Nosocomial and community transmission of measles virus genotype D8 imported by a returning traveller from Nepal

Kathryn M Weston,[1] Dominic E Dwyer,[2] Mala Ratnamohan,[2] Ken McPhie,[2] Sau-wan Chan,[2] James M Branley,[3] Lisa J Allchin,[1] Krishna P Hort[1]

Abstract

Measles is uncommon in Australia due to effective national vaccination strategies. In mid-2003, a cluster of nine cases of measles occurred in western Sydney. The index case was a 29-year-old traveller recently returned from Nepal. The case presented to hospital and transmitted the disease to two others in the Emergency Department. Further cases resulted from both community and nosocomial transmission. The median age of cases was 24 years, with three cases in children aged under four years. Only one person had a documented history of measles vaccination, a child who had received one dose of vaccine overseas. One case was a 2-month-old infant whose mother was immune and two cases were hospital staff members. Molecular analysis of measles virus isolates from four cases revealed the same D8 genotype, a strain previously identified in Nepal. Staff vaccination strategies implemented as a result of the outbreak were poorly patronised despite nosocomial transmission. As diseases such as measles become rare it is important to thoroughly investigate any outbreaks, and to maintain a high index of suspicion of measles, particularly in travellers presenting with a rash having returned from measles-endemic areas. Genetic analysis is important in tracing the origins of an outbreak, and to confirm relatedness between cases. The highly infectious nature of measles virus also underscores the need for appropriate infection control in minimising risk of nosocomial transmission. Such policies are of increasing importance with the emergence of novel viruses or the threat of pandemic influenza. *Commun Dis Intell* 2006;30:358–365.

Keywords: measles, nosocomial, genotype D8, transmission

Introduction

Measles is a highly infectious and serious disease responsible for significant morbidity and mortality in undeveloped countries.[1] In Australia, locally acquired measles is now uncommon, largely due to effective measles vaccination initiatives. Outbreaks are most often due to overseas acquisition of the virus with subsequent infection of susceptible individuals in Australia[2,3] or spread through conscientious objectors to vaccination.[4]

The reported incidence of measles has declined since the introduction of surveillance in 1991, to a record low level of 0.07 cases per 100,000 population in 2005.[5] While possible cases presenting with a measles-like rash are sometimes reported to the local public health unit (PHU) by general practitioners and hospital physicians, the majority of reported cases do not fit the case criteria for measles as defined by the NSW Health Department.[6] Moreover, confirmatory diagnostic testing is not ordered for most patients who present with a rash, confounding accurate determination of the incidence of vaccine preventable diseases such as measles and rubella in Australia.

Following the National Measles Control Campaign in 1998, immunity to measles amongst children aged 6–11 years in Australia increased from 84 per cent to 94 per cent.[7] However, there remains a high-risk population of young adults in Australia, born between 1975 and 1981, who may have not contracted measles during childhood due to its declining incidence,

1. Centre for Population Health, Sydney West Area Health Service, Penrith, New South Wales
2. Centre for Clinical Microbiology and Infectious Diseases Laboratory Services, Institute of Clinical Pathology and Medical Research, Westmead Hospital, Westmead, New South Wales
3. Nepean Hospital, Sydney West Area Health Service, Penrith, New South Wales

Correspondence: Dr Kathryn Weston, Centre for Population Health, Sydney West Area Health Service, PO Box 63, Penrith NSW 2751. Telephone: +61 2 4734 2022. Facsimile: +61 2 4734 3444. Email: westonk@wahs.nsw.gov.au

but who also may not have been vaccinated due to lower vaccine coverage at the time.[8] This population of young adults is therefore at risk of measles, as demonstrated in four outbreaks in Victoria, occurring between 1999[9] and 2003.[3] Such outbreaks amongst a susceptible population reinforce the need for continued surveillance and follow-up of cases of measles, rapid testing, and the maintenance of a high index of suspicion for measles amongst travellers presenting with a rash. In three of the outbreaks, the index case acquired measles overseas and imported the disease into Australia. The index case for the remaining outbreak was not identified.[3]

Outbreaks of measles can be characterised by genetic analysis of virus isolates. Sequence analysis of the haemagglutinin (H) gene and of the hypervariable region of the nucleoprotein (N) gene can help in identifying geographic sources of the disease, particularly in countries with few locally acquired cases and where effective immunisation strategies are in place. Studies in Canada, the United States of America and Australia have shown that the measles virus genotypes found in the outbreaks described in the reports resulted from importation of the virus rather than local acquisition.[10,11,12] Genetic relatedness between cases and reference to known strains is an important part of an outbreak investigation, and can assist in informing eradication and control strategies.

