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Author(s): J. MOSSONG and C. P. MULLER

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## Estimation of the basic reproduction number of measles during an outbreak in a partially vaccinated population

J. MOSSONG<sup>1,2\*</sup> AND C. P. MULLER<sup>3,4</sup>

<sup>1</sup> Department of Biological Sciences, University of Warwick, Coventry CV4 7AL, UK

<sup>2</sup> CRESIS, CRP-Santé, 57 route d'Arlon, L-1140 Luxembourg

<sup>3</sup> WHO Collaborative Centre for Measles, Laboratoire National de Santé, P.O. Box 1102, L-1011 Luxembourg, Luxembourg

<sup>4</sup> Medical Faculty, University of Tübingen, 72070 Tübingen, Germany

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### SUMMARY

From March to July 1996 a measles outbreak occurred in northern Luxembourg with 110 reported cases centered around two primary schools (85 cases) and the surrounding community (25 cases). Eighty four suspected cases were confirmed serologically. Vaccine coverage was estimated from questionnaire-based surveys at the two primary schools to be 70 and 76%, respectively. Vaccine efficacy during the outbreak was estimated to be 94.6% [95% confidence interval (CI) 90.4–97.0]. Using the information from the school surveys, we obtained estimates of the basic reproduction number of measles of 7.7 (95% CI 4.4–11.0) and 6.2 (95% CI 3.5–8.9), respectively. Assuming a 95% vaccine efficacy, these estimates correspond to minimal vaccine coverages of 91.6% (95% CI 81.4–95.7) and 88.3% (95% CI 75.5–93.4) which would have been necessary to minimize the chances of a major outbreak occurring. We can confirm that major outbreaks in similar school settings can only be prevented if vaccination coverage exceeds 90%.

### INTRODUCTION

In Luxembourg, routine vaccination with MMR vaccine was introduced in 1987. Measles control measures rely solely on routine immunization, recommended at the age of 15–18 months, which are performed free of charge by the paediatrician or family doctor. A second dose is now recommended at the age of 5–6 years. According to a representative survey of 6-year-old school children in 1992, vaccine coverage was estimated to be 80%. A more recent survey done in 1996 of children aged 26–30 months has shown that coverage has increased to 91.1% [1]. However, there is evidence that after the introduction of the MMR vaccine, some medical doctors have not recommended

its routine use and this has resulted in localized pockets of susceptibility in certain geographical areas. It is in this setting that we report a measles outbreak in the spring and early summer of 1996 which was based around two primary schools. In addition to the serological investigation, a questionnaire-based survey at the two primary schools was initiated to obtain information on the vaccination coverage and immune status of the population. From these surveys we also provide estimates of vaccine efficacy of MMR vaccine in a primary school setting. Furthermore, we give estimates of an important epidemiological parameter, the basic reproduction number of measles ( $R_0$ ) at the two schools. This measure of the contagiousness of the virus in combination with estimates of vaccine efficacy determines the vaccine coverage necessary to minimize the chances of a major outbreak.

\* Author for correspondence: CRESIS, CRP-Santé, 57 route d'Arlon, L-1140 Luxembourg.

## METHODS

### Case definitions for confirmed and suspected cases

Cases were classified as having typical clinical measles if their symptoms were in accordance with the CDC definition of a clinical case (i.e. a fever of  $\geq 38.3$  °C with a generalized maculopapular rash lasting at least 3 days and combined with at least one of cough, coryza, or conjunctivitis). Furthermore, wherever possible, blood samples were taken from patients for confirmation of infection by the detection of measles-specific IgM by ELISA (Enzygnost, Dade, Mannheim, Germany) with proven high sensitivity and specificity [2, 3].

Notification was ascertained in several ways. A measles hot-line was set up during the outbreak and advertized to doctors for notification of suspected cases. Other cases were identified during regular visits to the schools during the outbreak or were reported by family, friends or neighbours of known cases.

