Emergence of attenuated measles illness among IgG positive/IgM negative measles cases, Victoria, Australia 2008–2017

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Key points: Between 2008-2018 an increase in IgM-/IgG+ measles cases was observed in Victoria, Australia. Thirteen cases were identified and were commonly vaccinated, male adults, with attenuated illnesses, low viral loads, and high IgG titres. Onward transmission was documented from one case.

Abstract

Background. Waning measles immunity among vaccinated individuals may result in an attenuated illness and is considered less infectious. This study aims to compare the epidemiological, clinical, and laboratory profile of measles cases with waning immunity to other measles cases.

Methods. PCR-positive (+) measles cases notified to Victoria's Department of Health and Human Services (DHHS) from 2008–2017 with immunoglobulin (Ig)M and IgG tested at diagnosis were classified according to serology at diagnosis: IgG negative (-) [non-immune]; IgM+/IgG+ [indeterminate]; or IgM-/IgG+ [waning immunity].

Results. Between 2008–2017, 297 measles cases were notified of whom 190 (64%) were included in this analysis; 151/190 (80%) were non-immune at diagnosis, 26 (4%) were indeterminate and 13 (7%) had waning immunity. Between 2008–13 and 2014–17, the proportion of cases with waning immunity increased from 0/87 (0%) to 13/103 (13%) (p<0.001) and the diagnostic sensitivity of initial IgM fell from 93% to 81% (p=0.012), respectively. Seven (54%) waning immunity cases reported receiving measles-containing vaccines; one case had two documented doses and three cases had one documented dose. Compared to non-immune and indeterminate cases, waning immunity cases were more likely to be male; less likely to report fever, coryza, and cough; and had lower burden of virus (higher Ct values on respiratory specimens). Among IgG+ cases, waning immunity cases had higher IgG titres than indeterminate cases (mean optical density [OD] values 1.96 vs. 0.71, p=0.004). Onward transmission from one waning immunity case to two infant household contacts too young for vaccination was documented.

Conclusions. Waning immunity among measles cases (IgM-/IgG+ at diagnosis), associated with secondary vaccine failure and modified clinical illness, is emerging in Victoria with transmission potential.

Keywords: measles; secondary vaccine failure; measles vaccine; measles elimination; immunity

Introduction

Measles, a highly infectious viral disease for which there is a safe and effective vaccine, caused an estimated 110,000 deaths in 2017, mostly children aged less than 5 years.(1) Measles vaccines have been available in Australia since 1968, with vaccination of children aged 12–23 months funded in all states and territories by 1972 and two-doses of measles-containing vaccine funded nationally from 1992.(2) The last recorded measles death in Australia occurred in 1995 and in 2014, Australia was declared measles eliminated by WHO.(3, 4) Despite high vaccine coverage in Australia, non-immune travellers and their contacts continue to be at risk of measles infection. Of the 340 measles cases notified in Australia in 2014, 41% were imported, 34% import-related, and the remaining 25% were from unknown sources.(5)

Measles infection confers lifelong protection from further episodes of clinical measles, and measles vaccine is highly immunogenic. Vaccine efficacy in Australia is estimated to be 96.7% (95% confidence interval [CI] 94.5–98.0%) for one dose and 99.7% (95%CI 97.9–99.2%) for two doses of measles vaccine.(6) Although infrequent, vaccine failures do occur. In 2014, 53 notified measles cases in Australia were classified as vaccine failures; 11 had received two doses and 42 had received one dose of measles containing vaccine.(5) Vaccine failure can either be primary, where a vaccine recipient does not develop protective immunity following vaccination, or secondary, where the protective immunity that develops post-vaccination wanes over time. The phenomenon of waning immunity following measles vaccination has been recognised for around 50 years.(7) In highly immunised populations such as Australia, a lack of natural boosting of antibody levels through exposure to circulating wild-type measles likely contributes to secondary vaccine failures.(8, 9)

Differentiation between primary and secondary vaccine failure is possible if measles antibodies are detected following vaccination and before measles disease. However, serological testing post-vaccination is not routine. At the time of measles diagnosis, secondary vaccine failure is suggested by the detection of measles virus by PCR along with detection of measles-specific immunoglobulin G (IgG) in the absence of measles-specific immunoglobulin M (IgM), and/or detection of high avidity IgG antibodies to measles. People with secondary vaccine failure have been shown to have an early robust IgG response, a transient or absent IgM response, and may have an altered clinical presentation.[9] In a recent study of secondary vaccine failure measles cases in California, those who had received ≥2 doses of measles vaccine demonstrated a modified clinical illness with lower rates of hospitalization, cough, coryza, conjunctivitis and fever than cases who had received one dose of measles vaccine or were unimmunised.(10)

