Original Report

A mathematical model to measure the impact of the Measles Control Campaign on the potential for measles transmission in Australia

C. R. MacIntyre,[1] N. J. Gay,[2] H. F. Gidding,[1] B. P. Hull,[1] G. L. Gilbert,[1,3] and P. B. McIntyre[1]

Background: The aims of this study were to determine the impact of the Australian Measles Control Campaign (MCC) on the transmission dynamics of measles by calculating the reproductive number (R) before and after the MCC, and to predict measles control in Australia in the future.

Methods: A national serosurvey was conducted before and after the MCC. Sera were tested for anti-measles IgG using enzyme immunoassay (EIA). A mathematical model, using serosurvey results and vaccine coverage estimates, was used to calculate the change in R after the MCC.

Results: The values of R calculated before and after the MCC were 0.90 and 0.57. At vaccine coverage levels indicated by the Australian Childhood Immunisation Register (ACIR), the value of R will exceed 1 (the epidemic threshold) in 2007–2008 nationally, and sooner in some regions of Australia. Coverage of at least 84% with two doses of MMR is required to sustain measles control.

Conclusions: The Australian MCC had a significant impact on the transmission dynamics of measles. However, current vaccine coverage levels may result in indigenous measles transmission by 2007. Sustained efforts are required to improve coverage with two doses of MMR and to ensure elimination of indigenous measles transmission.

INTRODUCTION

Australia conducted a national Measles Control Campaign (MCC) in the second half of 1998. The $30 million campaign was designed and funded by the Department of Health and Family Services of the Commonwealth of Australia (now the Department of Health and Aging), and was a joint initiative with the States and Territories. It aimed to increase measles vaccination coverage. The MCC was the first stage in a longer-term strategy to eliminate measles from Australia and help achieve the World Health Organization's goal of world-wide eradication between 2005 and 2010. Globally, measles is among the leading causes of death, and is responsible for more deaths than road traffic accidents or lung cancer.[1]

The MCC was conducted when the age for the second dose of measles–mumps–rubella (MMR) vaccine was lowered from 10–16 years to 4–5 years (prior to

[1]National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, The New Children's Hospital, Westmead, NSW, Australia; [2]PHLS Communicable Disease Surveillance Centre, Colindale, London, UK; [3]Institute for Clinical Pathology and Microbiology Research, Westmead Hospital, Westmead, NSW, Australia.

Address correspondence to Dr C. R. MacIntyre, NCIRS, Children's Hospital at Westmead, Locked Bag 4000, Westmead, NSW, Australia 2145.

E-mail: rainam@chu.edn.au

Corresponding Editor: Robert Gilman, Baltimore, MD, USA

school entry), and was accompanied by a major media program. The MCC had three components: (1) all primary school-aged children were offered MMR vaccine regardless of their existing immunization status; (2) reminder letters were sent to parents of children aged 12–42 months whose first dose of MMR vaccine (scheduled at the age of 12 months) was due or overdue, according to the Australian Childhood Immunisation Register (ACIR); and (3) an information pack was sent to secondary school students and their parents to encourage students to obtain a second dose of MMR.

It was found that over 95% of 1.78 million school children aged 5–12 years were vaccinated during the MCC.[2,3] More than 1.33 million of these children were vaccinated in the school program, which reached 8783 schools throughout Australia.[2]

Transmission of any disease depends on the infectivity of the agent, the duration of infectivity, rates of contact, and the susceptibility of contacts.[4] The combined effect of these factors is summarized by R, the effective reproductive number, which is the average number of secondary cases produced by a typical case in a given population. When R is greater than 1, cases increase from one generation to the next, and an epidemic ensues. When R is less than 1, cases decrease from one generation to the next. Thus the epidemic threshold is defined as $R=1$. For acute diseases that confer immunity such as measles, R oscillates around 1 in an epidemic cycle, where an epidemic begins when R is greater than 1. After the onset of the epidemic, R

declines as the pool of susceptible individuals is reduced. When R is reduced to less than 1, the number of cases declines, and the epidemic ends. Indigenous transmission (endemicity) will be eliminated if R is maintained below the epidemic threshold (i.e. R less than 1).[5] Thus, measurement of R gives an indication of measles control.

