The Broad Street Pump

June 2019

Issue 51

A Centre for Infectious Diseases and Microbiology - Public Health (CIDM-PH) and Marie Bashir Institute for Infectious Diseases & Biosecurity (MBI) publication

Laboratory diagnosis of measles virus – a change in paradigm?

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The World Health Organization (WHO) declared that measles virus (MeV) was eliminated in Australia in 2014,(1) largely due to the widespread availability and implementation of the live attenuated MeV vaccine. In Australia, MeV vaccines have been available since 1968, and the current two dose vaccination schedule was introduced in 1992.(2) As part of the National Immunisation Program, the first dose is provided as the measles-mumps-rubella vaccine at 12 months, followed by the second dose at 18 months of age as the measles-rubella-varicella vaccine.(3) All unvaccinated adults born after 1966 are recommended to have two doses of vaccine at least four weeks apart, unless there is serological evidence of immunity from wild-type MeV infection.

A single vaccination is estimated to be 93% effective at preventing MeV infection, increasing to 97% with two doses.(4) There are high vaccination rates against MeV in Australia (93% of all two year olds were fully vaccinated in 2017(5)). However, protective immunity may not always develop despite the receipt of two vaccine doses. Primary (whereby immunity never develops post vaccination) or secondary (associated with waning immunity post vaccination due to limited exposure to circulating wild-type MeV) vaccination failure poses a threat to the prevention of transmission of disease.(2) As susceptible persons are the natural reservoir for on-going MeV transmission, MeV is endemic in areas of low vaccine uptake, such as low to middle income countries. In addition, vaccine controversies (such as worse outcomes following Dengvaxia vaccination in those that have not been previously infected with dengue virus in the Philippines) affect public confidence and uptake of all vaccines,(6) further contributing to large MeV outbreaks.

Inside this issue

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In Australia, the importation of measles by foreign visitors or non-immune returned travellers from areas where MeV is endemic results in multiple localized and typically small outbreaks due to secondary local transmission to non-immune contacts.(1,2) Simultaneous outbreaks may occur across different jurisdictions due to the travel patterns of Australian visitors. At the time of writing, there have been 109 MeV notifications reported to the National Notifiable Disease Surveillance System in 2019.(6) Most of the cases have been from New South Wales (NSW; n=36), Australia's most populous state, which also receives the most number of travellers to Australia.

MeV infection typically presents as a self-resolving febrile illness characterised by a morbilliform rash, and can lead to complications in 30% of cases, including pneumonia, encephalitis, and rarely death.(8) In Australia, a confirmed case of measles requires either clinical and epidemiological evidence or definitive laboratory confirmation via one of the following; isolation of measles virus, detection of virus by nucleic acid testing (NAT), IgG seroconversion or a significant increase in antibody levels, except if the person had received MeV vaccine eight days to eight weeks prior to the collection of the convalescent sera.(9)

Laboratory confirmation of MeV is essential to accurately monitor the epidemiology of measles and to implement effective control strategies. Detection of MeV-specific IgM antibody on acute-phase sera is the most widely available test, but is not without limitations. 90% of persons with acute MeV infection will develop detectable IgM three days after the onset of rash, peaking at 7-10 days and generally becoming undetectable at eight weeks.(10) In one study, testing sera collected <72 hours after rash onset has a false negative rate of 33%.(1) The false positive rate of MeV-specific IgM testing in a highly vaccinated and low prevalence population is estimated at 4%; cross-reactivity from other viruses including human parvovirus, rubella virus and human herpesvirus 6, and to rheumatoid factor have been described. The IgM response in MeV vaccination failures may also be absent. IgG antibodies are similarly detectable within three days of rash onset, peaking at four weeks and persist for life.(10) The presence of IgG indicates past infection or vaccination.(11) Previous MeV infection is considered to provide lifelong immunity.(2)

