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How Australia's measles control activities have catalyzed rubella elimination

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Abstract

Background: By 2017, rubella had been officially eliminated in Australia. This success was attributed to Australia's longstanding national immunization programme and two enhanced measles immunization activities using measles, mumps, and rubella (MMR) vaccines — the Measles Control Campaign (MCC) and the Young Adult MMR Campaign (YAC). Our study describes the impact of these activities on rubella incidence, and its elimination in Australia.

Methods: Aggregate national serological survey data were assigned to birth cohorts, and mean, median, and age-group estimates calculated and analyzed against MMR immunization coverage estimates (1998–2018) and rubella notifications (1993–2018). Three-year cumulative incidences were calculated by birth cohort.

Results: The serological surveys revealed high and stable levels of rubella immunity among females, but estimates for three male cohorts were lower. Since 2007, MMR immunization coverage among children aged 24–27 months has remained above 90% for both doses. The 3-year cumulative incidence of rubella declined across all birth cohorts following the MCC and the YAC.

Discussion: Using MMR vaccines to address measles immunity gaps had the additional benefit of controlling rubella in Australia. Both the MCC and YAC shifted rubella epidemiology, accelerating the interruption of endemic transmission. Countries should consider combined measles and rubella vaccines for all catch-up activities.

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Ethical approval
No formal ethical approval was required for this work, as it is was a re-analysis of published data.

Competing interests
None of the authors have any conflict of interest to declare.

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Keywords

rubella; vaccines; epidemiology; elimination; Australia

Introduction

Rubella is an acute viral infection, considered to be mild, and commonly characterized by low-grade fever, rash, and malaise (Centers for Disease Control and Prevention, 2015; Reef, 2015). Severity of the disease increases with age, with complications such as encephalitis (estimated as 1/6000 cases) occurring more frequently in adults (Reef, 2015). Viral infection during pregnancy can also affect the development of the fetus and result in spontaneous abortion, stillbirth, or birth defects. Congenital rubella syndrome (CRS), a group of malformations classically presenting as combinations of visual, auditory, or cardiac anomalies, is estimated to occur in up to 90% of infants whose mothers were infected with the rubella virus during the first 10 weeks of pregnancy (Reef, 2015).

Australia, where the congenital consequences of rubella infection were first identified (Burgess, 1991), introduced immunization against rubella in 1971 to prevent CRS, targeting females aged 12–14 years and susceptible women prior to pregnancy (National Centre for Immunisation Reasearch and Surveillance, 2019) This programme reduced CRS cases from an estimated 120 cases annually to fewer than 20 per year by the mid-1980s (Cheffins et al., 1998; Menser et al., 1985). In 1989, Australia included a single dose of a measles-mumps-rubella (MMR) vaccine at 12 months of age for all children, and in 1992 replaced the adolescent female dose with a second MMR dose for all individuals aged 10–14 years (National Centre for Immunsiation Reasearch and Surveil lance, 2019) In 1997, the Australian federal, state and territorial governments established the National Immunisation Program (NIP) (Australian Government Department of Health, 2018), which included MMR vaccines. Over the last two decades, the schedule for MMR vaccines in Australia has been revised several times to reflect the changes seen in the epidemiology of these viruses. In addition to the NIP, Australia conducted two free, large MMR immunization programs to reduce the incidence of measles — the measles control campaign (MCC) in the second half of 1998 and the Young Adult MMR Campaign (YAC) from 2001–2002.

The MCC was conducted to ensure measles immunity in cohorts that were passed over when the age range for the second MMR dose was lowered in 1998 from 10–16 years to 4–6 years (Gidding, 2005; Turnbull et al., 2001). It targeted primary school children aged 5–12 years, and was implemented nationally as a school-based catch-up programme. Documented as exceptionally successful, this campaign immunized 75% of enrolled school children and increased measles serological immunity by 10% among the targeted ages to 94% nationally (Turnbull et al., 2001). A serological campaign evaluation documented an immediate increase in measles immunity in children aged 1–18 years nationally, to 90%, and an 8% increase in rubella immunity to 91 % (Gilbert et al., 2001). The MCC reduced measles incidence in Australia, which has been sustained (Gidding, 2005). More than a decade later, in 2012–2013, another serological survey documented high rubella immunity, with 93% seroprevalence in the age groups targeted by MCC (Edirisuriya et al., 2018).

