

# Twice vaccinated recipients are better protected against epidemic measles than are single dose recipients of measles containing vaccine

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**Abstract**

**Objective**—To study measles risk after revaccination.

**Design**—A population-based case-control study during an epidemic season.

**Main outcome measure**—Relative serologically confirmed measles risk.

**Participants and methods**—153 vaccinated cases, mostly from rural areas, were serologically confirmed as measles at the central laboratory in 1988–89. A randomly selected group of 453 controls from either municipalities of vaccinated cases or from areas where measles attack rate was >600/10<sup>5</sup>, was identified via the population registry. Vaccination and measles histories of cases and controls were determined from official vaccination cards.

**Results**—Once and twice vaccinated had crude relative risk 15.6 and 2.3 compared with thrice vaccinated. When cases who had received their first vaccination at less than 14 months of age were omitted from analysis, once vaccinated had 4.0 (95% CI 1.2, 16.6) times higher age adjusted measles risk compared with twice vaccinated. When, omission was extended to cases from one particular municipality where even revaccinees had high measles risk during an explosive outbreak the corresponding risk ratio was 17.8 (2.8, 67.8).

**Conclusions**—Twice vaccinated have better protection against epidemic measles compared with single dose recipients.

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immunity<sup>7–9</sup> (secondary vaccine failures; time since vaccination), and interval between vaccinations.

**Methods**

SETTING AND VACCINATION IN FINLAND

The setting for the study was the whole of Finland, an affluent Nordic country, with 5.1 million inhabitants.

In Finland, children are vaccinated free of charge by public health nurses at child health care centres. Each vaccination is registered on the child's health card kept at the centre and in a vaccination card kept at home. The health card is transferred from the centre to the school nurse when the child begins school.

All children born between 1973 and 1981 should have received the attenuated Schwarz strain measles vaccine (Rimevax, SmithKline Biologicals, Rixensart, Belgium), but only about 70% coverage was achieved.<sup>4,5</sup> Preschool children born before 1973 also occasionally received this monovalent vaccine. Since 1982, the trivalent measles, mumps, and rubella vaccine (MMR II, Merck and Co, Inc, West Point, PA, distributed in Finland as Virivac, SBL Vaccine AB, Stockholm, Sweden) containing the More Attenuated Enders-Edmonston strain of measles virus has been used exclusively, and administered first at 14–18 months and again at 6 years.<sup>4,6</sup> Thus children born between 1975 and 1981 were targets of both the monovalent and trivalent vaccination programmes, receiving the Schwarz strain at 14 months and exceptionally the first MMR at 2 to 5 years from 1983 to 1986, and then the second MMR at six years. The interval required between successive MMR vaccinations was at least six months. There were 562 000 children born between November 1975 and June 1984 under computerised surveillance. Non-vaccinated children aged 7–11 years were traced and vaccinated at schools in 1985.<sup>5</sup> Since 1986, 19 year old conscripts have been targeted (table 1).

OUTBREAK

During the comprehensive national MMR vaccination programme measles became rare, but pockets of susceptible non-vaccinated people born mostly in the early 1970s remained in rural sparsely populated areas. The last outbreak in Finland began in a municipality on the west coast after a 16 year old girl developed clinical measles on 15 September 1988. Next, a cluster of measles cases

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Indisputable individual level evidence that measles revaccinations increase protection is still lacking, and there is little information upon which to base optimised revaccination schedules,<sup>1</sup> though it has recently even internationally been recommended that there is a need to implement revaccinations against measles.<sup>2</sup>

A two dose measles vaccination policy to improve coverage and correct sporadic primary vaccination failures<sup>3</sup> (deficient seroresponse) was adopted by Finland in 1982.<sup>4,6</sup> This provides an exceptional opportunity to study the epidemiology of vaccine failures, against a background of decades of meticulously kept vaccination records, and effective serological surveillance of measles. We studied whether revaccinated people are better protected compared with single dose recipients in epidemic conditions, with an interest in waning

