

Epidemiological Surveillance and Control of Rubella in Singapore, 1991-2007

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Abstract

Introduction: We reviewed the epidemiological features of rubella in Singapore and the impact of the national immunisation programme in raising the population herd immunity against rubella, with special reference to females in the reproductive age group, and in the elimination of congenital rubella syndrome (CRS). **Materials and Methods:** Epidemiological data on all reported cases of rubella and CRS were obtained from the Communicable Diseases Division and Central Claims Processing System, respectively, at the Ministry of Health. Coverage of the childhood immunisation programme against rubella was based on the immunisation data maintained by the National Immunisation Registry, Health Promotion Board. To assess the herd immunity of the population against rubella, 4 serological surveys were conducted from 1989 to 1990, in 1993, 1998 and 2004. **Results:** The incidence of rubella has decreased significantly from the peak of 13.3 per 100,000 population in 1996 to 1.8 per 100,000 in 2007. CRS has virtually disappeared. With more than 92% to 93% of primary school leavers and preschool children annually vaccinated against rubella since 1976 and 1990, respectively, the level of susceptibility to rubella among women in the reproductive age group has gradually decreased from 44% in 1975 to 28% in 1985, and maintained at between 10% and 20% from 1987 to 1998. A considerable proportion (15.8%) of women 18 to 44 years of age remained susceptible to rubella infection in 2004. **Conclusion:** Rubella prevention and control has been successfully implemented. However, the relatively high level of susceptibility to rubella among women in the reproductive age group continues to be of concern. More public awareness and health educational efforts are needed and every opportunity should be taken to ensure that all susceptible women are identified and protected against the infection.

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Key words: Congenital rubella syndrome, Immunisation, Serological surveys

Introduction

Rubella is a mild febrile viral exanthematous disease transmitted through droplets or direct contact with the nasopharyngeal secretion of an infected person. It is of public health importance because of the teratogenic effects of the virus on the developing fetus. When rubella is contracted in the first trimester of pregnancy, it can cause multiple organ defects in the fetus and result in congenital rubella syndrome (CRS), miscarriage or fetal death.¹ The risk of congenital anomalies is rare when maternal infection occurs after the 20th week of pregnancy.² Up to 50% of infections may be sub-clinical or unapparent, and thus are unrecognised.³

CRS used to be an important public health problem in

Singapore.⁴ The incidence of CRS at Kandang Kerbau Maternity Hospital following a community-wide outbreak in 1969 reached 8.5 per 100,000 deliveries from November 1969 to December 1971.⁵ A post-outbreak serological survey of the female adult population revealed an immunity level against rubella of only 50% to 60%.⁶ The low seroprevalence of rubella in women 15 to 40 years of age was confirmed in a study conducted between January 1975 and December 1979 when 44% to 51% of 2965 subjects tested negative for rubella haemagglutination-inhibition antibody.⁷ Another 2 outbreaks of rubella occurred in 1975 and 1978, both started among national servicemen returning from overseas training and rapidly spread from

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army camps to the general population.⁸ To eliminate CRS, monovalent rubella vaccine was first introduced into the national immunisation programme for pre-adolescent female primary school leavers (aged 11 to 12 years old) in November 1976. This was subsequently extended to male primary school leavers and national service recruits in April 1982 as periodic outbreaks of rubella with high sickness-absenteeism among national servicemen had affected training schedules.⁹ Moreover, infected soldiers continued to be a potential source of infection to susceptible females in the reproductive age group.⁸

In January 1990, the selective rubella vaccination was extended to include all children of 1 year of age when the childhood immunisation programme against measles using the monovalent measles vaccine was replaced by the trivalent measles, mumps and rubella (MMR) vaccine. The monovalent rubella vaccine given to both male and female primary school leavers continued until it was replaced by the second dose of MMR vaccine in 1998.

The objectives of this study were to review the epidemiology of rubella in Singapore, the impact of the rubella immunisation programme on the elimination of CRS and the immune status of the population against rubella, with special reference to women in the reproductive age group.