This paper describes a cluster of nine cases of measles in western Sydney that presented in mid-2003. The genetic analysis of the measles virus obtained from specimens, the role of transmission through the hospital Emergency Department, and the importance of vaccination are discussed.

Methods

Case definition

The case definition for a confirmed case of measles was clinically defined measles-like illness with laboratory confirmation by one of the following: detectable measles virus-specific IgM or IgG seroconversion in serum, detection of measles virus antigen by immunofluorescence or measles virus RNA by polymerase chain reaction (PCR) from respiratory swabs or serum, or isolation of measles virus from blood, swabs or aspirates. Symptoms of clinically-defined illness included rash, cough, coryza and temperature over 38°C.[6]

Outbreak investigation and contact tracing

PHU officers investigating the outbreak followed response protocols outlined in the NSW Health Notifiable Diseases Manual.[6] Local general practitioners, infectious diseases physicians and emergency departments were alerted and provided with information about isolation and laboratory testing of suspected cases. PHU staff undertook contact tracing of patients following presentations to the Emergency Department (3 cases) and a general practice (2 presentations by one case). If the period of time from exposure to follow-up was short enough for vaccination or immunoglobulin prophylaxis to be effective, adults aged between 18 and 32 years were advised to receive measles, mumps and rubella (MMR) vaccination, and children aged under 12 months were offered immunoglobulin. These age groups were targeted as being susceptible to measles as the adults may have not contracted measles during childhood or not have been vaccinated, and the infants were too young to have received the first dose of MMR vaccine. Older children who had not received two doses of MMR vaccine were also advised to be vaccinated.

Hospital Infection Control staff contacted staff members at the hospital who were exposed to an infectious case. Those aged 32 years or younger were advised to receive MMR vaccination.

Laboratory diagnosis

Nasopharyngeal specimens, or nose and throat swabs, were collected from patients presenting with clinically-defined measles-like illness. For measles antigen detection, acetone-fixed smears of swabs were stained with measles-specific monoclonal antibodies (Chemicon International, Temecula, USA) and fluorescein isothiocyanate-conjugated anti-mouse immunoglobulin in an indirect immunofluorescence assay.

Vero cell monolayers in tube cultures were inoculated with 0.2 ml suspension of respiratory tract samples, incubated at 37°C and observed daily for cytopathic effects (CPE) characteristic of measles virus. Cultures showing CPE were confirmed by staining with measles-specific monoclonal antibodies described above.

A diagnostic measles PCR was performed using nucleoprotein (N) region primers in a nested format (outer sense 5'TACCCTCTGCTCTGGAGCTATGCC3', outer antisense 5'CTCGCACCTAGTCTAGAAG3' and inner sense 5'TATCACTGCCGAGGATGCAAG3', inner antisense 5'TGTCTGAGCCTTGTTCTTCCG3'). Total RNA was extracted from 200 µl serum using the Roche High Pure RNA kit (Roche Diagnostics, Germany). First round amplification was performed using Hot Start Amplitaq gold DNA taq polymerase and buffer (Applied Biosystems, Branchburg, New Jersey, USA) supplemented with 2.0 mM $MgCl_2$, 0.2 mM of each dNTP, 0.2 µM of both primers and cycling profiles of denaturation at 95°C (1 minute), annealing at 53°C (40 seconds), and extension at

72°C (1 minute) for 30 cycles. For the nested PCR, 1 µl of the outer product was amplified under similar conditions, except with an annealing temperature of 61°C. PCR amplicons of 379 nucleotides were visualised by electrophoresis on 1.5 per cent agarose gel, followed by sequencing for confirmation and comparison to other outbreak and reference measles sequences.[12,13]

Testing for measles-specific IgM and IgG serum antibodies was performed using the Enzygnost (Dade Behring, Germany) enzyme immunoassay according to the manufacturer's instructions.

