Mumps and rubella: a year of enhanced surveillance and laboratory testing

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SUMMARY

In Victoria (Australia) surveillance for mumps and rubella has historically been passive, with most notified cases clinically diagnosed. In July 2001, the Victorian Department of Human Services implemented an enhanced surveillance system focusing on improved laboratory testing. We tested 85% of notifications and only 9% of all mumps and 27% of rubella notifications were laboratory confirmed. While most notified cases were children who had been clinically diagnosed, we found most laboratory-confirmed cases were in adults. The positive predictive value of the clinical case definition was low: mumps (10%); rubella (22%). These results highlight the value of laboratory confirmation of the diagnosis when mumps and rubella are rare, failure to do so is likely to overestimate disease incidence.

INTRODUCTION

Mumps and rubella, once common childhood diseases, have been markedly reduced due to the widespread use of safe and effective vaccines. In Australia, monovalent vaccines have been available since 1969 for rubella and 1980 for mumps [1]. Trivalent measles, mumps and rubella (MMR) vaccine became available in 1989, and two doses have been recommended in the Australian Standard Vaccination Schedule for males and females since 1994 [1]. Subsequently, reported cases of mumps and rubella have declined from an estimated 59 000 and 43 000 cases in 1969 [2] to 212 and 312 in 2000 [3] respectively.

Despite improving MMR vaccination coverage in Victorian children aged 2 years (78% in 1994/1995 [4] and 92% in 2000 [5]), a review of mumps and rubella epidemiology in Victoria, between 1993 and 2000, showed notifications persisted for children who should have been protected by MMR vaccine [6]. During this time, surveillance of both diseases was passive and the majority of notifications were based only on a clinical diagnosis.

Enhanced surveillance programmes for vaccine-preventable diseases have demonstrated that the positive predictive value (PPV) of clinical diagnosis decreases when the disease incidence is low [7–9]. Enhanced mumps surveillance in Texas [9] and the United Kingdom [10] showed that, despite a large proportion of notified cases being laboratory tested, only 3 and 7% respectively were laboratory confirmed. Enhanced rubella surveillance in England and

Wales in 1994 demonstrated that only 29% of cases tested were laboratory confirmed [11].

The Victorian Department of Human Services (Australia) implemented an enhanced surveillance system for mumps and rubella cases in July 2001. The programme focused on confirming the diagnosis for all mumps and rubella notifications. Here, we report the results from the first 12 months of this programme. Specifically, we focus on age-specific numbers of notifications and vaccination history by case status. We also evaluate the National Health and Medical Research Council's (NHMRC) surveillance clinical case definitions for mumps and rubella [12].

METHODS

The programme of enhanced surveillance for mumps and rubella was introduced in Victoria at the beginning of July 2001. The programme consisted of follow-up interviews with the notifying clinicians and the case, or if the patient was a child, with the parent or guardian. Demographic data, clinical symptoms and mumps or rubella vaccination history were obtained.

The case or the parent/guardian was asked to retrieve the vaccination history from personal health or vaccination records where available. When available, we retrieved MMR vaccination histories from the Australian Childhood Immunisation Register (ACIR) [13, 14]. The ACIR commenced operation in January 1996 and records details of vaccinations given to Australian children less than 7 years of age. The vaccination history was classified as coming from a validated (specified date of vaccination from health or vaccination record, ACIR) or non-validated source (parental recall only).

We attempted to identify possible sources of infection. A cluster was defined as two or more epidemiologically linked cases. A sporadic case was defined as a single case that could not be linked to another case. We classified cases as imported if the source of exposure occurred outside Australia, otherwise cases were classified as locally acquired.

A serum specimen was sought from each notified case for confirmation of the clinical diagnosis. Where no previous laboratory test had been performed, we offered the services of a paediatric phlebotomist who conducted home visits to collect specimens at no cost to the patient.

Sera were tested for mumps virus or rubella virus IgM and IgG at the Victorian Infectious Diseases Reference Laboratory (VIDRL) using commercial enzyme immunoassays (See Table 1). If the original test was performed at another laboratory, we requested remaining sera from mumps virus or rubella virus IgM-positive specimens be forwarded to VIDRL for reference laboratory testing.

