a predominantly perihilar distribution.

TABLE 2. Patient Characteristics, Microbiology Features, and Outcome in 8 Patients With Measles Pneumonitis and Proven Bacterial Pulmonary Superinfections

Sex/Age (yr)	SAPS II	ID	CRD	Prior ABT*	Chest Imaging Results	Time Span† (d)	Setting of Infection	MB Sampling‡	MB Results	ABT§	MV Duration¶ (d)	VP**	ICU LOS†† (d)	Final Outcome
M/27	6	N	N	SP	CT	BIO	12	CAP	BSPC	H. influenzae	AMX	N	N	3	Alive
M/28	21	N	IA	AMX	X-ray	BIO	11	VAP	BAL	H. influenzae	AMC	10	N	17	Alive
M/23	32	N	N	AMC	X-ray	BIO	13	VAP	BAL	MSSA	AMC	3	N	2	Alive
M/30	30	N	IA	N	X-ray	NI	14	VAP	BAL	P. aeruginosa	IMP, CIP	29	N	42	Alive
M/16	28	N	N	N	X-ray	NI	10; 20	CAP; VAP	BAL; BAL	N. meningitidis; MSSA	AMC; OXA	32	N	41	Alive
F/30	37	Y	N	CRO, LVX	CT	BIAO	10; 15	CAP; VAP	BAL; BAL	MSSA; P. aeruginosa	TZP, LVX, LZD, ATM, GM; ATM, CS, RMP, AN	29	Y	41	Died
M/24	27	N	N	N	X-ray	RAO	1	CAP	UA	S. pneumoniae	CTX, SP	3	N	5	Alive
M/19	40	Y	N	AMC	CT	BIO	35	VAP	BAL	E. cloacae	IMP, AN	26	Y	33	Died

Abbreviations: ABT = antibiotic therapy, AMC = amoxicillin and clavulanic acid, AMX = amoxicillin, AN = amikacin, ATM = aztreonam, BAL = bronchoalveolar lavage, BIAO = bilateral interstitial opacities, BIO = bilateral interstitial opacities, BSPC = bronchoscopy-guided protected catheter, CIP = ciprofloxacin, CRD = chronic respiratory disease, CRO = ceftriaxone, CS = colimycin, CT = computed tomography, CTX = cefotaxime, GM = gentamicin, ID = immunosuppression, IMP = imipenem, LVX = levofloxacin, LZD = linezolid, MB = microbiologic, MSSA = methicillin-sensitive *Staphylococcus aureus*, N = no, NI = normal, OXA = oxacillin, RAO = right-sided alveolar opacities, RMP = rifampicin, SP = spiramycin, TZP = tazocilline, UA = urine antigen (*Streptococcus pneumoniae*), VP = vasopressor, Y = yes.

*Antibiotic therapy prior to ICU admission.

†Time elapsed between the onset of rash and microbiologic documentation, in days.

‡Sampling method for microbiologic documentation.

§Antibiotic therapy during ICU management.

¶Duration of mechanical ventilation, in days.

**At any given time of the course of the ICU management, epinephrine or phenylephrine infusion rate >2 mg/h.

††Length of stay in the ICU, in days.

Airway Bacterial Superinfection and Causative Microorganisms

Clinical characteristics, microbiology features, and outcome among the 8 patients with measles pneumonitis and proven bacterial superinfection are displayed in Table 2.

In patients admitted for respiratory symptoms, 17 patients had received antibiotic therapy before ICU admission. Only 4 patients did not receive antibiotics at any time during their medical management. Ten episodes of pulmonary bacterial superinfection were documented in 8 patients, including 4 cases of CAP and 6 cases of VAP. Two of these patients were immunocompromised; none was pregnant. The following bacteria were recovered: *Haemophilus influenzae* (n = 2), methicillin-sensitive *Staphylococcus aureus* (MSSA) (n = 3), *Pseudomonas aeruginosa* (n = 2), *Enterobacter cloacae* (n = 1), *S. pneumoniae* (n = 1), and *Neisseria meningitidis* (n = 1). Of note, 1 patient developed pulmonary aspergillosis following chemotherapy for stage IV non-Hodgkin lymphoma.

Upper Airway Involvement in Measles

Nineteen patients (52.8%) had symptoms consistent with pharyngitis due to measles. One patient had bacterial pharyngitis consecutive to beta-hemolytic *Streptococcus*. Sinusitis occurred in 2 instances, with proven *Neisseria meningitidis* superinfection in 1 case. MSSA was responsible for measles-related tracheobronchitis superinfection in 1 patient. One case of otitis media was reported.

Severe Respiratory Failure in the Setting of Measles Pneumonitis

Of 11 patients who required support with mechanical ventilation, 9 went on to develop ARDS. According to the Berlin definition, 5 patients met the criteria for severe ARDS, 2 patients could be classified as moderate ARDS, and 2 additional patients as mild ARDS.[69] None of the 5 pregnant women required mechanical ventilation. Among the patients with ARDS, extraalveolar air leak complications occurred in 4 cases and 5 patients died, all of whom were severely immunocompromised. There was no case of air leak complication among patients with measles pneumonitis who did not require mechanical ventilation. Four patients progressed to refractory hypoxemia which did not respond to combined therapeutics including prone positioning (n = 4), NO (n = 4), and ECMO (n = 4).

Extraalveolar Air Leak Complications

Extraalveolar air leak complications affected 4 patients, representing an incidence of 11.8% in the group of patients affected by measles pneumonitis. All of the patients were nonsmokers, and none had experienced pneumothorax before measles infection. Two patients had a history of respiratory disease: 1 patient was known for having bronchiectasis and the other, intermittent asthma. There was no evidence in any case for iatrogenic and/or traumatic pneumothorax. All of the patients were using mechanical ventilation and had ARDS at diagnosis. Extraalveolar air leak disease developed following ICU admission, and thus was not the motive for intensive care management. The condition manifested itself as unilateral pneumothorax in 2 cases, pneumomediastinum in 1 case, and combined pneumothorax and pneumomediastinum in 1 case. In this group, 2 patients died during the course of ICU management, albeit none as a direct consequence of air leak disease.

Neurologic Complications Associated With Measles

Details of clinical and laboratory investigations are presented in Table 3. Neurologic complications following measles infection consisted of 3 cases of PIE, 1 case of probable MIBE, and 1 case of intracerebral hemorrhage. The latter is not detailed in Table 3, because no direct connection could be established between measles infection and the occurrence of intracerebral hemorrhage. There was no reported case of subacute sclerosing panencephalitis. None of these patients with neurologic complications had received the full course of immunization against measles. Examples of magnetic resonance imaging (MRI) morphologic findings are shown in Figure 3.

