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Measles immunity and response to revaccination among secondary school children in Cumbria

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SUMMARY

The prevalence of antibody to measles virus in 759 children aged 11–18 years attending a secondary school in Cumbria was measured using a salivary IgG antibody capture assay. Serum IgG antibody levels were measured using a plaque reduction neutralization assay in subjects whose saliva was antibody negative. Vaccination histories were obtained from the child health computer and general practice records. A total of 662 pupils (87% of those tested) had detectable measles-specific IgG in saliva. Of the remaining 97, 82 provided blood samples and 29 had serum neutralizing antibody levels above 200 mIU/ml. After adjusting for non-participation rates, the proportion considered non-immune (no IgG in saliva and $\leqslant$ 200 mIU/ml in serum) was 9% overall, ranging from 6% in vaccinated children to 20% in unvaccinated children. Measles–mumps–rubella vaccine was given to 50 children of whom 38 provided post-vaccination serum and 32 saliva samples. Thirty (79%) had a fourfold or greater rise in serum neutralizing antibody and 28 (88%) developed IgG antibody in saliva. Half of the children considered non-immune by antibody testing would have been overlooked in a selective vaccination programme targeted at those without a history of prior vaccination. A programme targeted at all school children should substantially reduce the proportion non-immune since a primary or booster response was achieved in three quarters of previously vaccinated children with low antibody levels and in all unvaccinated children. While it is feasible to screen a school-sized population for immunity to measles relatively quickly using a salivary IgG assay, a simple inexpensive field assay would need to be developed before salivary screening and selective vaccination could substitute for universal vaccination of populations at risk of measles outbreaks. The salivary IgG assay provided a sensitive measure of a booster response to vaccination.

INTRODUCTION

In 1992, outbreaks of measles among children aged $\geqslant$ 9 years and over began to be reported from a number of areas of the United Kingdom [1–4]. The outbreaks were attributed to incomplete measles vaccine coverage in older children, together with a reduced opportunity for acquisition of natural immunity through exposure to measles because of declining

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incidence that followed the introduction of measles–mumps–rubella (MMR) vaccine in October 1988. Analysis of seroepidemiological data in combination with mathematical modelling predicted a major resurgence of measles in school age children unless steps were taken to immunize susceptible individuals, particularly those in secondary schools [5–7]. Two options were considered; either to target vaccination at all children without a history of prior measles vaccination or to attempt to immunize all children irrespective of vaccination history.

To assess the potential effect of a non-selective vaccination campaign to correct the deficit in population immunity to measles, we conducted a study of measles antibody prevalence in a large school in West Cumbria in which there had not been recent measles. The study aimed to compare susceptibility rates in children with and without a history of measles vaccination, and to measure the boosting achieved by re-vaccination. The feasibility of using salivary antibody assays to screen for susceptibility to measles was also investigated.

METHODS

Field work

The name, address and date of birth of the 879 children attending the school were obtained from the school's registration computer. Vaccination histories were obtained either from the local health authority child health computer (about 80% of children) or, for children not traced in this way, by requesting local general practitioners (GPs) to provide details. These data sources were then manually linked to the master database. After obtaining ethical approval, all parents were sent a letter explaining the aims of the project and asking for informed consent. School nurses visited the school and collected saliva samples using a sponge swab [9] from 759 children whose parents agreed to their participation. Children whose saliva samples contained no detectable measles-specific IgG were asked to provide a 10 ml sample of venous blood. This was collected at school by one of the investigators. Children who had a serum measles-specific IgG level $\leqslant$ 200 mIU/ml were considered susceptible to measles [10] and were offered MMR vaccine. With informed consent, vaccine was administered and another 10 ml sample of venous blood and a saliva sample was obtained 4 weeks after vaccination.