For mumps notifications, rubella virus IgG and measles virus IgG testing were performed as markers of previous MMR vaccination, and Epstein–Barr virus (EBV) IgM and IgG testing were performed for differential diagnosis (See Table 1). For rubella notifications, measles virus and parvovirus IgM and IgG testing were performed for differential diagnosis (See Table 1). Confirmatory and differential diagnosis tests were performed at VIDRL.

Depending on the serology result, vaccination history, and whether the case fitted the NHMRC's surveillance clinical case definitions for mumps and rubella, each case was classified as confirmed mumps or rubella or otherwise according to the criteria in Table 2. The criteria were framed around those used for enhanced measles surveillance in Victoria [15]. The NHMRC's surveillance clinical case definitions were evaluated using cases where both clinical information and laboratory test results were available.

Data were collated and analysed using Epi-Info version 6.04d and Excel (Microsoft Corporation).

RESULTS

In the first 12 months of enhanced surveillance, serum was collected from 63 out of 74 (85%) mumps notifications and 100 out of 118 (85%) rubella notifications. For mumps, only 7/74 (9%) notifications were classified as laboratory confirmed (Fig. 1). For rubella, 32/118 (27%) notifications were classified as laboratory confirmed (Fig. 2). See Table 2 for the classification of the remaining mumps and rubella notifications. Table 3 shows serological results by age group. Approximately one third of all mumps notifications and one half of all rubella notifications were from children under 5 years of age. Serum collection rates were similar across age groups for both mumps and rubella, ranging from 75 to 96% for mumps and 67 to 100% for rubella.

For both diseases, there was a general trend of increasing laboratory confirmation with increasing age and there was a statistically significant difference between laboratory-confirmation rates for those aged 20 years and above compared to those aged less than 20 years (mumps, $P < 0.001$; rubella, $P < 0.001$).

Table 1. *Test, method, sensitivity and specificity of laboratory kits used by VIDRL for enhanced mumps and rubella surveillance*

Test	Method	Manufacturer (country)	Manufacturer quoted	
			Sensitivity (%)	Specificity (%)
Mumps virus IgM	EI	Dade Behring's, Enzygnost (Marburg, Germany)	95	99·8
Mumps virus IgG	EI	Dade Behring's, Enzygnost (Marburg, Germany)	95·4	93·7
Rubella virus IgM	EI	Beckman Coulter – ACCESS (Fullerton, USA)	100	100
Rubella virus IgG	EI	Beckman Coulter – ACCESS (Fullerton, USA)	98	99
Human parvovirus IgM	EI	Biotrin parvovirus B19 (Dublin, Ireland)	86	95
Human parvovirus IgG	EI	Biotrin parvovirus B19 (Dublin, Ireland)	100	100
EBV IgM	EI	DiaSorin (Saluggia, Italy)	96	98
EBV nuclear antigen	EI	DiaSorin (Saluggia, Italy)	98	98·9
EBV IgG	EI	DiaSorin (Saluggia, Italy)	96·7	99·4

EBV, Epstein–Barr virus.
EI, Enzyme immunoassay.

Fig. 1. Mumps notifications by type, Victoria, July 2001 to June 2002. □, Clinical; ▨, laboratory rejected; ■, laboratory confirmed.
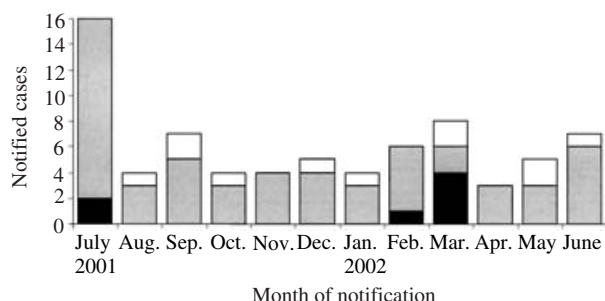

Fig. 2. Rubella notifications by type, Victoria, July 2001 to June 2002. □, Clinical; ▨, laboratory rejected; ■, laboratory confirmed.