Measles virus genotyping

For measles genotyping, total RNA was extracted using the Roche High Pure RNA kit (Roche Diagnostics, Germany) from either the swab samples, or from 200 µl of serum or Vero cells infected with measles virus harvested when CPE involved at least 30 per cent of the cell monolayer. RNA from serum and swabs was eluted in 50 µl and from infected Vero cells in 100 µl of elution buffer. A 456-nucleotide (nt) sequence coding for the carboxy-terminal of the nucleoprotein (N) gene and the full length (1,854 nt) of the haemagglutinin (H) gene were amplified in a single round PCR from four isolates. Amplicons were sequenced in both directions using sequencing primers described elsewhere.[14]

Nucleotide sequences of the N and H genes were aligned using the Clustal W (1.7) program and phylogenetic trees were generated by the Phylip program (Phylogeny Inference Package version 3.5) using the DNA distance matrix program (version 3.57) followed by neighbour-joining tree. Treeview (version 1.5) was used to draw the unrooted trees. Access to these programs was through www.angis.org.au, the website of the Australian National Genomic Information Service (ANGIS). The reference measles strains and Genbank Accession numbers used in the phylogenetic analyses are listed in the Table.[12,13]

Table. Measles genotypes used for the genetic characterisation of the outbreak isolates

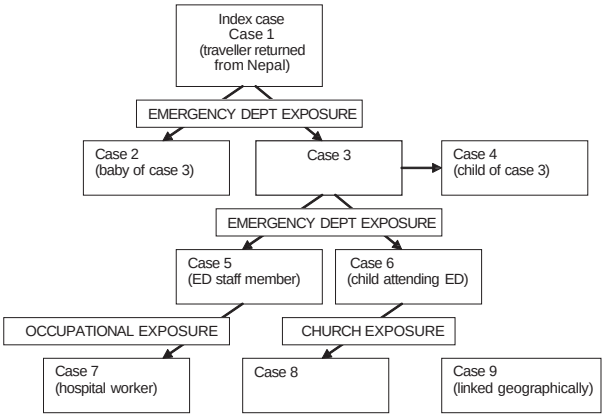
Reference strain	Genotype	Haemagglutinin gene, Genbank Accession no.	Nucleoprotein gene, Genbank Accession no.
Edmonston-wt.USA/54	A	U03669	U01987
Yaounde.CAE/12.83	B1	AF079552	U01998
Libreville.GAB/84	B2	AF079551	U01994
Ibadan.NIE/97/1	B3	AJ239133	AJ232203
New York.USA/94	B3	L46752	L46753
Tokyo.JPN/84/K	C1	AY047365	AY043459
Erlangen.DEU/90	C2	Z80808	X84872
Maryland.USA/77	C2	M91898	M89921
Bristol.UNK/74 (MVP)	D1	Z80805	D01005
Johannesburg.SOA/88/1	D2	AF085198	U64582
Illinois.USA/89/1	D3	M81895	U01977
Montreal.CAN/89	D4	AF079554	U01976
Palau.BLA/93	D5	L46757	L46758
Bangkok.THA/93/1	D5	AF009575	AF079555
New Jersey.USA/94/1	D6	L46749	L46750
Victoria.AUS/16.85	D7	AF247202	AF243450
Illinois.USA/50.99	D7	AY043461	AY037020
Manchester.UNK/30.94	D8	U29285	AF280803
Janakpur.NEP/2.99/1	D8	AJ250061	AJ250069
Victoria.AUS/12.99	D9	AY127853	AF481485
Kampala.UGA/3.01	D10	AY923214	AY923203
Goettingen.DEU/71	E	Z80797	X84879
Madrid.SPA/94 SSPE	F	Z80830	X84865
Berkeley.USA/83	G1	AF079553	U01974
Amsterdam.NET/49.97	G2	AF171231	AF171232
Gresik.INO/17.02	G3	AY184218	AY184217
Hunan.CHN/93/7	H1	AF045201	AF045212
Beijing.CHN/94/1	H2	AF045203	AF045217

