Mary E. Ramsay
Shamez Ladhani

*Corresponding author. Department of Primary Care and Public Health, Room 332, Reynolds Building, Imperial College London, Charing Cross Campus, London W6 8RF, UK. Tel.: +44 0207 5948703.
E-mail address: christina.atchison11@imperial.ac.uk (C. Atchison)

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The PHE Rotavirus Surveillance Network includes[a] Dr Rohini Manuel[b], Dr Duncan Clark[b], Dr John Magee[c], Dr Husam Osman[d], Dr Anthony D. Hale[e], Dr Hamid Jalal[f], Dr Mark Farrington[f], Dr Martin L'Estrange[f], Dr Ed Kaczmarski[g], Dr Andrew Turner[g], Dr Emanuela Pelosi[h], Dr Peter Hawtin[h], Dr David Carrington[i], Dr Adam Finn[i]

[b] *Public Health Laboratory London, Barts Health NHS Trust, London E1 2ES;* [c] *Public Health Laboratory Newcastle, Freeman Hospital, Newcastle NE7 7DN;* [d] *Public Health Laboratory Birmingham, Heart of England NHS Foundation Trust, Birmingham B9 5SS;* [e] *Public Health Laboratory Leeds, Leeds Teaching Hospitals NHS Trust, Leeds LS1 3EX;* [f] *Public Health Laboratory Cambridge, Addenbrooke's Hospital, Cambridge CB2 0QW;* [g] *Public Health Laboratory Manchester, Manchester Royal Infirmary, Manchester M13 9WZ;* [h] *Public Health Laboratory Southampton, Southampton General Hospital, Southampton SO16 6YD;* [i] *Public Health Laboratory Bristol, Bristol BS2 8EL*

Polyvalent immunoglobulins in neonates after perinatal exposure to measles Benefits and long-term tolerance of immunoglobulins

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Mayet and colleagues[1] describe a measles outbreak in France in the French military forces, during the major outbreak reported in France from 2008 to 2011, that involved >20,000 notified cases. Unexpectedly, more than 40% of them were young adults,[2] including pregnant women.[3] Because measles is responsible for high morbi-mortality in newborns, administration of polyvalent immunoglobulins is recommended in neonates born from non-immune pregnant mothers exposed in late pregnancy. However data regarding the tolerance and efficacy of polyvalent immunoglobulins in this specific group are lacking. We here report on the immediate and long-term tolerance and potential efficacy of polyvalent immunoglobulins administered to 7 neonates in this setting during an outbreak that occurred in our maternity ward in 2011.

Measles during pregnancy is associated with a higher risk of maternal pneumonia and related-death, along with fetal loss and prematurity.[4–6] Maternal measles occurring within 10 days before delivery may also lead to congenital infections, defined by a measles onset in the first 10 days of life.[7] Congenital measles was associated with a fatality rate of 30–50% before the polyvalent immunoglobulins era, and exposes infants to an increased risk of subacute sclerosing panencephalitis with earlier onset (*i.e.* below 2 years of age[8]). Newborn infants exposed postnatally and born from non-immune mothers are also at higher risk for severe neonatal measles and complications.[9]

Post exposure prevention is therefore key in non-immune pregnant women and their neonates. Live measles virus vaccination is contraindicated in pregnant women. It is also not recommended in neonates because of their immunological immaturity. Human polyvalent immunoglobulins have proven efficient to prevent or attenuate measles in children older than 6 months.[9–11] As a part of the French Plan for measles elimination, polyvalent immunoglobulins administered intravenously (IGIV) are recommended since 2005 in France after exposure to measles in pregnant women and neonates, although they have not been specifically evaluated in these settings.[9–11] The French recommendations include IGIV administration to neonates of non-immune mothers up to 6 days after exposure in two situations: (i) maternal measles within 10 days before delivery and (ii) direct exposure. The recommended dosage was initially of 400 mg/kg and was reduced in August 2011 to 200 mg/kg, ensuring the infusion of a minimum of 15 UI/kg.[12] Preliminary data reported a short-term protective effect of IVIG administered in 2 neonates whose mothers developed measles after birth.[3] Long-term outcome after neonatal IVIG has been only reported in one infant[13] and the preventive efficacy of neonatal administration of IVIG on sub-acute sclerosing pan-encephalitis is unknown.

In February and March 2011, we experienced a nosocomial outbreak in the Obstetrics ward of our hospital that evolved in 3 waves (Fig. 1). Measles was diagnosed in a 16 weeks gestation (WG)-pregnant woman attending the outpatient clinics (case 1). She and her baby did not receive IVIG, and her term newborn did not develop measles.

