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A study of maternally derived measles antibody in infants born to naturally infected and vaccinated women

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SUMMARY

Maternal, cord and infant measles antibody levels were measured and compared in a group of 411 vaccinated mothers and 240 unvaccinated mothers, and their babies, between 1983 and 1991. Maternal and cord sera were tested by haemagglutination inhibition and/or enzyme-linked immunosorbent assay, and plaque reduction neutralization tests were also used to test infant sera. Geometric mean titres were significantly higher in the unvaccinated than in the vaccinated mothers ($P < 0{\cdot}001$). Infants born to mothers with a history of measles had higher antibody levels at birth than infants of vaccinated mothers and, although the difference narrowed over time, continued to have higher levels up to 30 weeks of age. Between 5 and 7 months of age significantly more of the children of vaccinated mothers had plaque reduction neutralization antibody levels below that which would interfere with vaccination. As the boosting effect of circulating natural measles disappears, earlier measles vaccination may need to be considered, perhaps as part of a two-dose policy.

INTRODUCTION

The persistence of specific antibody, passively acquired from the mother contributes to seroconversion failures following measles vaccination in children under the age of 12 months [1–4]. This mechanism may also account for the lower efficacy observed when measles vaccine is administered between 12 and 15 months than after the age of 15 months [5]. Measles vaccine is not recommended in Canada and the UK until the second year of life [6, 7] and in the USA the recommended age for the first dose is between 12 and 15 months [8].

Immunity following natural infection confers higher antibody levels than those following vaccination [9–12] and infants born to vaccinated mothers acquire a lower level of measles antibody, which disappears at an earlier age, than infants born to mothers who have had natural measles infection [9–15]. Therefore, children born to vaccinated mothers may be vulnerable to natural measles infection and be able to respond to measles vaccine at a younger age than infants of unvaccinated mothers [9, 10, 12–17]. In the future, as the proportion of mothers who have been vaccinated increases, it may be possible to reduce the recommended age of measles vaccine, for all or for selected groups of children [9, 10, 12–14]. The aim of this study was to provide data which would assist in identifying the optimum age for vaccinating UK children in the future. We measured maternal, cord and infant levels of measles antibody in a cohort of

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UK women with a documented history of measles vaccination, and compared this to mothers with a history of natural measles.

METHODS

Vaccinated mothers

About 2500 UK-born women, immunized in 1964 with live Schwarz measles vaccine as part of the Medical Research Council (MRC) Study [18], are under annual follow up. In 1983 these women were asked to return a card if they became pregnant, consenting to the collection of paired cord and maternal blood at the time of delivery. This was then organized through the consultant obstetrician under whom the mother was booked. Since 1988 a further consent form has been sent to these mothers requesting follow up heel prick blood specimens from their infants at 8–30 weeks of age. These have been arranged by writing to the GP.

Unvaccinated mothers

Mothers were recruited from three sources for comparison. During 1989–90 women born before 1960 (and therefore too old to have received routine measles vaccine) were recruited postnatally by health visitors in Redbridge and north Hertfordshire. Maternal and infant samples were collected by a study nurse or doctor at between 8 and 30 weeks after birth. In 1990–1, a second group of women were recruited antenatally by study nurses in north Hertfordshire. This group was widened to include women born before 1960 and younger women with a history of natural measles and no history of measles vaccine. Paired cord and maternal samples were collected at the time of birth and follow up samples were taken between 8 and 30 weeks after birth. The third group of women recruited were the female partners of the male participants in the MRC vaccine trial. Those eligible were women born before 1960 or with a history of measles and no history of measles vaccine. These women were recruited antenatally and follow up performed as for the vaccinated cohort.

Laboratory methods

Maternal and cord and infant sera were tested haemagglutination inhibition (HAI) or enzyme-linked immunosorbent assay (ELISA). Initially, all sera were tested on a continuous basis by HAI and, if sufficient of volume of the sample was available, sera was also tested by ELISA. After 1989, samples were tested continuously by ELISA alone, rather than HAI, because of the higher sensitivity of the ELISA test [19]. Infant sera were tested according to the same protocol but any volumes remaining were stored at −20 °C for later batch-testing by plaque reduction neutralization (PRN) tests.

The tests were performed at the National Institute for Biological Standards and Control (HAI and PRN) and at the Virus Reference Division of the PHLS (ELISA). The HAI test was performed with baboon red blood cells, using classical methodology [20]. End point titres were taken as the highest dilution of serum, producing inhibition of agglutination of red blood cells by a fixed amount of virus. Sera were tested using a commercial ELISA (Behring Enzygnost OW LN 13). Measles specific IgG was quantified in mIU/ml by comparing the optical density readings of a titration of test serum with that of serum 66/202, the International Standard serum for measles [21].

