Interruption of rubella virus transmission in Australia may require vaccination of adult males: evidence from a Victorian sero-survey

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Abstract

Prior to the introduction of rubella vaccine to Australia in 1970 rubella was primarily a disease of primary school aged children. Vaccination programs have subsequently altered rubella age and sex susceptibility. Between July 2001 and June 2002, 85 per cent of the 32 laboratory-confirmed cases of rubella ascertained from enhanced surveillance in Victoria were males aged 20–42 years. This study aimed to determine rubella susceptibility by age group and sex in Victoria and to examine the implications of susceptibility for the interruption of circulating rubella virus. Rubella immunoglobulin G concentrations were determined for 934 residual diagnostic sera stored at the Victorian Infectious Diseases Reference Laboratory using a standard commercial enzyme immunoassay. Susceptibility was analysed by age groups defined by previous and current Australian rubella immunisation schedules. Among all subjects aged 1–55 years, males were more susceptible to rubella infection than females (10.2% vs 2.6%, p<0.0001). Although this sex difference occurred in all age groups, it was unlikely to be explained by sampling variation in sera from subjects aged 23–44 years, for whom rubella vaccine had been recommended only for girls aged 10–14 years and rubella susceptible women post-partum. Australia's past rubella immunisation policies have resulted in a susceptible cohort of adult males. If rubella virus transmission is to be interrupted in Australia, consideration needs to be given to a rubella vaccination program targeting men aged 17–44 years. A campaign, targeting both men and women in a similar age group has recently been successful in Costa Rica. *Commun Dis Intell* 2004;28:69–73.

Keywords: rubella, susceptibility, age group, sex

Introduction

Prior to the introduction of vaccination, rubella infection was generally a very common but relatively benign infection of primary school aged children. However 80 per cent of infections during the first eight weeks of pregnancy result in congenital rubella syndrome (CRS).[1] Rubella vaccine, which is thought to confer life long immunity, was first licensed in 1969 in the United States of America and the following year in Australia.[1,2] In 1971 a campaign aimed at vaccinating girls aged 10–14 years and women who were found to be susceptible to rubella post-partum was introduced in Australia.[2] This campaign was successful in reducing the incidence of CRS. Before the introduction of rubella vaccination about 120 cases of CRS occurred each year, equivalent to a case rate of 1 per 2,200 live births. Between 1993 and 1997 the incidence of CRS had decreased to approximately 1 in every 67,000 live births.[3] In 1997 there was one case where the infant had defects associated with congenital rubella and another case in 1999 where the infant had no defects. There were no further cases until 2003 when two cases, both with congenital rubella defects, were reported from Queensland.[4]

During the 1980s and 1990s a change from selective to universal rubella vaccination occurred in many industrialised countries, facilitating the potential eradication of circulating rubella virus.[5] In Australia, the schoolgirls only rubella vaccine program was replaced in 1993 by measles-mumps-rubella (MMR) vaccine for both boys and girls between the ages of 10 and 16 years. This was effectively a second dose of the MMR vaccine, the first having replaced measles-mumps for 12-month-old infants in 1989.[2] It is however, unlikely that many children would have received both the infant and adolescent vaccine doses. In 1998, in conjunction with the national Measles Control Campaign, the recommended age for the second dose of MMR was reduced from 10–16 years to 4–5 years. After the Measles Control Campaign, rubella susceptibility in people aged 1–18 years dropped from 17 per cent to

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9 per cent. However, young adult males were more susceptible to rubella than females in both pre- and post-campaign testing.[6]

Sequential changes to rubella immunisation policies in Australia have altered the age groups most at risk of infection. This is reflected in results from Victoria of the first 12 months of enhanced rubella surveillance, conducted between July 2001 and June 2002, when 29 (85%) of the 32 laboratory-confirmed cases of rubella were males aged 20–42 years.[7] We performed a sero-survey using residual sera at the Victorian Infectious Diseases Reference Laboratory (VIDRL) to determine if cases identified by enhanced surveillance were reflective of sex and age group susceptibility in Victoria. We also aimed to examine the implications of susceptibility for the interruption of circulating rubella virus in Victoria and, by implication, Australia. Interruption of rubella transmission has been achieved in Finland[8] and is a goal of the Pan American Health Organization.[9]

Methods

From all residual sera submitted for diagnostic testing at VIDRL between January and October 2002, a convenience sample of 934 sera from subjects aged 1–55 years at the time of specimen collection, was retrieved. Subjects who had been tested for any illness characterised by a rash, including measles or rubella, were excluded from the sample. Ethics approval for this study was obtained from the Ethics Committee of the Royal Melbourne Hospital Research Foundation.

