Australian vaccine preventable disease epidemiological review series: rubella 2008–2012

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Abstract

Introduction: Since the introduction of universal rubella vaccination in 1989, the incidence of rubella and congenital rubella syndrome (CRS) in Australia has declined significantly. Worldwide, there has been a focus on elimination, with the region of the Americas declaring rubella elimination in 2011. This study aims to review Australian rubella epidemiology for the 2008–2012 period, in the context of historical and international trends.

Methods: Notification, hospitalisation and mortality data were sourced from the National Notifiable Diseases Surveillance System, the National Hospital Morbidity Database and the Australian Bureau of Statistics (ABS). Data analysis focused on 2008–2012 for notifications and 2008–2011 for hospitalisations and deaths. ABS population data were used to calculate rates.

Results: The average annual rubella notification rate in Australia from 2008–2012 was 0.18 per 100,000 and the average annual hospitalisation rate was 0.03 per 100,000 from 2008–2011. One case of CRS was notified in 2012 and 1 hospitalisation with a principal diagnosis of CRS was recorded in 2008. The median age of rubella notifications was 29 years and 37% of notifications were for infections acquired overseas.

Discussion: Rubella continues to be well controlled in Australia and CRS is rare. The low incidence and increasing proportion of imported cases and other evidence suggest that elimination has been achieved; however, for formal verification of rubella elimination the expansion of genotypic surveillance will be required. Ongoing rubella control needs to focus on improved surveillance, maintenance of high levels of vaccine coverage, vaccination of at-risk populations in Australia, and regional and global efforts towards rubella elimination. *Commun Dis Intell* 2015;39(1):E19–E26.

Keywords: epidemiology; rubella; vaccine preventable diseases

Introduction

Rubella is a vaccine preventable, usually mild infection. However, infection during pregnancy is associated with a range of congenital abnormalities known as congenital rubella syndrome (CRS). The principal aim of vaccination campaigns worldwide is to prevent CRS, which remains a common cause of fetal abnormalities in rubella endemic regions.[1]

Rubella is caused by rubella virus, which is a member of the Togaviridae family, genus *Rubivirus.* Rubella is transmitted by contact with nasopharyngeal secretions, either through droplet or direct contact. The incubation period ranges from 12 to 23 days.[2,3] Rubella usually manifests as a mild non-specific febrile illness characterised by a non-confluent maculopapular rash, lymphadenopathy, headache, sore throat, cough and conjunctivitis. Arthralgia and arthritis are the most common complications. More serious complications, including encephalopathy and haemorrhage, occur rarely. Up to 50% of infections are asymptomatic. Infection during the first trimester of pregnancy is associated with spontaneous abortion or CRS in 85% of cases. Congenital abnormalities associated with CRS include cataracts, heart defects, sensorineural deafness, low birth weight and neurological defects.[3,4]

Rubella vaccines have been licensed in Australia since 1969, initially as a monovalent vaccine containing attenuated rubella virus, given to schoolgirls aged 10–14 years and susceptible women prior to pregnancy. From 1989, the measles-mumps-rubella (MMR) vaccine was introduced to the National Immunisation Program (NIP) schedule for all infants. From 1993, a 2nd dose of MMR vaccine was added to the NIP schedule for both boys and girls at 10–14 years of age, with a school-based catch-up program for this age group from 1993 to 1998.[5] The 2nd dose of MMR was moved to 4–5 years of age in 1998 and then replaced in 2013 with a dose of measles-mumps-rubella-varicella (MMRV) vaccine given at 18 months of age (Table 1 for full details of funded rubella vaccination programs in Australia).[6] Protection against rubella is long-term.[7]

The epidemiology of rubella in Australia changed following the introduction of universal rubella vaccination. There was a marked decline in the average annual notification rate from 14.8 per 100,000 population between 1993 and 1998 to 0.23 per 100,000 between 2005 and 2007. This was

Table 1: Nationally funded rubella vaccination programs in Australia[5]

Year	Program	Target age
1971–1993	Selective vaccination of schoolgirls	12–14 years
1989–1992	Universal 1-dose MMR	1 year
1993–1998	Universal 2-dose MMR	1 and 10-14 years
1993–1994	Selective school based catch-up for one cohort of males and females	10-14 years
1998-2013	Universal 2-dose MMR	1 and 4-5 years
1998	Measles Control Campaign – one-off school-based catch-up MMR	5-12 years
2013 onwards	Universal MMR + MMRV	1 year and 18 months

MMR   Measles-mumps-rubella vaccine.