Materials and Methods

Case Surveillance

The epidemiological data of all cases of rubella notified to the Ministry of Health (MOH) under the Infectious Disease Act from 1991 to 2007 were collated and analysed. The clinical criteria for the diagnosis of rubella were provided in a guidebook that was made available to all medical practitioners.¹⁰

Cases of CRS among infants born in Singapore and therapeutic abortions performed for rubella infections were identified from the Central Claims Processing System, a national inpatient discharge database which covered all hospitals in Singapore. The discharge diagnosis was based on the International Classification of Diseases, Ninth Revision (ICD-9), code 771.0. A case of CRS was defined as a clinically compatible case with a positive laboratory test [isolation of rubella virus or seroconversion or presence of rubella-specific immunoglobulin M (IgM) antibody]. All the CRS cases detected were investigated.

Immunisation Coverage

The annual MMR immunisation coverage of each cohort of Singapore citizens and permanent residents aged 2 years old from 1995 to 2007 was obtained from the National Immunisation Registry (NIR). In the case of primary school leavers, data on the proportion of children aged 11 to 12 years immunised against rubella were obtained from the

School Health Service of Youth Health Division, Health Promotion Board.

Serological Surveys

To assess the herd immunity of the population against rubella, 4 seroepidemiological surveys were conducted; the first from 1989 to 1990 just prior to the introduction of the trivalent MMR vaccine into the national childhood immunisation programme,¹¹ the second in 1993,¹² the third in 1998¹³ and the last in 2004.¹⁴ In the first 3 surveys, blood samples were collected from healthy children and adults aged between 6 months and over 45 years old at designated government polyclinics after consent had been obtained. Rubella agglutination IgG antibodies were analysed by the microparticle enzyme immunoassay (Abbott-Rubella IgG 2.0) at the Department of Pathology, Singapore General Hospital.

The last survey was based on stored blood samples of the National Health Survey (NHS 2004)¹⁵ collected between September and December 2004. The NHS 2004 was approved by the Institutional Review Board (IRB) Ethics Committee of the Health Promotion Board, Singapore. Details of the survey which was representative of the general population aged 18 to 74 years old have been described elsewhere.¹⁶ All eligible participants had consented to have their residual sera used for further research. Sera from these participants, stored at -80°C at the Department of Pathology, Singapore General Hospital, were sent to the Department of Laboratory Medicine, National University Hospital for analyses. The titre of rubella IgG antibody was determined using Abbott AXSYM system rubella IgG assay (Abbott Park, IL), a microparticle enzyme immunoassay. A titre of 10 IU/mL or greater was considered positive.

Statistical Analysis

For the calculation of annual age-specific incidence rates, the denominators used were the corresponding estimated mid-year populations compiled by the Department of Statistics, Singapore. The annual incidence rates of infants with CRS were calculated based on the number of live-births of the corresponding years obtained from the Registry of Births and Deaths.

Differences in rubella seropositivity rates by age, gender and ethnicity were computed and tested for statistical significance using the Z-test for 2 independent proportions. Univariate analysis was performed using χ^2 test for categorical data. Multivariate analysis using logistic regression was also carried out to identify socio-demographic profiles significantly associated with the presence of rubella seropositivity. Statistical analyses were performed using SPSS Software Version 15.0 (SPSS Chicago, IL). A *P* value less than 0.05 was considered statistically significant.

Results

Epidemiology

A 3-year cyclical pattern in rubella incidence was observed during the period from 1991 to 1999, with high incidence in 1993 (12.8 per 100,000 population), 1996 (13.3 per 100,000 population) and 1999 (10.9 per 100,000 population) (Fig. 1). This was followed by a significant decline to an incidence of 2.1 per 100,000 population in 2003 ($P < 0.05$, χ^2 test for trend), and 1.8 per 100,000 population in 2007.

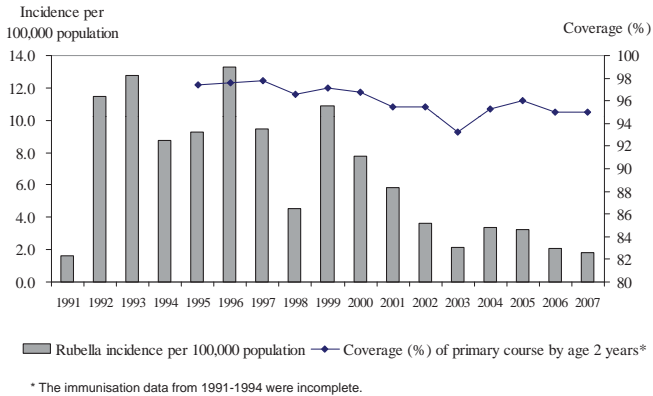


Fig. 1. Rubella incidence (per 100,000 population) and MMR immunisation coverage, 1991-2007.

