

## **Measles vaccine efficacy during an outbreak in a highly vaccinated population: Incremental increase in protection with age at vaccination up to 18 months**

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### SUMMARY

During a large measles outbreak in Quebec City in 1989, two investigations conducted in parallel evaluated the relative risk of measles and measles vaccine effectiveness with respect to age at vaccination. The study was a school-based case-control study including 563 cases and 1126 classmate controls. The second was a cohort study of the siblings of school cases including 493 siblings aged between 1 and 19 years. The relative risks (RR) of measles were similar in both settings and the trend towards increased vaccine efficacy with increasing age at vaccination was highly significant ( $P < 0.001$ ). Vaccine efficacy rose from 85% in children vaccinated at 12 months of age to  $\geq 94\%$  in those vaccinated at 15 months and older. Even for children vaccinated at or after 18 months of age, the RR of measles was reduced when compared with children vaccinated between 15 and 17 months of age (RR 0.61, CI 95% 0.33–1.15). Small changes in the timing of initial measles vaccination can have a major impact on vaccine efficacy.

### INTRODUCTION

In the past two decades the influence of age at vaccination on measles vaccine efficacy has been studied intensively. Several studies have demonstrated improved efficacy when vaccination is delayed from 12 to 15 months of age [1] but this effect has not been observed consistently [2, 3]. Because of the small size of these studies, most investigators have had to group children before and after a certain age to identify differences. Convincing evidence of a month by month trend for increasing vaccine efficiency is still lacking.

The optimal age for measles vaccination remains a topic of debate in the developed world and official recommendations vary widely from country to country. For example, measles vaccination in Sweden is recommended at 18 months of age [4], in the United Kingdom and the USA between 12 and 15 months

[5, 6], in Canada at 12 months of age [7], and the World Health Organization recommends vaccination at 9 months of age in the developing countries. Maternally derived measles antibodies are thought to be the major cause of primary vaccine failure when measles vaccine is given at early ages [8]. The presence of maternal neutralizing antibodies is strongly associated with vaccine failure and titres of passively acquired antibodies decline progressively after birth [9]. Other factors which may influence the efficacy of measles vaccination in young children include nutritional status, maturation of the immune system, the route of the vaccine delivery and vaccine dose.

During the 1989 measles outbreak in the Quebec City area, we took the opportunity to re-evaluate the impact of age at vaccination on vaccine efficacy in a large number of children.

#### METHODS

In the Quebec City area (population 600 000), measles vaccine is available free of charge to all infants through regional clinics or private physician offices and measles vaccine coverage has been reported to exceed 99% [10]. Despite this high level of vaccine coverage, a major measles outbreak occurred in 1989 during which 1363 cases were reported. The overall attack rate was 223 per 100 000, with age specific attack rates of 460, 1550 and 689/100 000 in the 5–9, 10–14 and 15–19 year age groups respectively. This outbreak was not restricted to financially disadvantaged populations and cases occurred in all socio-economic strata. Twenty-five percent (342/1363) of the cases were serologically confirmed by the presence of IgM or a fourfold increase in IgG titres. The remaining 1021 (75%) met the Canadian public health surveillance definition of measles: a generalized rash lasting 3 days or more, a temperature of 38.3 °C or more if measured, and one of the following signs: coryza, conjunctivitis or cough [11]. Prior to inclusion in this study, all cases were reconfirmed by public health physicians or nurses through contact with either the parents or the treating physician of the affected child.

#### *Type of study*

Two studies were performed in parallel: a case-control, school-based study and a family cohort study.

#### *Case-control, school-based study*

Elementary schools in the Quebec City area, with at least three measles cases, were selected for the study ( $n = 32$ ). Authorities at five schools refused to provide access to the school registries and these schools were excluded. Ten of the 14 high schools in the area with ten or more cases of measles were randomly selected and all agreed to participate. All cases from the study schools were included. In the elementary schools, each case was matched with two classmate controls. In the high schools, two controls were selected at random in the grade of each case if the attack rate in the grade was 5% or greater. If the attack rate was less than 5%, controls were selected randomly from students attending at least eight class hours per week with the case. Students who had a history of clinical measles before the 1989 outbreak were not eligible to be controls. Eighteen children in the elementary setting and 64 in the high schools had such a history and were excluded. Children

without a verifiable measles vaccination record (33 cases, 24 controls) or those vaccinated with measles vaccine strains other than Moraten (1 case, 7 controls), were also excluded. Thus from 563 cases and 1126 controls, 529 cases and 1095 controls were included in the analysis (Table 1).