MMRV   Measles-mumps-rubella-varicella vaccine.

accompanied by an increase in the median age of notifications and a decrease in the male to female notification rate ratio.[8–11]

This study aims to review Australian rubella epidemiology from 2008 to 2012, in the context of historical and international trends.

Methods

Data sources

Notifications

The National Notifiable Diseases Surveillance System (NNDSS), established in 1991, collects de-identified information about notifiable diseases from Australian states and territories. Confirmed and probable cases of rubella and CRS are notifiable under public health legislation in each state and territory. A confirmed case of rubella requires laboratory definitive evidence including either detection of rubella virus (viral culture or nucleic acid testing) or confirmatory serology (IgG seroconversion or ≥ 4-fold rise in IgG titre). A probable case of rubella requires clinical evidence and an epidemiological link to a laboratory confirmed case. A confirmed case of CRS requires definitive laboratory evidence in the infant (detection of rubella virus by culture or nucleic acid testing, or positive IgM confirmed by a reference laboratory). A probable case of CRS requires clinical evidence (compatible defects in the infant) and laboratory suggestive evidence in the mother or infant.[12] For this analysis, data were obtained from NNDSS for all notifications with a diagnosis date between 1 January 1993 and 31 December 2012. The diagnosis date is derived from the date of onset, or, where not supplied, the earliest date recorded among these fields: date of specimen, date of notification, or date when the notification was received. Analysis focused primarily on the 1 January 2008 to 31 December 2012 period, with notifications from 1 January 1993 included where relevant for trends.

Hospitalisations

Hospitalisation data were obtained from the National Hospital Morbidity Database, maintained by the Australian Institute of Health and Welfare. Administrative, demographic and clinical information about patients admitted to public and private hospitals in Australia are collected from hospital discharge summaries. For this analysis, all hospitalisations with admission dates between 1 January 2008 and 31 December 2011 (the most recent data available) were included. Eligible hospitalisation admissions were identified using the International Statistical Classification of Diseases and Related Health Problems, 10th revision, Australian Modification (ICD-10-AM) code B06 (rubella) and P350 (CRS), where listed as the principal or other diagnosis.

Mortality

Mortality data were obtained from the Australian Bureau of Statistics (ABS). Data where the underlying cause of death was recorded as rubella, using ICD-10 code B06 (rubella) were included in this analysis.

Population estimates

National, jurisdictional and age-specific mid-year estimated resident population data were obtained from the ABS.

Data analysis

For notifications, variables extracted for analysis included confirmed or probable status, year of diagnosis, age, sex, state or territory of residence, laboratory diagnosis method, vaccination status, Indigenous status and place of acquisition. For hospitalisations, variables extracted for analysis included primary or other diagnosis, year of admission, age, sex, state or territory of residence,

Indigenous status, complications and length of hospital stay. The outbreak reference field was not included in the analysis due to poor data quality.

Rates were calculated using ABS population data and are presented as annual average rates per 100,000 total population or population in age, sex or geographical subgroups as appropriate. Male to female notification rate ratios were calculated by age group with 95% confidence intervals. Trends in median age were analysed using the Kruskal-Wallis rank test. Summary statistics including median and range were calculated for age and length of hospital stay. Analysis and presentation of data was conducted using SAS, Microsoft Excel 2010 and Stata.

Ethics approval was not required for this review as de-identified aggregate population based data were summarised for routine public health surveillance only.