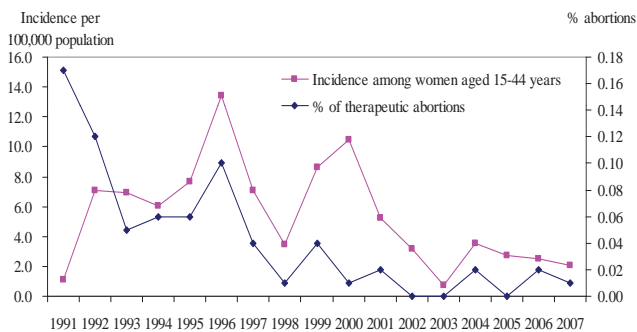


Fig. 2. Rubella incidence of women aged 15-44 years (per 100,000 population) and proportion of therapeutic abortions performed on account of rubella infections, 1991-2007.

The incidence rate was highest in preschool children aged below 5 years which constituted 24.1% to 38.1% of the reported cases, except in 1999 and 2000 (Table 1). The higher incidence rate in older children and adults in these 2 years was due to several institutional outbreaks (2 or more epidemiologically related cases) involving mainly unvaccinated foreign students, office and factory workers. Most of the cases (55%) in the 0 to 4 year-old age group were contributed by infants below 1 year of age who are not eligible for MMR vaccination.

The mean annual incidence rate of foreigners (6.8 per 100,000) was higher than that of each of the 3 major ethnic groups of local residents (Chinese, 4.0 per 100,000; Malays, 4.9 per 100,000; Indians, 1.3 per 100,000). The overall rate for males (4.9 per 100,000) was higher than that for females (4.1 per 100,000).

The incidence of rubella among women in the reproductive age group of 15 to 44 years old had decreased from 13.5 per 100,000 population in 1996 to 2.1 per 100,000 population in 2007 (Fig. 2). Correspondingly, the proportion of therapeutic

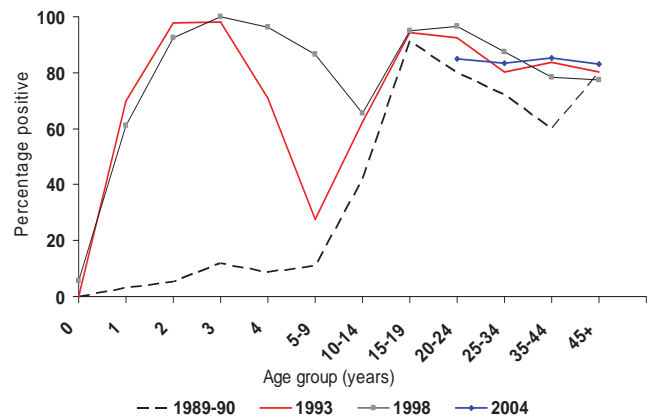


Fig. 3. Age-specific prevalence of antibody to rubella in Singapore, based on serological surveys conducted in 1989-90, 1993, 1998 and 2004.

Table 1. Age-Specific Incidence Rates per 100,000 Population of Reported Rubella Cases, 1998-2007

