

# MEASLES WITH A POSSIBLE 23 DAY INCUBATION PERIOD

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## Abstract

Measles virus (MV) eradication is biologically, technically and operationally feasible. An essential feature in understanding the chain of MV transmission is its incubation period, that is, the time from infection to the onset of symptoms. This period is important for determining the likely source of infection and directing public health measures to interrupt ongoing transmission. Long measles incubation periods have rarely been documented in the literature. We report on a previously healthy 11-year-old Australian boy who was confirmed with measles genotype D9 infection following travel in the Philippines. Epidemiological evidence supported an unusually long incubation period of at least 23 days and virological evidence was consistent with this finding. Although public health control measures such as post exposure prophylaxis, isolation and surveillance of susceptible individuals should continue to be based on the more common incubation period, a longer incubation period may occasionally explain an unexpected measles case. *Commun Dis Intell* 2012;36(3):E277–E280.

Keywords: measles, incubation period, elimination, epidemiology, genotyping

## Introduction

Measles virus (MV) eradication is biologically, technically and operationally feasible as demonstrated in the Region of the Americas and countries in every other region.<sup>1</sup> A number of countries have already declared endemic measles eliminated, while others, including Australia, are presently gathering evidence to confirm interruption of endemic MV transmission.<sup>2,3</sup> In these countries, laboratory and/or epidemiological confirmation of every case is ideally required. This allows: the origin of cases as local or imported to be identified, particularly if genotyping is available; the size and duration of outbreaks to be determined; risk groups requiring public health action to be recognised; and existing public health activities to be reviewed.

An essential feature in understanding the chain of MV transmission is its incubation period, that is, the time from infection to onset of symptoms. This period is important for determining the likely source of infection and directing public health measures to interrupt ongoing transmission. Infectious disease and public health texts and global guidelines

currently stipulate that the incubation period for measles infection is 7–18 days, but rarely as long as 19–21 days. This article reports on a measles case in a previously healthy child with a possible incubation period of at least 23 days.

## Case presentation

An 11-year-old Philippines-born male with no previous significant medical history developed a cough on 19 May 2011, followed by fever (39°C) on 20 May. On 22 May he developed a typical generalised measles rash that began behind his ears before spreading to his face and trunk. Fever and cough remained present at rash onset.

On hospital paediatric review on 23 May he was febrile (39°C), had a red, blanching non-itching and non-tender rash covering his entire body, exhibited a persistent cough, had prominent coryza and conjunctivitis, and Koplik spots were noted on his buccal mucosa. After receiving 500 mg of paracetamol orally and having blood and urine collected, he was discharged home with a request to remain isolated. His MV serology was IgM positive/IgG not detected, thereby confirming the clinical diagnosis of measles infection. He made a full recovery.

## Epidemiological investigation

The child was notified to the Hunter New England Population Health Unit on 23 May 2011. An epidemiological investigation was initiated the following day on the basis of the serological confirmation as measles, which is a notifiable disease under the *New South Wales Public Health Act 2010*. A detailed travel history, both international and domestic, was sought, exhaustive contact tracing was conducted in Australia, and his close (household) contacts were serologically investigated. Measles polymerase chain reaction (PCR) testing was only conducted for the case.

The child had travelled with three family members to the Philippines, returning by air to Sydney on 27 April. His travel companions included his mother (aged 45 years) and his 2 older brothers, aged 17 and 18 years. The family spent 2 weeks in the Philippines and returned to Sydney with a 24-hour stopover in Hong Kong, during which time they remained at the airport.

The family was unable to specifically identify a direct exposure to anyone with clinical measles during their visit to the Philippines, the stop-over in Hong Kong or in the period between returning to Australia and the onset of symptoms. The only close contacts the case had after returning to Australia were his mother, the 2 older brothers, a 16-year-old Australian-born step-sister, her 15-year-old friend, an aunt and her male partner, and his maternal grandmother. None of these individuals had experienced a febrile illness prior to the onset of symptoms in the case. Serological testing for MV-specific antibodies showed that all were IgM negative/IgG positive, suggesting previous infection or vaccination (Table 1).

**Table 1. Measles virus antibodies of household contacts**

Family member	IgM	IgG	Date of serology
18 year old brother	<1.0	113	24/05/2011
17 year old brother	Equivocal	109	24/05/2011
16 year old stepsister	<1.0	5	24/05/2011
Mother	<1.0	61	24/05/2011
Aunt	<1.0	29	25/05/2011
Partner of aunt	<1.0	4	25/05/2011
Friend of sister	<1.0	27	25/05/2011
Grandmother	<1.0	27	24/05/2011

The immunisation status of the case and his two Philippines-born brothers was not available on the electronic Australian immunisation register, and their mother had no physical records or memory of them being vaccinated in the Philippines as children or experiencing measles-like symptoms.

No measles cases had been identified in the Hunter New England health district in the 2 months prior to this case. There were 5 known cases of measles in New South Wales in the 23 days prior to the onset of symptoms. Two of these cases were identified as infected with measles genotype D4 and one of these cases had subsequently infected a quarantined sibling. Two cases in an adjoining health district were identified in a pair of siblings who had travelled to France and Italy. No typing was available for them, however, they and their family had not travelled out of their local area after returning to Australia on 1 May.