In Victoria, Australia (population 6.3 million in 2017), measles notification to the Victorian Department of Health and Human Services (DHHS) is mandatory upon initial diagnosis or clinical suspicion.(11) Immediate public health action, including case confirmation and management of contacts, is undertaken according to national guidelines.(12) Using notification and laboratory data from Victoria from 2008–2017, we aim to describe the occurrence of measles in people with serological evidence of waning measles immunity, and to compare the demographic, clinical and laboratory profile of measles cases with serological evidence of waning measles immunity to those without serological evidence of prior immunity.

Methods

We assessed measles cases notified to the Victorian DHHS from January 2008 to December 2017. Cases were included if they had measles RNA detected by PCR, and both measles-specific IgM and IgG tested on a specimen collected no later than the date of specimen collection for the PCR testing. Cases were classified according to their serology at diagnosis:

- Non-immune: IgG not detected (IgG- [IgM either detected or not detected])
- Indeterminate: IgM and IgG detected (IgM+/IgG+)
- Waning immunity: IgM not detected, IgG detected (IgM-/IgG+)

We reviewed surveillance data from DHHS, which includes notification data from clinicians and laboratories for all cases, and data from hospital discharge summaries and case / clinician interviews where available. Measles virus genotype, cycle threshold (Ct) values, and optical density (OD) values, where included when available.

Demographics (age, sex, country of birth), clinical features (hospitalisation, rash, cough, coryza, conjunctivitis, Koplik spots, source for onward transmission of measles virus), and Ct values were compared between the three groups. IgG OD titres were compared between the 'indeterminate' [IgM+/IgG+] and 'waning immunity' [IgM-/IgG+] groups. The diagnostic sensitivity of measles-specific IgM was calculated as the proportion of included PCR-positive measles cases with IgM detected at the time of first PCR detection. Multivariable models were developed to examine each of the following outcomes: temporal changes in IgM sensitivity, Ct values (from respiratory specimens) and OD values. A P-value of <0.05 was considered statistically significant. Data were analysed using StataMP 15. More detailed methods are available in the Supplement.

As this was an analysis of routinely collected surveillance data for public health purposes, human research ethics committee approval was not sought.

Results

From 2008–2017, 297 measles cases were notified in Victoria. The annual number of cases ranged from two in 2008 to 71 in 2014 (median 33.5 cases/year). Overall, 107 (36%) notified measles cases were excluded due to no PCR result (n=10), a negative PCR result (n=30), or serology not tested at diagnosis (n=67).

Waning immunity cases. Of the 190 included measles cases, 13 (7%) were classified as waning immunity, 26 (14%) as indeterminate (IgM+/IgG+), and 151 (80%) as non-immune (IgG-). From 2008–2013, no waning immunity cases were identified (0/87), compared to 2014–2017 when 13% (13/103) waning immunity cases were identified (p=0.001) [Figure 1]. Seven waning immunity cases (54%) were acquired in Australia and three cases (23%) were acquired in the Philippines [Table 1]. One case of waning immunity had received two documented doses of measles-containing vaccine, three cases had one documented dose, and four cases stated they were vaccinated but were unable to provide documentation of vaccine receipt (one of these cases was immunocompromised) [Table 1]. Rash was present in all waning immunity cases, but was noted to be atypical in 5/11 cases (45%) for whom the rash was described. One waning immunity case was the source for two further cases, both household contacts aged <12 months (too young for routine measles vaccination). A measles genotype was available for 10 waning immunity cases; all three cases from 2014 were identified as genotype B3, and all seven cases from 2015–17 were identified as genotype D8.

Demographics and clinical manifestations. Waning immunity cases were more likely to be male than non-immune and indeterminate cases [Table 2], and less likely to have fever, coryza and cough than non-immune and indeterminate cases. Waning immunity cases were diagnosed closer to rash onset (median 0 days from rash onset to collection of the PCR-positive specimen) than indeterminate and non-immune cases (median 3.5 and 2 days, respectively, p<0.001). There was no statistically significant difference in the proportion of cases in each group that were hospitalised or were a source of onward transmission of measles virus, or in the genotypes of cases in each group.