Analysis of samples

Saliva samples were tested for measles-specific IgG using a G-antibody capture radioimmunoassay (GACRIA) [11]. Saliva samples were considered positive if they gave a test/negative control ratio of $> 2{\cdot}1$ [11]. Serum and saliva samples were tested for measles-specific IgM by M-antibody capture radioimmunoassay (MACRIA) as previously described [11] and for measles-specific IgG by plaque reduction neutralization (PRN). The PRN method was similar to previously described methods [12] with two minor modifications. The loss strain of measles virus, isolated in USSR in 1988, was used as a challenge virus [13]. Sera were tested twice and measles-specific IgG was quantified in mIU/ml by comparing the titre of test serum required to reduce the number of plaques by 50% with that of serum 66/202, the international standard serum for measles [14]. The threshold sensitivity of the assay was *c.* 25 mIU/ml.

Statistical analysis

Seroconversion was defined as a change from undetectable to positive measles antibody or as a fourfold rise in antibody level after vaccination. If accompanied by the detection of measles specific IgM, the seroconversion was considered a primary response to vaccination; seroconversion/boosting without IgM was considered a secondary response. The log post vaccination antibody levels of the responders were regressed against sex, vaccination status and response type (primary v. secondary) using normal errors regression. Changes in the proportion susceptible with time since vaccination, age at vaccination and sex were investigated by logistic regression.

RESULTS

Vaccination histories were available for 772 (88%) pupils of whom 643 (73% of total) had been previously vaccinated, 129 (15%) were unvaccinated and the remaining 107 (12%) were of unknown vaccination status (Table 1). A total of 759 children provided saliva samples of whom 97 (13%) were negative for measles-specific IgG. Eighty-two of the latter provided serum samples and, of these, 53 (65%) had antibody levels $\leqslant$ 200 mIU/ml. These 53 children were offered MMR vaccine, and 45 accepted; a further 5 children with serum levels above 200 mIU/ml were also given MMR vaccine. Of these 50 children, 38 provided a serum sample and 32 a saliva sample after vaccination.

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Table 1. *Measles IgG antibody prevalence results in saliva and serum by vaccination status*

	Number of pupils	Gave saliva sample		Saliva IgG antibody positive		Saliva IgG antibody negative			Estimated susceptibles in school	
		No.	(% of total)	No.	(% of pupils tested)	Serum IgG antibody > 200 mIU/ml	Serum IgG antibody* ⩽ 200 mIU/ml	No blood sample	No.	(%)
Vaccinated	643	576	(90)	514	(89)	24	30	8	38	(6)
Unvaccinated	129	97	(75)	75	(77)	2	14	6	26	(20)
Not known	107	86	(80)	73	(85)	3	9	1	12	(11)
Total	879	759	(86)	662	(87)	29	53	15	76	(9)

* Includes seronegatives.

Table 2. *Response to vaccination according to pre-vaccination neutralization antibody titre*

Pre-vaccination antibody level (mIU/ml)	Antibody response to vaccination			
	Primary (IgM positive)	Secondary (IgM negative/IgG boost)	No response	Total
Negative	6	3	0	9
⩽ 200	3	16	5	24
> 200	0	2	3	5
Total	9	21	8	38

Prevalence of measles antibody

Of children who provided salivary samples, 97 (13%) were negative for salivary IgG. These represented 62 (11%) of vaccinated children, 22 (23%) of unvaccinated children and 13 (15%) of those of unknown vaccination status. Of the 82 salivary antibody negative children from whom blood samples were obtained 29 (35%) had serum antibody levels > 200 mIU/ml. Thirty (56%) of vaccinated children had serum antibody levels ⩽ 200 mIU/ml compared with 14 (88%) of unvaccinated children and 9 (75%) of those whose vaccination status was unknown. Children who had been previously vaccinated were more likely to provide salivary samples than those of unknown vaccination status or unvaccinated children (Table 1). In the total school population, after adjusting for participation rates according to vaccination status, 76 children (9%) were estimated to have antibody levels ⩽ 200 mIU/ml (6% of vaccinated, 20% of unvaccinated pupils and 11% of unknowns). Overall, 38 (50%) of the estimated 76 with levels ⩽ 200 mIU/ml were children with a history of vaccination.