Confirmed cases

Mumps

The seven laboratory-confirmed cases included four males and three females. Two cases were aged 21 and 22 years, with the other five cases aged between 50 and 55 years. The median age of confirmed mumps cases was 51 years. Of these seven cases: four reported not being previously immunized with a mumps virus-containing vaccine and the vaccination status was reported as being unknown for the three other cases. No epidemiological links between cases could be identified, and none of the cases acquired their infection from overseas.
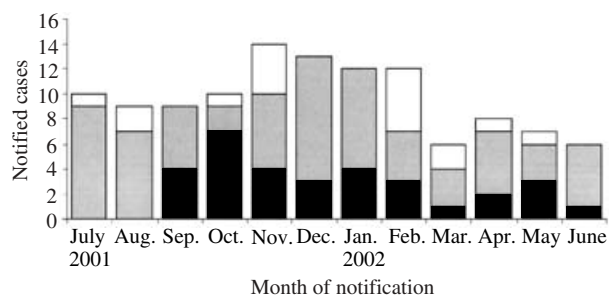
There were two other cases who tested positive for mumps virus IgM virus, but had received a mumps virus-containing vaccine less than 45 days prior to specimen collection date and were therefore classified as laboratory rejected.

Rubella

There were 32 laboratory-confirmed cases consisting of 28 males and 4 females, median age 22 years (range: 2–42 years). Twenty-three cases (72%) were males born between 1969 and 1981. Of the 32 cases, one case (3%) reported having two doses of rubella virus-containing vaccine, 23 (72%) had not been previously vaccinated and vaccination status was reported as

Table 2. *Classification of notified mumps and rubella cases by the enhanced surveillance programme*

Classification	Mumps	Rubella
(1) Laboratory confirmed	• Serum is positive for mumps virus IgM and the patient has not received a dose of MMR within 45 days of specimen collection, **or** • Detection of mumps virus from a clinical specimen by culture or nucleic acid test, **or** • IgG seroconversion or rise in antibody level or titre to mumps virus	• Serum is positive for rubella virus IgM and the patient has not received a dose of MMR within 45 days of specimen collection [32, 33], **or** • Detection of rubella virus from a clinical specimen by culture or nucleic acid test, **or** • IgG seroconversion or rise in antibody level or titre to rubella virus
(2) Laboratory rejected	• Serum is negative for mumps virus Igm with sample collected at least 7 days after parotid or salivary gland swelling [18], **or** • Serum is negative for mumps virus IgM but positive for mumps virus IgG, **or** • Serum is positive for a parotitis-causing pathogen (e.g. Epstein–Barr virus	• Serum is negative for rubella virus IgM with sample collected at least 5 days after rash onset [19, 20, 34, 35], **or** • Serum is negative for rubella virus IgM but positive for rubella virus IgG, **or** • Serum is positive for other rash-causing pathogen (e.g. human parvovirus, measles)
(3) Epidemiologically linked to a laboratory-confirmed case	Neither (1) nor (2) above **and** an epidemiological link to a laboratory-confirmed case has been established	
(4) Clinically compatible	Neither (1), (2) nor (3) **and** the case satisfies the NHMRC's surveillance clinical case definition for mumps [12]: 'A clinically compatible illness (swelling of the parotid or other salivary glands lasting two days or more without other apparent cause)'	Neither (1), (2) nor (3) **and** the case satisfies the NHMRC's surveillance clinical case definition for rubella [12]: 'A generalized maculopapular rash and fever and one or more of – Arthralgia/arthritis **or** – Lymphadenopathy **or** – Conjunctivitis'
(5) Not clinically compatible	Neither (1), (2), (3) nor (4) **and** the case does not satisfy the NHMRC surveillance clinical case definition for mumps or rubella	
(6) Not classifiable	There are insufficient data available to allow classification in either category (1), (2), (3), (4) or (5)	

unknown for the remaining eight cases (25%). One case of rubella was imported from Ethiopia.

Two clusters of rubella, involving five patients, were identified. The first cluster occurred in August 2001 and involved two male adult flatmates. Neither reported previous rubella vaccination. The timing of the onset dates in these two cases suggested transmission of infection from one flatmate to the other, but the original source of infection for the first flatmate was not able to be identified. The second cluster occurred in October 2001 and involved three adult males from the same workplace, all with similar onset dates. None reported previous rubella vaccination, and a source of infection was not found.

Serum samples from three cases tested positive for rubella virus IgM but had received a rubella virus-containing vaccine less than 45 days prior to specimen collection date and were therefore classified as laboratory rejected.