The aims of this study were to determine the impact of the MCC on the transmission dynamics of measles by calculating R before and after the MCC, and to predict measles control in Australia in the future.

METHODS

Serosurvey

The serosurvey methods have been described in detail previously.[6] Briefly, approximately 3000 sera, that would otherwise have been discarded, were obtained from diagnostic laboratories throughout Australia before and after the MCC, from children aged 1–18 years. In addition, a further 2025 sera collected before the MCC from subjects aged 19–49 years were tested for measles IgG antibody. Since older age groups were not targeted in the campaign, it was assumed that there would be no significant change in seroprevalence in this group.

Within each 1-year age group, States and Territories were sampled proportionally to their population size. Sample sizes were calculated to achieve confidence intervals of approximately ±5% for each age group, based on the expected level of immunity to measles. Approximately equal numbers of sera from males and females were tested.

Sera were tested and results interpreted according to the manufacturer's instructions using the Enzygnost (Behring Diagnostics, Marburg, Germany) anti-measles IgG enzyme immunoassay (EIA), at the Institute of Clinical Pathology and Medical Research, Sydney, Australia. Results were classified as positive, negative, or equivocal. A sensitivity analysis was done, in which data were analyzed initially with the equivocal results grouped with the positive results and then with the negative results. The rationale for this is that equivocal results usually indicate low, but not necessarily protective, levels of vaccine-induced antibodies.[6,7]

When calculating susceptibility to measles, results were age standardized to adjust for disproportionate sampling from different age groups. As the serosurvey was only conducted on people aged 1 year or over, and knowing that maternal antibodies to measles persist in the first 6 months of life, we assumed 50% susceptibility in children aged less than 1 year. The highest age of people tested was 49 years. The susceptibility to measles in people aged over 49 years was assumed to be the same as that for people aged 45–49 years, as older adults have been almost universally exposed to natural infection. Serosurvey results were used to model both pre- and post-campaign values of R.

Vaccine coverage estimates

Vaccine coverage estimates were obtained using the ACIR.[8] The ACIR is a national register which records the immunization status of all children aged 0–7 years for scheduled vaccines. Australia has universal health insurance coverage known as 'Medicare'. When a child is enrolled in Medicare after birth, they are automatically included in the ACIR. General practitioners (GPs) receive incentive payments for immunizing children and for notifying immunisations to the ACIR, and parents receive a Child Immunisation History Statement when the child is 12 months old, which outlines all the immunizations that the child has received. Parental incentives are also in place, with a maternity immunization allowance and childcare benefits being linked to immunization. The ACIR was first established in 1996, so that coverage data at 4 years of age are available only for the first birth cohort of children born in 1996. These data were used to estimate susceptibility to measles and to estimate future population trends in R. To predict measles control in the future, we used the ACIR MMR coverage data at 12 months and 4 years as a 'worst case scenario' (assuming that ACIR data represent the minimum possible coverage). We selected levels of coverage with two doses of MMR that are required to provide adequate herd immunity (94%) as our 'best case scenario'. We selected a level of vaccine coverage midway between the best and worst case scenarios as a third, intermediate scenario.

Postcode data were used to examine coverage by Divisions of General Practice (DGPs), which are geographically defined administrative areas. There are 123 DGPs in Australia, and 90% of GPs belong to a DGP. We modeled changes in R for selected DGPs with high and low MMR coverage around Australia.

Modeling

The population was stratified into five age groups: 0–4, 5–9, 10–14, 15–19, and 20+ years. The proportion susceptible in each age group x_i before and after the MCC was estimated from the seroprevalence data. Projections of the proportion susceptible in subsequent years were based on the post-MCC susceptibility in each cohort, on the assumption that no immunity would be acquired through natural infection. In new cohorts, the proportion susceptible was estimated from the expected vaccine coverage and vaccine efficacy (assumed to be 90% after one dose, and 99% after two doses).