Additional suspected cases, for whom no blood samples were available, were later identified from a school questionnaire distributed to all parents of children attending the two primary schools in Reuler and Winrange. Parents were requested to supply information on their children's history of past measles infection as well as history of measles immunization by either including a copy of a vaccine certificate or indicating the date of vaccination. Teachers agreed to collect the questionnaires and return them to the investigators.

The number of immune and susceptible children after the epidemic were ascertained using the information parents provided from the survey. Susceptibles were defined to be those children who had not received vaccine and who had no previous experience of measles. We considered as immune those children who were not cases and who were either vaccinated or had experienced measles infection previously. Children whose immune status could not be determined from the survey were excluded for the purposes of estimating the basic reproduction number.

### Statistical methods

Vaccine efficacy was estimated according to the criteria set by the World Health Organization for the field evaluation of vaccine efficacy. We calculated vaccine efficacy separately for the cohorts in either school as well as a pooled estimate using the formula:  $VE = 1 - AR_v/AR_u$  where  $AR_v$  and  $AR_u$  are the attack

rates among the vaccinated and unvaccinated children, respectively. Confidence intervals for vaccine efficacy were obtained with Epi-Info, V. 6 [4].

Heterogeneity in  $R \times C$  contingency tables was checked using either Fisher's exact test or a Monte-Carlo version of Fisher's exact test if the exact test proved to be too computationally intensive. Calculations were performed on a PC using StatXact-3, V. 3.1 (Cytel Software Company, MA). The Monte Carlo estimates of mean and 99% CIs of the  $P$  value were based on 100000 generated tables.

The minimal vaccination coverage  $P$  necessary for minimizing the chances of a major epidemic was estimated using the formula  $P = (1 - 1/R_0)/VE$ , where  $R_0$ , the basic reproduction number of the infection, is the average number of secondary cases due to an index case in a completely susceptible population [5] and  $VE$  represents vaccine efficacy. Although this result stems from the analysis of deterministic models, it is nevertheless a useful reference for stochastic outbreaks. The effective reproduction number  $R$  was simply defined to be the product of the basic reproduction number and the actual proportion of the total population which is susceptible.

To estimate the basic reproduction number  $R_0$  we followed the approach by Becker [6] which uses three statistics of the epidemic: the final number of cases ( $C$ ), the number of susceptibles before the epidemic ( $S$ ) and the total community size ( $N$ ). As most transmissions can be expected to occur inside the schools, we take  $N$  to be the total number of pupils at either school. The mean estimate,  $\hat{R}_0$ , is then given by the formula

$$\hat{R}_0 = \frac{N-1}{C} \sum_{i=S-C+1}^S 1/i, \quad (1)$$

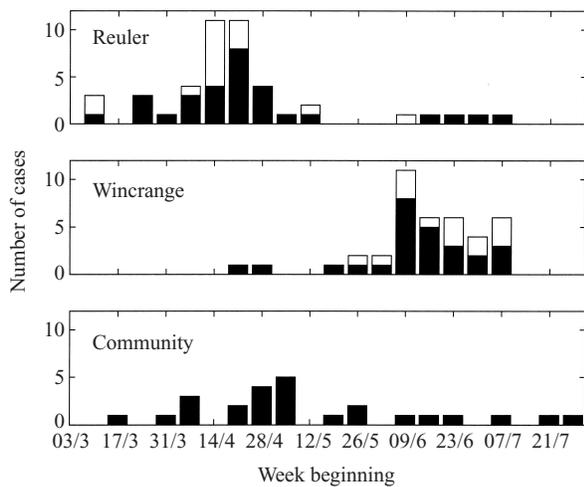
with standard error

$$SE(\hat{R}_0) = \frac{N-1}{C} \left( \sum_{i=S-C+1}^S 1/i^2 + \frac{C\hat{R}_0^2}{(N-1)^2} \right)^{1/2}. \quad (2)$$

## RESULTS

### Description of the outbreak

A total of 110 suspected cases of measles were reported from 1 March to 20 July 1996 over a period of 20 weeks. Eighty five (77.9%) of the reported cases attended primary schools in two villages (Winrange and Reuler) in a rural area of Northern Luxembourg. Both in terms of size and class structure, the two



**Fig. 1.** Epidemic curve with weekly number of cases based on onset of rash. Suspected cases are shown in white and confirmed cases in black.

schools were similar: 343 and 363 pupils were registered at Wincrange and Reuler, respectively, divided among 20 classes. Most of the remaining 25 cases occurred in the nearby community of the two schools in siblings of pupils.