Table 1 Measles attack rate during the 1988–9 epidemic, and proportion of children daily meeting over nine other children or school mates

| Age          | Daily attendance    | Proportion meeting daily >9 children | Attack rate per 10 <sup>5</sup> | MMR vaccination |
|--------------|---------------------|--------------------------------------|---------------------------------|-----------------|
| 0–9 months   | Home, maternal care | Low                                  | 22.2                            | —               |
| 9–13 months  | Home, maternal care | Low                                  | 306.7                           | —               |
| 14–23 months | Day care or home    | 6*                                   | 98.0                            | First           |
| 2 years      | Day care or home    | 14*                                  | 23.3                            | First†          |
| 3 years      | Day care or home    | 18*                                  | 30.0                            | First†          |
| 4 years      | Day care or home    | 24*                                  | 38.3                            | First†          |
| 5 years      | Day care or home    | 46*                                  | 41.7                            | First†          |
| 6 years      | Day care or home    | 59*                                  | 13.3                            | Second          |
| 7–12 years   | Elementary schools  | High                                 | 12.5                            | First‡          |
| 13–19 years  | Various schools     | High                                 | 270.7                           | First‡§         |
| 20–29 years  | Work                | —                                    | 18.0                            | —               |
| 30–39 years  | Work                | —                                    | 1.5                             | —               |
| 40+ years    | Work                | —                                    | 0.1                             | —               |
| Total        | —                   | —                                    | 25.6¶                           | —               |

\*Among 45 000 vaccinees in 1983. †Those over 18 months of age by 1983 were exceptionally allowed to be vaccinated. ‡70 000 non-vaccinated children aged 7–10 years were traced and vaccinated in 1985, and the 11–13 year old girls' monovalent rubella programme became an MMR programme targeted at both sexes in 1988. §19–20 year old conscripts vaccinated since 1986. ¶451 diagnoses made in commercial laboratories not included.

emerged 100 kilometers to the north. The epidemic shifted both north and south; it peaked in northeast Finland in February 1989, then continued southeast, and the southern-most regions were affected in April–May 1989.

During the outbreak, 1748 measles cases were reported; 1297 of them were confirmed by uniform serological criteria in the National Public Health Institute and the remainder by varying criteria in virology laboratories of five universities. The epidemic is depicted by a slowly propagating curve of measles cases with some peaks.

#### CASES

There were 153 serologically confirmed and vaccinated measles cases during the epidemic, whose mean age was 10.1 years, range 2 to 22. They were identified and confirmed as follows. A nationwide MMR vaccine failure notification programme operating since 1982 in the government reference laboratory only, provided a series of 85 measles cases.<sup>6</sup> Single monovalent measles vaccine failures were not notified to this programme. A serological surveillance programme for measles was launched in 1987 and the National Public Health Institute provided diagnostic services free of charge to both public and private health sectors,<sup>6</sup> and gave 68 mainly monovalent vaccinated measles cases for this study. Cases were included when the time from the last vaccination to the onset of symptoms exceeded 90 days.

The surveillance procedures required that whenever measles was suspected, paired serum

samples of the case were sent for serological confirmation to the National Public Health Institute. Measles was defined as a fourfold increase in IgG antibodies in paired serum samples using a haemagglutination inhibition technique.<sup>10</sup> If only one sample was available, diagnosis required an increase in specific IgM antibodies by enzyme immunoassay (EIA) (Enzygnost IgM/EIA Behringwerke, Marburg, Germany). All cases were IgM positive.

#### CONTROLS

The original series comprised 518 and the final series with complete data 453 controls who did not catch measles during the epidemic. They were selected as follows. At first, confirmed measles cases were removed from the sampling frame. Then the controls were selected from the same age range as the cases, including those who had passed first vaccination age (that is, 19 months) 90 days before the epidemic period. The controls' age range definition was in practice too wide and 24 controls originally chosen in the two control series appeared too young. They were not approached.

Four controls from each case's municipality, and additional 258 controls from high attack rate municipalities (at least 600 per 100 000) were randomly selected from the National Population Registry. For example, if there were four vaccination failures in a low attack rate municipality (<600 per 100 000) 16 controls were randomly picked.

At the time of control sampling, 65 vaccine failures identified by the serological surveillance programme were available and confirmed. Additional 85 cases from the vaccine failure notification programme (and three cases from the serological surveillance programme) were later provided by serological data. Their area of residence satisfied the sampling criteria. Furthermore, in both series the vaccination status of controls was almost identical (data not shown) because of the uniform nature of the Finnish vaccination system. Thus, selection of additional controls was considered unnecessary.