Postinfectious Encephalomyelitis

The 3 patients who developed neurologic symptoms in the setting of PIE did so within 1 week of the onset of measles. There was no evidence of underlying immunosuppression in these patients. On ICU admission, all 3 patients had the typical morbillous rash along with fever. In 2 cases altered mental status, without any evidence of epilepsy, was the predominant symptom. In the third case, initial clinical assessment was suggestive of meningitis, and the patient experienced 1 seizure, confirmed by electroencephalogram (EEG). On cerebral spinal fluid (CSF) analysis, mild lymphocytic pleocytosis and hyperproteinorachia were observed in every case. Imaging consisting of brain CT scan and brain MRI performed respectively on day 1 and day 16 following the onset of neurologic manifestations was deemed normal. In 1 case, brain and medulla MRI T2-weighted coronal fluid-attenuated inversion recovery (FLAIR) sequence depicted a diffuse hyperintense signal of the medulla indicative of myelitis. Chest imaging did not unveil any evidence for pneumonitis on admission. Mechanical ventilation was warranted in 2 cases as a result of neurologic failure. Concurrent measles pneumonitis affected 2 patients.

Measles Inclusion Body Encephalitis

A 37-year-old kidney transplant recipient presented with an episode of focal seizure affecting the right upper limb followed by grand mal seizure. One month before his admission, the patient had resumed hemodialysis following kidney graft failure as a result of transplant glomerulopathy, without concurrent reinforcement of the immunosuppressive regimen.

On admission, the patient was stuporous but both his hemodynamic and respiratory conditions were normal. A history of possible measles cross-transmission was noted 3 months before the first neurologic symptoms, but the patient denied any rash over that period. Notable neurologic examination findings included motor aphasia, paralysis of the left lower limb, and clonic seizure of the right upper limb. A brain MRI substantiated hyperintense signals affecting the right thalamus and peduncle along with similar lesions affecting the cortico-subcortical regions of the right temporal lobe, right occipital lobe, and left frontal lobe on the FLAIR sequence. The CSF analysis was unremarkable. The patient's immunosuppressive regimen of mycophenolate mofetil 250 mg twice daily and prednisone 7 mg once daily was withheld.

Because of a gradual decline of the patient's consciousness, without evidence of epilepsy on iterative EEG, he was placed under mechanical ventilation a week after his admission. Sequential serologic testing for measles demonstrated unequivocal seroconversion with positive IgM and immunoglobulin G (IgG) antibodies on 2 plasma samples contemporaneous with the neurologic symptoms, whereas a third sample

TABLE 3. Characteristics of 4 Patients With Neurologic Complications Due to Measles

Sex\Age (yr)	Comorbid Condition	First Neurologic Symptom	Time Span: Measles Onset – First Neurologic Symptoms* (d)	CNS Imaging	Time Span: Measles Onset – CNS Imaging† (d)	Results	CSF Examination	EEG Pattern	Diagnosis Neurologic Complication	Measles Pneumonitis‡	Final Outcome
M/24	None	Delirium	7	MRI	26§	Nl	10 RBC; 226 WBC; 85% Ly; P: 1.44; G: Nl	NP	PIE	Y	Bilateral paraparesis bladder dysfunction
M/16	None	Nuchal rigidity, photophobia	4	CT scan	5	Nl	2 RBC; 232 WBC; 99% Ly; P: 1.91; G: Nl	Epileptiform discharges	PIE	N	Alive, no sequelae
M/16	None	Delirium, paraparesis, acute urinary retention	7	MRI, T2	7	Foci of hyperintensity of the medulla	0 RBC; 86 WBC; 70% Ly; P: 1.76; G: Nl	Slow wave abnormalities	PIE	Y	Bilateral paraparesis bladder dysfunction
M/37	Kidney transplant	Bilateral upper limb clonus	NR	MRI, T2	7	Foci of hyperintensity right thalamus right subcortical temporal lobe, right cerebral peduncle	11,400 RBC; 11 WBC; 86% PMN; P: 1.76; G: Nl	Slow wave abnormalities	MIBE	N	Normal mental status; infrequent myoclonus

Abbreviations: G = glucose content, Ly = lymphocyte count, Nl = normal, NP = not performed, NR = not relevant, P = protein content in g/L, PMN = polymorphonuclear leukocyte count, RBC = red blood cells count, WBC = white blood cells count.

*Time elapsed between the onset of measles, as defined by occurrence of rash, and first neurologic symptoms, in days.
†Time elapsed between the onset of measles, as defined by occurrence of rash, and acquisition of MRI, in days.
‡Co-occurrence of measles pneumonitis.
§A brain CT scan performed the day after the onset of neurologic symptoms was deemed normal.
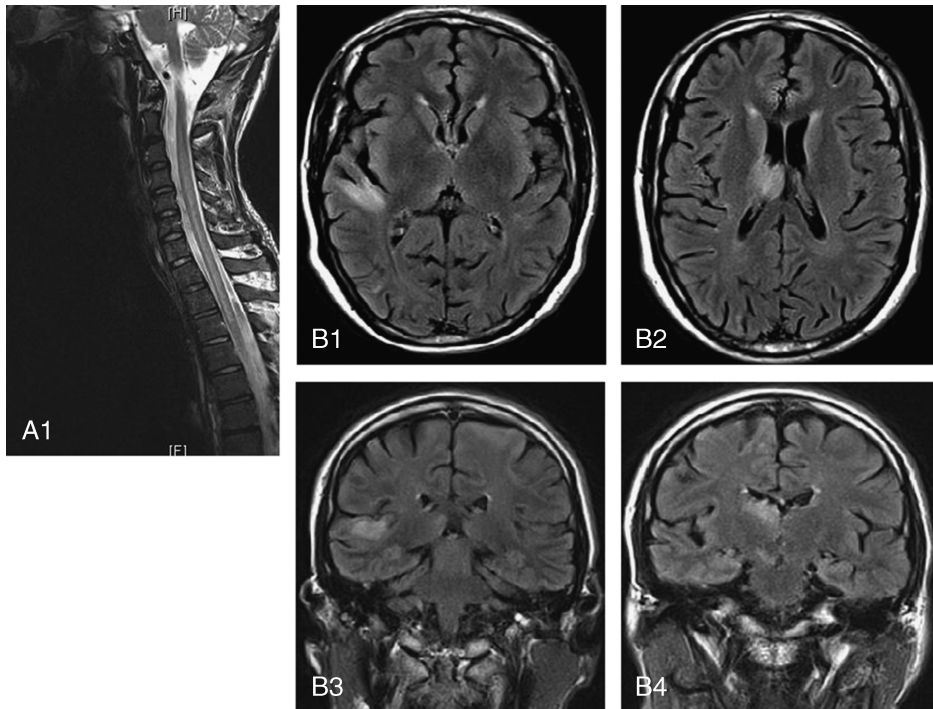
FIGURE 3. Examples of CNS MRI in patients with measles-related neurologic complications. A1. Image from a 16-year-old patient with no prior medical history, admitted to the ICU with postinfectious myelitis: T2-weighted sequence shows diffuse hyperintensities of the cervical and dorsal medulla consistent with myelitis. B. Images from a 37-year-old kidney transplant patient with acute encephalitis, on admission to the ICU: axial and coronal T2-weighted FLAIR sequences show hyperintensities of the right thalamus (B2, B4) and of subcortical white matter of the right temporal lobe (B1, B3).

collected 5 months before the neurologic symptoms was negative. A brain biopsy procedure was initially considered but was not carried out because of the satisfactory course of the patient's neurologic condition following treatment discontinuation. Accordingly, a control brain MRI performed on day 10 revealed partial resolution of the aforementioned abnormalities.