The sample size was determined by the expected measles immunity in specific age-groups defined by past Australian measles immunisation policies,[10] since the sample was primarily designed to estimate changes in measles immunity following the immunisation campaign targeting young adults.[11]

Sera from approximately equal numbers of male and female subjects were tested at VIDRL for rubella-specific IgG using the Beckman Access Immunoassay System (Beckman Instruments, Chaska, MN, USA). In accordance with the manufacturer's instructions, subjects were considered protected from rubella virus infection if the IgG concentration was >15 IU/ml and susceptible if <10 IU/ml. Initially equivocal specimens (10–15 IU/ml) were re-tested. Equivocal results on final testing were regarded as susceptible.

We have assumed rubella vaccination strategies will have affected rubella immunity in the population and have further assumed that age-specific immunity in the population would be reflected in the convenience sample. Analysis of rubella immunity was thus based on the presumed effect of changes in rubella immunisation policy on different age groups (Table).[2] Rubella vaccination history was unknown for all subjects for whom sera were tested and analysis was based on rubella vaccination recommendations rather than vaccination history. For instance, if a rubella containing vaccine was recommended at 12 months, it was assumed the vaccine would have been given at 12 months. However, because vaccination policies were in place over a number of years, they applied to children in a wider age range in 2002 than the specific age recommended for vaccination, effectively allowing for vaccination to have occurred later than recommended. There was thus an extended opportunity for immunisation policies to affect population immunity. For the purposes of grouping the data, 10–14-year-old girls in the school-based program between 1971 and 1992 and boys and girls aged 10–16 years between 1993 and 1998, were treated as if all vaccines had been recommended at age 13.

The chi-squared or Fisher's exact test was used for the comparison of categorical variables and exact binomial confidence intervals were calculated around proportions.

Results

About 6.5 per cent of all 934 sera tested lacked protective antibodies to rubella, with males being 3.9 times (95% CI, 2.1–7.3) more susceptible to rubella infection than females (10.2% vs 2.6%, p<0.0001) (Table). There was no significant difference in rubella susceptibility of males (p=0.85) or females (p=0.46) by age group.

Although the point estimate of male susceptibility was higher than the point estimate for females in the age groups 1–5 years (11.1% vs 0%, p=0.12), 6–16 years (9.7% vs 5.3%, p=0.25) and 44–55 years (6.0% vs 2.1%, p=0.32), this may have been explained by sampling variation in smaller samples. There was no difference in rubella vaccination policy by sex for these three age groups (Table). However, the sex difference in susceptibility was very unlikely to be due to sampling variation in the 23–44 year age range who had attended school when the rubella immunisation strategy was to target only adolescent girls. In this age range, 11.2 per cent of males were susceptible to rubella compared with 1.8 per cent of females (p<0.0001). Those aged 17–22 years had attended school when both boys and girls were eligible for MMR vaccination and, in this group, 10.3 per cent of males were susceptible to rubella compared with 2.8 per cent of females (p=0.07).

The sample did not demonstrate a difference in rubella immunity between males aged 1–22 years for whom at least one dose of rubella vaccine had been recommended and males aged 23–44 years for whom no rubella vaccine had been recommended (10. 5% vs 11.6%, p=0.76). There was a small residual rubella susceptibility of approximately two to three per cent in women of child bearing age (Table).

Discussion

This study has shown that about 6.5 per cent of the sample of residual sera collected from the Victorian population aged 1–55 years lacked protective antibodies to rubella. Males were about four times more likely than females to be susceptible to rubella infection. The epidemiology of rubella in Victoria is now similar to that of measles, a disease predominantly affecting young adults.[10] In the last three measles outbreaks in Victoria between 1999 and 2002, the median age of cases has varied between 22 and 25 years.[12,13,14] The median age of rubella cases from enhanced rubella surveillance in Victoria was 22 years.[7]

Although the results from this study are from an analysis of residual sera, they are likely to be applicable to the wider Victorian community. We have previously shown no significant population health difference between susceptibility to a number of vaccine preventable diseases comparing a convenience sample of residual diagnostic sera and sera obtained from a three-stage random cluster survey in Victoria.[15] Moreover, the findings from enhanced rubella surveillance[7] and a long-term survey of pregnant women in Victoria,[16] support the results from this study.