In an adapted form of the PRN test [22], the challenge virus was incubated with a doubling dilution series of the test serum from 1/4 to 1/128. After 90 min at room temperature, the virus-antibody mixture was titrated in a plaque assay using Vero cells in 24-well plastic plates [23]. After 10 days incubation at 35 °C the cell monolayers were fixed, stained with crystal violet and the number of plaques in each well counted. Each assay also contained wells inoculated with challenge virus only. The end point titre of each test serum was determined as the dilution producing a 50% reduction in the number of virus plaques; this was calculated based on probit analysis [24]. The Philadelphia-26 strain of measles was used as challenge in that test. The International Standard for measles serum was included in every assay and measles titres converted into mIU/ml [21].

Analysis

Log-transformed titres were analysed for the three tests separately. Comparison of the two groups was performed for year of sample, maternal age, gestational age and birth weight of the infant. Maternal antibody levels were compared, adjusting for age, between vaccinated and unvaccinated groups and investigating the effect of year of sample and the timing of the maternal sample (whether it was taken at the time of delivery or at least 8 weeks postnatally).

The differences between cord and maternal antibody levels for each child (that is the placental concentration factor) were compared between vaccinated and unvaccinated mothers, adjusting for the maternal age, gestational age, birth weight and infant's sex. To compare antibody decay in the two groups of infants, antibody levels were then regressed against the age of the infant at the time of sampling, and the regression lines were compared for infants of vaccinated and unvaccinated women. Geometric mean antibody levels and the proportions of infants with levels thought to be protective against wild virus disease (200 mIU/ml) [25], and levels thought to interfere with vaccine response (50 mIU/ml) [26], were compared within different age categories of the two sets of infants.

Regression analyses were undertaken using normal errors regression, allowing for censoring of titre values – that is those which were reported as below the lower limit or above the upper limit of the reported range for that test, using established methods [27]. In this method censored observations are not assigned values but contribute the appropriate tail probabilities to the likelihood.

RESULTS

The study included 404 babies from vaccinated mothers and 245 from mothers with natural measles. The 207 mothers for whom a history of measles infection was uncertain were excluded from the analysis. The groups were not strictly comparable in that the mothers with natural measles were recruited between 1989 and 1993, whereas the vaccinated mothers were recruited between 1983 and 1993, but the latter group included 61% recruited after 1989. The mean age of mothers was 26 (S.D. 2·6) years in the vaccinated and 30 (S.D. 3·7) years in the unvaccinated group. The mean gestational age was 40 (S.D. 1·4) weeks, and the mean birth weight 3·4 (S.D. 0·49) kg, in both groups. For the vaccinated group, 56% of the infants were female compared to 50% of infants born to the unvaccinated group.

Maternal antibody

The analyses of mothers' antibody levels are based on results available for 640 pregnancies. HAI results were available for 506 mothers and ELISA results for 309. Maternal antibody levels increased significantly with age of mother for vaccinated ($P < 0·001$) and unvaccinated ($P = 0·044$) groups when measured by ELISA but not by HAI. Geometric mean titres, adjusted for censoring, were significantly higher in the measles than in the vaccinated group for both ELISA and HAI tests ($P < 0·001$), after adjusting for age (Table 1). A higher proportion of the mothers in the vaccinated than in the natural measles group had antibody levels indicating susceptibility to measles by ELISA testing (< 200 mIU/l), 37/161 (23%) and 10/148 (7%) respectively ($P < 0·001$). Similarly, a higher proportion of mothers in the vaccinated group had HAI levels below the cutoff, 24/298 (8%) compared to 5/208 (2%) in the group with natural measles ($P < 0·05$).

Maternal-cord antibody levels

Cord antibody level results were available for the following tests: ELISA ($n = 190$), HAI ($n = 385$). Antibody levels in the cord samples were higher than those in the maternal samples by a factor of 1·68 (95% confidence interval 1·57–1·80) by ELISA, 1·85 (95% confidence interval 1·67–2·06) by HAI. The concentration gradient was not significantly associated with maternal age or vaccination status, or the infant's sex, birth weight, or gestational age.