The epidemic curve (Fig. 1) shows how the outbreak started at the primary school in Reuler before spreading into the rest of the community and eventually sparking off another epidemic at the primary school in Wincrange. It is interesting to note however, that transmission seems to have been interrupted at both schools. Although the reasons for these interruptions are somewhat unclear, it is possible that school holidays (Easter break from 6 to 21 April and Pentecost break from 26 May to 5 June 1996) have played a role. A recent study employing molecular techniques has identified that the measles virus isolated from both schools belonged to the same genetic strain [7]. Since the two schools are geographically close (10 miles), it is probable that some transmission occurred between the schools at the peak of the epidemics.

The median age at infection of all reported cases was 8 years. Five cases occurred in infants less than 2 years old and four cases in adults. Eighty four blood samples were taken from the 110 suspected cases and all contained measles-specific IgM, providing evidence of recent measles infection. No blood samples were available from the other 26 suspected cases. Among the 84 serologically confirmed cases, 79 (94%) had typical clinical measles according to the CDC case definition, but 5 did not meet all of the criteria. Among the 8 (9.5%) cases which occurred among

immunized individuals, 2 children (25%) did not have typical clinical measles compared to 3 (4%) among 76 unvaccinated cases ( $P = 0.095$ ).

### Post-outbreak school surveys

From the 709 pupils registered at the two schools, 599 (84.5%) questionnaires were returned. Either a copy of the vaccination certificate or the date of vaccination was given for 415 (94.7%) of the 438 children reportedly vaccinated.

Vaccination and infection status prior to the outbreak is shown in Table 1. At Reuler, 25 (8.4%) of respondents had a previous history of measles and 227 (76.4%) were vaccinated. At Wincrange, 28 (9.2%) gave a history of previous measles infection and 211 (69.9%) had received immunization. Inspection of the dates and ages at previous infection suggests that neither school had experienced a major outbreak in the 1990s. Allowing for the overlap between the vaccinated and previously infected group, at least 16.5% of children at Reuler and 22.2% at Wincrange could be considered susceptible before the outbreak.

The actual proportion of susceptibles that were infected differed slightly between the two schools at the class level. Whereas infection rates were homogeneous at Wincrange ( $P = 0.5369$ ; 99% CI 0.5328–0.5410), there is a significant difference at Reuler ( $P = 0.0197$ ; 99% CI 0.0186–0.0208). Figure 2 shows this infection pattern after classes have been grouped into yearly grades indicating that higher measles transmission occurred among younger children at Reuler primary school.

At Reuler, 10 cases of measles occurred among the 217 vaccinated children, compared with 35 cases among 64 unvaccinated children yielding a vaccine efficacy of 91.6% (95% CI 83.9–95.6). At Wincrange, 2 cases were recorded among 203 vaccinated children, compared with 41 cases among 79 unvaccinated children giving an estimate of 98.1% vaccine efficacy (95% CI 92.3–99.5). By pooling the two schools together, we obtain an overall vaccine efficacy of 94.6% (95% CI 90.4–97.0), which is comparable to estimates reported in the literature from outbreaks in developed countries [8]. Moreover, vaccine efficacy was found not to differ significantly between grades.