The WHO reports 24 current MeV genotypes, including the genotype A vaccine strain (MeVA). NAT can be performed on nasopharyngeal or urine samples, and is the most sensitive and specific diagnostic method to detect MeV during an acute infection.(11) Following MeV vaccination, approximately 5% of vaccine recipients develop a self-resolving, MeV-like illness (with symptoms including fever and rash) 5-12 days after vaccination, which is not considered transmissible.(11) During this time, MeVA may be detected from upper respiratory tract or urine samples. Of note, a recent study has shown that MeVA may be detected in upper respiratory tract samples up to 784 days post vaccination.(7)

Real-time polymerase chain reaction assays can be used to detect MeV and to differentiate between wild-type MeV and MeVA. This substantially reduces the turnaround time in the laboratory to determine MeVA strains, which have traditionally required the use of sequencing methods. Rapid discrimination between MeVA and wild-type MeV is useful to guide individual case management and public health responses regarding the use of MeV vaccine and/or normal human immunoglobulin as post-exposure prophylaxis in susceptible contacts. Up until May 2019, 2433 individuals with suspected MeV infection have undergone MeV NAT at NSW Health Pathology-ICPMR, with 28 (1.2%) and 22 (0.9%) wildtype strains and MeVA cases detected, respectively.

The increased availability of NAT for the diagnosis of MeV infection has shed new light on the interpretation of MeV-specific serology. As outlined in the table below, of 36 MeV cases in NSW this year, IgM and IgG were detected in the sera of seven persons collected between 0-6 days after the onset of rash. Three of the seven persons received at least one dose of MeV vaccine; two of them received two doses. MeV vaccine history were not available in the remaining four persons. One person reported previous MeV infection many years prior.

Of the 36 cases, IgM but not IgG was detected in the sera of 10 persons collected between 0-14 days after the onset of rash. Two of the ten persons were known to have received at least one dose of MeV vaccine, supporting the recommendation of at least two doses of vaccine to ensure optimal protection. Of interest, IgG was not detected in one person that had received two doses of MeV vaccine, indicating vaccine failure. In the same person, IgM was also not detected, although sera were collected on the day prior to the onset of rash.

Table. Laboratory results of persons infected with measles virus in New South Wales, 2019

IgM	IgG	Day(s) serology taken from rash onset	PCR Nose/Throat Swabs	PCR Urine	Genotype	Vaccination History
ND	ND		Pos	Pos	D8	Unknown
ND	ND		Pos	Neg	B3	Yes - unknown if 1 or 2 doses
Nil	ND		Pos	Pos	D8	No
ND	ND		Pos	Pos	D8	No
ND	ND		Pos	Pos	D8	No (Too young)
ND	ND		Pos	ND	D8	No (Too young)
Pos	Neg	3	Pos	Pos	B3	Unknown
Pos	Pos	6	Pos	Pos	B3	Unknown
Pos	Pos	3	Pos	ND	B3	Yes - Fully
ND	ND		Pos	ND	B3	Unknown
Pos	Neg	14	Pos	ND	B3	Yes - 1 dose only for age
Pos	Pos	1	Pos	Pos	B3	Yes - Fully on AIR
ND	Pos	2	Pos	Pos	D8	Unknown
Pos	Neg	0	Pos	Pos	B3	No (Too young)
Pos	Neg	1	Pos	ND	D8	No (Too young)
Pos	Pos	2	Pos	Pos	B3	No - Reports previous infection
ND	ND		Pos	ND	B3	Unknown - likely as child
Pos	Neg	1	Pos	Pos	D8	Unknown
Equivocal	Neg	0	ND	Pos	D8	No
Pos	Neg	0	Pos	Pos	D8	Yes - unknown if 1 or 2 doses
Neg	Pos	1	Neg	Pos	Non-typeable	Unknown
ND	ND		Pos	ND	D8	No (Too young)
ND	ND		Pos	ND	D8	No (Too young)
Neg	Neg	-1	Pos	Pos	D8	Yes - Fully on AIR
Pos	Pos	3	Pos	Pos	D8	Unknown - likely as child
Pos	Neg and Equivocal	3	Pos	Pos	N/A	No
Pos	Neg and Equivocal	0	Pos	Pos	N/A	No
ND	ND		Pos	ND	D8	Yes - Fully on AIR
Pos	Pos	1	ND	ND	N/A	Yes - unknown if 1 or 2 doses
ND	ND		Pos	Pos	B3	No
ND	ND		Pos	ND	N/A	Unknown - likely as child
Pos	Neg	2	Pos	ND	B3	Unknown
Pos	Pos	0	ND	Pos	B3	Unknown
Pos	Neg	1	Pos	Pos	D8	Unknown
Neg	Pos	N/A	Pos	Neg	D8	Unknown
ND	ND		Pos	Neg	D8	Yes - Fully