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The YAC was aimed at adults aged 18–30 years to improve measles immunity among those who had not been eligible for MMR immunizations through the NIP or targeted immunization activities, or may have received only one dose of MMR vaccine (Campbell, 2000). Free MMR vaccines were offered to eligible individuals through general practitioners and other vaccination providers in 2001–2002 (Kelly et al., 2007). Unlike the MCC, which was a nationally run programme, the YAC was managed by each state and territory in Australia, with funding provided by the federal government. It is unknown what proportion of the targeted population was immunized during the YAC, but it was considered less successful for measles when compared with the MCC.

Estimates from a Victoria-specific measles serosurvey conducted in 2002 showed no immediate evidence of increased measles immunity in the YAC targeted population (Kelly et al., 2007). However data from national rubella serosurveys in 2007 and 2012–13 estimated rubella immunity to be around 90% in those eligible for YAC (1971–1983) (Edirisuriya et al., 2018; Song et al., 2012). Moreover, the 2007 serosurvey demonstrated that the rubella immunity gap between the sexes was reduced by 6% in those eligible for the YAC, compared with 2002 data, but not in those 5 years older than this cohort (Song et al., 2012)

Our study describes the impact of the MCC- and YAC-enhanced measles control activities on the incidence of rubella in Australia, and discusses how these activities led to Australia achieving the elimination of endemic rubella.

Methods

MMR immunization coverage estimates

MMR immunization coverage estimates were accessed from the Australian Immunisation Register (AIR), by dose, for children aged 24–27 months and 60–63 months, between December 1998 and December 2018.

Serological surveys

Edirisuriya et al. shared the aggregate national serological survey data from 1999, 2002, 2007, and 2012 (Edirisuriya et al., 2018). These surveys used a random sample of stored diagnostic specimens, stratified by patient age group, sex, and state or territory of residence. Enzygnost (Behring Diagnostics, Marburg, Germany) anti-rubella IgG enzyme immunoassay (EIA) was used with serological positivity set at 7 IU/ml (Edirisuriya et al., 2018; Gilbert et al., 2001). Age-group estimates were used to assign values by birth year. Next, the means, medians, and ranges were calculated for all individuals over 1 year of age. Birth cohorts were assigned according to the age eligibility for the MCC and YAC as follows: (1) those too young for either campaign, born in or after 1994; (2) those eligible for MCC, born 1986–1993; (3) those potentially missed by either campaign, born 1984–1985; (4) those eligible for YAC, born 1971–1983; and (5) those too old for either campaign, born in or before 1970.

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Notifications

Rubella cases diagnosed between 1993 and 2018 were accessed from Australia's National Notifiable Disease Surveillance System (NNDSS). Rubella cases in the NNDSS include laboratory-confirmed cases and cases that meet clinical and epidemiological case definitions (Communicable Diseases Network Australia, 2019). Where year of birth was not recorded, it was estimated from the reported age at onset and the date of diagnosis. Notifications were stratified by age, sex, diagnosis year, and birth cohorts, as described above. Rates were calculated using the Australian Bureau of Statistics estimated residential population (Australian Bureau of Statistics, 2018). Poisson regression in SAS™ was used to calculate the estimated percent reduction in reported rubella cases in the 3 years before and after the MCC (1995–1997 and 1999–2001) and YAC (1998–2000 and 2003–2005) within birth cohorts. 95% confidence intervals for the estimated percent reductions were calculated based on a normal distribution on the log scale.