Age group (y)	1998 (n = 179)	1999 (n = 432)	2000 (n = 312)	2001 (n = 242)	2002 (n = 152)	2003 (n = 88)	2004 (n = 141)	2005 (n = 139)	2006 (n = 90)	2007 (n = 83)
0-4	21.5 (30.2)	11.5 (6.5)	2.5 (1.9)	28.0 (27.3)	25.2 (38.1)	14.5 (36.4)	15.7 (24.1)	19.4 (29.5)	14.9 (34.4)	11.0 (27.7)
5-9	4.4 (6.7)	3.3 (2.1)	6.7 (5.8)	5.6 (6.2)	4.1 (7.2)	1.2 (3.4)	0.4 (0.7)	2.8 (5.0)	1.2 (3.4)	0.0 (0.0)
10-14	6.6 (8.4)	7.8 (4.4)	25.3 (20.2)	6.1 (6.6)	10.7 (19.1)	2.9 (9.1)	3.7 (7.1)	2.6 (5.0)	1.5 (4.4)	1.1 (3.6)
15-24	5.2 (17.9)	20.5 (28.7)	13.2 (26.3)	6.4 (16.9)	4.2 (17.1)	2.3 (15.9)	3.7 (16.3)	2.9 (13.7)	2.8 (21.1)	2.5 (21.7)
25-34	3.9 (19.5)	11.3 (22.9)	11.3 (31.7)	5.2 (19.0)	1.9 (11.2)	2.0 (19.3)	4.0 (24.1)	3.4 (20.9)	2.5 (24.4)	2.2 (25.3)
35-44	2.9 (11.7)	12.2 (21.1)	4.6 (11.2)	5.8 (18.6)	1.3 (6.6)	1.1 (9.1)	2.5 (13.5)	2.9 (15.8)	0.4 (3.4)	0.9 (8.4)
45-54	1.1 (5.6)	6.3 (14.3)	0.9 (2.9)	1.2 (5.4)	0.1 (0.7)	0.5 (6.8)	1.7 (14.2)	1.1 (10.1)	0.6 (8.9)	0.8 (13.3)
Total	4.6 (100.0)	10.9 (100.0)	7.7 (100.0)	5.8 (100.0)	3.6 (100.0)	2.1 (100.0)	3.4 (100.0)	3.3 (100.0)	2.0 (100.0)	1.8 (100.0)

Figures in brackets refer to percentage of total cases in the corresponding year.

Table 2. Incidence of CRS and Therapeutic Abortions Performed on Account of Rubella Infection, 1991-2007

Year	CRS		Total no. of abortions	No. of therapeutic abortions performed on account of rubella infections	
	No.	Per 1000 live-births		No.	(%)
1991	1	0.02	17,798	30	0.17
1992	4	0.08	17,073	21	0.12
1993	4	0.08	16,476	8	0.05
1994	2	0.04	15,690	10	0.06
1995	2	0.04	14,504	9	0.06
1996	2	0.04	14,365	15	0.10
1997	0	0.00	13,827	5	0.04
1998	0	0.00	13,838	2	0.01
1999	2	0.05	13,753	6	0.04
2000	0	0.00	13,754	2	0.01
2001	2	0.05	13,140	3	0.02
2002	1	0.02	12,749	0	0.00
2003	0	0.00	12,272	0	0.00
2004	0	0.00	12,070	2	0.02
2005	1	0.03	11,482	0	0.00
2006	0	0.00	12,032	3	0.02
2007	0	0.00	11,933	1	0.01

abortions performed on account of rubella infections had decreased from 0.10% in 1996 to 0.01% in 2007. The overall correlation between the incidence of rubella among women aged 15 to 44 years old (per 100,000 population) and proportion of therapeutic abortions performed on account of rubella infections from 1991 to 2007 was found to be statistically insignificant ($P > 0.05$). However, there were some years that the pattern corresponded quite well, such as in 1996.

The incidence of CRS declined from 0.08 per 1000 live-births in 1992/1993 to 0.03 per 1000 live-births in 2004 (Table 2). No cases of CRS were reported in 1997, 1998, 2000, 2003, 2004, 2006 and 2007. The number of therapeutic abortions performed on account of rubella infections also dropped markedly from 30 cases in 1991 to 1 in 2007.

Immunisation Coverage

The annual MMR immunisation coverage among Singapore citizens and permanent residents at 2 years of age had been maintained at a high level (93% to 98%), even in 2003 when an outbreak of severe acute respiratory syndrome (SARS) occurred (Fig. 1).¹⁷ In the case of primary school leavers, the annual coverage rate had been above 93% (93% to 96%).

Seroepidemiology

A total of 500 children and adults between 6 months and over 45 years of age were tested for rubella IgG antibody during the 1989 to 1990 survey. The seroprevalence of rubella was low in children below 10 years of age (7% to 11%). It doubled from 42% in the 10 to 14 year-old age group to 90% in the 15 to 19 year-old age group and maintained at above 80% in adults, except in the 35 to 44 year-old age group which had a prevalence of 60% (Fig. 3).