Forty one controls had either not returned questionnaire or their health card could not be located in school (see later). Thus, the size of the final combined control series was 453 cases; their mean age was 10.0 years, range 2 to 22. Among the controls, 80 teenagers and young adults had a previous history of measles irrespective of the vaccination status (table 2),

Table 2 Relative risk (RR) of measles among once and twice vaccinated compared with three times vaccinated in Finland during the 1988–89 epidemic

| Prior measles history | Vaccinated | Cases      | Controls | Crude |             | Adjusted* |              |
|-----------------------|------------|------------|----------|-------|-------------|-----------|--------------|
|                       |            |            |          | RR    | (95% CI)    | RR        | (95% CI)     |
| No                    | Thrice†    | 3 (2)‡     | 64       | 1.0   | —           | 1.0       | —            |
| No                    | Twice      | 10 (4)‡    | 93       | 2.3   | (0.6, 11.0) | 7.1       | (2.1, 19.9)  |
| No                    | Once       | 140 (12)‡  | 192      | 15.6  | (4.9, 78.6) | 16.3      | (2.6, 138.5) |
| Yes                   | Any        | —          | 80       | —     | —           | —         | —            |
| No                    | No         | 1053 (13)§ | 24       | —     | —           | —         | —            |
| Total                 |            | 1206       | 453      | —     | —           | —         | —            |

\*Averaged over five age strata, and all vaccinations given <14 months of age omitted. †Reference category for relative risk estimates. ‡In parentheses the number of reported failures from one municipality with the highest attack rate (2200/10<sup>5</sup>) and very low vaccine efficacy even among the revaccinees<sup>14</sup>. §1053 non-vaccinated measles cases were reported to the serological surveillance programme in the 2–22 year age range.

24 of the controls did not have a measles vaccination history nor previous measles history.

#### DATA ON CASES AND CONTROLS

The vaccination status and measles history of each case was checked from health cards by nurses or physicians at the case's health care centre or school, which was derived from the surveillance programmes.

The health centre or school of controls was not available from registries, but the control's address was provided by the Population Registry. Data on vaccination status and measles history of the controls were obtained by mail questionnaire and checked from the vaccination card at home. In a case of non-response or lost card, the nearest health care centre or school was approached for a photocopy of the health card. The data were based on the card at home in 71%, a photocopy of the card from health centre or school in 14%, and 7% of subjects were sure about their vaccinations and gave exact dates. The response rate for the controls was 92%.

#### INFECTION PRESSURE

Average infection pressure in a municipality during the outbreak was calculated by dividing the number of measles cases by the population. The high pressure criteria (attack rate  $>600/10^3$ ) used in selection of controls and subsequent data analyses correspond to the attack rate during the peak years before the vaccination programmes.<sup>4,6</sup>

The infection pressure on an individual cannot be measured directly. Daily contacts with other children allow crude estimates of the number of possible virus exposures according to the classic Reed-Frost model.<sup>11</sup> Data on daily contacts were not collected for the cases and controls. A notion of infection pressure was obtained by estimating it indirectly for pre-school children by each year of age from a separate national sample of 45 000 children whose mothers reported the number of daily child contacts to nurses during visits in 1983.

#### STATISTICAL METHODS

Relative risks of measles among once and twice vaccinated compared with thrice vaccinated, and time and vaccination age related relative risks were estimated by odds ratios, and the corresponding confidence intervals calculated by an exact method.<sup>12</sup> All analyses dealing with additional protection by revaccinations (only controls' vaccinations that preceded the outbreak period were considered) were stratified by low ( $<600/10^3$ ) or high ( $>600/10^3$ ) infection pressure areas and by different daily attendance groups (table 1) to evaluate confounding resulting from differences in exposure. Daily attendance groups were stratified as follows: preschool children, three two year age categories within elementary schools, and children and young adults no longer in elementary schools. Not a single twice MMR vaccinated case among most intermingling 6 year olds (table 1) was reported within the youngest age strata. Few older children ( $>12$  years) were twice vaccinated and even they got additional

protection from revaccination. Crude and Mantel-Haenszel age adjusted<sup>13</sup> relative risks of once and twice compared with thrice vaccinated are presented omitting all cases and controls who received the first monovalent vaccination before 14 months of age. Finally cases from one municipality where even revaccinees had high measles risk (up to 80%) were omitted because of the very special nature of this particular setting.<sup>14</sup>