Results

Immunization coverage and immunity by serology

Immunization coverage estimates with the first dose of MMR in children aged 24–27 months have increased since reporting began in 1998, becoming stable between 93% and 95% since 2013 (Figure 1). Estimates for MMR second dose coverage have been slightly more varied, ranging from 80% to 94% for children aged 60–63 months, and 89% to 94% for children aged 24–27 months. MMR second dose estimates declined from 93% in 2013 to 89% in 2014, but increased and stabilized at 93% by 2016. The temporary dip in estimates for the second MMR dose in 2014 has been attributed to the coverage of this dose being assessed at 24–27 months for the first time (Hull et al., 2017).

The serological surveys included individuals born between 1950 and 2010, who were aged 10–70 years in 2020. Results from these serosurveys showed that there had been a high and constant level of immune protection among females (median range, 92–98%) (Figure 2). Males were estimated to have had 4–13% lower immunity than females in the birth cohorts of 1960 through 1987 (median range, 84–95%). The lowest rubella serological protection was 84% among males born between 1980 and 1983.

Incidence

Since 1995, the incidence of rubella has declined dramatically in Australia (Figure 1), dropping below 1 notification per 100 000 population. Since 2014, fewer than 20 rubella cases have been reported each year in Australia, resulting in an annual notification rate below 0.1 per 100 000 population. Major changes in the incidence of rubella over the past 25-year period have corresponded with the implementation of the mass immunization campaigns and changes to the NIP, as shown in Figure 1.

Before the implementation of the MCC in 1998, the proportional age-distribution of rubella cases during 1993–1999 was concentrated among the birth cohorts who were either eligible for the YAC (birth cohort 1971–1983; range 39–55%) or those too old for either campaign (birth cohorts ≤ 1970 (range 23–32%) (Figure 3). Although cases occurred in birth cohorts

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eligible for the MCC (1986–1993), these were low in comparison (range 8–15%). Following the implementation of the YAC in 2000–2001, a noticeable decline in rubella cases was seen across all birth cohorts (Figure 4). The proportions of rubella cases reported in two cohorts — those too young for vaccination (birth cohort ≥ 1994) and those eligible for MCC (birth cohort 1986–1993) — varied, but increased overall from low in 2002 (ranges 2–24% and 2–31%, respectively) to pre-dominant during 2015–2018 (ranges 12–40% and 18–41%, respectively) (Figure 3).

Following implementation of both the MCC and YAC, the 3-year cumulative incidence of rubella cases declined across all defined birth cohorts (Table 1). Following the implementation of the MCC, reductions in the 3-year cumulative incidence ranged from 67% to 95%. The birth cohort with the largest percentage decline following this campaign included those not eligible for either the MCC or YAC (missed; birth cohort 1984–1985), with a 95% decline (95% CI: 93–97%]. The post-3-year cumulative incidence of rubella in the birth cohort eligible for the MCC dropped by 94% (95% CI: 92–95%) compared with the cumulative incidence in the 3 years preceding its implementation. Declines in the 3-year cumulative rubella incidence following the implementation of the YAC ranged from 79% to 96%, with the largest reduction occurring in the ‘too young’ cohort at 96% (95% CI: 93–98%). For the birth cohort eligible for the YAC, the 3-year cumulative incidence decreased by 91% (95% CI: 88–93%).

Discussion

Over the past 25 years, there have been marked changes in rubella epidemiology across Australia. Our review shows that rubella incidence among birth cohorts targeted by the MCC and YAC fell noticeably following both these activities. The first Australian national serological survey was instituted in 1999 to monitor the impact of the MCC on measles and rubella immunity among the targeted cohorts.

Subsequent serological surveys for rubella provided similar findings, resulting in three cohorts of immunity from the different rubella control strategies: natural immunity (born pre-1960), direct female protection (born 1960–1987), and rubella elimination (born 1988–2010). This final group was eligible for a childhood MMR vaccine for all children and also MCC in the 1998 catch-up campaign to accelerate measles elimination (Gilbert et al., 2001). Rubella immunity benefited significantly from the MCC by a direct 8% boost in serological immunity in those younger than 18 years of age (Gilbert et al., 2001).