Laboratory results. Among included cases, the diagnostic sensitivity of measles-specific IgM fell from 93.1% (95%CI: 85.6%–97.4%) between 2008–2013 to 80.6% (95% CI: 71.6%–87.7%) between 2014–2017 (p=0.012), getting as low as 50.0% (95%CI 21.1%–78.9%) in 2017 [Figure 2]. The observed reduction in the diagnostic sensitivity of IgM per year of the study period remained following adjustment for days from rash onset to specimen collection (adjusted odds ratio [aOR] per year 0.76 [95%CI 0.60–0.95], p=0.018). Ct values were available on respiratory specimens for 119/190 included

cases. The mean Ct value for waning immunity cases (32.3) was higher than non-immune cases (25.6) and indeterminate cases (26.3) [Figure 3a], indicating lower virus burden among waning immunity cases. OD values, available for 29 IgG+ cases, were higher among waning immunity cases (IgM-) than indeterminate cases (IgM+) (mean 1.96 vs. 0.71, p=0.004) [Figure 3b]. The differences in Ct value and OD remained following adjustment for days from rash onset to specimen collection [Table 3].

Discussion

Measles among individuals with serological evidence of waning immunity is an emerging issue in Victoria, Australia, with 13 cases identified between 2014–17 and none in the preceding six years. These cases pose a series of challenges, including clinical recognition (cases often present with an attenuated clinical illness), laboratory diagnosis (they have low / absent IgM titres) and public health follow-up (we documented onward measles virus transmission from one waning immunity case). Waning immunity cases will likely represent an increasing proportion of notified measles cases in years to come.

The IgM-/IgG+ serological profile of our 'waning immunity' group is consistent with secondary vaccine failure. In countries such as Australia that have achieved measles elimination, vaccinated individuals are less likely to have natural boosting of their measles antibodies through exposure to circulating wild-type measles, resulting in waning of specific antibodies.(14-16) Secondary vaccine failures have been reported to be more likely to have IgM titres that are absent, low or delayed, along with high IgG titres.(14) Avidity testing – not available in Victoria during this study period – could distinguish between a recent primary infection (low avidity) and secondary vaccine failure (high avidity IgG antibodies).(17, 18)

The waning immunity group had higher Ct values on RT-PCR of respiratory samples, indicating lower virus burden in the respiratory tract, as well as lower rates of upper respiratory tract symptoms (cough and coryza). Similarly, in a recent outbreak in Yamagata, Japan, Ct values were significantly higher among 'modified measles' compared to 'typical measles' cases.(19) This supports historical observations that onward transmission from secondary vaccine failure measles cases are less likely.(20) However, modelling estimates suggest the effective reproduction number (R) for modified measles exceeded the epidemic threshold of one during the early (pre-intervention) phase of an outbreak in Okinawa, Japan, albeit lower than the estimated R for typical measles (ratio typical:modified measles 1.74).(21) Importantly, we documented onward transmission from one

waning immunity case to two unvaccinated infants, which is similar to a recent Californian study in which three of 26 secondary vaccine failure cases with documentation of ≥2 doses of measles vaccine were the source for further measles cases.(10) Similarly, onward transmission was documented from one 'modified measles' case in Yamagata who had received one dose of measles-containing vaccine.(22) This means that the health-care and public-health follow-up of measles cases to identify and manage non-immune contacts must occur for IgG-positive measles cases.

According to Australian public health guidelines, contacts are considered immune to measles if they were born before 1966 (unless available serological results indicate IgG-negative) or have documented evidence of being fully vaccinated against measles (two doses of measles-containing vaccine, at least 4 weeks apart, at age ≥12 months), detectable measles-specific IgG, or laboratory-confirmed prior measles.(12) Our findings challenge the assumption of immunity among those who are fully vaccinated against measles and those with measles-specific IgG. The proportion of contacts who are fully vaccinated and/or IgG-positive and go on to develop measles is presumably low, but not zero. Measles contacts who are fully vaccinated and/or IgG-positive and their health-care providers should be made aware that they could develop measles, and that the clinical presentation could be modified. Similar to others, we reported measles cases with serological evidence of waning immunity often had atypical rash and were less likely to have fever, coryza, and cough. Our finding that those with waning immunity were diagnosed closer to rash onset than the non-immune group was surprising. One possibility is that rash onset (or recognition of an atypical rash) was delayed in the waning immunity group.