Other Clinical and Laboratory Complications Associated With Measles

The most prevalent laboratory complication was lymphopenia, affecting 24 of 28 (85.7%) patients for whom a lymphocyte count was readily available on admission. Potential confounding factors involved HIV infection (n = 1), immunosuppressive regimen (n = 2), and chronic malnutrition (n = 1). The median lymphocyte level was 515 mm^3 (IQR, 315–815 mm^3). Other complications included diarrhea (n = 5, 14.7%), rhabdomyolysis (n = 9, 26.5%), hepatitis (n = 3, 8.8%), and thrombocytopenia (n = 9, 26.5%). Aminotransferase plasma levels were augmented in 18 (50%) of the patients. In 1 case, a patient developed acute renal failure consecutive to severe rhabdomyolysis, in the absence of seizures, with a CK pick level of 94,100 IU/L. The patient was managed with supportive care and did not require renal replacement therapy. On the whole, the aforementioned complications were mild, since no patient developed acute liver failure (median alanine aminotransferase level, 118 IU/L; IQR, 111-796 IU/L), or bleeding complications (median platelet levels, 126,000/mm^3; IQR, 105,000–140,750/mm^3) and rhabdomyolysis was asymptomatic in all other cases (median CK levels, 770 IU/L; IQR, 577–1173 IU/L).

Antiviral and Immunomodulatory Therapies

Variables related to measles-directed treatment are depicted in Table 4. A total of 8 patients received at least 1 of the following treatments: ribavirin (n = 4), IVIG therapy (n = 5), plasma therapy (n = 1), steroids (n = 4), or vitamin A treatment (n = 1). Primary indication was measles pneumonitis complicated by ARDS (n = 4) or severe hypoxemia (n = 1).

Among these 8 patients, 2 patients were started on antiviral treatment as a result of PIE and another patient as a result of MIBE. The median time between the disease onset and treatment initiation was 14 days (IQR, 7.0–21.5 d). In patients with respiratory failure, the patient's ventilatory condition worsened in every case despite different combinations of therapies, including intravenous ribavirin in 3 cases (see Table 4). Ultimately, 1 patient survived while the others died due to refractory hypoxemia or multiorgan failure. One patient with PIE was treated with a combination of plasma exchange and steroid pulse therapy. Only slight motor improvement was observed following treatment completion. Another patient with seizures related to PIE underwent a course of IVIG therapy. He was symptom free on discharge from the hospital. Finally, 1 patient with MIBE received ribavirin but the treatment was prematurely interrupted after 3 days after reassessment of the indication.

No adverse event related to antiviral treatment was reported, with the exception of 1 episode of intravascular hemolysis ascribable to ribavirin at day 21 of treatment. This adverse effect was deemed severe enough to warrant definitive withdrawal of the treatment. After discontinuation of ribavirin the hemolysis fully receded.

TABLE 4. Disease Course in 8 Patients With Measles-Directed Therapy

Sex/Age (yr)	SAPS II	ID	Indication for Therapy	Ribavirin			Vitamin A		IVIG			Plasma Exchange			Steroids				Response	Final Outcome
				Time Span* (d)	DOT (d)	Dose (mg)	Time Span* (d)	Dose (IU)	Time Span* (d)	DOT (d)	Dose (mg)	Time Span* (d)	DOT (d)	Dose†	Drug	Time Span* (d)	DOT (d)	Dose (mg)		
M/18	40	Y	ARDS	1	6‡	1225	19	100,000							MP	18	1	120	-	Died
M/16	39	N	PIE																++	Full recovery
M/16	28	N	PIE						5	1	50				MP	9	3	1000	+	Disabled
M/27	47	Y	Pn	36	2	1225			10	3	28								-	Disabled
F/30	37	Y	ARDS						23	5	20								-	Died
F/18	41	Y	ARDS						10	2	100				MP	20		180	-	Died
M/19	40	Y	ARDS	14	4	1200			14	4	30	15	8	10	HC	40	11	100	-	Died
M/37	64	Y	MIBE	NR	3§	1300													NR	Partial recovery

Abbreviations: DOT= duration of treatment, HC = hydrocortisone hemisuccinate, ID = immunosuppression, MP = methylprednisolone, N = no, NR = not relevant, Pn = Pneumonitis, Y = yes.

*Time elapsed between onset of measles, as defined by onset of morbillous rash, and initiation of therapy, in days.

†Number of plasma exchanges.

‡Treatment withheld due to measles specific treatment-related adverse effects.

§Treatment prematurely stopped due to fear of adverse effects and insufficient evidence of efficacy.

Follow-Up

Four patients died during ICU management; all as a consequence of refractory ARDS. On follow-up 1 patient had severe chronic respiratory failure related to a fibrosing sequelae 6 months following measles pneumonitis complicated with ARDS. Two patients had mild gait disorder due to mild lower limb paraparesis along with bladder dysfunction 3 months after having developed encephalitis and myelitis ascribable to measles. Following discontinuation of the immunosuppressive treatment, the patient with MIBE steadily improved over the next 20 days with a perfect recovery of both his mental status and motor deficit. Only infrequent myoclonic jerks were noted at 1 month follow-up.

Among the 5 pregnant patients, the course of pregnancy was uneventful in 3 cases with delivery of live infants at the expected term. One patient underwent cesarean delivery prompted by fetal growth restriction after 38 weeks of gestation, and another developed preeclampsia at 40 weeks of gestation, which mandated urgent vaginal delivery. No neonatal complication was found, and both mother and offspring were doing well at follow-up.

DISCUSSION

In the current retrospective study we report 36 cases of severe measles infection confirmed by laboratory testing and requiring ICU management. To our knowledge, it is the largest series of severe measles infection in a high-resource health care setting. Most of the cases affected young adults (median age, 29.2 yr; IQR, 27.2–34.2 yr) and occurred during the first 6 months of 2011 (n = 26; 72.2%), and mirrored the yearly and seasonal national epidemics.[21] The predominant clinical picture was measles-related interstitial pneumonitis (n = 32), whereas neurologic symptoms occurred in 4 cases. Two different scenarios could be delineated in this group of patients. Overall, a benign evolution was noted in most cases (n = 23, 69.7%). However, in a small subset of immunocompromised patients we observed a severe course with frequent bacterial superinfections, a possible propensity for barotraumas, a high mortality rate (11.7%), and diagnostic caveats including a subacute and gradual progression of respiratory symptoms and a missing or atypical morbillous rash. The clinical expression of measles-induced neurologic complications is varied and often misleading, and patients can be left with severe neurologic impairments.