The success of the MCC has been well documented, with rubella serological immunity following the campaign estimated to be around 94% for pre-school-aged children (2–5 years) and 95% for primary school-aged children (6–12 years) (Gidding, 2005; Gilbert et al., 2001) Our review corroborates these findings, with declines in the 3-year cumulative incidence and high rubella immunity seen among the MCC-eligible cohort. Our study noted that declines also occurred in the 3-year cumulative incidence in the non-MCC-eligible birth cohorts (range 67–95%), demonstrating the effectiveness of the MCC campaign on rubella transmission.

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Serosurveys examining the seropositivity of measles and rubella in Victoria in 2002 suggested that the impact of YAC was suboptimal, with little gain in measles or rubella immunity among the targeted cohorts (Kelly et al., 2007; Kelly et al., 2004). Funded in the 2000–2001 financial year by the federal government, the YAC was a population-based programme managed by individual states and territories, rather than being nationally coordinated, leading to variations in its implementation. Whilst it is agreed that the YAC began in 2001, it is unclear precisely when the campaign concluded across the country (Campbell, 2000; Kelly et al., 2007). Evidence from the national rubella serosurveys from 2002 and 2007 suggest that the YAC had more of an impact on rubella immunity than previously thought. First, there was a 6% reduction in sex-discrepant immunity between males and females among the YAC-eligible cohort (Song et al., 2012), suggesting that around 6–12% of the target population may have received a rubella-containing vaccine. Second, by using MMR vaccines to eliminate measles in Australia, rubella immunity was concurrently targeted and improved. Serological evidence has shown national rubella immunity has remained above and exceeded the herd immunity threshold of 83–85% (Fine, 1993), interrupting local transmission.

Our review of the impact the YAC had on the incidence of rubella in Australia found a marked decline in the 3-year cumulative incidence, not only in those eligible for the YAC, but also in the infant population. Cases of rubella infection in infants fell from 11 cases in 2001 to zero in 2002, for the first time. Between 2003 and 2018, there were only four cases of rubella infection reported in infants, suggesting that immunity towards rubella had increased among parents and caregivers. This was further supported by the low numbers of CRS cases ($n = 11$) reported between 2003 and 2018 (Australian Department of Health, 2021). With the exception of two babies born in the first half of 2003, associated with a localized outbreak in the state of Queensland (Forrest et al., 2003), the remaining nine CRS cases reported were babies of overseas-born mothers who had migrated to Australia and were unvaccinated (Fielding, 2008; Franklin and Rowe, 2014; NNDSS Annual Report Writing Group, 2009, 2015a, 2015b; Owen et al., 2007; Yohannes et al., 2006) Our findings differed from those of previous reports (Edirisuriya et al., 2018; Gidding et al., 2003; Kelly et al., 2004) and suggested that the YAC campaign aided in further boosting rubella immunity.

In 2012, the World Health Organization (WHO) released the Global Measles and Rubella Strategic Plan 2012–2020 (World Health Organization, 2012), which set the target for measles and rubella elimination in five WHO regions by the end of 2020. Unfortunately, this target had not been met at the time of writing, with only the Americas region sustaining rubella elimination at the end of 2020. In 2018, the WHO Strategic Advisory Group of Experts on Immunization indicated that rubella control was lagging, and highlighted that although global coverage of rubella-containing vaccines exceeded 50% in 2017, this coverage varied substantially among the WHO regions (Strategic Advisory Group of Experts on Immunization, 2018). Australia is one of only six countries in the Western Pacific region to have achieved the elimination of both endemic measles (in 2014) and rubella (in 2017) (World Health Organization, 2019, 2021). While both the MCC and YAC aimed to increase immunity against and eliminate measles in Australia, using MMR vaccines in these

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campaigns improved rubella immunity, particularly among the male population, leading to its elimination.