The results are also likely to be broadly applicable Australia wide. With minor exceptions, vaccination policies in Australian states have been similar in the last 50 years. Measles susceptibility has been previously shown to be similar in young adults from Victoria[10] and Australia,[17] suggesting the same may be true for rubella susceptibility. This appears to be borne out by a comparison of rubella susceptibility in Australians aged 16–18 years, and the results of this study. After the Measles Control Campaign in 1999, only 2 per cent of Australian females aged 16–18 years were susceptible to rubella, compared with 18 per cent of males.[6] In this study, with sera collected in 2002, 3 per cent of Victorian females aged 17–22 years were susceptible to rubella, compared with 10 per cent of Victorian males. Persons aged 16–18 years in 1999 would be aged 19–21 years in 2002, so the two samples should be broadly comparable.

There was no apparent difference in rubella susceptibility comparing males who had received at least one dose of a vaccine containing rubella and those who had received no rubella vaccine. While this may have been due to sampling variation, it may also be due to a lower uptake of MMR vaccination

Table. Susceptibility to rubella infection in sera collected from Victoria, reflecting previous and current rubella vaccination strategies

Age group (years) in 2002	Immunisation policy for vaccines containing rubella	Males		Females		P-value males vs females	All	
		Tested	Susceptible N (%) (95% CI)	Tested	Susceptible N (%) (95% CI)		Tested	Susceptible N (%) (95% CI)
1–5	Measles-mumps-rubella (MMR) at 12 months	36	4 (11.1%) (3.1–26.1)	27	0 (0%) (0–12.8)	0.12	63	4 (6.3%) (1.8–15.5)
6–16	MMR at 12 months and second dose MMR at 4–5 years or as part of Measles Control Campaign	93	9(9.7%) (4.5–17.6)	95	5 (5.3%) (1.7–11.9)	0.25	188	14 (7.4%) (4.1–12.2)
17–22	Measles-mumps at 12 months and MMR for boys and girls aged 10–16 years in school-based program	68	7 (10.3%) (4.2–20.1)	71	2 (2.8%) (0.3–9.8)	0.07	139	9 (6.5%) (3.0–11.9)
23–44	School girl only (10–14 years) rubella program	224	25 (11.2%) (7.4–16.0)	222	4 (1.8%) (0.5–4.5)	<0.0001	446	29 (6.5%) (4.4–9.2)
44–55	No rubella vaccine routinely recommended	50	3 (6.0%) (1.3-16.5)	48	1 (2.1%) (0.1–11.1)	0.32	98	4 (4.1%) (1.1–10.1)
All ages	Various	471	48 (10.2%) (7.6–13.3)	463	12 (2.6%) (1.3–4.5)	<0.0001	934	60 (6.4%) (4.9-8.2)

by boys, presumptive evidence for which has been shown for MMR vaccine uptake in the school based program in South Australia.[18]

Because man is the only host for rubella virus[1] it has been suggested that interrupting the transmission of wild-type rubella virus could prevent CRS.[19] This has been accomplished in Cuba using a combined strategy of vaccinating children and adult women.[20] However, in the late 1990s in the United States of America and Mexico, 80 per cent of rubella cases occurred in males aged 15–44 years, primarily of Hispanic ethnicity.[21] For successful elimination of circulating rubella virus, in addition to providing universal vaccination in childhood, vaccination strategies will need to address the issue of residual rubella susceptibility in those countries like Australia where adolescent and adult males provide a reservoir for the virus.[19] This approach was successful in Costa Rica in May 2001, with the completion of a campaign targeting both males and females aged 15–39 years, with a measles-rubella (MR) vaccine. MR coverage achieved in the campaign was 87 per cent in the 30–34 year age group and greater than 90 per cent in all other target age groups.[22]

Since the monovalent rubella vaccine was licensed in Australia in 1970, rubella vaccination strategies have moved from a selective to a universal approach that has the potential to eliminate rubella infection. However, in Australia and other countries with similar past rubella vaccination strategies, adult males are a susceptible reservoir for circulating rubella virus. If Australia were to aim for interruption of rubella transmission in the near future, consideration would need to be given to a rubella vaccination program targeting adult males who were aged 17–44 years in 2002. This is a similar age range to the young adults targeted in Australia's measles vaccination campaign using MMR vaccine.[11] This age group is difficult to reach in a population based program.

With only two cases of CRS in Australia between 1997 and 1999 and no cases between 2000 and 2002, it may have been assumed that Australia's rubella immunisation policies were moving towards successful prevention of rubella infection among pregnant women.[4] However, two cases of CRS in 2003, where both infants were born to young Caucasian Australian-born mothers, suggests there is no room for complacency in rubella control.[4] Continuation of Australia's current rubella vaccine policy will not interrupt rubella virus circulation until all of Australia's population has been eligible for two doses of rubella vaccine. With an average life expectancy in Australia approaching 80 years, this may not happen until mid way through the century. It may be time to review Australia's approach to rubella immunisation.