Respiratory Complications

Measles Pneumonitis and Chest Imaging

A radiographic pattern of interstitial lesions is recognized as characteristic of measles pneumonitis. Our findings are in agreement with previous reports since 23 patients (69.7%) with measles pneumonitis presented with radiographic abnormalities consistent with interstitial lesions. It should be noted that data regarding radiographic assessment of measles pneumonitis are predominantly based on chest X-ray examination, coming either from settings in which CT scans are not readily available or from studies dating from the pre-CT scan era.[26,57,68] In most of the 9 patients who had CT scans on admission, the abnormalities displayed were bilateral micronodular lesions or ground-glass opacities. Whether these patterns are specific of severe measles pneumonitis or simply ascribable to sample bias requires further investigation. Another debatable issue is the reliability of chest imaging to correctly identify patients with bacterial superinfection. Our results are inconclusive, primarily because of the small number of patients with CAP (n = 4). As shown in Table 2, there did not seem to be any unambiguous pattern suggestive of superinfection: 2 patients had normal

chest X-ray exams, 4 patients had bilateral interstitial opacities, 1 had right-sided alveolar opacities, and 1 had bilateral mixed alveolar and interstitial opacities.

However, other studies have addressed this question and demonstrated that the presence of a lobar consolidation or dense infiltrate is neither sensitive nor specific of bacterial coinfection.[26,57] A possible explanation regarding the poor discriminatory performance of chest imaging may reside in the possible natural history of measles-associated interstitial pneumonitis. The dynamic pattern of lesions, as highlighted by the results of repeated scans in 2 patients with measles-associated ARDS, suggests that lobar consolidation might result from the progressive coalescence of micronodular lesions, whether bacterial superinfection occurs or not.

Lower Airway Tract Bacterial Superinfection

In the current study, lower airway tract superinfections affected only 8 patients (24.2% of patients with respiratory symptoms). This incidence dropped to 12.1% when only patients with CAP are considered—in other words, when we discarded cases of pneumonia likely to be related to nosocomial factors in addition to measles pneumonitis. This relatively low incidence of bacterial pneumonia, especially when compared to other studies, where as many as 50% of patients were reported to have bacterial superinfection,[15,68] may be ascribable to "preemptive" antibiotic therapy (51.5% of patients with respiratory symptoms). In line with this hypothesis, patients with documented pulmonary superinfections either had not been exposed to prior antibiotic therapy (n = 2) or had inappropriate therapy with regards to the microbiologic results (n = 4). In fact, prophylactic antibiotic therapy has previously been considered as a way to reduce the burden of lung bacterial superinfection, primarily in African children.[15] Although there was a small trend favoring antibiotic prophylaxis in a recent metaanalysis, no definite conclusion could be reached given the poor quality of the studies.[31] Furthermore, the stringent case definition for bacterial pneumonia, which included mandatory positive microbiologic results, may well have led to an underestimation of the true incidence of bacterial pneumonia.

Measles Virus-Related Immunosuppression

Another key finding of the present study was the state of lymphopenia, which affected 24 of 28 (85.7%) patients for whom a lymphocyte count was readily available, at ICU admission. Mechanisms by which measles is able to induce lymphocyte depletion include the following: apoptosis in both infected and uninfected lymphocytes,[55] enhanced adhesion of lymphocytes in secondary lymphoid organ,[51] or loss of precursors through thymic epithelial cell infection.[5] Additionally, MV interferes with lymphocyte function by suppressing T-cell proliferation,[42] damping IL-2 responses,[9] and negatively impacting downward signaling.[6] Functional alteration of the innate immunity has also been assumed with reports of a decline of NK cell activity[27] and compromised dendritic cell chemotaxis.[2] This state of immunosuppression, which starts soon after the onset of the morbillous rash, is age dependant and tends to last longer in adults.[56] This, in turn, exposes these patients to a greater risk of superinfection and subsequent complications, and may, in part, explain the incidence of severe disease in this age group.

Respiratory Impairment in Different Subsets of Patients

One of the key findings of the current study is the poor outcome associated with measles infection in the setting of host immunosuppression. All immunocompromised patients progressed towards ARDS, and 4 died. High measles case mortality in the context of HIV coinfection has been previously reported in African children, where malnutrition is often an additional concern,[58] but there is a paucity of data regarding adult patients in countries with a high standard of health care.[32] Why immunocompromised hosts are so vulnerable to MV infection remains to be fully elucidated,[62] but studies in both human patients and other primates point to a delayed virus clearance in case of concurrent immunosuppression,[28,63] suggesting that immunocompromised patients might be exposed to the virus' deleterious effect for an extended period of time. Accordingly, patients who developed ARDS as a consequence of measles-induced ARDS did so in the later stage of the disease as reflected by the delay between initial symptoms and ICU admission (median, 10 d; IQR, 6–19 d). Whether severe respiratory impairment in this subset of patients results from the direct consequence of the virus per se or to late bacterial superinfection, as speculated by some authors, remains to be determined.[39]

Additionally, immunocompromised patients exposed to MV are likely to develop a specific histopathologic pattern affecting the lung known as Hecht giant cell pneumonia, as was documented in 1 case in the current study.[17,46] Autopsy findings in this setting include degeneration of bronchial and bronchiolar epithelium, interstitial pneumonia, and giant cells in the alveolar wall.[8,41] Furthermore, the adverse effect of MV on the patient's immune status might combine with the patient's underlying immunosuppression, thus increasing the risk of superinfection.

Finally, measles infection in immunocompromised patients can be especially deceiving, with otherwise uncommon complications, and the hallmark rash may be limited or absent.[32,45] In other words, the diagnosis of measles-induced ARDS should be considered in immunocompromised patients even in the absence of the morbillous exanthema, once other causes have been ruled out and after assessment of the patient's immunization status and of local measles epidemics.

Whether risk factors recognized for severe H1N1 infection, namely obesity, chronic respiratory disease, and pregnancy, also apply to measles-induced pneumonitis could not be assessed accurately in the current study given its size. Nonetheless, it should be noted that 26.7% of the patients with measles pneumonitis (n = 9) had a prior history of chronic respiratory impairment, a figure close to those reported in severe H1N1 infection. However, chronic respiratory disease consisted mainly of intermittent asthma (n = 6). Obesity did not seem to convey any risk for severe disease, affecting only 3 patients. Pregnancy has been repeatedly reported as being associated with severe H1N1 infection,[38] and this may also hold true in measles.[16] In the current study 5 (13.9%) patients were pregnant, all of whom enjoyed a relatively benign course of the infection with no severe respiratory or neurologic complications, despite requiring admission to the ICU.

Of note, in the setting of pregnancy, measles is known to cause fetal growth restriction, premature birth, or spontaneous abortion.[13,16] With respect to these complications, the course of measles was eventless in all but 1 patient who underwent cesarean delivery because of fetal growth restriction after 38 weeks of gestation.

Air Leak Complications

Another frequent adverse event observed during measles infection was the occurrence of extraalveolar air leak complications. Although the pathogenic process responsible for this complication remains to be ascertained, a parallel can be drawn with patients who developed pneumothoraces as a result of

severe acute respiratory syndrome (SARS) or *Pneumocystis jirovecii* pneumonia.[76] In both conditions histopathologic studies have documented extensive pulmonary injury, as well as tissue necrosis and cystic lesions in the case of *Pneumocystis jirovecii* infection, factors said to promote the occurrence of air leak disease.[20,22,52,61] Likewise, on routine follow-up chest CT scan examination, disseminated cystic lesions in both lungs were observed in 1 case of measles pneumonitis complicated with ARDS (see Figure 2, panel B2). Likewise, necropsy examinations of patients diagnosed as having measles have shown evidence of diffuse lung injury, including necrosis of type-I pneumocyte, although this latter feature was found predominantly in immunocompromised patients with Hecht giant cell pneumonia.[46] In keeping with these results, of 4 patients with air leak disease in the current study, 2 were immunocompromised.