The potential for measles transmission was summarized by the effective reproduction number, R, the average number of secondary cases produced by a typical infective agent.[9] R depends on the transmission potential for measles in a totally susceptible population and on the proportion susceptible in each age group. R_{0ij} is the average number of secondary cases in the ith age group caused by an infectious individual in the jth age

group if all individuals in the ith age group are susceptible to infection. Values for R_{0ij} from previous studies in the UK and Canada were used:[10]

$$(R_{0ij}) = \begin{bmatrix} 0.96 & 0.43 & 0.43 & 0.43 & 0.43 \\ 0.48 & 4.99 & 1.80 & 0.48 & 0.48 \\ 0.48 & 1.80 & 7.48 & 0.48 & 0.48 \\ 0.48 & 0.48 & 0.48 & 8.73 & 0.48 \\ 5.23 & 5.23 & 5.23 & 5.23 & 5.23 \end{bmatrix}$$

If only a proportion x_i of the ith age group is susceptible to infection, then R_{ij}, the number of secondary infections in that group caused by an infectious individual in the jth age group, is given simply by $R_{ij} = R_{0ij} x_i$. The overall R is calculated as the leading eigenvalue of the next-generation matrix R_{ij}.[11]

Ethics approval

The serosurvey was approved by appropriate institutional ethics committees and the state-wide Health Confidentiality and Ethics Committee of the New South Wales Health Department.

RESULTS

Using serosurvey results when equivocal results were grouped with positive results, the values of R calculated before and after the MCC were 0.90 and 0.57, respectively. When equivocal serology results were classed as negative, the values of R were 1.25 before, and 0.93 after, the MCC.

Figure 1 shows the notifications of measles before and after the MCC, and shows that measles notifications declined after the MCC. Figure 2 shows the serosurvey results by age before and after the MCC. Immunity to measles improved in the target age groups after the MCC. Figure 3 shows the predicted R for measles up to 2010 in Australia for varying levels of vaccination coverage. In the worst case scenario (based on ACIR vaccine coverage data and assuming no improvement in coverage), 13% of 5–12-year-olds and 19% of 1–5-year-olds will be susceptible by 2006. The vaccination levels used in the various scenarios are shown in Table 1. Figure 4 shows the R values for selected DGPs in Australia, and shows the projected time when each will exceed the epidemic threshold if vaccination coverage remains at current levels. There is a wide variation in the level of measles control between DGPs.

DISCUSSION

The Australian MCC was successful in reducing susceptibility to measles in the target age groups, as demonstrated by the serosurvey results. Modeling shows that the MCC was successful in interrupting transmission of measles in Australia, as demonstrated by a reduction

of R below the epidemic threshold. However, if ACIR data, which we presented as the worst case scenario, are correct, and there is no improvement in coverage, R will exceed the epidemic threshold by 2007. In this case, another catch-up campaign will be needed in 2005–2006, targeting pre-school and school-aged children who have not received two doses of MMR. However, studies suggest that the ACIR underestimates coverage by 4–7%,[12] and if the ACIR data were adjusted for such levels of underreporting, the true coverage for two doses would be 73–75%. If this is the case, the epidemic threshold will be crossed in 2010. This scenario is still significantly worse than our 'best case' scenario.

Our study also showed a large amount of variation in coverage levels between DGPs in Australia, with coverage of two doses ranging from 40% to 77%. Our modeling indicates that some DGPs may already be exceeding the epidemic threshold for measles. We have not excluded differential underreporting as a factor in this apparent variation, and intend to feed back results to individual DGPs and ask for their assistance in interpreting the results.

One reason why coverage with two doses of MMR may be low is that the second dose, unlike with all previous scheduled vaccines, is not subject to an incentive payment for medical practitioners. In 1998, incentive payments for medical practitioners were introduced for scheduled vaccines at 2, 4, 6, 12 and 18 months, but not for the 4-year MMR dose.[8]

Parental and provider factors may also play a role in low uptake of the second dose of MMR. A UK study showed that MMR vaccination, particularly the second dose, is not perceived to be important for children's health.[13] A survey of the attitudes of medical practitioners to MMR vaccination showed that there was significant misinformation and confusion regarding the need for a second dose, with only 20% of practitioners stating that they would unequivocally recommend the second dose to a wavering parent.[14]

Mathematical modeling has shown that a catch-up campaign must be used in conjunction with high levels of coverage achieved through a routine two-dose schedule, and that a catch-up campaign alone has only transient benefits.[10] The success of the Australian MCC must be consolidated by improving and maintaining