In total, 145 contact pregnant women were identified, including 15 that were non-immune to measles (10%). Among those 15 susceptible mothers, 9 were exposed more than 2 weeks before delivery. They did not develop measles, and delivered healthy uninfected babies. The six

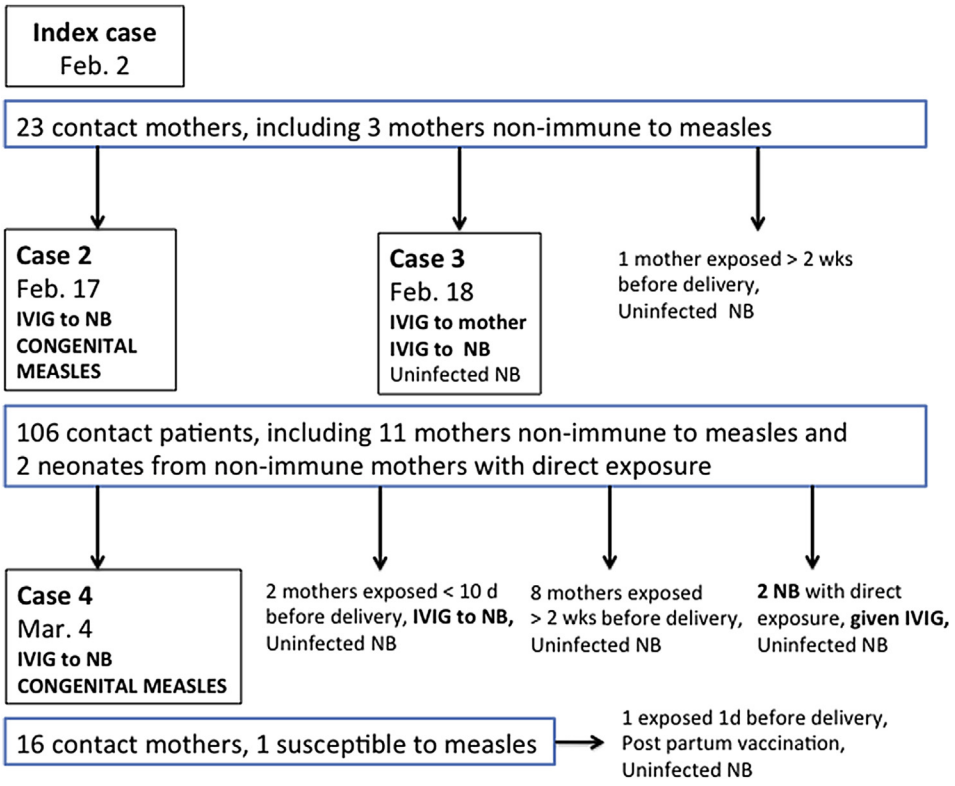

Figure 1 Transmission pattern of maternal cases, 02 February—04 March 2011. IVIG: polyvalent intravenous immunoglobulins; NB: newborn; Wks: weeks; d: days.

other non-immune pregnant women were exposed within 10 days before delivery. Three of them developed measles at term. The first one received IVIG at D2 of eruption (38WG) (case 3), and delivered 8 days later an uninfected baby who also received IVIG immediately at birth (400 mg/kg, according to current recommendations). The newborn remained uninfected (clinically + negative saliva PCR at birth). The second mother (case 2) delivered the first day of eruption and did not receive IVIG. Her baby remained asymptomatic but had positive saliva PCR at D0. He received IVIG immediately at birth. The third mother (case 4) developed measles the day after delivery. She reported a past history of measles vaccination (1 dose) in infancy. She did not receive IVIG. Her baby was asymptomatic at birth, but his saliva measles virus PCR was positive at D3. He received IVIG at D4 and developed a typical skin rash with Koplick's spots at D5, without any severe complication. Altogether, all the 3 neonates born from mothers with perinatal measles received IVIG after exposure: one remained uninfected and no severe congenital infection was reported in the 2 others. At three-year follow-up, evolution was uneventful and neurodevelopment was considered normal for all of them.

Among the 3 remaining non-immune mothers exposed within 10 days before delivery, none received IVIG antenatally: 2 of them had their newborns treated by IVIG at birth; these neonates had negative saliva PCR at birth and remained asymptomatic after IVIG infusion. The last mother delivered the day after exposure and received vaccination with uneventful subsequent outcome for her and her baby.

Finally, two additional neonates from non-immune mothers received IVIG at birth, because of a direct postnatal measles exposure in the maternity ward: they both remained asymptomatic.

Immediate tolerance of IVIG (400 mg/kg, according to current national recommendations) was good for all neonates, as reported in other settings.[14] Follow-up data was available at 3 years for 6/7 IG-treated children (including all infected newborns); all had a normal evolution without any detected neurodevelopmental impairment.

In sharp contrast with previous observations that reported the high mortality rate of neonatal measles,[8] these cases argue for the potential beneficial effects of IVIG administered to neonates after direct postnatal exposure (0/2 contamination) and to children born from mothers with measles within 10 days before delivery (no severe congenital infection). Outcome at 3 years following administration was favorable. In a situation where randomized trials would be either unethical or impossible because of its rarity, our observations provide long-term data supporting current recommendations on prophylactic IGIV to limit the burden of congenital and neonatal measles.

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