Since all air leak events occurred in patients using mechanical ventilation in the setting of ARDS, we cannot rule out barotrauma as either an important cofactor or the primary culprit, all the more because the ventilatory settings were not recorded when air leak disease occurred. However, the high rate of air leak disease in the current study as well as a growing body of evidence[1,34,66] should urge physicians to use lung-protective ventilation.

Upper Respiratory Tract Infection

It should be emphasized that the spectrum of airway infection related to measles is vast and includes the upper airway tract. In the current study we found 1 case of tracheobronchitis, 1 case of otitis, and 2 cases of sinusitis. Similar to measles pneumonitis, upper airway infection can arise either due to direct viral infection or bacterial superinfection in adults.[3,26] In the current study, bacterial coinfection or superinfection was documented in 3 patients. Although upper airway infection may not appear as a primary concern in patients with organ failure in the ICU, physicians should be aware of these measles-associated manifestations as they may lead to bacterial superinfection.

Neurologic Complications Associated With Measles

Postinfectious Encephalomyelitis

Measles encephalitis is regarded as a rare complication occurring in only approximately 0.1% of cases, but both morbidity and mortality rates are high, and the overall prognosis may be worse in adults than in young children.[7,64,73] Accordingly, in our series, 2 patients displayed severe motor impairment at follow-up. Measles gives rise to a myriad of clinical manifestations in the setting of PIE; seizures, meningitis, multifocal neurologic deficit including signs of myelitis, and an altered mental status, such as was observed in our 3 patients, rank among the most commonly reported symptoms.[64] In all 3 patients, mild lymphocytic pleocytosis and hyperproteinorachia on CSF examination were noted as in previous reports.[71]

The key pathogenic mechanism in PIE is believed to be demyelination mediated by an autoimmune process during the stage of recovery from infection, generally within 2 weeks of the exanthema.[30] In the current study we were not able to confirm these results, because none of the 3 patients with PIE was tested for the presence of MV in the CSF by PCR. Accordingly, distinctive neuropathologic features, including perivascular inflammation and demyelination, resemble the features of experimental allergic encephalitis.[25] Furthermore, experimental data support the occurrence of T cell-mediated hyperactivity against myelin base protein during the course of the disease.[30] In line with this interpretation, both clinical and imaging features of the disease bear a strong resemblance to acute disseminated encephalomyelitis (ADEM).[72]

In 1 case of PIE, an MRI performed on day 7 following initial symptoms demonstrated a diffuse hypersignal affecting the cervical, dorsal, and lumbar medulla on T2 FLAIR sequence, findings consistent with ADEM, as illustrated in Figure 3. Brain imaging investigations were negative in the 2 remaining patients. However, in 1 case the sole brain imaging performed was a CT scan, a notoriously insensitive technique to detect the white matter lesions characteristic of ADEM.[79] In the other patient, the MRI imaging was undertaken almost a month after the initial symptoms, therefore transient lesions may have been missed.[29] However, how and why MV elicits an autoimmune response is not clear.[53]

Measles Inclusion Body Encephalitis

MIBE affects immunocompromised hosts between 5 weeks and up to 6 months after the onset of measles. So far, 5 cases have been reported in kidney transplantation recipients.[82] If only a brain biopsy can definitively ascertain the diagnosis of MIBE, the following clinical and laboratory investigations can lend support to this hypothesis: a) normal CSF analysis, b) history of epilepsy both focal and generalized, c) seroconversion during the course of the neurologic disorder, and d) significant clinical improvement after withholding the immunosuppressive regimen. Once again, timely modulation of the patient immunosuppression is critical for both triggering and stalling the neurologic disease progression, at least in the setting of MIBE. This is consistent with previous reports of MIBE in which this complication arises only in case of severe cell-mediated impairment, which causes virus persistence in the central nervous system (CNS) before neurologic symptoms. Apart from transplantation, other clinical settings favorable to MIBE occurrence include mainly HIV infection, chemotherapy for hematologic malignancies, and immunosuppressive therapies for autoimmune diseases.[32,82]

Laboratory Test Disorders

Mild laboratory abnormalities including thrombocytopenia and elevation of CK levels and aminotransferases are common findings in measles infection; they seldom give rise to any overt clinical complication but reflect the systemic nature of measles infection.[40] Thrombocytopenia develops in the early stages of the infection, presumably as a consequence of megacaryocyte infection by the virus itself.[59] Bleeding complications as a result of thrombocytopenia have been known to occur, but rarely account for major hemorrhage.[3] Likewise, elevated aminotransferase levels were frequent, affecting 50% of patients, and they could indicate either ongoing rhabdomyolysis (26.5%), or, less commonly, measles-associated hepatitis (8.8%). As reported previously,[3,85] liver failure as a result of measles is exceptional, and was not observed in the current study. Asymptomatic rhabdomyolysis is another frequent metabolic disturbance, although its precise mechanism remains elusive.[36,85] Only on a few occasions can rhabdomyolysis be severe enough to induce acute renal failure, such as in 1 patient in the current study.[74,86] Finally, lymphopenia is highly prevalent, as exemplified in this study, where it affected 24 of 28 patients (85.7%) for whom a lymphocyte count was readily available on admission. Both its physiopathology and its significance have been reviewed previously.

Epidemiologic Considerations With Regard to Immunization Issues

France has engaged in a bid to promote widespread measles vaccination since 1983 when a single injection of measles

vaccine was officially included in the vaccination schedule for infants aged 12–15 months.[10] In the span of 9 years, immunization against measles rose from 32% (1984) to 80% (1994), while at the same time measles ceased to be an endemic disease among children, and a sharp decline in its associated morbidity and mortality was recorded.[10] However immunization rates then stalled at about 80%, and it was not until 1996 that a second injection was added to the schedule as part of a noncompulsory "catch up" program designed for unvaccinated individuals, but also following reports highlighting the risk of waning immunity in the single injection strategy. Yet, immunization still had not reached sufficient levels by the time the 2009–2011 measles outbreak struck France.[21]

Not surprisingly, most of the patients who developed measles in the current series were young adults. First, because it is well-known that patients from this age group tend to present with more severe measles-associated complications. Second, because in accordance with previous data, all patients who had vaccination status documented (n = 26) either were not vaccinated at all (n = 19) or had received only a single injection of the vaccine (n = 7). Twenty-eight patients (78%) were born during the critical 1980–1996 period, in a time of poor immunization rates. We can concluded that measles epidemics are largely a reflection of insufficient vaccination coverage, and our results are convergent with evidence stemming from other European countries.[48,49]

Third, it is now clear that an immunization coverage rate short of 95% is unlikely to provide "herd protection" or to impede the circulation of measles virus in small groups of unvaccinated subjects, given the virus' extremely contagious nature.[43] As a consequence, these pockets of susceptible individuals act as a reservoir capable of fueling new outbreaks during which unprotected young adults are greatly exposed, hence the gradual shift in the clinical pattern of measles from a childhood and generally benign infection to a lethal disease affecting young adults. Efforts to reinforce measles immunization through vaccination programs have been fraught with resistance from individuals or small communities opposed to vaccination for various reasons including scientific misinformation,[78] religious beliefs or customs,[4,33] misperception of the disease,[67] or exaggerated concerns regarding its safety.[11]

Another source of concern is the impact of global travels, which may contribute to measles importation.[48] However the current study does not lend support to this mechanism since all cases of measles were indigenously acquired.