Results

Rubella

Notification and hospitalisation trends

From January 2008 to December 2012, there were 201 notified cases of rubella, of which 185 (92%) were confirmed and 16 (8%) were probable cases. The average overall annual notification rate (prob-able and confirmed cases combined) was 0.18 per 100,000. The annual number of rubella notifications has remained stable and low since 2004 (Figure 1). No seasonal pattern was seen over the 2008–2012 period (data not shown).
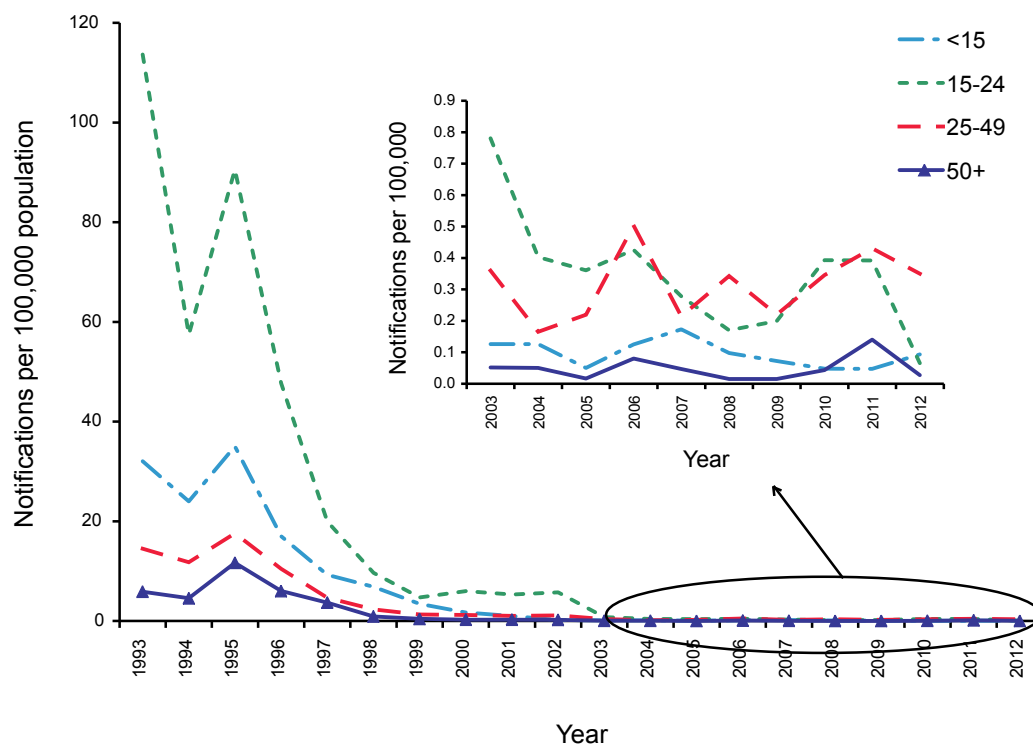
There were 30 hospitalisations due to rubella infection between January 2008 and December 2011; an average annual rate of 0.03 per 100,000 (Table 2). Of the 30 hospital separations, 15 had a principal diagnosis of rubella, an average annual rate of 0.02 per 100,000.

Age and sex distribution

Rubella notification rates have declined markedly in all age groups since 1993 (Figure 1). The median age of notified cases between 2008 and 2012 was 29 years. Between 1993 and 2012 there was an increase in the median age from 18 to 32 ($P < 0.001$).

From 2008 to 2012, the highest age-specific average annual rate of rubella notifications in men was in the 30–39 years age group (0.53 per 100,000); in women it was in the 20–29 years age group (0.52 per 100,000). The overall male to female notification rate ratio was 1.3:1 (95% CI 1.0–1.8) from 2008 to 2012. However, the rate of notifications in males was significantly higher than females only in the 30–39 years age group (RR = 2.3, 95% CI 1.3–4.2) (Figure 2).
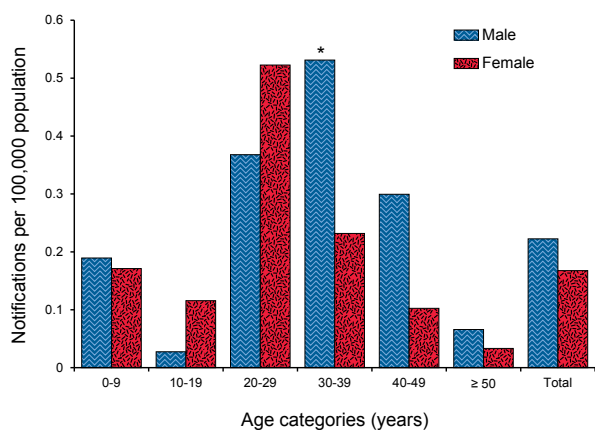
Figure 1: Rubella notification rates, Australia, 1993 to 2012, by age group

There were 69 notified cases of rubella in women of child bearing age (15–44 years) from 2008 to 2012 at an average annual rate of 0.30 per 100,000. Within this group the highest average annual rate of notifications was in women in the 25–29 years age group (0.63 per 100,000).