Infants' antibody levels

Infant antibody level results were available for the following tests: ELISA ($n = 231$), HAI ($n = 268$), and PRN ($n = 120$). Antibody levels were higher in children of unvaccinated than in children of vaccinated mothers, for all three tests. Geometric mean antibody levels (95% confidence interval) by ELISA were 44·6 (35·1, 56·7) and 125 (106, 151) in children born to vaccinated mothers and unvaccinated mothers respectively. Allowing for censoring in the ELISA and HAI results, antibody levels in infants born to both groups of mothers fell with increasing age of the infants. Separate slopes for infants born to each group of mothers suggested some narrowing of the difference over time, and this narrowing was significant for HAI ($P = 0·001$) but not for ELISA or PRN. A higher proportion of children born to vaccinated mothers than mothers with natural measles had HAI antibody levels below the test cut-off; 85/124 (69%) in the vaccinated group compared to 75/144 (52%) in the natural measles group. Using the more sensitive ELISA, a higher proportion of children had antibody levels below that which would interfere with response

Table 1. *Maternal measles antibody titres in sera collected from vaccinated mothers and from mothers infected with wild measles virus (United Kingdom, 1983–91)*

	Mothers with a record of measles vaccination			Mothers with a history of natural measles		
Measles antibody tests	Number	Geometric mean levels	95% confidence limits	Number	Geometric mean levels	95% confidence limits
ELISA (mIU)	161	426	358–506	148	882	737–1055
HAI (reciprocal titre)	298	12·4	10·8–14·2	208	43·7	37·0–51·6

Table 2. *The effect of age on the mean measles antibody levels of infants born to vaccinated and naturally infected mothers (United Kingdom, 1983–91)*

	PRN* (mIU/l)							
	Vaccinated				Measles			
Infants' age (days)	*n*	Geometric mean levels (95% confidence interval)	⩾ 50	⩾ 200	*n*	Geometric mean levels (95% confidence interval)	⩾ 50	⩾ 200
⩽ 120	14	116 (68–199)	12	4	19	404 (250–652)	18	16
121–150	25	102 (67–155)	22	7	12	376 (206–688)	12	10
⩾ 151	19	61 (38–98)	10	3	30	133 (91–195)	25	8
Total	58	89 (68–119)	44	14	61	230 (173–307)	55	42

* Plaque reduction neutralization.

to vaccine (50 mIU/l): 40/93 (43%) in the vaccinated group compared to 31/138 (22%) in the group with history of natural measles ($P < 0{\cdot}01$). In the group of children aged 150 days or more, a higher proportion of infants of unvaccinated than of vaccinated mothers had PRN levels which would interfere with vaccination ($P < 0{\cdot}05$) (Table 2).

DISCUSSION

This study confirms previous work which has demonstrated lower measles antibody levels in vaccinated adults than in those with a history of natural measles [5, 9, 11]. This difference is apparent using three different assays and after allowing for age. As demonstrated in US mothers, measles antibody is concentrated across the placenta [9] and the concentration factor does not differ between the vaccinated and unvaccinated mothers. In this unique group of women with a documented vaccination history, we have shown that children of vaccinated mothers are born with lower measles antibody levels and have lower antibody levels up to the age of 5 months than the babies of unvaccinated mothers. As previously suggested [10], the difference between babies of unvaccinated and vaccinated mothers may narrow with age. Interpretation of changes with time is difficult due to increasing censoring.

Almost half of the children of vaccinated mothers aged 5 months or over, however, had PRN antibody levels below that thought to interfere with response to measles vaccine. In previous studies in the UK and Canada over 90% of children of vaccinated mothers had antibody levels below the test cut-off at 6–7 months of age [10, 13, 17]. The higher proportion of antibody negative infants in these studies may reflect the choice of cut-off or the sensitivity of the assay, the older age of the infants sampled, or it may be due to real differences between the populations. Maternal antibody levels may have been boosted by the continuing extensive circulation of natural measles in the UK, in contrast to Canada [10, 28]. This boosting may be reflected in greater persistence of antibody in the infant.

In the developed world, measles vaccination is given over the age of 12 months because of failure to seroconvert and poor protection offered in infants vaccinated at an earlier age. The evidence for this is based on infants born predominantly to unvaccinated mothers [2, 4, 29] and higher seroconversion rates can be achieved in infants of vaccinated mothers at or below 12 months [9, 14]. In addition, with the increasing use of two dose measles vaccine policies [29], the risk of primary vaccine failure after one dose of vaccine may be less important to the overall control of measles. Revaccination of children vaccinated under 12 months of age has been shown to be protective [31, 32], and therefore early measles vaccine as part of a two dose schedule is an attractive option.

Measles vaccine was introduced for routine immunization in the UK in 1968, but coverage remained low throughout the 1970s and early 1980s [33]. Until the next century, therefore, the majority of UK mothers will have had natural measles, and those mothers who have been vaccinated may have had their antibody levels boosted by exposure to natural measles. As measles vaccine coverage increases, cases which occur in children under the age of scheduled vaccination will assume greater importance. Earlier vaccination at the same age in all districts has the potential to prevent some of these cases and to facilitate the achievement of higher levels of courage. The introduction of a two-dose measles vaccination policy, which has been recommended in the UK [34], would be an opportunity for re-addressing the age of the first dose. This will require periodic reevaluation, as the effect of boosting wanes, to assess the most appropriate age.