Measles-Directed Therapy: Focus on Ribavirin

Ribavirin represents the only genuinely antiviral treatment tested in the clinical setting of measles infection. An in vitro study has highlighted its ability to interfere with the virus' replication cycle.[75] However, clinical studies related to adult patients with measles pneumonitis remain scarce, with variable drug administration routes,[19] and few have been conducted using sound methodology.[83] During a measles epidemic, Forni et al[19] reported 6 adult patients with severe respiratory compromise related to measles infection. Five patients exhibited respiratory improvement following initiation of intravenous ribavirin therapy. In immunocompromised patients, experience with ribavirin is at best anecdotal and success has been varied in patients with pneumonitis or MIBE.[32,50,80] In the current case series, only 2 patients, both of whom were immunocompromised and had severe measles pneumonitis, had a protracted course of ribavirin. Although ribavirin therapy was initiated promptly after the onset of the disease, both of these immunocompromised patients' respiratory conditions progressed to ARDS, and, ultimately, death. In 1 case, the treatment was withheld after 6 days because of ribavirin-induced hemolysis. In 1 patient affected by MIBE, ribavirin was withdrawn just 2 days after initiation as a result of insufficient evidence to sustain its indication (see Table 4).

Study Limitations

To the best of our knowledge, the current study represents the largest assessment of measles-related complications and their management in the setting of an ICU. Nevertheless, several limitations should be underlined.

First, the study suggests possible risk factors for severe measles, first and foremost of these being immunodepression. However, because of the small size of the study population, statistical analysis could not be performed, and presumed risk factors for severe disease could not ascertained. Consequently, these results await confirmation from either larger studies or case-control studies. For similar reasons, the connection between measles and some potentially specific complications, such as extraalveolar air leak disease, remains speculative.

The pattern of complications induced by measles, including the proportions of lethal and adult cases and neurologic and other complications, has been known to differ from 1 area to another; access to health care resources is 1 of the major determinants. Thus, it is not known whether the spectrum of complications and suspected risk factors of severe disease described in the current study are applicable to other regions of the world.[23,77]

Despite efforts devoted to gathering as many cases of measles as possible, the case collection was not exhaustive. Consequently, we may have underestimated the true incidence of severe measles requiring ICU management and some of its complications.

Conclusion

Measles is a disease with protean clinical manifestations, among which respiratory and neurologic complications, such as ARDS and PIE, are the most dreaded. Special attention is warranted for immunocompromised individuals, as measles occurring in this setting can lead to life-threatening complications that may require ICU management. Diagnosis of measles infection in the immunocompromised patient can be challenging in the face of specific complications and absent or atypical morbillous rash. When managing patients with measles pneumonitis using mechanical ventilation, physicians should be aware that these patients may be predisposed to barotrauma. Airway bacterial superinfection, likely to be favored by MV-induced immunosuppression, represents an additional concern and should be actively sought for each time a patient presents with severe respiratory impairment. Immunomodulatory therapy and antiviral treatment with ribavirin may play a role in the management of patients affected by PIE and measles-induced ARDS, but further investigations are needed before they can be considered a standard of care. Until then, primary prevention by adequate vaccination remains the most effective therapeutic means during community-wide outbreaks.

REFERENCES

1. Abramson O, Dagan R, Tal A, Sofer S. Severe complications of measles requiring intensive care in infants and young children. *Arch Pediatr Adolesc Med.* 1995;149:1237–1240.

2. Abt M, Gassert E, Schneider-Schaulies S. Measles virus modulates chemokine release and chemotactic responses of dendritic cells. *J Gen Virol*. 2009;90:909–914.

3. Ackerman Z, Ackerman E, Shouval D. Measles: clinical and laboratory observations in young adults during an epidemic. *South Med J*. 1988;81:1396–1400.

4. Anis E, Grotto I, Moerman L, Warshavsky B, Slater PE, Lev B, Israeli A. Measles in a highly vaccinated society: the 2007-08 outbreak in Israel. *J Infect*. 2009;59:252–258.

5. Auwaerter PG, Kaneshima H, McCune JM, Wiegand G, Griffin DE. Measles virus infection of thymic epithelium in the SCID-hu mouse leads to thymocyte apoptosis. *J Virol*. 1996;70:3734–3740.

6. Avota E, Avots A, Niewiesk S, Kane LP, Bommhardt U, ter Meulen V, Schneider-Schaulies S. Disruption of Akt kinase activation is important for immunosuppression induced by measles virus. *Nat Med*. 2001;7:725–731.

7. Baba Y, Tsuboi Y, Inoue H, Yamada T, Wszolek ZK, Broderick DF. Acute measles encephalitis in adults. *J Neurol*. 2006;253:121–124.

8. Becroft DM, Osborne DR. The lungs in fatal measles infection in childhood: pathological, radiological and immunological correlations. *Histopathology*. 1980;4:401–412.

9. Bell AF, Burns JB, Fujinami RS. Measles virus infection of human T cells modulates cytokine generation and IL-2 receptor alpha chain expression. *Virology*. 1997;232:241–247.

10. Bonmarin I, Levy-Bruhl D. Measles in France: the epidemiological impact of suboptimal immunisation coverage. *Euro Surveill*. 2002;7:55–60.

11. Casiday R, Cresswell T, Wilson D, Panter-Brick C. A survey of UK parental attitudes to the MMR vaccine and trust in medical authority. *Vaccine*. 2006;24:177–184.

12. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2002;165:867–903.

13. Chiba ME, Saito M, Suzuki N, Honda Y, Yaegashi N. Measles infection in pregnancy. *J Infect*. 2003;47:40–44.

14. Classification of measles cases and categorization of measles elimination programs. *MMWR Morb Mortal Wkly Rep*. 1983;31:707–711.

15. Duke T, Mgone CS. Measles: not just another viral exanthem. *Lancet*. 2003;361:763–773.

16. Eberhart-Phillips JE, Frederick PD, Baron RC, Mascola L. Measles in pregnancy: a descriptive study of 58 cases. *Obstet Gynecol*. 1993;82:797–801.

17. Enders JF, Mc CK, Mitus A, Cheatham WJ. Isolation of measles virus at autopsy in cases of giant-cell pneumonia without rash. *N Engl J Med*. 1959;261:875–881.

18. Filia A, De Crescenzo M, Seyler T, Bella A, Ciofi Degli Atti ML, Nicoletti L, Magurano F, Salmaso S. Measles resurges in Italy: preliminary data from September 2007 to May 2008. *Euro Surveill*. 2008;13.

19. Forni AL, Schluger NW, Roberts RB. Severe measles pneumonitis in adults: evaluation of clinical characteristics and therapy with intravenous ribavirin. *Clin Infect Dis*. 1994;19:454–462.