Despite Australia's excellent vaccination coverage which has resulted in a reduction the annual incidence of measles from a peak of 2,742/100,000 in 1925 to 0.4/100,000 from 2005–2001 and elimination of endemic measles virus transmission,(4, 24-27) a proportion of Australians remain susceptible to measles. We found males were over-represented in the waning immunity group. Women might be more likely to receive a second (or subsequent) dose of measles-containing vaccine to protect against congenital rubella or because of differences in health-seeking behaviour. Measles transmission modelling based on historical serological data indicates that Australia, along with other high-income countries such as Italy and Singapore, could experience an increase in measles incidence.(27) In Australia, measles seropositivity dropped from 91.9% in 1996–1999 to 80.8% in 2012–2013, with the calculated effective reproduction number (R) exceeding one for the first time in recent history (1.70 in 2012–2013, compared to 0.57–0.90 in from 1996–2007).(16) In the 2012–2013 serosurvey, the lowest seropositive proportion (70.0%) was in the 1992–1998 birth cohort. Consequently, the Victorian Government currently funds measles-containing vaccine for

young adults without documented evidence of two doses of measles-containing vaccine or serological evidence of immunity.(28) Our study demonstrates that measles cases also occur in young adults with detectable measles-specific IgG. In South Korea, there have been calls for a routine third dose of measles-containing vaccine in young health care workers due to a high proportion of vaccinated but potentially measles susceptible young adults.(29, 30) Instituting a third dose of measles-containing vaccine for young adults in Australia (either routine or restricted to high-risk groups such as travellers and health-care workers) might improve seropositivity rates and reduce the measles cases in young adults, including 'waning-immunity' cases. The effectiveness of additional doses of measles vaccine warrants further study as the post-vaccination antibody response among children with waning immunity has been reported to be modest and transient.(31)

Although measles virus vaccine strains are genotype A, they produce cross-protective neutralising antibodies across all measles genotypes.(32, 33) Neutralization titres are lower following vaccination than following natural measles virus infection.(34) It was interesting to note that all 10 of the 'waning immunity' group for whom measles genotype was available were either B3 or D8. Genotype B3 was responsible for an outbreak among vaccinated healthcare workers in the Netherlands in 2014, in which an index case with the Tonbridge strain B3 measles virus transmitted to one vaccinated healthcare worker, while an index case with Tonbridge C339T variant resulted in six HCW cases (five vaccinated HCWs).(35) Genotype D8 has also been noted to cause illness among vaccinated individuals in Indonesia (with sequencing revealing the strains to be 99% similar to other D8 strains circulating in the region at the time) and in the US.(20, 36) Although we did not detect a statistical difference between occurrence of the B3 and D8 genotypes between groups, and B3 and D8 genotypes were among the dominant circulating genotypes during our study period,(37) it does raise the question of whether mutations in the infecting measles virus contributed to secondary vaccine failure in these groups. Some groups have advocated epitope monitoring be included in measles surveillance,(38) although to date this has not been routine in Victoria.

One limitation of this study was the inability to accurately classify those who were IgM+/IgG+ at diagnosis, who we labelled as 'indeterminate'. Our analysis indicates this group is more similar to the 'non-immune' group than the 'waning immunity' group. More time had elapsed between rash onset and diagnosis in this indeterminate group, giving time for both IgM and IgG antibodies to develop, and they had lower OD values and lower Ct values than the 'waning immunity' group (both adjusted for time between rash onset and specimen collection). It is possible, however, that a small number of these individuals represented secondary vaccine failures and belong in the 'waning immunity' group, as small amounts of IgM may be produced during a secondary immune response.(17) It is