### Laboratory investigation

SIEMENS Enzygnost™ assay was used to detect measles IgM and IgG in the case and his close contacts (Table 2). Urine and throat swab samples from

the case were positive by real-time PCR (RT-PCR) for MV using Applied Biosystems® Taqman® Fast Universal PCR mastermix (2X) by Life Technologies. Molecular characterisation to determine the genotype of the virus involved sequencing a 450 nucleotide (nt) region of the viral nucleoprotein (N) gene as previously described.<sup>4</sup> The entire haemagglutinin (H) gene was also sequenced to enable a more detailed comparison with other measles strains circulating in 2011. Briefly, PCR products were purified using ExoSAP-IT PCR clean-up kit (GE Healthcare) according to the manufacturer's instructions. Purified PCR products were sequenced in the forward and reverse directions.<sup>4</sup> Nucleotide sequences were analysed on the Bio-Edit Sequence Alignment Editor software<sup>5</sup> and MV genotype determined using the National Center for Biotechnology Information (NCBI) on-line nucleotide blast program.

**Table 2. SIEMENS Enzygnost™ assay values**

Assay	Value (Index)	Interpretation
IgM	<0.5	Negative
	0.5–1.0	Equivocal
	>1.0	Positive
IgG	<1.0	Negative
	1.0–2.0	Equivocal
	>2.0	Positive

Case nucleotide sequences were submitted to Genbank, accession.number JX679861

Sequencing of the N gene identified the MV genotype as D9. The N gene nt sequences of 6 MVs from cases in the Philippines, five occurring during January and February 2011, and one occurring in April 2011, were compared with the case N gene sequence (Philippines N sequences provided by the National Reference Laboratory (NRL)-Measles, Research Institute for Tropical Medicine, Philippines). The 6 Philippine N gene sequences differed by a maximum of 3 nt from each other and from the local case.

Partial N gene and complete H gene nt sequences from the case and 3 D9 MV strains circulating during the first quarter of 2011 in New South Wales were also compared. One New South Wales MV strain differed by 1 nt in the N gene and 6 nts in the H gene to the case strain sequence. Two New South Wales strains had identical N and H sequences that differed from the case by 3 and 6 nts in the N and H gene, respectively.

## Discussion

The epidemiological evidence supports a measles exposure in the Philippines as the source of this child's measles infection and the virological evidence is consistent with this hypothesis. All 29 genotyped measles cases from the Philippines between January 2010 and June 2011 were D9 strains (personal communication, Youngmee Jee, Western Pacific Regional Office of the World Health Organization). Comparison of N and H gene sequences of the case strain and strains from New South Wales (N and H sequences) and the Philippines (N gene only) were consistent with importation from the Philippines. As sequencing of MV genes other than N and H becomes more widely available, specific geographical location of individual cases' place of infection will be more readily possible.<sup>6</sup> Molecular sequencing methods have been identified as a research priority as we move towards measles elimination.<sup>7</sup>

The Hunter New England region of New South Wales, Australia, has a documented high quality enhanced measles surveillance system that meets the indicators recommended for elimination.<sup>8</sup> This suggests that general practitioners are unlikely to have missed other measles cases in the region if they presented for treatment. Although this scenario cannot be completely eliminated, undetected cases in the community would have likely resulted in additional cases due to the infectious nature of measles.

The case's 17-year-old brother had an equivocal IgM test (index 0.5–1.0) but a high IgG value. This suggests a previous infection but sequential IgG values may have assisted to confirm that he did not experience a subclinical case of measles and serve as the source of infection in Australia.

As the child's measles exposure most likely occurred in the Philippines or in transit no later than 27 April, the period to onset of symptoms on 19 May represents an incubation period of at least 23 days. Long measles incubation periods have rarely been documented in the literature, possibly in part because in measles endemic areas it can be difficult to ascertain the exact time of exposure. This complicates the accurate determination of incubation periods, and serial intervals or rash onset dates may then be used as a proxy for the incubation period. The incubation period is longer than the serial interval as the infectious period commences prior to symptom onset (personal communication, Professor Natasha Crowcroft, Health Canada).

An observational study in rural Kenya<sup>9</sup> demonstrated infrequent incubation periods of up to 24 days and observations on measles transmission in a fever hospital in 1931 documented infrequent incubation periods up to 25 days.<sup>10</sup>

The log-normal distribution of directly-transmitted infectious disease incubation periods (with the distribution dramatically skewed to the right) is well recognised.<sup>11</sup> The 99th percentile of the lognormal distribution for the measles incubation period is 22.3 days (95% CI 20.8–23.9) and thus an incubation period of 23 days should occasionally occur.<sup>12,13</sup> These unusually long incubation periods may reflect variations in infectious dose, pathogen replication time or degree of susceptibility.<sup>14</sup>

## Conclusion

Measles elimination demands careful review and classification of each confirmed measles case as locally acquired, imported or import-related. Although public health control measures such as post exposure prophylaxis, isolation and surveillance of susceptible individuals should continue to be based on the common incubation period, a longer incubation period may occasionally explain an unexpected measles case.

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