#### *Family cohort*

The families of the school cases described above were contacted to create a cohort of exposed siblings. From the 563 school-cases, 504 siblings between the ages of 1 and 19 years without a prior history of measles were recruited. In 11 families, one sibling had developed measles prior to the school (primary case), at the same time or within 6 days of the school case (coprimary cases). The siblings (11) of these families were excluded to avoid bias towards families with higher attack rates. Thus 493 siblings of the school cases were included in the cohort. These children were followed for a period of 3 weeks from the disease onset in the school case. Siblings with no vaccination records (10) or vaccinated with measles strains other than Moraten (21) were excluded from the analysis of age at vaccination (Table 1).

#### *Collection of data*

A phone survey was conducted between 1 December 1989 and 14 February 1990 by seven trained interviewers. Each subject's parents were asked to read information recorded in the standard vaccination booklet provided at birth for all children in Quebec. Information collected included the brand name of the vaccine, the date of vaccination and the identification of the provider (private physician *v.* public health nurse). If the vaccination record was not available, written authorization to consult the medical record was sought.

Monovalent, bivalent and trivalent Merck Frosst measles vaccines used before the introduction of the MMR II® in 1979 all contained the same measles component (at least 1000 TCID<sub>50</sub> of Moraten strain) and are referred to as MMRI. The MMRI does not differ from MMR II by its measles component but includes a new stabilizer and a new rubella strain. Age at vaccination was calculated by rounding down fractional months between birth and the vaccination date.

#### *Statistical analysis*

Relative risks (RR) of measles according to age at vaccination and 95% confidence intervals were calculated directly in the cohort and estimated from the odds ratio (OR) in the case-control study [12]. Associations were assessed for confounding with both conditional and unconditional logistic regression. The models included the age at vaccination, sex, vaccination with MMRI *v.* MMR II and the provider. Because the coefficients of crude analysis were not changed in the multivariate models, only the crude analysis will be shown. Linear trend was evaluated with Mantel Haenszel  $\chi^2_{\text{trend}}$ .

In the family cohort, vaccine efficacy for each age at vaccination *j* (VE<sub>*j*</sub>) was calculated according to the following equation:

$$VE_j = \frac{\text{Attack rate unvaccinated} - \text{attack rate vaccinated}_j}{\text{Attack rate unvaccinated}}$$

Table 1. *Vaccination status of participants by setting*

	Unvaccinated	Vaccinated once with Moraten strain	Vaccinated twice with Moraten strain	Excluded from analysis		Total
				No record	Other vaccine strains	
Schools						
Cases	54	471	4	33	1	563
Controls	0	1074	21	24	7	1126
Family						
Cases	17	41	0	3	0	62
Total	17	441	4	10	21	493

## RESULTS

*Case-control, school-based study*

A total of 563 cases were identified in 37 schools with a total student body of 23997 yielding a crude attack rate of 2.3%. Elementary schools provided 215 cases (attack rate 2.0%) and high schools provided 348 cases (attack rate 2.6%). The mean age of cases was similar for cases and controls (12.3 years). The mean age at vaccination was 12.7 months for cases and 13.6 months for controls. The risk of measles in children vaccinated before 12 months of age was slightly greater than the risk in those vaccinated at 12 months (Table 2). However, 70% of cases and 81% of controls vaccinated before 12 months of age were immunized within 2 weeks of their first birthday. Children vaccinated at 13 months were at significantly lower risk of acquiring measles than children vaccinated at 12 months (RR = 0.55,  $P < 0.001$ ). Children vaccinated at 15 months of age or older were at lower risk of developing measles than those vaccinated at 13 and 14 months of age (RR = 0.58,  $P = 0.002$ ). The risk of measles decreased still further when children vaccinated after 17 months of age were compared with those vaccinated between 15 and 17 months of age, but this difference did not reach statistical significance (RR = 0.62,  $P = 0.10$ ). The overall trend for decreased risk of measles with older age at vaccination was highly significant ( $P < 0.001$ ) (Table 2). Although not numerous, children who got two doses of measles vaccine received them at various ages and were protected as well as those who received a single dose at 15 months of age or older (RR = 0.98,  $P = 1.0$ ). All the associations were similar for boys and girls.

Since cases and controls were matched by school class and were therefore similar for age and the type of vaccine delivered (MMR I or MMR II), these data cannot address the possible influence of elapsed time since vaccination or the vaccine formulation.