Results

Outbreak details

Details of the outbreak are shown in Figure 1. The index case, Case 1, a 29-year-old male, presented to the Emergency Department of a large teaching hospital in June 2003 with a three-day history of fever, cough and feeling unwell. He presented with a morbilliform rash, fever, cough, coryza and temperature over 38°C. He was asked to return the next day whereupon his condition had worsened and he was admitted. The case had returned from Nepal via a stop-over in Bangkok seven days before his first presentation. A travel history was taken on admission and a number of conditions considered. The case claimed to have had measles previously and to have been vaccinated against measles in the past. He had not been vaccinated with MMR immediately prior to the trip to Nepal. Measles was considered as a possible diagnosis upon his first presentation and he was isolated. Upon his second presentation, however, no specific infection control procedures were implemented. The local PHU was not notified and a public holiday long weekend provided an additional delay before measles was confirmed.

Figure 1. Transmission of measles between cases



Upon confirmation of measles, Emergency Department contacts of Case 1 were notified of the risk of measles. It was too late for immunoglobulin prophylaxis. Two contacts from the one family (Cases 2 and 3, aged 2 months and 27 years respectively) developed measles with the rash appearing between 8 and 16 days post-contact. Case 3 was the father of Case 2. Subsequently, measles was transmitted to a 15-month-old sibling of Case 2 (Case 4) who was not vaccinated against measles. The 17-year-old mother, whose immune status was indicated by measles-specific IgG in a serum sample, did not contract measles.

Case 3 presented to the Emergency Department and, despite being promptly isolated, transmitted the infection to an Emergency Department staff member (Case 5, aged 30 years) and a 3½-year-old child (Case 6) who was being treated in the Emergency Department. Both developed a rash 11 days after contact. Another staff member subsequently developed measles (Case 7, aged 38 years), the likely source being Case 5.

The 3½-year-old child (Case 6) visited a church whilst infectious and transmitted measles to an unvaccinated adult (Case 8, aged 24 years) who developed a rash 14 days after contact. An additional case (Case 9, aged 21 years), living in the same geographical area as the other cases, was notified to the local PHU prompting investigation of possible exposures. If Case 9 was linked to any of the other cases, the timing of symptoms indicated that infection could only have been through contact with Case 8. However the nature of any such contact could not be determined. It is possible that other cases occurred in the area but were not diagnosed as measles or were not notified.

The median age of cases was 24 years (range 2 months to 38 years), with three cases in children aged under 4 years.

Clinical and laboratory details

All cases except the infant (Case 2) presented with rash, fever, and cough. The infant presented with rash, fever and coryza. Koplik spots were detected in four patients. Six patients also presented with conjunctivitis. Abnormal liver function tests were noted in all adult cases tested (n=4), an uncommon manifestation of measles.[15] All patients had at least one laboratory test confirming measles virus infection. All cases were confirmed cases according to NSW Health criteria.[6] Four of the six adult cases and one of the three child cases required hospitalisation for between two and five days.

The incubation period of the infant's illness (Case 2) was short, with the rash occurring eight days post-contact. The period between contact and rash for the 3½-year-old child (Case 6) was 11 days. The other child (Case 4) contracted measles from Case 3 or Case 2 and the exact date of transmission was unknown. The adults for whom precise details of contact were known developed a rash between 11 and 16 days post-exposure.

Vaccination status

Only one person (Case 6) had documented evidence of measles vaccination, having received a dose of vaccine overseas. The other two children in the outbreak were unvaccinated either because they were

too young (Case 2) or parental choice (Case 4). Of the six adult cases, three thought they had received one dose of vaccine (Cases 1, 3, 9), two thought they had measles in childhood (Cases 1, 8) and one thought that measles serology had been previously tested and that immunity was adequate (Case 5). No details of the vaccination or disease history were obtained for Case 7.