*PCR: polymerase chain reaction; ND: not done; Pos: positive; Neg: negative; pt: patient; AIR: Australian Immunisation Register
N/A: not available

IgG but not IgM was detected in the sera of two persons collected within three days of the onset of rash, reflecting waning immunity. The vaccination status of these two persons are unknown, and it is likely that the detectable IgG is accounted for by MeV vaccine rather than wild-type MeV infection, as infection is more likely to result in protective immunity. Furthermore, it has been shown that MeV infection may be attenuated in those that have received two doses of vaccine but with secondary vaccine failure, with less symptoms and lower rates of hospitalisations when compared to unvaccinated or single dose vaccine recipients.(2) There is also reduced transmission of MeV infection in persons with attenuated MeV infection, with a reduction in the viral load and duration of viral shedding from the upper respiratory tract.(2)

In summary, the serological findings of the MeV cases in NSW when correlated with NAT challenges the paradigm that the presence of detectable IgG antibodies confer protective immunity. The issues of vaccine failures and waning immunity have substantial public health impact, as such persons may be infected with, and transmit MeV. Further research into the immune responses following wild-type MeV infection and vaccination are awaited. In the meantime, the use of MeV vaccine should continue to be promoted by policy makers and healthcare providers to prevent resurgence of measles.

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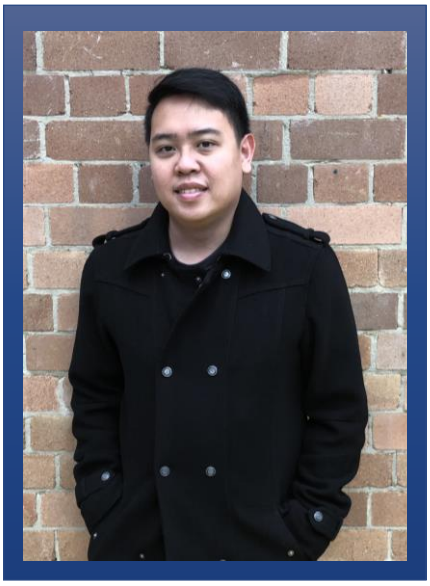
Staff Profile

Dr Eby Sim

Eby completed his PhD, a collaborative project with CSIRO Agriculture and Food, at the ithree institute in The University of Technology Sydney. Utilising a genomics approach, his research was focused on Shiga toxin-encoding bacteriophages and its contribution to pathogenicity in *Escherichia coli* O157. He was also involved in the investigation of a potential mechanism for the evolution of pathogenesis in an *Escherichia coli* O157 isolate.

During his Post-Doctoral appointment at the ithree institute, Eby expanded his investigation into the evolution of pathogenesis to include Shiga toxin-producing *Escherichia coli* isolates regardless of serotype. He also started utilising long read sequencing technology on the PacBio platform to resolve genomes for downstream comparative genomic investigations. Apart from the aforementioned, he was also involved in the optimisation of methods for phage DNA extraction and extraction of DNA suitable for PacBio sequencing. Eby recently joined NSW Health Pathology and the Centre for Infectious Diseases and Microbiology – Public Health team, and his research is focused on utilising Nanopore Sequencing, a portable long read sequencing platform, for the rapid identification and characterisation of pathogens of clinical and public health significance.



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