The median age of hospitalisations with any diagnosis of rubella from 2008 to 2011 was 26 years. The median age of hospitalisations with a principal diagnosis of rubella was 15 years. The male to female rate ratio of hospitalised cases with any diagnosis of rubella from 2008 to 2011 was 1.4:1 (95% CI 0.6–3.0).

Figure 2: Rubella notification, Australia, 2008 to 2012, by age category and sex

* Statistically significant difference.

Geographical distribution

From 2008 to 2012, notifications of rubella were distributed across the jurisdictions, except in the Northern Territory, where no cases were notified. The average annual jurisdiction-specific notification rate from 2008 to 2012 ranged from 0.00 per 100,000 in the Northern Territory to 0.28 per 100,000 in Western Australia. The average annual hospitalisation rate from 2008 to 2012 varied by jurisdiction ranging from 0.00 per 100,000 in Western Australia to 0.33 per 100,000 in the Northern Territory.

The apparent discrepancy between rubella notification and hospitalisation rates in the Northern Territory may be due to the different methods of data collection and classification used for these datasets, in the context of a small number of cases.

Severe morbidity and mortality

From 2008 to 2011, 156 hospital bed days were associated with diagnostic codes for rubella. Thirty-seven of these bed days were recorded for hospitalisations where the principal diagnosis was rubella. The median length of stay in hospital was 2 days for all rubella hospitalisations and 1 day for hospitalisations with a principal diagnosis of rubella.

From 2008 to 2011, the hospitalisation to notification rate ratio was 0.25 (95% CI 0.16–0.37). The average annual hospitalisation rate was highest in the 0–9 years age group (0.07 per 100,000, 8 hospitalisations). Complications arising from rubella infection were recorded for 7 out of 30 hospitalisations. The complications were distributed throughout different age groups (Table 2).

Table 2: Rubella hospitalisations, complications and length of stay , Australia, 2008 to 2011, by age group

Age	Rubella (any diagnosis) hospitalisations		Rubella with neurological complications	Rubella with other complications	Rubella without complications	Median LOS per admission
	n	Rate per 100,000 population	n	n	n	Days
0-9	8	0.07	0	1	7	1
10-19	2	0.01	0	0	2	2.5
20-29	8	0.05	0	2	6	2.5
30-39	5	0.03	0	0	5	3
40-49	2	0.01	0	1	1	5
50+	5	0.01	1	2	2	5
Total	30	0.03	1	6	23	2

LOS   Length of stay.

Deaths

There were no deaths recorded as due to rubella from 2008 to 2011.

Place of acquisition

Place of acquisition was documented for 143 of 201 rubella notifications (71%) from 2008 to 2012. Of the 201 notifications, 55 (27%) were imported from overseas and 88 (44%) were locally acquired. Countries of acquisition included Vietnam, Indonesia, England, The Philippines, China, Sri Lanka, India, South Africa and Zimbabwe.

Indigenous status

Indigenous status was known for 155 of 201 (77%) rubella notifications from 2008 to 2012. Two (1%) notifications of rubella were recorded as Aboriginal or Torres Strait Islander.

Indigenous status was recorded for 28 of 30 rubella hospitalisations from 2008 to 2011. Two hospitalised cases were recorded as Aboriginal or Torres Strait Islander. Neither of these cases had a principal diagnosis of rubella.

Vaccination status

Vaccination status was recorded for 142 of 201 (71%) notifications between 2008 and 2012. Of these, 51 (36%) were recorded as unvaccinated, 16 (11%) as fully vaccinated, 7 (5%) as partially vaccinated, 2 (1%) as 'not applicable', and 66 (46%) as having unknown vaccination status. Completeness of vaccination status by state or territory during the 2008–2012 period ranged from all 34 of Queensland notifications to 7 of 64 New South Wales notifications. Data completeness for this field at the national level was above 70% in each year over this period.