In the 1993 survey, sera from 909 children and adults aged 6 months to over 45 years old were analysed. The seroprevalence increased from 69.9% in 1 year-old infants to 97.9% in children aged 2 to 3 years old. It then declined to 70.8% in the 4 year-olds and 27.5% in children aged 5 to 9 years old. The seroprevalence was 62.5% in older children aged 10 to 14 years of age and it attained a very high level of 94.4% in the age group of 15 to 19 years old before it dropped again to 80.3% in adults above 45 years of age (Fig 3).

The serological survey conducted in 1998 coincided with the implementation of the 'catch-up' measles vaccination programme for adolescents aged 12 to 18 years old using the MMR vaccine in 1997, and the introduction of the second dose of MMR vaccine to all primary 6 school children in 1998.¹⁸ Sera obtained from 928 children and adults from 6 months to over 45 years of age were tested. The seroprevalence was between 87.4% and 96.6% among those aged 15 to 34 years old, and then maintained at 77.3% to 78.4% in adults aged above 35 years old (Fig 3).

Compared to the serological survey conducted prior to the introduction of the trivalent MMR vaccine in 1990, there had been a significant increase in the overall prevalence of antibody to rubella among healthy children and adults aged between 6 months and over 45 years old from 47.6% in 1989 and 1990 to 71.7% in 1993, and 80.2% in 1998 ($P < 0.05$, χ^2 test for trend). The increase in seroprevalence in the 5 to 9 year-old age group was most marked across all surveys; the seroprevalence in this age group was 27.5% in 1993, which was more than double that in 1989 and 1990 (11.0%), and it increased by more than 3 times to 86.4% in 1998 ($P < 0.05$, χ^2 test for trend). The seroprevalence in the 10 to 14 year-old age group was also significantly higher at 62.5% in 1993, compared to 42% in 1989 and 1990 ($P < 0.05$). The antibody prevalence in the 15 to 24 year-old age group increased from 85% in 1989 and 1990 to 93.4% in 1993 and 95.8% in 1998 ($P < 0.05$, χ^2 test for trend).

In NHS 2004, of 4152 adult resident population aged 18 to 74 years old tested for rubella IgG antibody, 84.0% (95% CI, 82.9%-85.1%) were seropositive. While the proportion of women aged 15 to 44 years old susceptible to rubella infection decreased from more than 20% in the

period of 1989 to 1990 to 17% in 1993, and 13.6% in 1998, a significant proportion of women in the reproductive age group remained susceptible to rubella infection (15.8% seronegative) in 2004. There was no significant ethnic difference in susceptibility to rubella among this group of women (Chinese, 15.8%; Malays, 13.8%; and Indians, 16.7%). Based on univariate analysis and multivariate analysis using logistic regression, no significant differences in socio-demographic profiles among women of all ages and women in the reproductive age group were found. Using “year of birth before 1964” (>12 years old in 1976) as a proxy indicator, no significant difference was detected in the seroprevalence among females born before or after 1964.

Discussion

The incidence of rubella has been declining from 13.3 per 100,000 in 1996 to 1.8 per 100,000 in 2007. This decreasing trend can be attributed to the comprehensive coverage of the childhood rubella immunisation programme in which more than 93% of children aged 1 to 2 years old are annually vaccinated. The impact of the national immunisation programme against rubella was also reflected in the findings of the periodic serological surveys conducted in the period of 1989 to 1990, 1993 and 1998 which showed increasing prevalence of rubella antibodies among preschool and primary school leavers vaccinated. Moreover, from the 1993 serological survey, the high seroprevalence of 93.4% in the 15 to 24 year-old age group confirmed the immunogenicity of the monovalent rubella vaccine. Between 91.3% and 98.7% of this age cohort was vaccinated with the monovalent rubella vaccine at 11+ years of age during the period of 1977 to 1993.¹²

Based on mathematical modelling, rubella virus transmission in children may be eliminated with a vaccination coverage rate of about 90%.¹⁹ In fact, outbreaks in army camps had virtually disappeared following routine vaccination of male primary school leavers and national service recruits in 1982.²⁰ More than 97% of a cohort of national service recruits tested in 1994 was found to possess rubella antibodies.²¹

Rubella continues to affect the unvaccinated population; viz infants below 1 year of age who are not eligible for immunisation, local residents who are not covered under the national immunisation programme which started in 1976 for female primary school leavers of 12 years of age, and foreign students and workers from countries where there is no immunisation programme against rubella or where the immunisation coverage may be low.