20. Franks TJ, Chong PY, Chui P, Galvin JR, Lourens RM, Reid AH, Selbs E, McEvoy CP, Hayden CD, Fukuoka J, Taubenberger JK, Travis WD. Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore. *Hum Pathol*. 2003;34:743–748.

21. Freymuth F, Vabret A. Measles, a re-emerging disease in France? *Clin Microbiol Infect*. 2011;17:793.

22. Fujii T, Nakamura T, Iwamoto A. Pneumocystis pneumonia in patients with HIV infection: clinical manifestations, laboratory findings, and radiological features. *J Infect Chemother*. 2007;13:1–7.

23. Gadoth N. Subacute sclerosing panencephalitis (SSPE) the story of a vanishing disease. *Brain Dev*. 2012;34:705–711.

24. Gee S, Cotter S, O'Flanagan D. Spotlight on measles 2010: measles outbreak in Ireland 2009-2010. *Euro Surveill*. 2010;15.

25. Gendelman HE, Wolinsky JS, Johnson RT, Pressman NJ, Pezeshkpour GH, Boisset GF. Measles encephalomyelitis: lack of evidence of viral invasion of the central nervous system and quantitative study of the nature of demyelination. *Ann Neurol*. 1984;15:353–360.

26. Gremillion DH, Crawford GE. Measles pneumonia in young adults. An analysis of 106 cases. *Am J Med*. 1981;71:539–542.

27. Griffin DE, Ward BJ, Jauregui E, Johnson RT, Vaisberg A. Natural killer cell activity during measles. *Clin Exp Immunol*. 1990;81:218–224.

28. Hicks JT, Sullivan JL, Albrecht P. Immune responses during measles infection in immunosuppressed Rhesus monkeys. *J Immunol*. 1977;119:1452–1456.

29. Hollinger P, Sturzenegger M, Mathis J, Schroth G, Hess CW. Acute disseminated encephalomyelitis in adults: a reappraisal of clinical, CSF, EEG, and MRI findings. *J Neurol*. 2002;249:320–329.

30. Johnson RT, Griffin DE, Hirsch RL, Wolinsky JS, Roedenbeck S, Lindo de Soriano I, Vaisberg A. Measles encephalomyelitis—clinical and immunologic studies. *N Engl J Med*. 1984;310:137–141.

31. Kabra SK, Lodha R, Hilton DJ. Antibiotics for preventing complications in children with measles. *Cochrane Database Syst Rev*. 2008:CD001477.

32. Kaplan LJ, Daum RS, Smaron M, McCarthy CA. Severe measles in immunocompromised patients. *JAMA*. 1992;267:1237–1241.

33. Kasper S, Holzmann H, Aberle SW, Wassermann-Neuhold M, Gschiel H, Feenstra O, Allerberger F, Schmid D. Measles outbreak in Styria, Austria, March-May 2009. *Euro Surveill*. 2009;14.

34. Lagunju IA, Orimadegun AE, Oyedemi DG. Measles in Ibadan: a continuous scourge. *Afr J Med Med Sci*. 2005;34:383–387.

35. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA*. 1993;270:2957–2963.

36. Leibovici L, Sharir T, Kalter-Leibovici O, Alpert G, Epstein LM. An outbreak of measles among young adults. Clinical and laboratory features in 461 patients. *J Adolesc Health Care*. 1988;9:203–207.

37. Lopez Hernandez B, Laguna Sorinas J, Marin Rodriguez I, Gallardo Garcia V, Perez Morilla E, Mayoral Cortes JM. Spotlight on measles 2010: An ongoing outbreak of measles in an unvaccinated population in Granada,Spain, October to November 2010: an ongoing outbreak of measles in an unvaccinated population in Granada, Spain, October to November 2010. *Euro Surveill*. 2010;15.

38. Louie JK, Acosta M, Jamieson DJ, Honein MA. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N Engl J Med*. 2010;362:27–35.

39. Loukides S, Panagou P, Kolokouris D, Kalogeropoulos N. Bacterial pneumonia as a suprainfection in young adults with measles. *Eur Respir J*. 1999;13:356–360.

40. Ludlow M, Allen I, Schneider-Schaulies J. Systemic spread of measles virus: overcoming the epithelial and endothelial barriers. *Thromb Haemost*. 2009;102:1050–1056.

41. Markowitz LE, Nieburg P. The burden of acute respiratory infection due to measles in developing countries and the potential impact of measles vaccine. *Rev Infect Dis*. 1991;13(Suppl 6):S555–561.

42. McChesney MB, Fujinami RS, Lampert PW, Oldstone MB. Viruses disrupt functions of human lymphocytes. II. Measles virus suppresses antibody production by acting on B lymphocytes. *J Exp Med*. 1986;163:1331–1336.

43. Moss WJ, Griffin DE. Global measles elimination. *Nat Rev Microbiol*. 2006;4:900–908.

44. Moss WJ, Griffin DE. Measles. *Lancet*. 2012;379:153–164.

45. Moss WJ, Monze M, Ryon JJ, Quinn TC, Griffin DE, Cutts F. Prospective study of measles in hospitalized, human immunodeficiency virus (HIV)-infected and HIV-uninfected children in Zambia. *Clin Infect Dis*. 2002;35:189–196.

46. Moussallem TM, Guedes F, Fernandes ER, Pagliari C, Lancellotti CL, de Andrade HF Jr, Duarte MI. Lung involvement in childhood measles: severe immune dysfunction revealed by quantitative immunohistochemistry. *Hum Pathol*. 2007;38:1239–1247.

47. Mulholland EK, Griffiths UK, Biellik R. Measles in the 21st century. *N Engl J Med*. 2012;366:1755–1757.

48. Muscat M. Who gets measles in Europe? *J Infect Dis*. 2011;204 (Suppl 1):S353–365.

49. Muscat M, Bang H, Wohlfahrt J, Glismann S, Molbak K. Measles in Europe: an epidemiological assessment. *Lancet*. 2009;373: 383–389.

50. Mustafa MM, Weitman SD, Winick NJ, Bellini WJ, Timmons CF, Siegel JD. Subacute measles encephalitis in the young immunocompromised host: report of two cases diagnosed by polymerase chain reaction and treated with ribavirin and review of the literature. *Clin Infect Dis*. 1993;16:654–660.

51. Nanan R, Chittka B, Hadam M, Kreth HW. Measles virus infection causes transient depletion of activated T cells from peripheral circulation. *J Clin Virol*. 1999;12:201–210.

52. Nicholls JM, Poon LL, Lee KC, Ng WF, Lai ST, Leung CY, Chu CM, Hui PK, Mak KL, Lim W, Yan KW, Chan KH, Tsang NC, Guan Y, Yuen KY, Peiris JS. Lung pathology of fatal severe acute respiratory syndrome. *Lancet*. 2003;361:1773–1778.

53. Norrby E, Kristensson K. Measles virus in the brain. *Brain Res Bull*. 1997;44:213–220.

54. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. *World Health Organ Tech Rep Ser*. 2000;894: i–xii, 1–253.