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References

1. Chantler J, Wolinsky JS, Tingle A. Rubella virus. In: Knipe DM, Howley PM, editors. *Fields Virology*. 4th edition. Philadelphia: Lippincott Williams and Wilkins, 2001:963–990.

2. Gidding HF, Burgess MA, Kempe AE. A short history of vaccination in Australia. *Med J Aust* 2001;174: 37–40.

3. Sullivan EM, Burgess MA, Forrest JM. The epidemiology of rubella and congenital rubella in Australia, 1992 to 1997. *Commun Dis Intell* 1999;23: 209–214.

4. Forrest J, Burgess M, Donovan T. A resurgence of congenital rubella in Australia? *Commun Dis Intell* 2003;27:533–536.

5. Bart KJ, Orenstein WA, Preblud SR, Hinman AR. Universal immunization to interrupt rubella. *Rev Infect Dis* 1985;7 Suppl 1:S177–S184.

6. Gilbert GL, Escott RG, Gidding HF, Turnbull FM, Heath TC, McIntyre PB, *et al*. Impact of the Australian Measles Control Campaign on immunity to measles and rubella. *Epidemiol Infect* 2001;127:297–303.

7. Guy RJ, Andrews RM, Kelly HA, Leydon JA, Riddell MA, Lambert S, *et al.* Mumps and rubella: a year of enhanced surveillance and laboratory testing. *Epidemiol Infect.* In press, 2004.

8. Peltola H, Davidkin I, Paunio M, Valle M, Leinikki P, Heinonen OP. Mumps and rubella eliminated from Finland. *JAMA* 2000;284:2643–2647.

9. World Health Organization, Department of Vaccines and Biologicals. Report of a meeting on preventing congenital rubella syndrome: immunization strategies, surveillance needs. Geneva: World Health Organization; 2000 12 – 14 January. Report No.: WHO/V&B/00.10.

10. Kelly HA, Riddell MA, Lambert SB, Leydon JA, Catton MG. Measles immunity among young adults in Victoria. *Commun Dis Intell* 2001;25:129–132.

11. Campbell M. Young adult measles vaccination [editorial]. *Commun Dis Intell* 2000;24:241–242.

12. Lambert SB, Morgan ML, Riddell MA, Andrews RM, Kelly HA, Leydon JA, *et al.* Measles outbreak in young adults in Victoria, 1999. *Med J Aust* 2000;173: 467–471.

13. Davidson N, Andrews R, Riddell M, Leydon J, Lynch P. A measles outbreak among young adults in Victoria, February 2001. *Commun Dis Intell* 2002;26: 273–278.

14. Counahan M, Tobin S, Andrews R, Robinson P, Chibo D, Riddell M. Measles—get vaccinated! *Vic Infect Dis Bull* 2003;6:33–34.

15. Kelly H, Riddell MA, Gidding HF, Nolan T, Gilbert GL. A random cluster survey and a convenience sample give comparable estimates of immunity to vaccine preventable diseases in children of school age in Victoria, Australia. *Vaccine* 2002;20:3130–3136.

16. Francis BH, Thomas AK, McCarty CA. The impact of rubella immunization on the serological status of women of childbearing age: a retrospective longitudinal study in Melbourne, Australia. *Am J Pub Health* 2003;93:1274–1276.

17. Gidding HF, Gilbert GL. Measles immunity in young Australian adults. *Commun Dis Intell* 2001;25:133–136.

18. Cheffins T, Chan A, Keane RJ, Haan EA, Hall R. The impact of rubella immunisation on the incidence of rubella, congenital rubella syndrome and rubella-related terminations of pregnancy in South Australia. *Br J Obstet Gynaecol* 1998;105:998–1004.

19. Hinman AR, Hersh BS, de Quadros CA. Rational use of rubella vaccine for prevention of congenital rubella syndrome in the Americas. *Rev Panam Salud Publica.* 1998;4:156–160.

20. Measles, rubella, and congenital rubella syndrome—United States and Mexico, 1997–1999. *MMWR Morb Mortal Wkly Rep* 2000;49:1048–1059.

21. Castillo-Soloranzo C, Carrasco P, Tambini G, Reef S, Brana M, de Quadros CA. New horizons in the control of rubella and prevention of congenital rubella syndrome in the Americas. *J Infect Dis* 2003;187 Suppl 1:S146–S152.

22. Morice A, Carvajal X, Leon M, Machado V, Badilla X, Reef S, *et al*. Accelerated rubella control and congenital rubella syndrome prevention strengthen measles eradication: the Costa Rican experience. *J Infect Dis* 2003;187 Suppl 1:S158–S163.