Outbreak investigation

A total of 496 people were identified as possible contacts at either the Emergency Department or general practitioner (GP) surgery. Of these, 184 contacts from the Emergency Department and 72 contacts from the GP surgery were in the 'at risk' age group of 18 to 32 years, or were infants aged under 12 months. Telephone contact was made with 61 per cent of the Emergency Department contacts and with 52 per cent of the GP surgery contacts. A letter was sent to the remainder. All contacts were provided with advice about the risk of measles and disease symptoms, and were recommended vaccination if necessary. There was difficulty in tracing all contacts presenting to both the Emergency Department and the general practice as some patients had not provided any or accurate contact details on presentation. PHU officers attempted to visit two families who could not be contacted by telephone, to advise parents about the need for immunoglobulin prophylaxis for exposed infants. One family was contacted in this way, while the other family had moved and could not be located.

PHU follow-up also involved providing information to contacts who had attended church with an infectious case. The church community of more than 500 members was provided with information in Arabic about the risk of measles, disease symptoms, and vaccination. A beauty salon and child-care centre were also contacted and provided with the same advice.

The hospital infection control team undertook contact tracing of 34 staff members who had possible exposure to measles and were in the risk age group of between 18 and 32 years. Seventeen of these staff members (50%) received MMR vaccination as a result. The remainder had either a past history of measles or measles serology indicating immunity. A staff health program recommending MMR vaccination was implemented at the hospital, targeting staff born after 1970. Information and education about measles and MMR vaccination were distributed by letter to susceptible staff, and to all staff through hospital networks including a staff newsletter and electronically. MMR vaccination was also offered at different locations throughout the hospital. Only 17 per cent of staff born after 1970 (134 out of 788 people identified from staff records) took the opportunity to receive MMR vaccination with 15 per cent of staff declining and 62 per cent not responding to the program. Only six per cent of those targeted indicated they had previously been vaccinated. A second staff health program, aimed at staff who did not respond to the first program and at new staff, identified 461 staff. Of these, three per cent had been previously vaccinated (14 people) and 14 per cent (63 people) received MMR. Ten per cent declined vaccination and 74 per cent did not respond to the program.