expected that avidity testing will become available in Victoria in coming years, and this will assist in assessment of secondary vaccine failures. Serological testing was undertaken at a number of different laboratories using different tests, which could have resulted in inconsistent classification of a small number of cases. Another limitation was the lack of well-documented vaccination history among many measles cases. It is hoped that with the recent expansion of the Australian Immunisation Register (AIR) from a childhood-only to whole-of-life immunisation register, vaccine coverage data across the entire population will gradually improve.(39) Record linkage between AIR and case notification data in Victoria would also facilitate assessment of measles vaccine failures. A further limitation was missing data among included cases, encompassing clinical data (e.g. date of rash onset and rash characteristics) and laboratory results (e.g. OD and Ct values, genotypes). The sample size was small, which could limit our power to detect significant differences between the groups. Finally, approximately one-third of all measles cases notified during the study period were excluded, mostly due to lack of serological testing at diagnosis, and we therefore could have missed some 'waning immunity' cases. This highlights the importance of performing both serological and PCR testing on suspected measles cases, where possible. Excluded cases were younger and less likely to be hospitalised, which could account for the lack of serological testing as less invasive specimens such as throat swab and urine can be used for PCR testing. The potential impact of this selection bias on our findings is likely to be minimal, as neither age nor hospitalisation differed significantly between groups for our included cases [see Supplement].

The occurrence of measles among people with serological evidence of waning immunity is increasing in Victoria. Despite modified clinical illness and lower respiratory virus burden, onward transmission was documented from one case, highlighting the need for public health follow-up of contacts. Use of both PCR and serology to diagnose measles among people who have been vaccinated and/or are IgG-positive will overcome issues with reduced sensitivity of measles-specific IgM in this group.(14, 40)

Secondary vaccine failures are likely to represent an increasing proportion of all measles cases in Australia, a country with high vaccination coverage and which achieved and has maintained measles elimination since 2014. It will be important to monitor this epidemiological trend and determine if further changes to public health, clinical, and laboratory practice are required, such as inclusion of additional measles-containing vaccines in the National Immunisation Program for some or all of the young adult population.

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Figure Legend

Figure 1: Number and classification of included measles cases by year, Victoria 2008–2017

Figure 2: Diagnostic sensitivity of measles-specific IgM at time of initial positive PCR, Victoria 2008–2017

*bars represent 95% confidence intervals

Figure 3: Measles virus cycle threshold (Ct*) and IgG titres by group, Victoria 2008–2017

3a) Measles virus cycle threshold (Ct) values from RT-PCR of respiratory specimens

3b) Measles-specific IgG titres (optical density [OD] values) for cases with IgG detected at diagnosis

Table 1: Waning immunity measles cases (PCR+, IgM-, IgG+), Victoria 2008–2017

Case Number	Year of diagnosis	Age (years), sex	Country of birth	Country of acquisition	Hospitalised	Fever	Rash	Rash atypical?	Conjunctivitis	Coryza	Cough	Koplik spots	Onward transmission	Vaccination history (year/s of vaccination)	Genotype	Ct (respiratory specimen)	IgG OD titre	Rash onset to diagnosis, days
1	2014	14M	Philippines	Philippines	N	Y	Y	N	N	Y	Y	N	N	x1 (2000)	B3	35	--	0
2	2014	30M	Uzbekistan	Philippines	Y	Y	Y	N	Y	Y	Y	Y	N	--	B3	24	--	0
3	2014	42M	UK	Philippines	Y	Y	Y	--	N	N	N	N	N	--	B3	29	0.88	0
4	2015	26M	Australia	Australia	N	Y	Y	Y	N	N	N	N	N	Vaccinated (SR)	D8	33	--	-4
5	2015	30M	Australia	Australia	N	Y	Y	Y	Y	Y	N	N	N	x1 (1985)	--	31	3.63	0
6	2015	31M	--	Australia	N	Y	Y	--	Y	Y	Y	N	Y (x2)	--	D8	--	2.03	0
7	2016	20M	Indonesia	Indonesia	N	N	Y	Y	N	N	N	N	N	--	D8	--	1.76	2
8	2016	33M	Poland	Australia	Y	N	Y	N	N	N	Y	N	N	Vaccinated (SR)	--	27	2.18	1
9	2016	40M	Australia	Australia	N	Y	Y	N	N	N	N	N	N	X2 (1976, 1983)	D8	40	--	1
10	2017	27F	Australia	Indonesia	N	N	Y	Y	Y	N	Y	N	N	x1 (1992)	--	40	--	2
11	2017	30M	Australia	Australia	N	Y	Y	N	N	N	Y	N	N	Vaccinated (SR), immunocompromised	D8	27	0.11	0
12	2017	34M	Australia	Australia	Y	N	Y	N	N	N	Y	N	N	--	D8	--	--	1
13	2017	59F	South Korea	South Korea	Y	N	Y	N	Y	N	N	N	N	Vaccinated (SR)	D8	37	3.24	0