### Estimating the basic reproduction number

From the survey, we identified 45 cases, 18 susceptible children and 219 immune children after the epidemic

Table 1. Measles vaccination and immune status in survey responders

Previous case	Vaccinated			Total
	No	Yes	Unknown	
	Reuler			
No	49	207	4	260
Yes	15	10	0	25
Unknown	2	10	0	12
Total	66	227	4	297
	Winchrage			
No	67	194	2	263
Yes	12	9	7	28
Unknown	2	8	1	11
Total	81	211	10	302

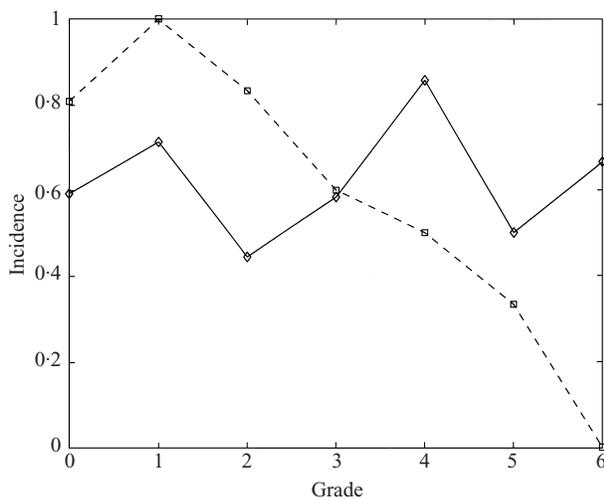


Fig. 2. Ratio of infectives to susceptibles (prior to outbreak) by school grade at Reuler (diamonds/solid line) and Winchrage (squares/dotted line). Grade 0 represents children at kindergarten.

at Reuler. The immune status of the remaining 81 children was unknown, either because their questionnaire was lacking information or because they failed to return their forms. At Winchrage, we noted 43 cases, 220 immune children, 28 children susceptible after the epidemic and 55 children with unknown immune status. If we only use those children with known immune status for the estimation of  $R_0$ , i.e. we do not include the non-responders in the calculations, we obtain estimates of  $R_0$  of 7.7 (95% CI 4.4–11.0) at Reuler, and 6.2 (95% CI 3.5–8.9) at Winchrage. At the beginning of the epidemic, the corresponding estimates of the effective reproduction number  $R$  are 1.7 (95% CI 1.0–2.5) at Reuler and 1.5 (95% CI 0.9–2.2), whereas at the end of the epidemic they are 0.5 (95% CI 0.3–0.7) at Reuler and 0.4 (95% CI

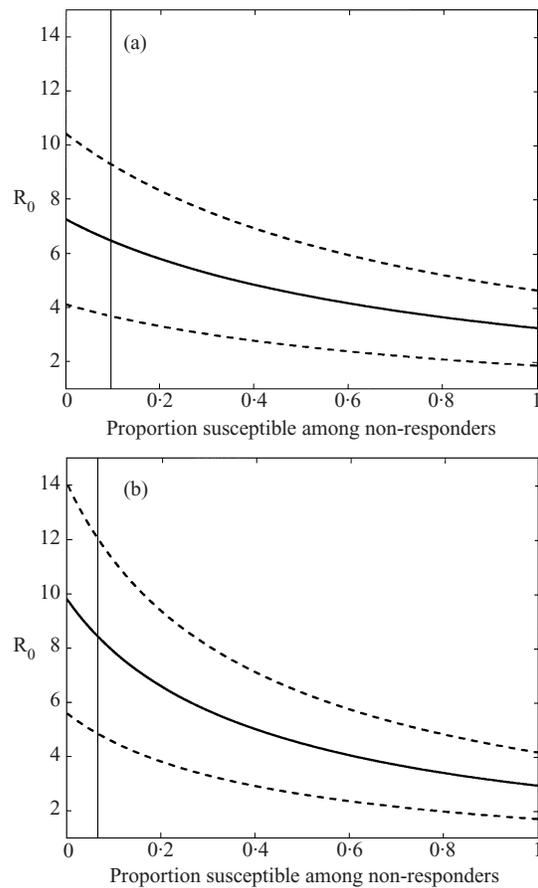


Fig. 3. Estimates of the basic reproduction number  $R_0$  at (a) Winchrage and (b) Reuler depend on the proportion of susceptibles among the survey non-responders. The solid line represents the mean estimate and the dotted lines the 95% confidence region for the mean. For comparison, the vertical line indicates the actual proportion of susceptibles among the survey responders.

0.2–0.6) at Winchrage. The low effective reproductive numbers at the start of the outbreaks could explain the relatively prolonged duration of the epidemics.