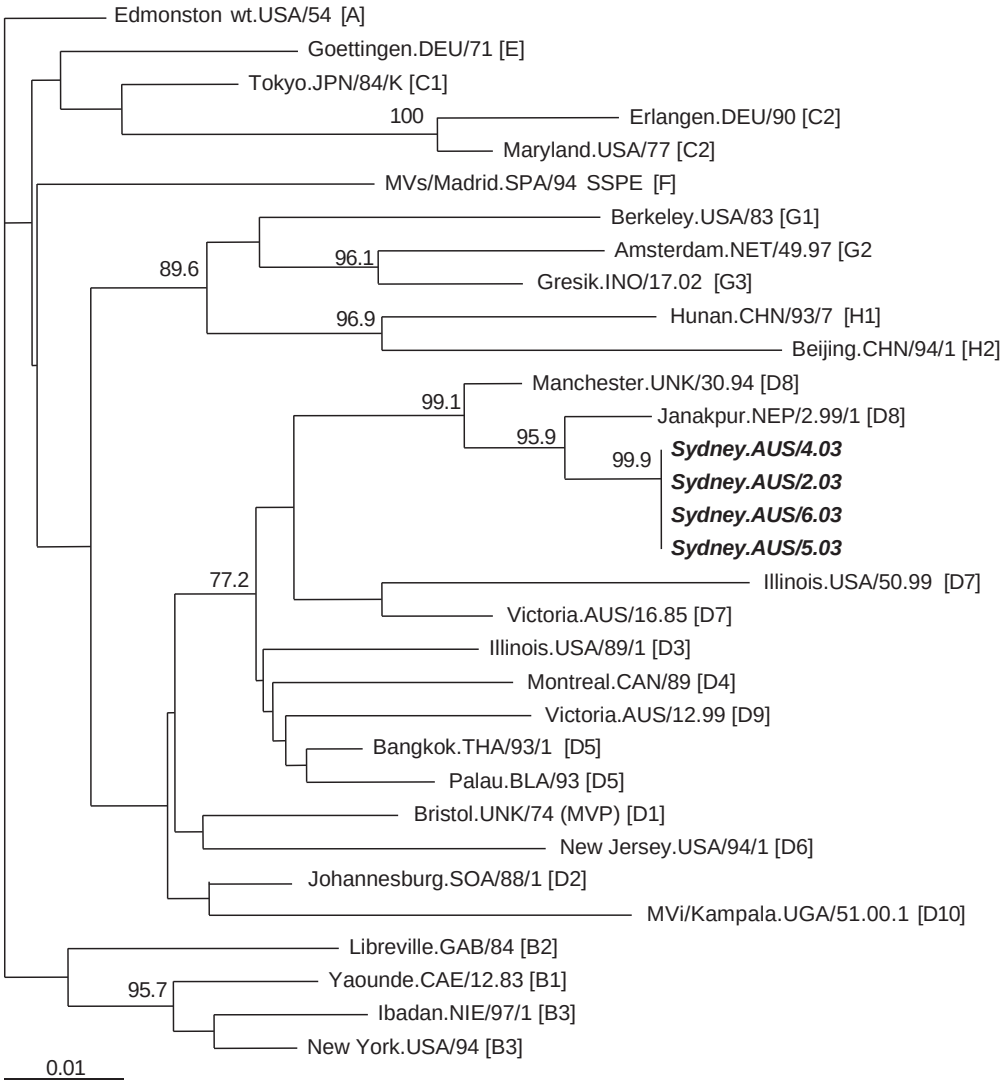
Genetic analysis of measles viruses

Measles virus was isolated from five patients (Cases 2, 3, 5, 7 and 8) including two cases from the same family. Sequencing of the N genes of four isolates (only one isolate from the family was sequenced) showed that they were identical, and were more closely related to a Nepalese measles genotype D8 (Janakpur NEP/2.99/1, Table) isolate[16] than to other sequences, (Figure 2).[12,13] Similar results were obtained with phylogenetic analysis of the H gene sequences (data not shown). The D8 genotype has occasionally been detected in Australia previously (the last time in early 2001), although the country of origin was not always available.[17] The D8 genotype was confirmed on RNA from three isolates sent to the Measles Reference Laboratory at VIDRL (Doris Chibo, personal communication). To confirm the specificity of the diagnostic PCR compared to measles virus isolation and antigen detection from respiratory tract specimens, a 355 nt sequence of the amplicon generated from serum of the index case showed 100 per cent similarity to the N gene sequence of one of the outbreak isolates, Sydney.AUS/4.03 (data not shown). The Genbank Accession numbers of the four sequences from this outbreak are DQ852617, DQ852618, DQ852619 and DQ852620.

Discussion

This paper describes a cluster of nine laboratory-confirmed cases of measles, eight of which were linked through contact. The index case had returned from Nepal three days prior to onset of fever and seven days prior to onset of rash. As the incubation time for measles is about 10 days, varying from 7 to 18 days to onset of fever and 14 days to onset of rash,[6] the most likely scenario is that the disease was acquired in Nepal. Phylogenetic analyses of the N and H regions of the measles viruses isolated from four cases indicated that sequences were most closely related to each other and the Janakpur. NEP/2.99/1 strain, a genotype D8 isolate of Nepalese origin,[16] further suggesting the acquisition of measles in Nepal and transmission to contacts in Australia. As outbreaks of measles become rarer in countries where vaccination programs have been effective, it is important to thoroughly investigate any incursions of disease. Genetic analysis of measles

Figure 2. Phylogenetic relationship based on the carboxy terminal end of the N gene (456nt) of the four Sydney isolates to recent isolates, Janakpur.NEP/2.99/1,[16] MVi/Kampala.UGA/51.00.1,[13] and other reference strains quoted by the WHO.[12]



Significant bootstrap values are indicated at the nodes (1,000 replicates, in %) of the unrooted tree. The isolates from this cluster are shown in bold. The scale indicates 1 per cent nt difference and [ ] denotes the genotypes of the reference strains.

isolates can aid in identifying the geographic and personal source of the outbreak, confirm relatedness of cases within outbreaks, and identify routes of transmission.[13,18]