Time since vaccination among controls was calculated to the median day of the outbreak. Analyses dealing with time since the vaccination and time between vaccinations were restricted to the MMR programme (only once vaccinated included) to avoid effect modification because of wild virus exposure,<sup>4,6,15</sup> and possible different immunogenic<sup>16</sup> and storage<sup>17-20</sup> properties, and because of previous low vaccination age. Twenty four of the 55 cases immunised with solely monovalent measles vaccine had received it in 1975 or 1976 before 14 months of age.

#### Results

Children aged 10-13 months and teenagers had the highest attack rates (table 1).

Those once vaccinated against measles in mono- or trivalent form had a 15.6 times higher risk of the disease (95% CI 4.9, 78.6) during the outbreak compared with those thrice vaccinated (table 2). Comparing once vaccinated to two and three times vaccinated combined, the relative risk was 8.8 (4.7, 17.6). Restricting the analyses to those immunised by trivalent MMR vaccine since 1982, once vaccinated subjects had a 5.6 (2.1, 18.5) higher risk of measles compared with the twice vaccinated (none were vaccinated three times). Adjustment over five age groups and restricting analyses to those vaccinated after 14 months of age did not materially change the results. When those cases who had received their first vaccination at less than 14 months of age were omitted, once vaccinated had 4.0 (1.2, 16.6) higher age adjusted measles risk compared with twice vaccinated.

When cases from one particular municipality where even revaccinees had high measles risk and also cases who had received their first vaccination at less than 14 months of age were omitted, once vaccinated had 17.8 (2.8, 67.8) higher measles risk compared with twice vaccinated after age adjustment. Only one thrice vaccinated case who had received her first vaccination at 11 months of age was reported outside the high risk municipality.

The risk of contracting measles increased linearly with time from vaccination among preschool children, but a weaker and statistically non-significant association emerged among school children. Pre-school children who were vaccinated more than four years previously had a 4.2 (1.4, 13.1) times higher measles risk compared with those vaccinated within the two years before outbreak.

Twice MMR vaccinated cases (all five cases were from the previously mentioned municipality where even revaccinees had measles risk) had a 1.6 years (0.4, 2.8) shorter mean interval

between vaccinations than the controls even when restricting comparison within elementary school children. When the time interval between vaccinations was arbitrarily divided into less than 2.5 years and 2.5 or more, the more closely revaccinated had a 22.8 (2.0, 1102.2) times higher measles risk compared with those revaccinated more apart. Thus, the twice MMR vaccinated individuals had complete protection in low attack rate areas. Almost all the twice MMR vaccinated in Finland were in low attack rate elementary schools during the 1988–89 epidemic season.

When restricting analyses among once inoculated monovalent vaccine recipients who all were no longer in low attack rate elementary schools, those vaccinated before 14 months of age had 2.7 (1.0, 8.0) higher risk of measles compared with those vaccinated after 14 months of age.

When taking only those age cohorts that first received monovalent measles vaccine and who were once revaccinated with MMR, those who were first vaccinated before 14 months of age had 3.5 (0.5, 25.2) times higher measles risk compared with those who received their first inoculation after 14 months of age.

### Discussion

The strength of this study compared with previous outbreak research<sup>19–42</sup> is the large number of serologically confirmed vaccine failures and the large proportion of twice and even thrice vaccinated subjects (about 170 000) in the population during an outbreak in an environment practically free of natural boosters for years. This is the first study directly assessing the effect of time between successive measles vaccinations, though the small number (five) twice vaccinated MMR failures all originated in one municipality with exceptional circumstances.