There were several potential limitations to our study. Cases of rubella received by the NNDSS did not include all rubella cases occurring in the community, as milder cases may not have presented to a medical practitioner, and a rubella diagnosis requires laboratory confirmation. However, this is unlikely to have changed substantially over time. Specimens for each serosurvey were opportunistically sampled from diagnostic samples collected from different laboratories during a specified historical period. Although representativeness may have fluctuated over time, the results from the first survey were in agreement with at least one prospectively collected random sample (Kelly et al., 2002).

Conclusion

Australian data show that the use of MMR vaccines to specifically address measles immunity gaps through targeted immunization campaigns achieved the additional benefit of controlling and eliminating rubella. While the impact of the YAC was considered suboptimal for measles, our study found that this campaign, along with the MCC, shifted the epidemiology of rubella and reduced its gender-immunity gap, accelerating the interruption of endemic rubella transmission in Australia. The Australian experience shows there is an unequivocal benefit in using combined measles and rubella vaccines when conducting measles control and elimination activities. As recommended by the WHO (World Health Organization, 2020), countries that have included rubella as part of their immunization schedule should use combined measles and rubella vaccines for all routine and supplemental immunization activities, particularly in response to the disruptions caused by the COVID-19 pandemic, to simultaneously eliminate the endemic transmissions of both viruses.

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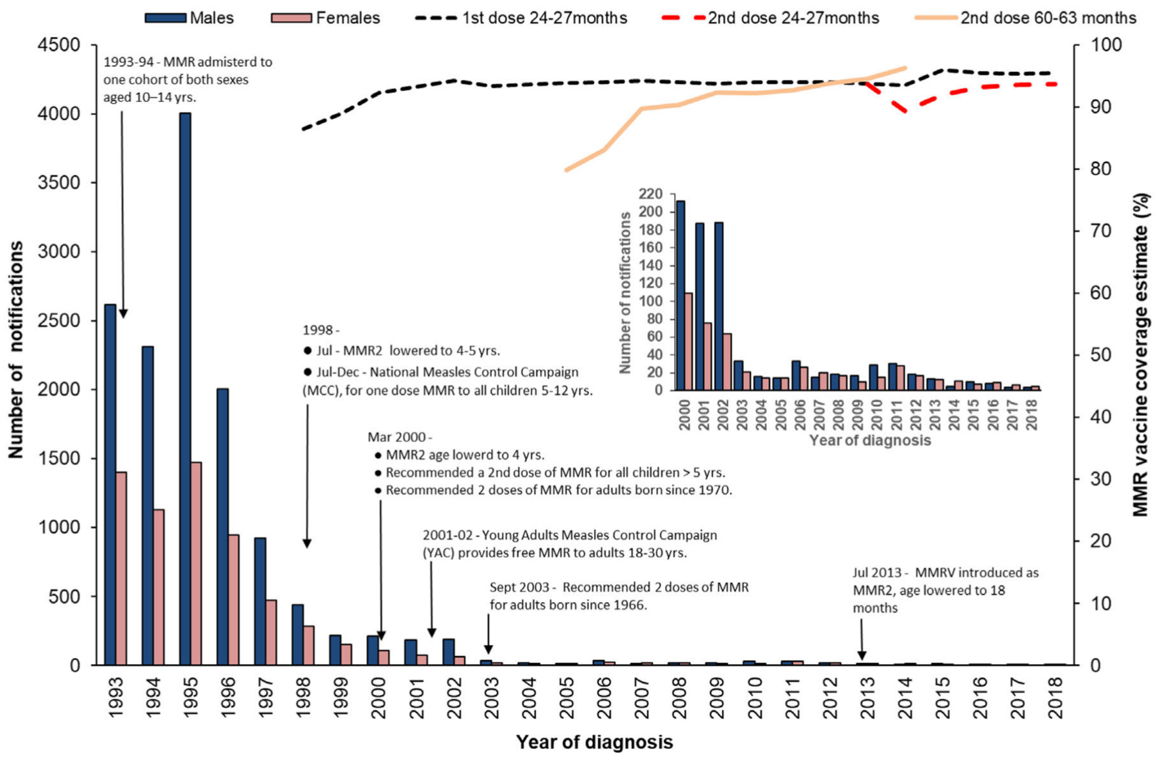

Figure 1.