Of the 365 males who gave a saliva sample, 319 (87%) were IgG antibody positive, the same proportion as in females (343 of 394); similarly, of the 35 males who gave serum samples, 12 (34%) had neutralizing antibody levels above 200 mIU/ml compared with 17 of the 47 (36%) females. The prevalence of salivary antibody increased with age from 389 of 464 (84%) in children aged 11–13 years to 213 of 234 (91%) in 14–15 year olds; 60 of the 61 (98%) children aged 16–18 years had detectable antibody in saliva.

Of children who provided salivary samples, only four were vaccinated below 12 months of age, and all were considered immune. Most children had been vaccinated 8–13 years before the survey (range 2–17 years). There was no significant trend in the proportion susceptible according to age at vaccination or time since vaccination (data not shown).

Response to vaccination

Table 2 shows the response to vaccination among the 38 children who provided post vaccination sera. A total of 30 children (79%) seroconverted or had a ⩾ fourfold rise in antibody level. Among the 33 children with a pre-vaccination level of 200 mIU/ml or below, 32 showed at least a twofold increase in titre and 32 had a post-vaccination level above 200 mIU/ml. Of the five children with pre-vaccination titres above

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Table 3. *Response to revaccination according to previous vaccination status*

Previous vaccination status	Antibody response to vaccination: Primary (IgM positive)	Secondary (IgM negative/IgG boost)	No response	Total
Vaccinated	2	15	5	22
Not vaccinated	6	2	0	8
Not known	1	4	3	8
Total	9	21	8	38

200 mIU/ml, two had a fourfold rise in titre (pre-vaccination level 230, 249 mIU/ml) and three did not (pre-vaccination level 572, 852, 916 mIU/ml); none developed an IgM response.

Among the 22 children who had been vaccinated previously, 17 (77%) showed a boost in titre (Table 3). Of the responders, unvaccinated children were more likely to have an IgM response than those who were previously vaccinated ($P = 0{\cdot}004$).

Geometric mean titres (GMTs) in post vaccination sera were significantly lower in secondary than primary responders, 1256 v. 3664 mIU/ml respectively; after adjusting for age, sex and prior vaccination the fold difference in GMT was 0·326, (95% confidence interval 0·136–0·785, $P < 0{\cdot}001$). Neither sex nor prior vaccination status had a significant effect on post-vaccination titres.

Post-vaccination saliva samples were tested from 32 of the 38 children from whom post-vaccination sera were taken; 28 of the 32 (88%) developed IgG antibody. One of the four children who remained IgG negative in saliva failed to show a boost in serum neutralizing antibody titre (post-vaccination level 118 mIU/ml); the other three had post-vaccination serum neutralizing antibody levels of between 384 and 966 mIU/ml. Of the nine children with IgM antibody in serum, only five had detectable salivary IgM antibody after vaccination.

DISCUSSION

In this secondary school population in West Cumbria, 76 (9%) of pupils were estimated to be susceptible to measles, the numbers ranging from 38 (6%) in previously vaccinated children to 26 (20%) in the unvaccinated. Overall, half of those considered susceptible had a history of vaccination. This illustrates the importance of having adopted a non-selective vaccination strategy in the recent UK MR vaccination campaign [5, 6]. The proportion susceptible, as judged by a negative IgG test on saliva and a serum neutralizing antibody level $\leqslant$ 200 mIU/ml was similar to that found in the national serological surveillance programme [5] for the same birth cohorts when tested by haemagglutination inhibition – a test which is an accepted serological correlate of protection. As the study school was in a district where a neighbouring school had experienced a large outbreak in 1992 [8], this confirms that susceptibility to measles in areas which experienced outbreaks in the run up to the national campaign was not atypical and that the pool of susceptible school children identified in the national surveillance programme had clinical and epidemiological significance.