An interesting aspect of this cluster was the occurrence of measles in a 2-month-old baby whose 17-year-old mother was immune. In most cases, maternal antibodies from measles infection or vaccination will protect newborns. Antibody levels wane after 6 to 9 months and measles vaccination is offered at 9 to 12 months in most countries. It has been suggested that infants of women who have received measles vaccine may experience earlier loss of maternal antibody than infants whose mothers were immune due to natural infection.[19] This may result in insufficient protection for these children prior to their scheduled vaccination. The mother of the infant in this case thought she had contracted measles when aged five years and living overseas. She also recalled missing a high school vaccination. It is therefore likely that her immunity was due to natural disease and, accordingly, her infant would be expected to have passive immunity. The fact that the child developed measles indicates that a diagnosis of measles in a very young child presenting with measles-like symptoms, although unexpected, should not be discounted. An interesting feature of the infant's illness was a short incubation period with the rash appearing only eight days after exposure. Incubation periods for measles are typically shorter in children.[20]

The index case did not have a documented history of measles vaccination and was in an age group at higher risk. The lack of documented vaccination history amongst all but one case reinforces the importance of vaccination as a protective measure against the disease. Furthermore, patient recall of vaccination or disease cannot be relied upon as sufficient evidence. In this outbreak the index case claimed to have been vaccinated and to have had clinical measles. These claims may have reduced the index of suspicion of measles in the Emergency Department despite the classical measles symptoms and recent travel history. The claims are also a likely reason for lack of MMR vaccination prior to travel to a measles-endemic area. The National Health and Medical Research Council recommends MMR vaccination for travellers born during or since 1966 who have not received two doses of MMR vaccine.[21] The importance of documented history of vaccination rather than patient recall should be emphasised to potential travellers seeking advice about travel vaccination.

One child in this cluster (Case 4) could have received MMR vaccination shortly after exposure, an action that may have prevented the disease. However, despite advice from the PHU, the child was not vaccinated and subsequently developed measles. Transmission within the Emergency Department played a significant role in this outbreak with contact at that site being responsible for five cases. The highly infectious nature of measles was demonstrated by the development of measles in a staff member who did not come into contact with the patient, but who entered the room fifteen minutes after it had been vacated. Guidelines from NSW Health indicate that susceptible persons should not have entered the room for two hours after the infectious case had left.[6] On the other hand, a properly protected workforce would obviate the need for such measures to protect staff and would allow hospital resources to be used efficiently. Healthcare workers should be aware of their vaccination status and ensure their vaccinations are up-to-date. The issues of nosocomial transmission of measles and the need for staff vaccination are not new.[22,23] However their importance is not always reflected in a proactive approach by healthcare workers to ensure they are properly protected. At this hospital, some staff members in the age group at higher risk were reluctant to be vaccinated with MMR, even after two colleagues had contracted measles at work. Programs to promote MMR vaccination to staff during and after the outbreak were poorly patronised by clinical staff, with a better response from non-clinical staff. Studies of healthcare workers have attributed poor uptake of influenza vaccine to factors including a lack of awareness of its importance and concern about side effects,[24] and a perception that the health care worker was 'healthy' and did not need the vaccine.[26] If the same or similar reasons are responsible for poor uptake of MMR vaccine amongst hospital staff, a strong promotional campaign backed by institutional strategies is needed to address the problem.

Clearly, crowded hospital environments such as Emergency Departments are risky places in terms of transmission of airborne diseases and this outbreak highlights the need for appropriate infection control procedures in the event of suspected measles. Such infection control policies and procedures are of increasing importance in the effective management of disease outbreaks, and to respond to the emergence of novel viral diseases such as severe acute respiratory syndrome, and avian influenza.

The delay in diagnosis and confirmation of the index case was problematic as it resulted in delayed contact tracing and follow-up. With low rates of measles notifications in Australia, the improbability of measles as a diagnosis may result in delays in laboratory testing and diagnosis, quarantine of the case, and contact tracing, vaccination or immunoglobulin treatment. Until measles is eradicated, vigilance is required amongst physicians treating patients who present with a rash, or who have recently returned from overseas. Early action in notifying public health authorities and infection control staff, and the timely provision of immunoglobulin or MMR vaccination to those at risk are crucial steps in minimising the risk of secondary cases.

Acknowledgements

The authors thank the staff at the former Wentworth Area Health Service Public Health Unit and Infection Control Department, NSW Health, and other Wentworth Area Health Service staff for their assistance during the measles outbreak.

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