National notification numbers for rubella, Australia, 1993–2018, including immunization points and MMR vaccine coverage estimates for children aged 24–63 months by year of diagnosis — Australia, 1998–2018.

Notes:

131 rubella notifications were excluded as sex was not reported.

MMR vaccine estimates for the first dose at 24–27 months were calculated using reported date of birth. These estimates may vary from published estimates from the Department of Human Services, which uses the date added to the AIR for assessments.

The age used to assess the vaccine coverage estimate of the second MMR dose changed in 2014 from 60–63 months to 24–27 months to align with changes made to the national immunization schedule for the administration of MMR vaccines.

Source: Rubella notifications from the National Notifiable Disease Surveillance System, extracted on August 14, 2019 and MMR coverage estimates provided by Australian Immunisation Register (AIR) quarterly coverage reports, extracted on July 3, 2019.

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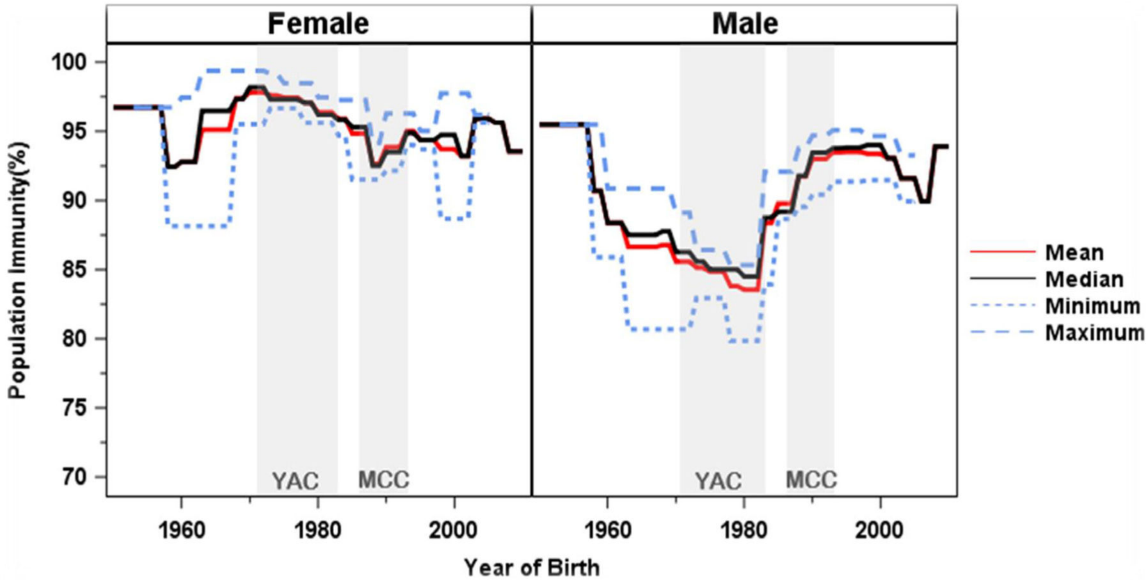

Figure 2.
Rubella seropositivity among Australians born in 1950–2010, as estimated by four national surveys conducted between 1999 and 2012, with MCC and YAC birth cohorts identified
Note: MCC = Measles Control Campaign (birth cohort 1986–1993); YAC = Young Adult MMR Campaign (birth cohort 1971–1983)
Source: National Centre for Immunisation Research and Surveillance rubella serosurvey, 2012–2013.