Table 1. Vaccine coverage estimates used in case scenarios for predicting R in the future

	Vaccine coverage		
	Best case scenario (%)	Middle scenario (%)	Worst case scenario (ACIR) (%)
2 doses by 5 years	84	77	70
1 dose by 5 years	12	16	20
0 doses by 5 years	4	7	10
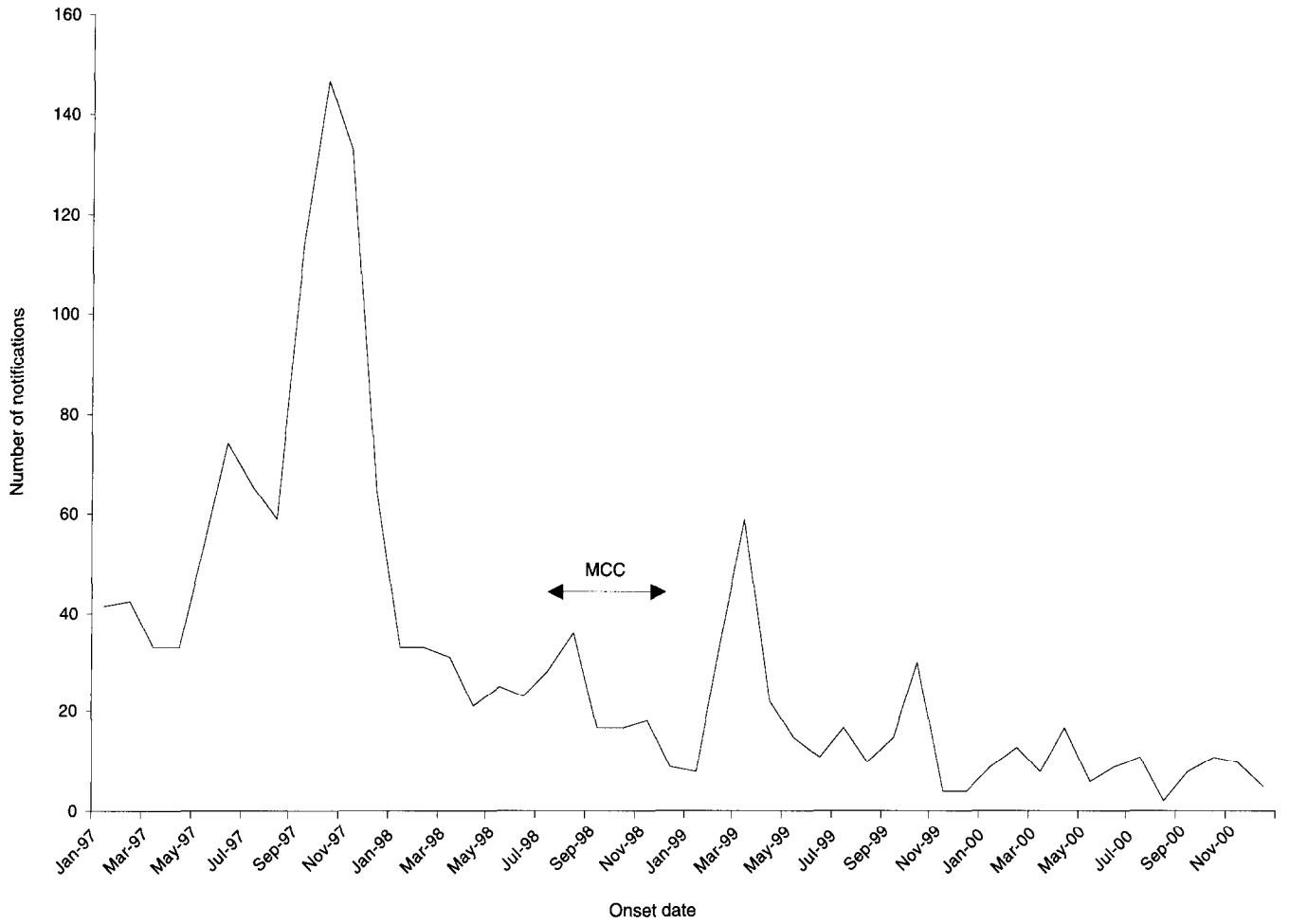
Figure 1. Measles notifications, Australia, 1997–2000.
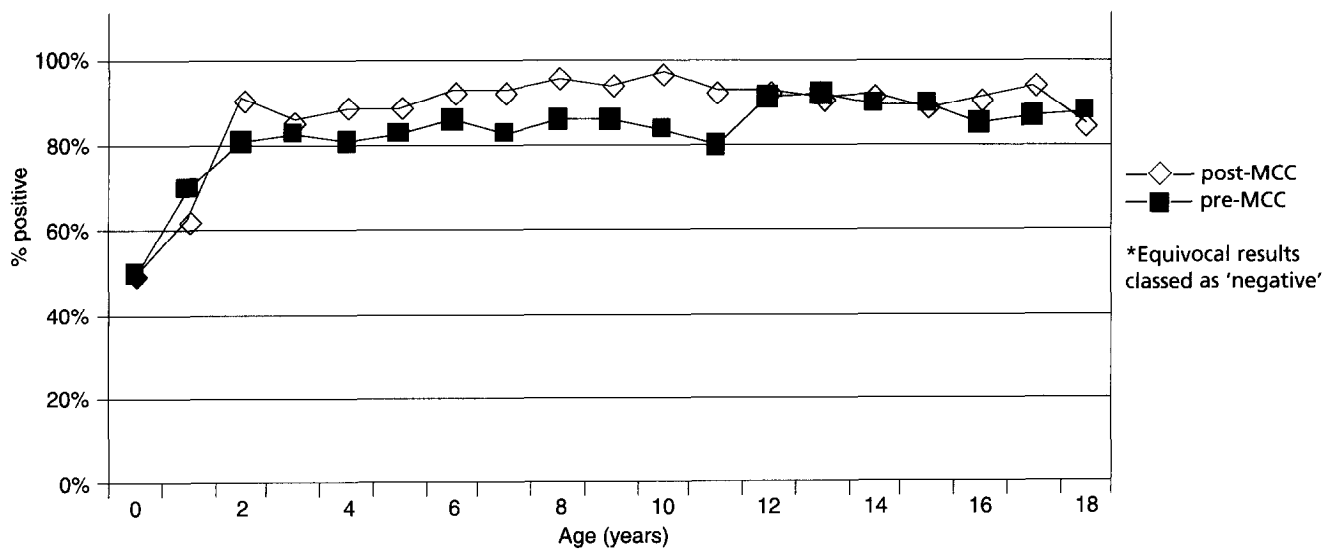
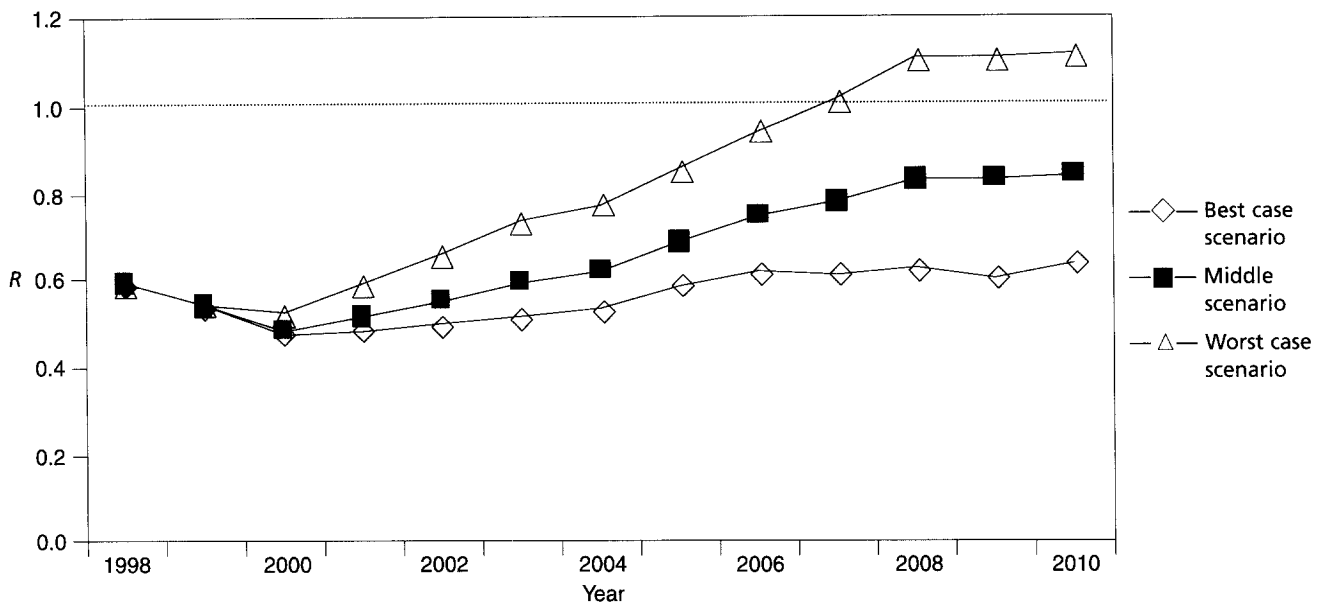**Figure 2.** Percentage-positive* for measles IgG before and after measles control campaign.