*Family cohort*

From the 493 siblings of school-cases, 62 sustained measles (12.7%). Among vaccinated siblings, the attack rate was 9.3% (41/441) while all unvaccinated siblings sustained measles (17/17). The mean age of siblings in the family cohort

Table 2. Relative risk (RR) of measles and vaccine efficacy (VE) according to age at vaccination

	Age at vaccination (months)						2 doses
	≤ 11	12	13	14	15-17	≥ 18	
<b>Schools</b>							
Cases	70	235	78	33	33	22	4
Controls*	107	352	211	120	136	147	21
RR†	0.98	Ref.	0.55	0.41	0.36	0.22	0.29
CI 95%	0.68-1.40	—	0.40-0.76	0.26-0.64	0.23-0.56	0.13-0.37	0.07-0.86
<b>Family</b>							
Cases	6	19	6	3	5	2	0
Total	36	128	73	55	80	69	4
RR†	1.10	Ref.	0.56	0.37	0.42	0.20	undef.
CI 95%	0.47-2.56	—	0.23-1.33	0.10-1.20	0.16-1.09	0.05-0.82	
VE	84	85	92	95	94	97	100
CI 95%	65-92	78-90	82-96	84-98	85-97	89-99	85-100

\* One subject was excluded because month of vaccination was unreadable in his record.

†  $\chi^2_{trend} = 66.9, P < 0.0001$ .

‡  $\chi^2_{trend} = 9.8, P = 0.002$ .

study was 10·5 years and was similar for children who eventually proved to be resistant or susceptible to measles. The mean age at vaccination was 12·8 months in those who developed measles and 14 months in those who remained healthy. The estimated vaccine efficacy in the family cohort was 85% for vaccination at 12 months of age, 92% in those vaccinated at 13 months of age and 97% in children vaccinated at 18 months or later (Table 2). The most important increase in efficacy occurred between 12 and 13 months of age. The point estimates of relative risk for developing measles comparing children vaccinated at > 12 months of age with those vaccinated at 12 months were similar to those in the school-based study (Table 2). In the family cohort, the risk of acquiring measles was significantly lower in those vaccinated at  $\geq 15$  months of age when compared with those vaccinated at 12 to 14 months of age (RR = 0·43,  $P = 0\cdot03$ ). No difference in the efficacy of the MMRI and MMR II was observed in the family cohort study after adjustment for age at vaccination and the elapsed time since vaccination. Sex did not confound or modify the risk of measles.

In both the school-based and the family cohort studies, the risk of measles was similar whether the vaccine was administered by public health nurse or by a physician in a private office.

#### DISCUSSION

This is the largest study to date demonstrating that age at vaccination is a major determinant of measles vaccine efficacy. The study suggests that small changes in the age at vaccination within the range of official recommendations of several developed countries can have a significant impact on the risk of measles and vaccine efficacy.

Estimates of vaccine efficacy are calculated by comparing attack rates in vaccinated and unvaccinated individuals. Since the control group in the school-based study contained no unvaccinated children, estimates of vaccine efficacy could only be made in the family cohort study. These estimates can be biased by several methodological flaws, four of which are thought to be critical [13]. (i) Sensitive and specific case definition, (ii) detection of all cases, (iii) ascertainment of vaccination status and (iv) comparability of measles exposure of vaccinated and unvaccinated individuals. In the current study, the case definition of measles was standard and would be expected to provide good sensitivity and high specificity during a major outbreak. Since measles can be clinically attenuated in subjects with partial vaccine-induced immunity, all studies of this kind are slightly biased to overestimate vaccine efficacy. In the family cohort study, it is unlikely that any measles cases were missed since secondary cases were actively sought. Ascertainment of vaccination status was carried out with great care and the procedures followed were identical for vaccinated and unvaccinated children. Finally, it is reasonable to assume that exposure to measles was uniform in the family cohort since this study was restricted to families in which a single primary case was identified. Although we cannot estimate vaccine efficacy in the school-based case-control study, the point estimates for the relative risk of measles in these children stratified by age at vaccination are strikingly similar to those observed in the family cohort study. This provides reasonable indirect evidence that the vaccine

efficacy estimates calculated from the family cohort study are sound. Exclusion of subjects with a prior history of measles may have no effect on the vaccine efficacy estimates or may lead to an overestimation of efficacy depending upon the mechanism of vaccine-induced protection [14]. However, exclusion of these children should not influence the estimates of relative risk between different ages at vaccination.