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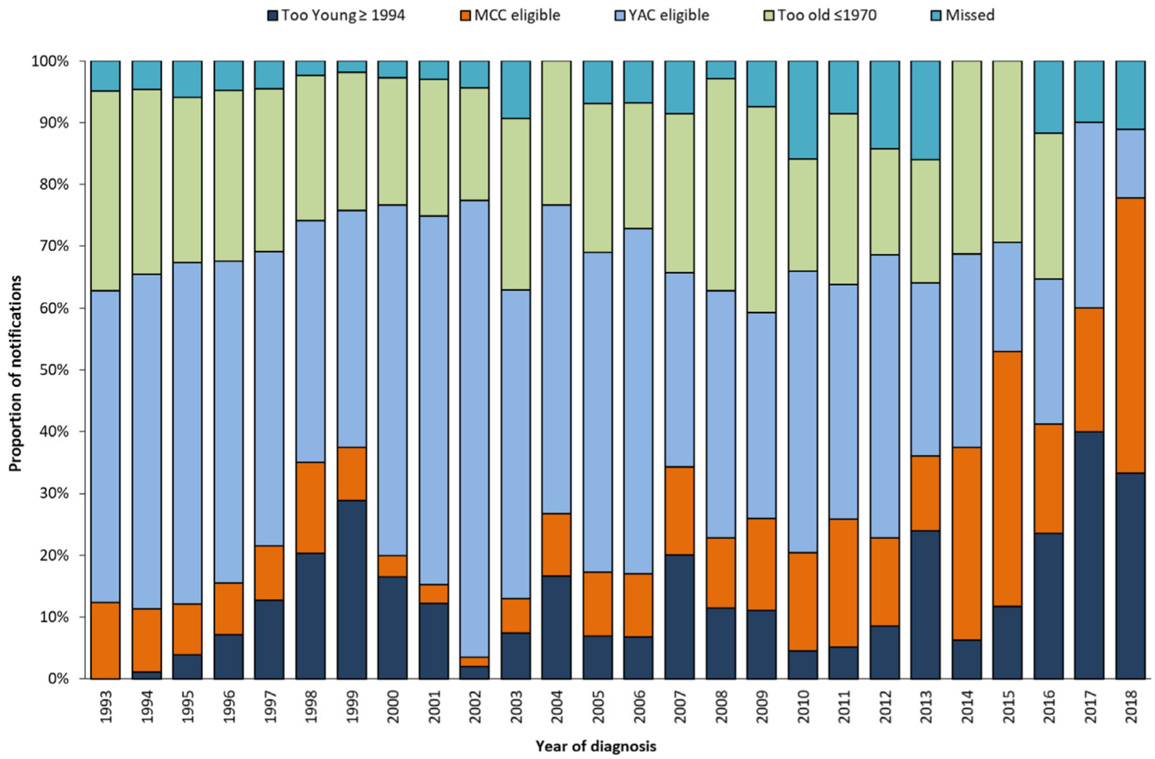

Figure 3.

Proportions of national rubella notifications by birth cohort vaccine eligibility and year of diagnosis, 1993–2018, Australia

Birth cohorts: too young — birth cohort ≥ 1994; MCC eligible — birth cohort 1986–1993; YAC eligible — birth cohort 1971–1983; too old — birth cohort ≤ 1970; missed birth cohort 1984–1985

Source: National Notifiable Disease Surveillance System, extracted on August 14, 2019.