Laboratory diagnosis method

The laboratory diagnosis method was recorded for 188 of 201 (93%) notifications between 2008 and 2012. Of these 169 (89%) were diagnosed by serology only, 17 (9%) by both nucleic acid testing and serology, and 1 (1%) by both culture and serology.

Congenital rubella syndrome

There was 1 notification of CRS between 2008 and 2012: a male aged less than 1 year of age notified in 2012 from the Northern Territory. The place of acquisition was recorded as Indonesia.

There was 1 hospitalisation with a principal diagnosis of CRS between 2008 and 2011, in a 1-month-old male in Victoria hospitalised for 2 days.

There were 72 hospitalisations with a secondary or other diagnosis of CRS from 2008 to 2011 contributing to a total of 608 bed days. The median length of stay was 4.5 days with a range from 1 day to 57 days. The median age at separation was 41 years, with a range of 0 to 71 years (the youngest case being a readmission of the 2008 case noted above, with the next youngest being 2 years of age).

Discussion

Between 2008 and 2012, rubella remained well controlled in Australia with an average annual notification rate of 0.18 per 100,000. The annual rubella notification rate has remained below 0.3 per 100,000 since 2003, following a marked decline in the late 1990s and early 2000s. This is well below the goal for rubella control of 1 per 100,000 endorsed by the Western Pacific Regional Office of the World Health Organization (WHO).[13]

The median age of rubella notifications in Australia between 2008 and 2012 was 29 years, compared with a median age of 27 years between 2005 and 2007 and 25 years between 2003 and 2005.[10,11] This trend of increasing age of notifications likely reflects the declining rates of rubella in children since routine MMR immunisation in infants was implemented.

The rate ratio of male to female rubella notifications during the 2008–2012 period overall was 1.3:1 (95% CI 1.0–1.8). However, this conceals differences between age categories. The male notification rate was significantly higher than the female notification rate in the 30–39 years age group (RR = 2.3, 95% CI 1.3–4.2). Men within this age group were not vaccinated in school based immunisation programs and are also likely to have had less opportunity to acquire natural immunity because of declining wild-type virus circulation due to the immunisation programs targeted at their female peers. This susceptible male population has been demonstrated in national serosurveillance data showing significant differences in seropositivity between males and females aged 25 to 40 years in 2007. The difference in seropositivity (female minus male) was statistically significant ($P < 0.001$) in the 25–29 years age group, the 30–34 years age group and the 35–39 years age group. The differences ranged from 8.7%–15.8%.[14] An over-representation of men in these age groups has also been described in recent outbreaks in Poland, Romania and Japan, which also had selective schoolgirl vaccination

policies.[15–17] Other under-vaccinated groups in Australia at risk of rubella include migrant and refugee populations.[18–20]

The average annual rubella notification rate in women of child-bearing age (15–44 years) during the 2008–2012 period was low—0.3 per 100,000—similar to that during the 2003–2007 period.[11,10] Rubella screening in pregnancy, a part of routine antenatal practice in Australia, is recommended to identify women who are non-immune, so that they can be vaccinated prior to future pregnancies.[21] Serological studies in pregnant Australian women report seropositivity of over 90%, but lower rates have been observed in women born in Asia, nulliparous women, women over 35 years of age and Aboriginal and Torres Strait Islander women living in rural areas.[22,23]

CRS is now rare in Australia. We identified 2 cases between 2008 and 2012: 1 CRS hospitalisation in 2008 and 1 notified case in 2012. This compares with a total of 9 CRS cases notified in the previous 6 year period, from 2002 to 2007.[11] The Australian Paediatric Surveillance Unit, which conducts active surveillance among paediatricians, as opposed to the passive surveillance that occurs via NNDSS, also identified 2 cases of CRS between 2008 and 2012; however both were reported in 2012.[24–28]

The low number of CRS cases documented underlines the success of the Australian rubella vaccination program. The incidence of CRS is estimated to have been 200 cases (1 in 2000 live births) annually between 1968 and 1976.[29] However, the global burden of CRS remains high, principally in countries yet to introduce rubella-containing vaccines. It is estimated that 103,068 CRS cases occurred globally in 2010, with the greatest burden in the African and South East Asian WHO regions (40,680 and 47,527 cases, respectively).[30]