Our data confirm and extend previous observations of an effect of the age at vaccination on vaccine efficacy [1, 3]. Our 90% overall efficacy is lower than the 95% estimates frequently reported [15–17]. However, this small difference is probably attributable to the older age at vaccination used in the USA where most of these reports originated. The large number of cases in our study allowed a convincing demonstration of incremental increases in protection between 12 and 18 months of age. Although the greatest change in protective efficacy was observed between 12 and 13 months of age, an improvement in protection was suggested even when children vaccinated at 18 months and older were compared with those vaccinated between 15 and 17 months of age. Since passively acquired antibodies are unlikely to persist at any significant titre beyond 15 months of age, this last observation raises the possibility that factors other than maternal antibodies, such as maturation of the immune system, can also play a role in measles failure in young children.

The relation between passively acquired antibody and vaccine efficacy is complex. Factors likely to influence this relationship include maternal age (i.e. likelihood of immunity from natural disease or from vaccination), circulation of wild-type virus (i.e. a natural booster), nutritional status, gestational age and frequency of other infectious illnesses in early infancy. The relative importance of these factors certainly varies from one population to another. Our study was performed in a relatively affluent, developed world setting in which 93% of the mothers were born before 1957 and presumed to have had natural measles immunity. Although measles vaccination coverage in Canada over the past 20 years has been good to excellent, the virus has continued to circulate widely up to 1990. Many of the mothers in our study were therefore likely to have had one or more prior natural exposures prior to giving birth to the study children. Similarly, the study children may also have been exposed to the wild virus one or more times after vaccination. It is well documented that such exposures can lead not only to classical disease but also to attenuated or asymptomatic infections which also increase vaccination-induced antibody titres [18, 19]. In a highly vaccinated population, the ratio of asymptomatic to overt cases can exceed 10 to 1 [19]. Regardless of the source of induction of antibody titres in the mothers, the kinetics of disappearance of passively acquired antibody in the child are likely to be similar in any given population. Therefore, while our results cannot be directly extrapolated to other populations differing in any of the parameters outlined above, we believe that the basic observation of a month-by-month incremental change in vaccine efficacy is important and has implications for vaccination policies world-wide. In populations protected exclusively by vaccination and free from circulation of wild-type virus, the curve of incremental increase in vaccine efficacy would probably be shifted to earlier ages. In the developing world, prematurity, malnutrition and increased infectious disease burden would shift this



curve to an earlier age but are counterbalanced by other factors such as younger maternal age, greater proportion of mothers with natural immunity and continued circulation of wild-type virus.

In any given population, however, it is likely that even minor change in the age at vaccination may have a major impact on vaccine efficacy. In a population similar to ours, for example, vaccination at 12 months of age (the current Canadian recommendation) is likely to leave as much as 15% of the population susceptible to measles infection. A seemingly trivial delay of 1 month would decrease the proportion of susceptibles to 8% and less than 5% would remain susceptible with a delay of 3 months or more. In a population such as our own, vaccination at 12 months of age would allow large numbers of 'vaccinated susceptibles' to accumulate over time. This pool of susceptibles has no doubt contributed to the major measles outbreaks which have occurred in Canada over the last decade despite high levels of vaccine coverage [20, 21].

Given the remarkably contagious nature of the measles virus, even 4% susceptibles in a large population may be enough to permit low-level circulation of wild-type virus and/or periodic epidemics [22]. Two-dose measles vaccination schedules may therefore be unavoidable in the pursuit of complete elimination of measles. Indeed, many countries have already adopted or are actively considering the adoption of two-dose strategies [23], in spite of some controversy over the protection induced by the second dose in subjects with low initial antibody response [24, 25]. However, even when a second dose of vaccine is to be administered, it seems reasonable to optimize the response to the first dose. This may be particularly relevant in countries like USA or Sweden which opted for schedule with long delay between the first and second doses of measles vaccine.

In conclusion, our data confirm that even small changes in the timing of initial measles vaccination can have a major impact on protection and vaccine efficacy. The optimal age at vaccination should balance the efficacy of the vaccine at different ages with the risk of acquiring measles before these ages. As the persistence of maternal antibody, measles vaccine efficacy and age-stratified incidence of measles are influenced by factors which change in different populations and, as none of these factors is static, it is clear that the 'optimal' age for measles vaccination is a moving target which shifts at different rates and even in different directions over time. Clearly, considerations of measles vaccine timing are more important in countries which rely on a single dose of measles than in those which have two dose schedules [11].

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