Although children with a history of vaccination comprised over half those considered susceptible, vaccinated children constituted only 12% of confirmed measles cases prior to the campaign [5]. Similarly, although susceptibility rates were only threefold lower in vaccinated than unvaccinated children in our study, attack rates in vaccinated children during the measles outbreak that occurred in the neighbouring school were tenfold lower in vaccinated than in unvaccinated children [8]. This suggests that some of the vaccinees in our study with low or negative antibody levels may nevertheless have been protected against clinical measles. This phenomenon has been demonstrated in a recent home contact study from Senegal in which vaccine efficacy against clinically typical measles in seronegative children vaccinated with a high titre preparation before 12 months of age was around 50% [15]. It is possible that IgM positive cases and those identified by the application of a clinical case definition during an outbreak investigation may not comprise the totality of infections in exposed vaccinees. The potential for vaccinated children with low antibody levels to transmit measles without developing clinical disease or an IgM response is still uncertain. None of the asymptomatic contacts in the Senegal study was

followed up serologically to investigate whether subclinical measles infection had occurred. However, one study from the USA suggests that many vaccinees with antibody levels below 200 mIU/ml are likely to experience a subclinical boost in antibody titre on exposure to measles [10]. Furthermore, serological evidence from Greenland suggests that persons infected subclinically may transmit measles virus [16].

As shown in other studies, individuals with no detectable antibody, and most of those with low antibody levels, will seroconvert [17, 18]. Previous studies have shown that vaccination of those with high antibody levels has little or no effect [18]; the lack of a fourfold rise in titre in the three individuals in our study with pre-vaccination levels > 500 mIU/ml is consistent with this. The increase in antibody levels after vaccination was lower in individuals experiencing a secondary than a primary response. Only 2 of the 15 children who had been vaccinated previously had an IgM response but the primary vaccine failure rate cannot be estimated from our data since such children may have seroconverted by prior exposure to measles. Similarly, the lack of an association between antibody prevalence and age at or time since vaccination is difficult to interpret without information on prior exposure.

The long-term effectiveness of childhood vaccination in preventing measles outbreaks will depend to some extent on the duration of the boost in immunity achieved in those whose antibody levels have declined. Other studies have shown that in 30–40% of individuals who show a secondary immune response to vaccination, antibody levels fall below that considered protective within a few years [17, 19]. Nevertheless, if all susceptible schoolchildren are revaccinated, the proportion with undetectable or low antibody levels can be reduced substantially. The resulting gain in antibody prevalence should be sufficient to interrupt transmission, at least in the short term [6, 7]. Continued serological surveillance of the population of England and Wales will be necessary to detect any repeated accumulation of susceptible schoolchildren in future. Introduction of a second dose of vaccine to reduce this risk is under consideration.

This study demonstrated the feasibility of screening a school-sized population for antibody to measles using a saliva test. Samples were collected over two school days by a team of four school nurses and one administrative officer. Salivary antibody screening was a better predictor of susceptibility to measles than vaccination history. If lack of documentation of prior vaccination had been used to identify those needing vaccine, 27% of the school would have been classed as in need of vaccination, instead of 9% as estimated by the two-stage screening procedure. Also, the susceptible vaccinated children (who represented 4% of the total school population), would have been missed. Relying on the results of salivary antibody assays would have reduced the proportion requiring vaccination to 13% (if 100% participation were achieved); thus only 4% of pupils would have been vaccinated unnecessarily. It is of interest that compliance with salivary testing was higher in children who had a documented history of vaccination suggesting that there are persisting differences between families who have accepted or rejected immunization in the past which could affect acceptance of a second dose of MMR vaccine if this is routinely offered in the future.

We did not formally assess the sensitivity and specificity of the salivary assay in this study, but its lack of sensitivity is indicated by the detection of > 200 mIU/ml of measles antibody in sera collected from 35% of children with negative salivary tests. In a previous study at this laboratory no false positives were detected although on small proportion of children with positive saliva samples had serum levels below 200 mIU/ml [20]. Other workers have reported the development of a sensitive and specific measles salivary assay [21]. However, a robust inexpensive field assay would need to be developed before salivary antibody screening and selective vaccination could substitute for universal vaccination of populations considered to be at risk for measles outbreaks. Development of detectable IgG antibody in saliva proved to be a sensitive measure of a serological response to vaccination. However, the sensitivity of salivary IgM detection after vaccination was only 4/9, which is lower than the 92% detected following natural measles [22]. This may reflect the lower intensity of the immune response following infection with the attenuated vaccine. Use of the salivary IgG assay to evaluate the response of a population to a vaccination initiative, such as the recent school based campaign, merits investigation.

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