Rubella elimination is a recent focus of the WHO. Elimination was announced in the Americas in 2011.[31] The European region has a revised target of elimination by 2015.[31] The Western Pacific Region, of which Australia is a member state, has endorsed a regional accelerated rubella control and CRS prevention goal to decrease rubella incidence to less than 10 cases per million population and CRS incidence to less than 10 cases per million live births by 2015 and has recently proposed a regional goal of rubella elimination, with the target year to be defined in the near future.[14,32]

The lines of evidence required to verify the elimination of rubella have been established by the American and European regions. These include epidemiology suggestive of elimination (low incidence of rubella and CRS, and the shift towards the predominance of sporadic, imported cases with limited spread) in the presence of quality surveillance; molecular epidemiology documenting interruption of endemic transmission; high levels of population immunity; and a sustainable national immunisation program.[33,34]

It can be argued that Australia meets all of these criteria, with the exception of molecular epidemiology documenting interruption of endemic transmission, due to the limited genotyping currently conducted. Our study shows low incidence of rubella and CRS. The proportion of imported cases increased from 9% to 27% of rubella notifications between 2005 and 2007[11] and 2008 and 2012 in Australia. We identified only 1 published report of a rubella cluster in Australia during the 2008–2012 period.

Immunisation coverage for rubella in Australia is high. In 2012, the percentage of children immunised with their 1st dose of rubella vaccine by 2 years of age and their 2nd dose by 5 years of age was 93.9% and 91.6% respectively.[35] Serosurveys confirm high levels of population immunity.[35] A study using Australian rubella notification, vaccine coverage, and serosurvey data calculated a reproduction number (R) less than 0.5, well below the epidemic threshold of 1.[14] A modelling study using multiple data sources, including Australian serosurvey data, estimated a 99% reduction in both rubella and CRS incidence and R ≤ 0.28, consistent with Australia having achieved rubella elimination.[36]

Formal verification of elimination of rubella in Australia will require improvements in surveillance for rubella and CRS. Nationally consistent follow-up of notifications is needed, with improved data quality on the place of acquisition and outbreak reference fields to demonstrate the source of infection and chains of transmission. The expansion of genotype surveillance will be needed to demonstrate the absence of endemic strains. Wider use of nucleic acid testing or culture will be required to generate specimens suitable for genotyping, given that most rubella notifications are currently diagnosed by serology.

Modelling suggests that rubella control in Australia is much less vulnerable to reductions in vaccine coverage compared with measles, with decreases in coverage of up to 15% estimated to have minimal impact before 2060,[36] However, high levels of vaccine coverage still need to be maintained, particularly to protect against the potentially severe consequences of CRS, as sporadic cases of imported rubella will continue to occur as long as rubella continues to circulate in other countries.

As of 2012, 62 of 194 (32%) WHO member states have yet to introduce rubella-containing vaccines in their immunisation schedule.[31]

There are a number of limitations of this study. The true burden of rubella in Australia is likely to be underestimated since up to 50% of rubella is asymptomatic[3] and not all symptomatic cases are diagnosed and notified. The current case definition for CRS in the NNDSS does not include spontaneous abortion and hence is unable to capture the full spectrum of disease due to congenital rubella infection. However, since methods of case ascertainment and definitions have remained constant since 2004, the trends described remain valid. In rubella notification data, completeness was poor for a number of fields including country of acquisition and vaccination status. Where the vaccination status field was complete, it was often recorded as unknown. This may reflect the difficulty in obtaining an accurate vaccination history from adults in the absence of a whole-of-life immunisation register. The discrepancy in CRS cases identified in NNDSS and APSU data may be due to different methods of case ascertainment and case definitions. ICD-10-AM codes used identify cases of rubella and CRS in the National Hospital Morbidity Database were assigned for hospital billing purposes and have not been validated to clinical diagnoses or case definitions, so may be susceptible to misclassification. However, again, methodology has remained consistent over time.

In conclusion, rubella incidence remains low in Australia and CRS is increasingly rare. Formal verification of rubella elimination in Australia will require the expansion of genotype surveillance. Ongoing rubella control requires good surveillance, maintenance of high levels of vaccine coverage, and support to regional and global efforts towards rubella control or elimination.

Acknowledgements

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