M – male; F – female; Y – yes; N- no; -- data not available; SR – self reported vaccination status, without documentation of date of measles vaccine

Table 2: Demographic and clinical features of measles cases by serology status at diagnosis, Victoria 2008–2017

	Waning immunity IgM- / IgG+ (N=13)		Indeterminate IgM+ / IgG+ (N=26)		Non-immune IgM- (N=151)		
Demographics and vaccination	n/N	(%)	n/N	(%)	n/N	(%)	p-value*
Age in years: Median (interquartile range [IQR])	30	(27–34)	22	(13–32)	26	(17–35)	0.142
Australian-born	6/12	(50.0)	19/26	(73.1)	95/148	(64.2)	0.388
Male	11/13	(84.6)	11/26	(42.3)	89/151	(58.9)	0.039
Clinical features							
Hospitalised	5/13	(38.5)	12/26	(46.2)	73/135	(54.1)	0.464
Rash present	13/13	(100)	26/26	(100)	149/149	(100)	1.000
Fever	8/13	(61.5)	25/26	(96.2)	134/148	(90.5)	0.008
Conjunctivitis	5/13	(38.5)	14/26	(53.9)	94/148	(63.5)	0.157
Coryza	4/13	(30.8)	21/26	(80.8)	108/148	(73.0)	0.005
Cough	7/13	(53.9)	22/26	(84.6)	135/148	(91.2)	0.001
Koplik spots	1/13	(7.7)	1/26	(3.9)	26/148	(16.9)	0.224
Days from rash onset to diagnosis: Median (IQR)	0	(0–1)	3.5	(2–6)	2	(1–3)	<0.001
Source for onward transmission of measles virus	1/13	(7.7)	9/26	(34.6)	39/151	(25.8)	0.190

* p-values refer to chi-square and Fisher's exact tests (categorical variables) and Kruskal Wallis tests (continuous variables)

Table 3: Measles virus cycle threshold (Ct) values [which have an inverse relationship to virus burden] and measles IgG optical density (OD) values by serology status at diagnosis, Victoria 2008–2017

Specimen type	Pre-existing immunity		N	Ct value		Univariate analysis			Multivariable analysis*		
				Mean (sd)		Co-efficient [95% CI]		p-value	Co-efficient [95% CI]		p-value
Respiratory	Non-immune	IgG-	95	25.6	(4.1)	Ref			Ref		
	Indeterminate	IgM+/IgG+	14	26.3	(5.6)	0.75	[-1.77–3.27]	0.557	-0.07	[-2.59–2.45]	0.955
	Waning immunity	IgM-/IgG+	10	32.3	(5.6)	6.76	[3.83–9.69]	<0.001	7.73	[4.78–10.68]	<0.001
Blood	Non-immune	IgG-	37	35.2	(3.7)						
	Indeterminate	IgM+/IgG+	5	38.4	(1.5)						
	Waning immunity	IgM-/IgG+	1	39	--						
Urine	Non-immune	IgG-	12	30.1	(5.3)						
	Indeterminate	IgM+/IgG+	4	33.0	(5.6)						
	Waning immunity	IgM-/IgG+	0	--	--						
Specimen type	Pre-existing immunity		N	OD value		Univariate analysis			Multivariable analysis*		
				Mean (sd)		Co-efficient [95% CI]			Co-efficient [95% CI]		p-value
Serum	Indeterminate	IgM+/IgG+	22	0.71	(0.82)	Ref			Ref		
	Waning immunity	IgM-/IgG+	7	1.96	(1.22)	1.25	[0.43–2.07]	0.004	1.27	[0.36–2.18]	0.008