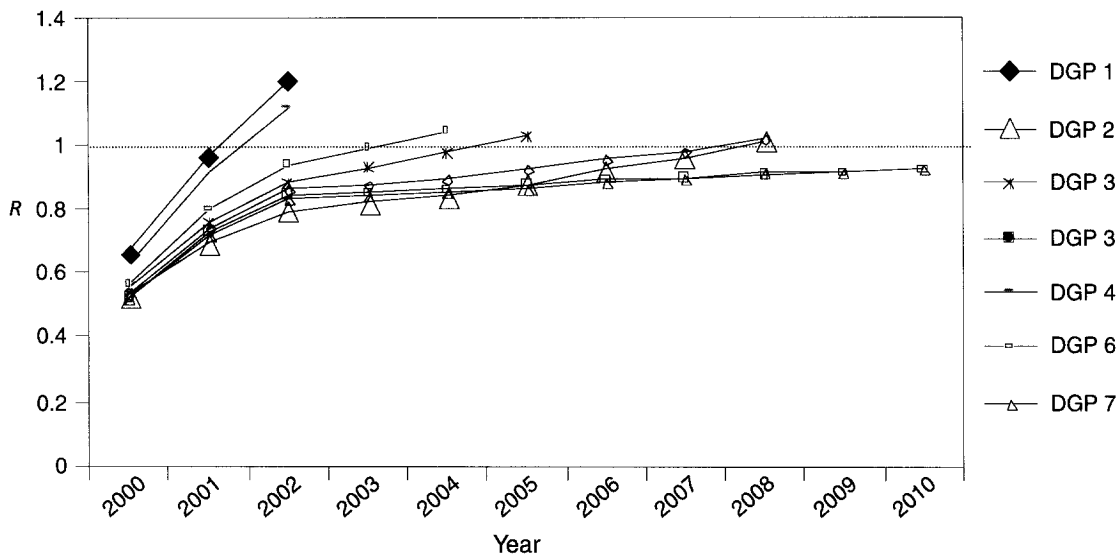**Figure 3.** Effect on *R* for measles of varying vaccination coverage.

Figure 4. *R* for selected Australian divisions of general practice.

high levels of coverage with two doses of MMR. Our study indicates that the ideal coverage target is at least 84%, with two doses at 5 years of age, and less than 4% of children unvaccinated at school entry. Efforts to achieve this target are particularly important in light of recent adverse media publicity about MMR vaccine and autism,[15] and the impact that this may have on coverage.[16,17]

The limitations of this study include those associated with an opportunistic serosurvey. Sera collected for diagnostic testing of other diseases may introduce a selection bias. However, comparisons between our results and those of a prospective serosurvey designed specifically to evaluate the MCC in one state of Australia, Victoria,[18] show comparable results, indicating

that the effects of such bias are minimal. The limitation of using ACIR data for the calculation of vaccination coverage relates to the degree of underreporting to the ACIR, leading to underestimation of coverage. We dealt with this by using the ACIR data as our 'worst case scenario', and using two other scenarios with higher levels of coverage. Mathematical modeling has some limitations, mainly the applicability of population contact patterns derived from the UK and Canada to an Australian setting. However, childcare and schooling patterns (which determine the highest levels of contact) are similar in these three countries.