The primary objective of the rubella immunisation programme is to prevent CRS.²² Such immunisation programmes have eliminated or greatly reduced the incidence of rubella and CRS in developed countries.^{23,24}

The World Health Organisation (WHO) has set a target to reduce the incidence of congenital rubella infection in the European Region to less than 1 per 100,000 live-births by 2010.²⁵ In Singapore, the incidence of congenital rubella dropped sharply from 16 cases in 1976 to 10 cases in 1983, 2 cases in 1987 and it has virtually disappeared in recent years.²⁰ The annual number of therapeutic abortions performed on account of rubella infection has also decreased from between 45 and 77 cases in the 1970s and 1980s to virtually none in the last few years. While Singapore is on track towards achieving the WHO target for the European Region, there is no room for complacency.

Of concern is the considerably high proportion of women of reproductive age who remain non-immune despite the high coverage of the childhood rubella immunisation programme over the last 3 decades. Although the level of susceptibility in women aged 15 to 44 years old has dropped from 44% in 1975 to 28% in 1985, and maintained at between 10% and 20% from 1987 to 1998, the NHS 2004 revealed that 15.8% of women aged 18 to 44 years old were non-immune to rubella infection. This level is relatively high compared to women of reproductive age (15 to 39 years old) in Australia and 16 countries in the WHO European Region in 2003, for example, it was 2.7% in Australia, 6.2% in England and Wales, 2.2% in Sweden,²⁶ and 9.6% among women of foreign nationality and 3.5% among the local population in Switzerland.²⁷ When compared with women of reproductive age in some Asian cities, Singapore has a non-immunity level higher than that in Taipei (10.9% in women aged 15 to 44 years old in 2004),²⁸ but lower than that in Seoul (26.9% in female university students aged 18 to 26 years old in 1996).²⁹

No significant difference in susceptibility to rubella was detected amongst women of the pre-vaccination cohort (pre-1964) and those of the post-vaccination cohort (post-1964). One possible explanation for this observation is the rise in immigrants and non-residents from rubella endemic countries in Singapore. As we do not have the breakdown of the residents in terms of Singapore citizens born in Singapore and Singapore permanent residents who originated from other countries where the rubella immunisation programme might not be as comprehensive as in Singapore, we are unable to fully examine the impact of high levels of immigration on the overall level of herd immunity in Singapore.

The growing immigration in developed countries is known to pose a higher risk of rubella virus transmission due to the introduction of groups of unprotected individuals.³⁰ The incidence rate of rubella among foreigners in Singapore is higher than that of local residents, and localised transmission has occurred in settings where unvaccinated susceptible populations congregate such as schools, factories and offices.

A high degree of vigilance should therefore be maintained in such settings where susceptible foreigners congregate.

Greater focus on protecting the population at greatest risk, that is, women in the reproductive age group is needed, as the risk of infection in pregnant women constitutes the public health burden of rubella.^{31,32} Every opportunity for health education and vaccination against rubella should be taken to ensure that all susceptible women, including immigrants and non-residents, are protected. Exposed pregnant women with low-level immunity to rubella could be at risk of re-infection of wild-type rubella.³³ The current rubella immunisation programme will be further strengthened and extended. These include premarital screening for rubella antibody to identify susceptible women before pregnancy,³⁴ and vaccination of susceptible women in the reproductive age group as part of the routine general medical and gynaecological outpatient care.³⁵ Foreign students should also be routinely checked not only for the compulsory measles vaccination, but also rubella vaccination which is offered voluntarily.

We would like to point out that in this study, only 14% to 32% of the reported rubella cases had the clinical diagnosis verified by laboratory tests. Rubella is clinically similar to a number of other viral infections. In an ad-hoc study of a sample of 114 notified cases of measles, 42.1% turned out to be rubella.³⁶ Moreover, in the interpretation of IgM antibody results, non-specific findings are not uncommon as the antibody may cross-react with other viral infections such as parvovirus B19, cytomegalovirus and Epstein-Barr virus.¹¹ It should also be noted that the serological surveys of the period of 1989 to 1990, 1993 and 1998 were not representative of the general population and that the laboratory tests for the detection of IgG rubella antibodies were not the same in the various surveys conducted. Nevertheless, these surveys have provided evidence of the changing trends in the age-specific seroprevalence of rubella following the introduction of the national childhood immunisation programme and the implications of the findings in women of reproductive age.

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