sd – standard deviation; -- data not available; Ref – reference category

* Linear regression models adjusted for days from rash onset to specimen collection
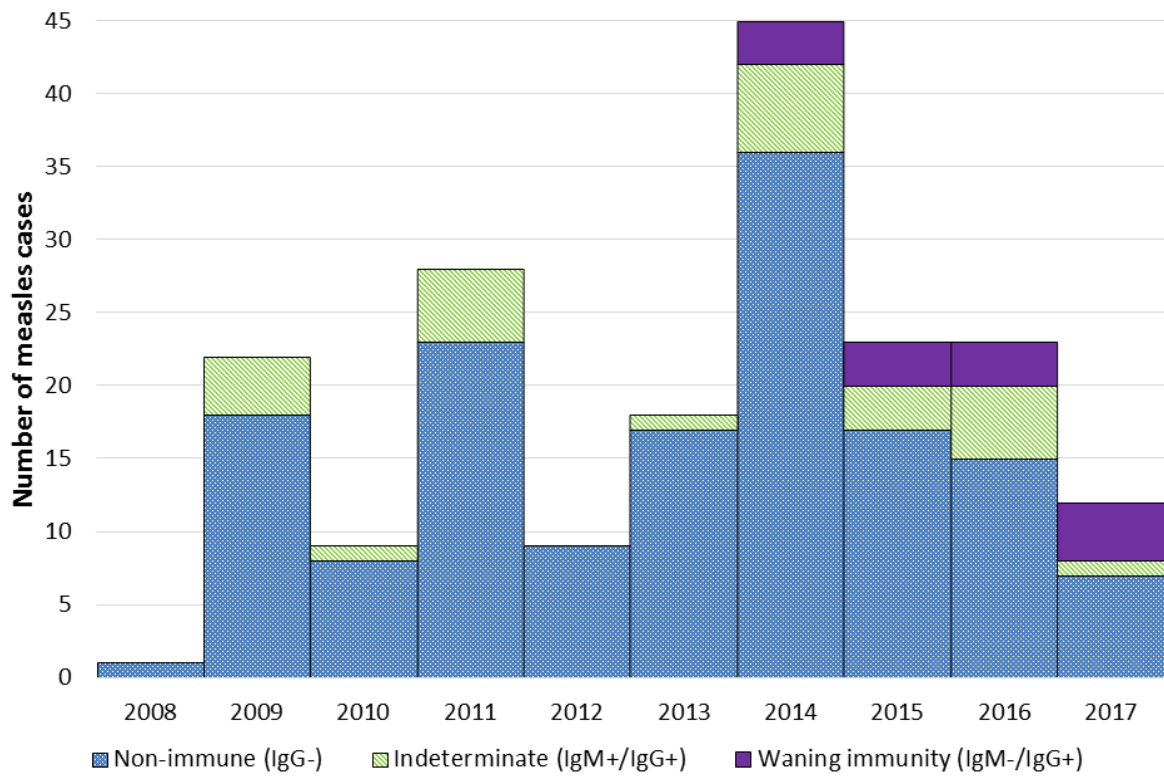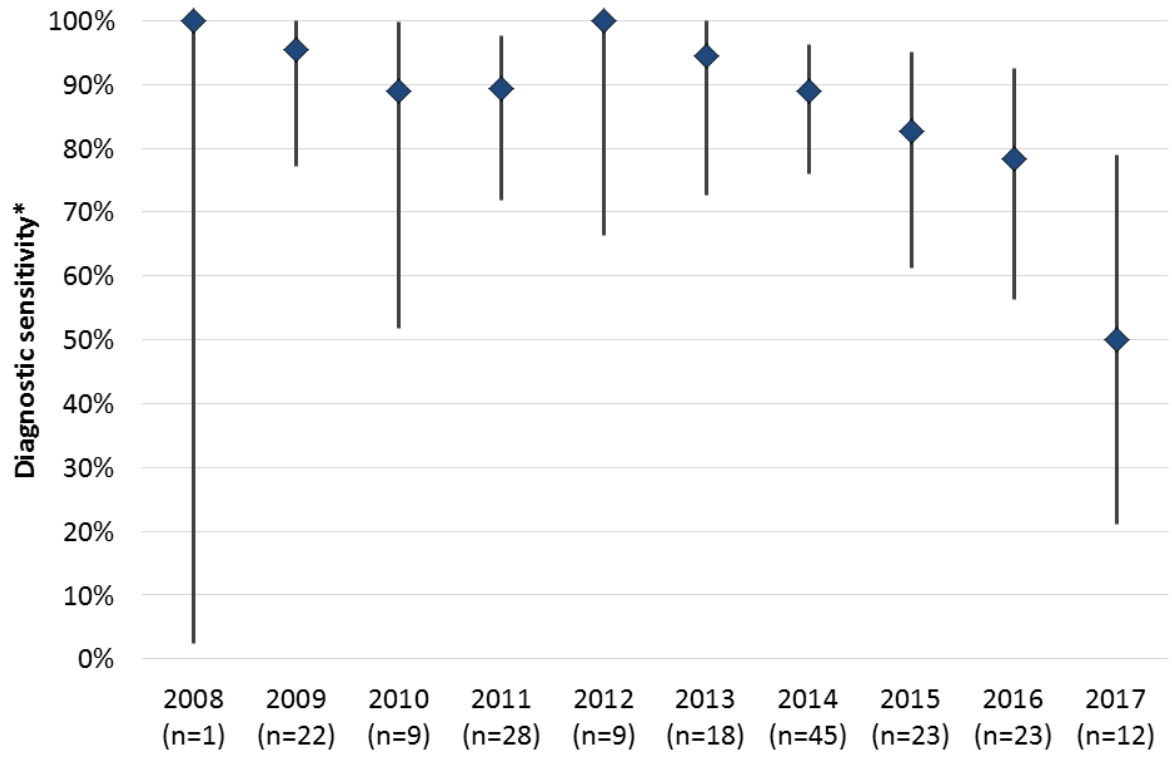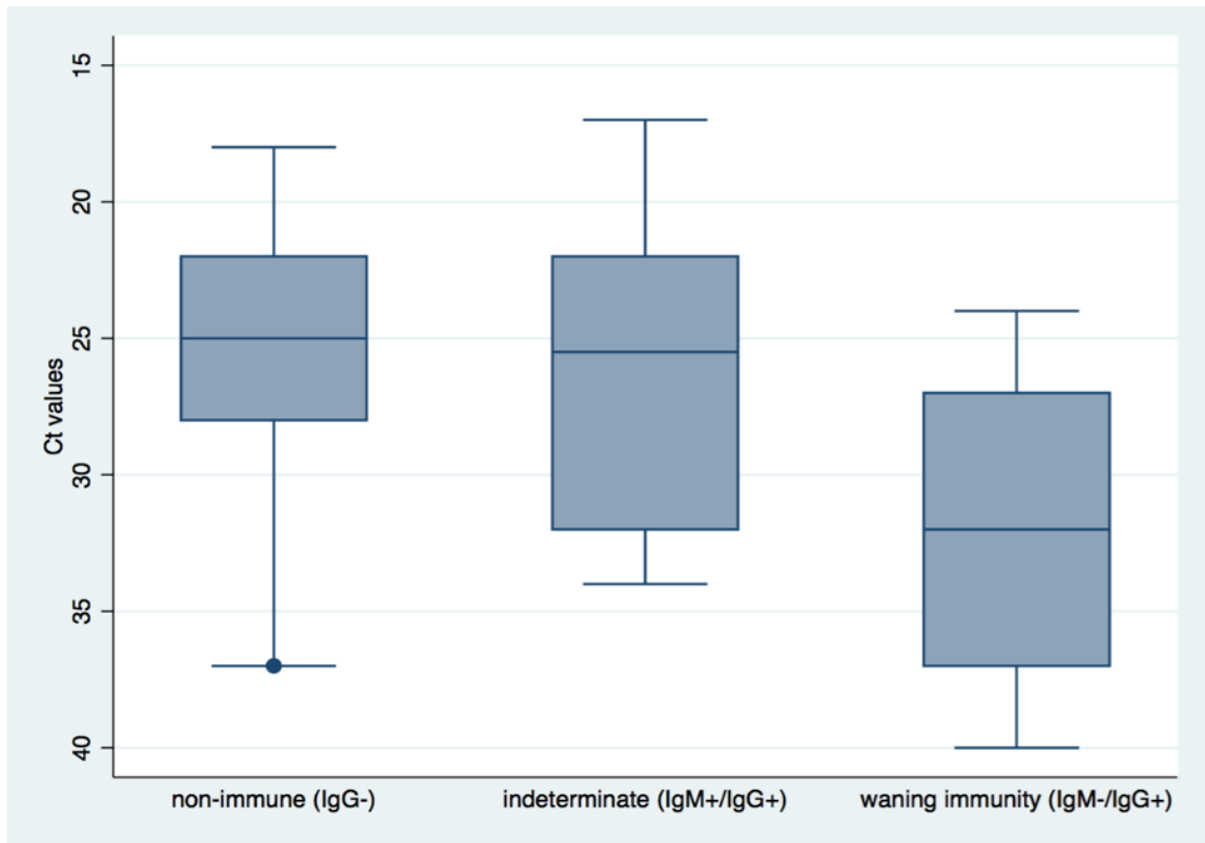
Figure 1

Figure 2

Figure 3a

Figure 3b