Non-cases (laboratory rejected)

Mumps

Fifty-five cases were rejected as mumps based on laboratory evidence. We tested 43 of these for EBV and seven (16%) were found to be positive. Of the laboratory-rejected cases; 18/55 (33%) were aged 1–4 years, 20/55 (36%) were aged 5–19 years and 17/55 (31%) were aged 20 years and older. In those aged less than 20 years, 34/38 (89%) of the laboratory-rejected cases had received at least one dose of mumps virus-containing vaccine; whereas of those aged 20 years and older, 7/17 (41%) were unvaccinated and for 9/17 (53%) vaccination status was reported as unknown.

Table 3. *Serological results by age group for notified cases of mumps and rubella, Victoria, July 2001 to June 2002*

Age (years)	Mumps						Rubella					
	Notified		Serologically tested		Laboratory-confirmed		Notified		Serologically tested		Laboratory-confirmed	
	n	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
<1	1	1	0	0	0	0	29	25	21	72	0	0
1–4	20	27	18	90	0	0	30	25	28	93	2	7
5–19	28	38	21	75	0	0	24	20	16	67	1	6
20+	25	34	24	96	7	29	35	30	35	100	29	83
Total	74	100	63	85	7	11	118	100	100	85	32	32

Rubella

Sixty-seven cases were laboratory-rejected as rubella, 62 were tested for parvovirus B19 IgM and 10 (16%) were found to be positive. Of the laboratory-rejected cases, 45/67 (67%) were aged under 5 years, 16/67 (24%) were aged 5–19 years and 6/67 (9%) were aged 20 years and above. In those aged less than 20 years, 32/41 (78%) of the laboratory-rejected cases had received at least one dose of rubella virus-containing vaccine (those under 1 year old were excluded as they were ineligible for the first dose of vaccine). Only 1/6 (17%) of those aged 20 years and older had received at least one dose of rubella virus-containing vaccine.

Confirmation of vaccination history

Mumps

Of 32 cases who had received at least one dose of mumps virus-containing vaccine, sera from 31 cases (96%) had mumps virus IgG detected and 100% had rubella virus and measles virus IgG detected (markers of previous MMR vaccination).

Eight cases reported being unvaccinated but six (75%) of these had mumps virus IgG detected. All six were aged 20 years and above, and born prior to the introduction of the mumps vaccine, indicating IgG was likely to be due to past exposure to wild virus.

Of those who were laboratory tested and for whom vaccination history was obtained from a validated source; 25/26 (96%) had mumps virus IgG detected. Of those from a non-validated source: 6/6 (100%) had mumps virus IgG detected.

Rubella

Thirty-five cases had received at least one dose of rubella virus-containing vaccine and all cases had rubella virus IgG detected. Six cases reported being unvaccinated and, when tested, only 1/6 (17%) had rubella virus IgG detected. All cases that were laboratory tested and reported being vaccinated (validated and non-validated sources) had rubella virus IgG detected.

Reference laboratory testing

Mumps

Of the seven mumps cases, five were initially confirmed by VIDRL. Two cases were originally positive for mumps virus IgM at other laboratories, but had insufficient serum for re-testing.

Rubella

Of the 32 rubella cases, 21 were initially confirmed by VIDRL and 11 were positive for rubella virus IgM at other laboratories but had insufficient serum for re-testing. There were two cases (subsequently reclassified as laboratory rejected) who tested positive for rubella virus IgM at a diagnostic laboratory but negative at VIDRL. Both cases tested positive for parvovirus B19 IgM at VIDRL.

Evaluation of NHMRC surveillance clinical case definition

Mumps

Of the 74 mumps notifications, 63 (85%) with both clinical information and laboratory results were used to evaluate the NHMRC surveillance clinical case definition. Sensitivity of the NHMRC surveillance clinical case definition was 86% and specificity 5%, while positive predictive value and negative predictive value were 10 and 75% respectively.

Rubella

Clinical information and laboratory results were available for 99 out of 118 (84%) rubella cases and were used to evaluate the NHMRC surveillance clinical case definition. Sensitivity of the clinical case definition was only 34%, specificity 42%, positive predictive value was 22% and negative predictive value 57%.

DISCUSSION

Our results demonstrate that when the incidence of mumps and rubella infections are low, as they currently are in Victoria, a clinical diagnosis of mumps or rubella that meets the NHMRC's surveillance case definition has a low positive predictive value; 10% for mumps and 22% for rubella. We were able to test 85% of mumps and rubella notifications, with only 9% of all mumps and 27% of all rubella notifications being laboratory confirmed. The majority of laboratory-confirmed cases were adults (not vaccinated or vaccination status unknown) and most laboratory-rejected cases were vaccinated children.