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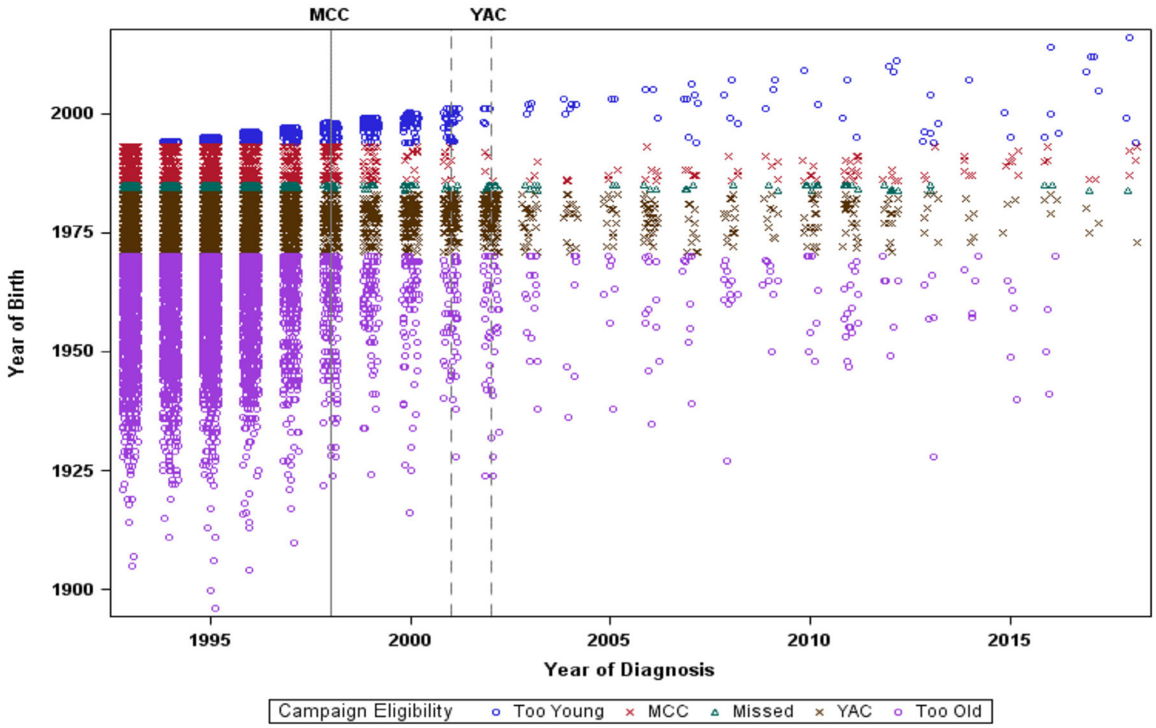

Figure 4.

Reduction in reported annual rubella infections (1993–2018) according to birth cohort and vaccination campaign eligibility, Australia

Notes: 1119 rubella notifications reported without a month and year of birth were excluded from the analysis.

Birth cohorts: too young — birth cohort ≥ 1994; MCC — birth cohort 1986–1993; missed — birth cohort 1984–1985; YAC — birth cohort 1971–1983; too old — birth cohort ≤ 1970

Source : National Notifiable Disease Surveillance System, extracted on August 14, 2019.

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Table 1

Percentage changes and confidence intervals for national rubella notifications by birth cohort vaccine eligibility, for the 3 years preceeding and following the MCC and YAC, Australia

Birth cohort eligibility (birth years)	**Pre-MCC3 cases[a]**	**Post-MCC3 cases[a]**	**Percentage change, MCC (95% CI)**	**Pre-YAC3 cases[b]**	**Post-YAC3 cases[b]**	**Percentage change, YAC (95% CI)**
Too young ≥ 1994	580	191	−67.1 (−72.0 to −61.2)	306	11	−96.4 (−98.0 to −93.4)
MCC 1986–1993	797	51	−93.6 (−95.2 to −91.5)	150	9	−94.0 (−96.9 to −88.2)
Missed 1984–1985	512	24	−95.3 (−96.9 to −92.9)	33	7	−78.8 (−90.6 to −52.0)
YAC 1971–1983	5096	480	−90.6 (−91.4 to −89.7)	607	57	−90.6 (−92.8 to −87.7)
Too old ≤ 1970	2583	206	−92.0 (−93.1 to −90.8)	318	29	−90.9 (−93.8 to −86.7)
Total	9568	952	−90.1 (−90.7 to −89.4)	1414	113	−92.0 (−93.4 to −90.3)

Source: National Notifiable Disease Surveillance System, extracted on August 14, 2019.

Notes: 1119 rubella notifications reported without a month and year of birth were excluded from the analysis.

MCC = Measles Control Campaign, YAC = Young Adult Measles Control Campaign

[a] Pre-MCC3 analysis, years 1995–1997; post-MMC3 analysis, years 1999–2001

[b] Pre-YAC3 analysis, years 1998–2000; post-YAC3 analysis, years 2002–2004