The validity could be questioned if twice and thrice vaccinated measles cases were underreported in vaccine failure surveillance. Had measles cases been sporadic this might have been a problem, as the reporting physician might not have made the correct diagnosis when the subject had a history of two or even three measles vaccinations. In an obvious outbreak situation, however, this type of reporting bias cannot explain our results. Essential non-response bias is unlikely as we had a very high response rate throughout. Information bias is excluded by the serological confirmation of cases and numerous cross checkings from previous double records of the vaccinations. Sound internal validity of the study is also reflected by the fact that low vaccination age not only among once vaccinated<sup>19 21–24 28 30–37 39 41</sup> but also among revaccinated<sup>42</sup> predicted vaccination failure.

The superiority of the two dose over the one dose strategy has been indirectly predicted from ecological,<sup>44</sup> and quasi experimental data,<sup>45</sup> and indirect individual level immunological data.<sup>37</sup> Conclusive evidence that revaccinated individuals have lower measles attack rates has so far been lacking,<sup>1</sup> though many outbreak reports suggest this interpreta-

tion.<sup>22 29–31 35 41 42</sup> Our study shows that routine revaccination gives more complete protection, even when the first vaccination is given after 14 months of age.

The common belief that successful measles vaccination induces lifelong immunity<sup>46–49</sup> has been the prevailing doctrine on which many national<sup>40 50–52</sup> and especially international<sup>46</sup> recommendations were based. This belief is based on historical analogy: after measles had been absent for a long time in Faroe Islands those who had had measles decades ago were not attacked.<sup>53</sup> Excluding isolated areas, a person's lifetime number of measles exposures used to be around 15 in the prevaccination era.<sup>54</sup> Vaccine induced antibody titres decline in low attack rate conditions,<sup>9 37 48 49 55–57</sup> whereas in reported measles exposures in the United Kingdom no such effect has been observed.<sup>51 52</sup>

The additional protection from revaccination is achieved by correcting either primary or secondary vaccine failures, or both. A longer time since single vaccination increased measles risk among pre-school children, suggesting waning immunity, though this association might be explained by a concomitant increase in the number of daily contacts and thus a greater possibility of catching measles. The latter interpretation is supported by the fact that time since vaccination did not clearly explain vaccine failure among older school children. It is however, possible that we were undersampling secondary vaccine failures, because all cases were IgM positive. This is thought to indicate virginity to infection,<sup>58 59</sup> though this has been questioned.<sup>60–63</sup>

Many studies have found that time since vaccination increases the risk of measles vaccine failure,<sup>21–23 25–27 29–32 35 36 41</sup> but this may have been because of the introduction of the new heat stabiliser in measles vaccines after 1979<sup>9 17–20 36</sup> or to previous low vaccination age.<sup>24 27 41</sup> Many studies<sup>28 33 38 39 58</sup> have not found that time since vaccination predicts vaccine failure. So far some circumstantial<sup>9 15 56 57 65</sup> and even some direct<sup>7 8 60</sup> evidence implies that waning vaccine induced immunity might become a true problem in conditions without natural boosters.

Vaccine induced virus replication is considered responsible for the defence response against measles.<sup>66</sup> Replication is probably weak or absent with high antibody titres, as high maternal or intentionally administered antibody titres interfere with measles vaccination.<sup>67</sup> It could be that antibody levels have to decline after measles vaccination to achieve a proper protection by revaccination, and this could explain why a short interval between vaccinations increased the risk of measles compared with a longer interval. Indeed, a 10 year interval has been shown to yield a more comprehensive and sustained immunological response compared with a short interval.<sup>56</sup> Recent observational data from the US have challenged this.<sup>42</sup> Obviously the fact that the five twice MMR vaccinated failures of whom four of five had a shorter than 2.5 year time period between vaccinations originated from one



municipality<sup>14</sup> with very special circumstances weakens our ability to make valid inferences about time periods between vaccinations.

This study further strengthens our belief that the key to the success<sup>4-6</sup> along with high achieved coverage<sup>5</sup> has been revaccination. In 1996 not a single measles case was diagnosed<sup>68</sup> from over 1000 studied serum samples, although almost two million Finns travel abroad annually and hundreds of thousands of tourists from high attack rate areas in the old Soviet Union visit Finland each year. All suspected measles cases require paired serological testing in Finland. Whether revaccination also boosts immunity is to be answered by future studies.

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