When disease incidence is low, parotitis – a classic feature of mumps – and a non-specific rash illness – similar to that caused by rubella – may often be due to other causes. Other viral infections that produce parotitis similar to that induced by mumps include EBV, parainfluenza, coxsackie, and influenza A viruses [16–18]; highlighted by 16% of our laboratory-rejected mumps cases being caused by EBV. Clinically similar illnesses to rubella may be caused by parvovirus, adenovirus, enterovirus and measles [19, 20], which was highlighted by 15% of laboratory-rejected rubella cases being caused by parvovirus B19. No cause of illness was found for the remaining laboratory-rejected cases.

Failure to conduct case investigations may lead to inaccurate conclusions if surveillance data are used to identify which age groups are at risk for specific vaccine-preventable diseases. In Victoria, between 1993 and 2000, the highest notification rates for mumps were in children aged 1–4 and 5–9 years; from 1998 to 2000 the highest notification rates for rubella were in children aged less than 5 years, and notifications in children were mainly clinically diagnosed [6]. Our results highlight that while the majority of suspected cases were among vaccinated children, once laboratory testing was undertaken these cases were rejected. This finding suggests that between 1993 and 2000 surveillance data for mumps and rubella, based largely on passive clinical notifications in younger age groups, were inaccurate, resulting in an overestimation of disease incidence.

We have demonstrated that confirmed cases were more likely to be adults – most unvaccinated or with vaccination status unknown. The median age of confirmed mumps cases was 51 years, and confirmed rubella cases were predominantly males (88%) and the median age was 22 years. The rubella susceptibility in young adult males can be attributed to not receiving a rubella virus-containing vaccine due to the targeted nature of the adolescent schoolgirl programme between 1971 and 1993 [21, 22] and lack of exposure or waning immunity to circulating wild virus. Similarly, the mumps susceptibility can be attributed to being born prior to the introduction of mumps vaccine in 1980 and either not having been exposed to the virus or immunity to wild virus infection has waned [23, 24]. Following measles outbreaks in this young adult age-group [25], the Commonwealth Government of Australia provided AUD$20 million for a MMR vaccination programme for young adults between 18 and 30 years of age in August 2001 [26]. No formal evaluation of the success of this programme has been published, however it is likely that poor penetration means rubella outbreaks will continue to occur in adult males currently aged in their 20s [21].

Our results suggest that nearly all cases of mumps and rubella within Victoria acquired their infection locally and for most a source of infection could not be identified. There were no clusters recognized for mumps and only two small clusters identified for rubella. The primary focus of this project was to confirm the diagnosis; however, laboratory-confirmed cases were unable to identify routinely a source of their infection. The asymptomatic nature of most rubella infections [27] may have precluded recognition of cases of rubella infection in contacts. Rubella has been identified as the next viral disease candidate for global eradication (after polio and measles) [28]. When Australia moves into a rubella elimination phase, attempting to identify a source of infection and chains of transmission will become more important. Molecular typing can then be utilized to document the rubella virus strains [29]. This has already been established as an important epidemiological tool in enhanced measles surveillance [30].

We recommend consideration be given to the use of laboratory testing for notified cases using the guidelines described in Table 2. These guidelines include

criteria for the timing and interpretation of testing to ensure results are accurate. Not all IgM antibody assays have a specificity of 100 %. This was highlighted by two cases of alleged rubella that tested positive to rubella virus IgM in non-reference laboratories, but were negative for rubella virus IgM at the reference laboratory and subsequently tested positive for parvovirus IgM. False-positive rubella virus IgM tests may occur among persons with certain viral infections (EBV, cytomegalovirus, or parvovirus B19) and among persons who are rheumatoid factor positive or pregnant [19, 20, 31]. This reiterates the importance of maintaining reference laboratory support for surveillance programmes.

The findings from enhanced mumps and rubella surveillance have demonstrated that due to widespread two-dose MMR coverage in Victoria, mumps and rubella virus circulation has dramatically declined, to a level below that suggested by passive surveillance. When mumps and rubella are rare, laboratory confirmation is recommended to ensure surveillance data-sets are accurate, do not overestimate disease incidence, and reflect the true age-specific incidence of disease. Accurate data are necessary to target vaccination interventions effectively and are critical to document progress towards eliminating indigenous mumps and rubella in Australia.

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