55. Okada H, Kobune F, Sato TA, Kohama T, Takeuchi Y, Abe T, Takayama N, Tsuchiya T, Tashiro M. Extensive lymphopenia due to apoptosis of uninfected lymphocytes in acute measles patients. *Arch Virol*. 2000;145:905–920.

56. Okada H, Sato TA, Katayama A, Higuchi K, Shichijo K, Tsuchiya T, Takayama N, Takeuchi Y, Abe T, Okabe N, Tashiro M. Comparative analysis of host responses related to immunosuppression between measles patients and vaccine recipients with live attenuated measles vaccines. *Arch Virol*. 2001;146:859–874.

57. Olson RW, Hodges GR. Measles pneumonia. Bacterial suprainfection as a complicating factor. *JAMA*. 1975;232:363–365.

58. Oshitani H, Suzuki H, Mpabalwani ME, Mizuta K, Numazaki Y. Measles case fatality by sex, vaccination status, and HIV-1 antibody in Zambian children. *Lancet*. 1996;348:415.

59. Oski FA, Naiman JL. Effect of live measles vaccine on the platelet count. *N Engl J Med*. 1966;275:352–356.

60. Parent du Chatelet I, Antona D, Freymuth F, Muscat M, Halftermeyer-Zhou F, Maine C, Floret D, Levy-Bruhl D. Spotlight on measles 2010: update on the ongoing measles outbreak in France, 2008–2010. *Euro Surveill*. 2010;15.

61. Pastores SM, Garay SM, Naidich DP, Rom WN. Review: pneumothorax in patients with AIDS-related Pneumocystis carinii pneumonia. *Am J Med Sci*. 1996;312:229–234.

62. Permar SR, Griffin DE, Letvin NL. Immune containment and consequences of measles virus infection in healthy and immunocompromised individuals. *Clin Vaccine Immunol*. 2006;13:437–443.

63. Permar SR, Moss WJ, Ryon JJ, Monze M, Cutts F, Quinn TC, Griffin DE. Prolonged measles virus shedding in human immunodeficiency virus-infected children, detected by reverse transcriptase-polymerase chain reaction. *J Infect Dis*. 2001;183:532–538.

64. Perry RT, Halsey NA. The clinical significance of measles: a review. *J Infect Dis*. 2004;189(Suppl 1):S4–16.

65. Pervanidou D, Horefti E, Patrinos S, Lytras T, Triantafillou E, Mentis A, Bonovas S, Panagiotopoulos T. Spotlight on measles 2010: ongoing measles outbreak in Greece, January-July 2010. *Euro Surveill*. 2010;15.

66. Piastra M, Onesimo R, De Luca D, Lancella L, Marzano L, De Rosa G, Pietrini D, Valentini P, Conti G. Measles-induced respiratory distress, air-leak and ARDS. *Eur J Clin Microbiol Infect Dis*. 2010;29:181–185.

67. Poethko-Muller C, Ellert U, Kuhnert R, Neuhauser H, Schlaud M, Schenk L. Vaccination coverage against measles in German-born and foreign-born children and identification of unvaccinated subgroups in Germany. *Vaccine*. 2009;27: 2563–2569.

68. Quiambao BP, Gatchalian SR, Halonen P, Lucero M, Sombrero L, Paladin FJ, Meurman O, Merin J, Ruutu P. Coinfection is common in measles-associated pneumonia. *Pediatr Infect Dis J*. 1998;17:89–93.

69. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, Camporota L, Slutsky AS. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307:2526–2533.

70. Recommendations from an ad hoc Meeting of the WHO Measles and Rubella Laboratory Network (LabNet) on use of alternative diagnostic samples for measles and rubella surveillance. *MMWR Morb Mortal Wkly Rep*. 2008; 57:657–660.

71. Reuter D, Schneider-Schaulies J. Measles virus infection of the CNS: human disease, animal models, and approaches to therapy. *Med Microbiol Immunol*. 2010;199:261–271.

72. Rima BK, Duprex WP. Morbilliviruses and human disease. *J Pathol*. 2006;208:199–214.

73. Schneider-Schaulies J, Meulen V, Schneider-Schaulies S. Measles infection of the central nervous system. *J Neurovirol*. 2003;9: 247–252.

74. Seibold S, Merkel F, Weber M, Marx M. Rhabdomyolysis and acute renal failure in an adult with measles virus infection. *Nephrol Dial Transplant*. 1998;13:1829–1831.

75. Shigeta S, Mori S, Baba M, Ito M, Honzumi K, Nakamura K, Oshitani H, Numazaki Y, Matsuda A, Obara T, et al. Antiviral activities of ribavirin, 5-ethynyl-1-beta-D-ribofuranosylimidazole-4-carboxamide, and 6′-(R)-6′-C-methylneplanocin A against several ortho- and paramyxoviruses. *Antimicrob Agents Chemother*. 1992;36:435–439.

76. Sihoe AD, Wong RH, Lee AT, Lau LS, Leung NY, Law KI, Yim AP. Severe acute respiratory syndrome complicated by spontaneous pneumothorax. *Chest*. 2004;125:2345–2351.

77. Simons E, Ferrari M, Fricks J, Wannemuehler K, Anand A, Burton A, Strebel P. Assessment of the 2010 global measles mortality reduction goal: results from a model of surveillance data. *Lancet*. 2012;379:2173–2178.

78. Smith A, Yarwood J, Salisbury DM. Tracking mothers' attitudes to MMR immunisation 1996-2006. *Vaccine*. 2007; 25:3996–4002.

79. Sonneville R, Demeret S, Klein I, Bouadma L, Mourvillier B, Audibert J, Legriel S, Bolgert F, Regnier B, Wolff M. Acute disseminated encephalomyelitisin the intensive care unit:clinical features and outcome of 20 adults. *Intensive Care Med*. 2008;34:528–532.

80. Stogner SW, King JW, Black-Payne C, Bocchini J. Ribavirin and intravenous immune globulin therapy for measles pneumonia in HIV infection. *South Med J*. 1993;86:1415–1418.

81. Tulchinsky TH, Ginsberg GM, Abed Y, Angeles MT, Akukwe C, Bonn J. Measles control in developing and developed countries: the case for a two-dose policy. *Bull World Health Organ*. 1993;71:93–103.

82. Turner A, Jeyaratnam D, Haworth F, Sinha MD, Hughes E, Cohen B, Jin L, Kidd IM, Rigden SP, MacMahon E. Measles-associated encephalopathy in children with renal transplants. *Am J Transplant*. 2006;6:1459–1465.

83. Uylangco CV, Beroy GJ, Santiago LT, Mercoleza VD, Mendoza SL. A double-blind, placebo-controlled evaluation of ribavirin in the treatment of acute measles. *Clin Ther*. 1981;3:389–396.

84. Waku-Kouomou D, Freymuth F, du Chatelet IP, Wild TF, Horvat B. Co-circulation of multiple measles virus genotypes during an epidemic in France in 2008. *J Med Virol*. 2010; 82:1033–1043.

85. Wong RD, Goetz MB. Clinical and laboratory features of measles in hospitalized adults. *Am J Med*. 1993;95:377–383.

86. Yamada H, Ono T, Kimura M. Rhabdomyolysis in adults with measles virus infection. *Am J Med*. 2000;108:600.