Assuming a 95% vaccine efficacy, these estimates correspond to vaccine coverages of 91.6% (95% CI 81.4–95.7) at Reuler and 88.3 (95% CI 75.5–93.4) at Winrange, respectively, which would have been necessary to minimize the chances of an outbreak occurring. Note that these minimal coverage estimates are 15–20% higher than the actual vaccine coverage which was 76.4% at Reuler and 69.9% at Winrange and similarly high levels have also been suggested by other authors [5].

However, it is necessary to point out that the above method for estimating  $R_0$  is very sensitive to the distribution of susceptibles and immunes among the non-responders. Figure 3 shows the mean and 95% confidence limits of  $R_0$  at the two schools as a function of the proportion of susceptibles among the non-responders assuming that all cases were identified during the epidemic, so that survey non-responders were either susceptible or immune. It is clear that estimates of  $R_0$  could increase substantially if all non-responders happened to be immune.

## DISCUSSION

While some developed and developing countries have been able to control or eliminate measles through intensive vaccination efforts (e.g. mass campaigns in the United Kingdom and the Americas, multidose regimes in the United States and Scandinavia), several authors [9–12] have stressed the need for all EU countries to increase coverage to target levels of 95% as recommended in the ‘Health for all in the year 2000’ programme of WHO Europe. The epidemic we have reported is therefore further evidence that vaccination levels of 70–75% are insufficient to prevent outbreaks, especially in school settings.

To our knowledge, no other study has previously attempted to estimate the basic reproduction number  $R_0$  of measles during an outbreak in a vaccinated population. Becker and Hasofer [13] applied a related but slightly more sophisticated technique to outbreak data from a measles epidemic in a German village in 1861. They obtained an estimate of  $R_0$  of the order of 10–11. The most commonly used method to estimate the basic reproduction number  $R_0$  relies on age-serological profiles obtained prior to the start of routine immunization rather than from outbreak data. Estimates of  $R_0$  derived using this technique have been of the order of 15[5], which is roughly twice the value of our estimates. We have several explanations for the apparent discrepancy between

these and our estimates. Our statistical technique for estimating  $R_0$  is very sensitive to the number of susceptibles remaining after the epidemic which we might have underestimated due to parental recall bias. We did not include survey non-responders in our calculations. As indicated in Figure 3, our estimates of  $R_0$  could increase substantially if all survey non-responders happened to be immune. Also the method for estimating  $R_0$  assumes no heterogeneity in mixing; each child has the same probability of contacting any other child, which does not take into account the class structure of schools, nor the contact patterns among siblings. Adding heterogeneity to mathematical models in the form of variable contact rates generally has the effect of increasing the basic reproduction number. The outbreaks at both schools were temporarily interrupted and this has not been considered in the estimation method. We have investigated this complication by only counting cases which occurred during the main epidemic and found that estimates of the basic reproduction number only changed marginally, especially with respect to the wide confidence intervals. We have only considered measles transmission within the schools, whereas it is quite likely that some transmissions have occurred outside of the school environment (e.g. from older to younger siblings at home). These out-of-school contacts are not taken into account for our estimation purposes, but could clearly increase the basic reproduction number.

Regardless of the possibility of underestimating the basic reproduction number, our estimates of  $R_0$  correspond to a vaccination coverage of greater than 90%, which would have been necessary to minimize the chances of an outbreak occurring.

More reliable estimates of  $R_0$  could only be obtained if a more detailed investigation of the immune status of the whole school population and possibly their family contacts had been initiated before and after the epidemic. Whereas questionnaire-based surveys are adequate to estimate vaccine coverage and vaccine efficacy, it is possible, as Lyons and colleagues [14] have pointed out, that we could have underestimated the proportion of immune children due to recall bias: some parents might not remember whether their child received measles vaccine or whether it had measles in the past. To improve estimates of the basic reproduction number, post-outbreak immunity should be serologically confirmed. A recently described immunoassay which relies on oral fluid samples [15] would be suitable if blood samples cannot be obtained.

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