Despite these limitations, mathematical modeling is useful in evaluating disease control, as it can summarize serologic profiles by a single parameter, the repro-

duction number *R*, which quantifies the level of herd immunity in the population, and allows prediction of epidemics.[9] This provides far more information than simple disease notification data or age–serologic profiles alone, and allows more rational planning of public health programs. Our study demonstrates that, in the absence of regular serosurvey data, knowledge of vaccine coverage can allow the monitoring of measles control. Australia is in a position to do this, with a centralized national register of immunization records.[8]

The WHO has set a target for global eradication of measles.[19] As individual countries and regions approach elimination, good surveillance is important, and can be enhanced by monitoring *R* over time.[5] In this context, elimination (or cessation of indigenous transmission of disease) can be considered to be achieved if *R* is maintained below 1.[5] In Australia, we need to improve vaccination coverage with two doses of MMR in order to achieve this in the long term. We believe that modeling is useful for translating serosurvey and vaccine coverage data into predictive tools to assist public health planning and policy.

REFERENCES

1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997; 349:1269–1276.

2. National Centre for Immunization Research and Surveillance of Vaccine Preventable Diseases. Australian measles control campaign 1998. Evaluation report. Sydney: University of Sydney, Royal Alexandra Hospital for Children, 1999.

3. McIntyre PB, Gidding HF, Gilbert GL. Measles in an era of measles control. Med J Aust 2000; 172:103–104.

4. Anderson RM, May MM. Infectious diseases of humans, dynamics and control. London: Oxford University Press, 1999:757.

5. De Serres G, Gay NJ, Farrington CP. Epidemiology of transmissible diseases after elimination. Am J Epidemiol 2000; 151:1039–1048; discussion 1049–1052.

6. Gilbert GL, Escott RG, Gidding HF, et al. Impact of the Australian Measles Control Campaign on immunity to measles and rubella. Epidemiol Infect 2001; 127(2):297–303.

7. Andrews N, Pebody RG, Berbers G, et al. The European Sero-Epidemiology Network: standardizing the enzyme immunoassay results for measles, mumps and rubella. Epidemiol Infect 2000; 125:127–141.

8. Hull BP, McIntyre PB, Heath TC, Sayer GP. Measuring immunisation coverage in Australia. A review of the Australian Childhood Immunisation Register. Aust Family Physician 1999; 28:55–60.

9. Gay NJ, Hesketh LM, Morgan-Capner P, Miller E. Interpretation of serological surveillance data for measles using mathematical models: implications for vaccine strategy. Epidemiol Infect 1995; 115:139–156.

10. Gay NJ, Pelletier L, Duclos P. Modelling the incidence of measles in Canada: an assessment of the options for vaccination policy. Vaccine 1998; 16:794–801.

11. Diekmann O, Heesterbeek JA, Metz JA. On the definition and the computation of the basic reproduction ratio R0 in models for infectious diseases in heterogeneous populations. J Math Biol 1990; 28:365–382.

12. Hull BP, McIntyre PB. A re-evaluation of immunisation coverage estimates from the Australian Childhood Immunisation Register. Communicable Dis Intelligence 2000; 24:161–164.

13. Pareek M, Pattison HM. The two-dose measles, mumps, and rubella (MMR) immunisation schedule: factors affecting maternal intention to vaccinate. Br J Gen Pract 2000; 50:969–971.

14. Petrovic M, Roberts R, Ramsay M. Second dose of measles, mumps, and rubella vaccine: questionnaire survey of health professionals. BMJ 2001; 322:82–85.

15. Wakefield AJ, Murch SH, Anthony A, et al. Ileal–lymphoid–nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet 1998; 351:637–641.

16. Mason BW, Donnelly PD. Impact of a local newspaper campaign on the uptake of the measles mumps and rubella vaccine. J Epidemiol Community Health 2000; 54:473–474.

17. Anderson P. Another media scare about MMR vaccine hits Britain. BMJ 1999; 318:1578.

18. 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.

19. Anonymous. Advances in global measles control and elimination: summary of the 1997 international meeting. MMWR Morbid Mortal Wkly Rep 1998; 47:1–23.