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REFERENCES

1. Black FL, Berman LL, Borgnono JM, et al. Geographic variation in infant loss of maternal measles antibody and in prevalence of rubella antibody. Am J Epidemiol 1986; **124**: 442–52.
2. Wilkins J, Wehrle PF. Evidence for the re-instatement of infants 12 to 14 months of age into routine measles immunization programs. Am J Dis Child 1978; **132**: 164–6.
3. Albrecht P, Ennis FA, Saltzman EJ, Krugman S. Persistence of maternal antibody in infants beyond 12 months: Mechanism of vaccine failure. J Pediatr 1977; **91**: 715–8.
4. Krugman S, Giles JP, Friedman H, Stone S. Studies on immunity to measles. J Pediatr 1965; **66**: 471.
5. ACIP. Measles Prevention: Recommendations of the Immunization Practices Advisory Committee (ACIP). MMWR 1989; **38**: S9 (1–18).
6. Guidelines for measles control in Canada. Canada Dis Wkly Rep 1991; **17**: 35–9.
7. Department of Health. *Immunisation against Infectious Disease*. London: HMSO, 1992.
8. CDC. Recommended Childhood Immunization Schedule – United States, January 1995. MMWR 1995; **43**: 959–60.
9. Lennon JL, Black FL. Maternally derived measles immunity in era of vaccine-protected mothers. J Pediatr 1986; **108**: 671–6.
10. Pabst HF, Donald WS, Marysysk RG, Carson MM, Chui LW-L, Joffres MR, Grimsrud KM. Reduced measles immunity in infants in a well-vaccinated population. Pediatr Infect Dis J 1992; **11**: 525–9.
11. Yeager AS, Harvey B, Crosson FJ, Davis JH, Ross LA, Halonen PE. Need for measles revaccination in adolescents: Correlation with birth date prior to 1972. J Pediatr 1983; **102**: 191–5.
12. Kakica MA, Venezia RA, Miller J, Hughes PA, Lepow ML. Measles antibodies in women and infants in the vaccine era. J Med Virol 1995; **45**: 227–9.
13. Jenks PJ, Caul EO, Roome APCH. Maternally derived measles immunity in children of naturally infected and vaccinated mothers. Epidemiol Infect 1988; **101**: 473–6.
14. Carson MM, Spady DW, Albrecht P, et al. Measles vaccination of infants in a well-vaccinated population. Pediatr Infect Dis J 1995; **14**: 17–22.
15. Ferson MJ, Whybin LR, Robertson PW. Pilot study of measles immunity in infants aged four to six months. Commun Dis Intell 1995; **19**: 30–1.
16. Kamat M, Pyati S, Pildes RS, et al. Measles antibody titres in early infancy. Arch Pediatr Med 1994; : 694–8.
17. Chui LWL, Maryusyk RG, Pabst HF. Measles virus specific antibody in infants in a highly vaccinated society. J Med Virol 1991; **33**: 199–204.
18. Medical Research Council. Measles Vaccine Committee. Vaccination against measles: a clinical trial of live measles vaccine given alone and live measles vaccine preceded by killed vaccine. BMJ 1966; **i**: 441–6.
19. Cremer NE, Cossen CK, Shell G, Diggs J, Gallo D, Schmidt NJ. Enzyme immunoassay versus plaque neutralisation and other methods for determination of immune status to measles and varicella-zoster viruses and versus compliment fixation for serodiagnosis of infections with these viruses. J Clin Micro 1983; **21**: 869–74.
20. Grist NR, Ross CA, Bell EJ. Diagnostic methods in clinical virology. Oxford: Blackwell Scientific Publications, 1974.

21. Forsey T, Heath AB, Minor PB. The 1st International Standard for anti-measles serum. Biologicals 1991; **19**: 237–41.
22. Albrecht P, Herrman K, Burns GR. Role of virus strain in conventional and enhanced measles plaque neutralisation test. J Virol Meth 1981; **3**: 251–60.
23. Mann GF, Allison MC, Copeland JA, Agostini CFM, Zuckermann AJ. A simplified plaque assay system for measles virus. J Biol Stand 1980; **8**: 219–25.
24. Finney DJ. Probit analysis. Cambridge: Cambridge University Press, 1971.
25. Chen RT, Markowitz LE, Albrecht P, Stewart JA, Mofenson LM, Preblud SR, Orenstein WA. Measles antibody: reevaluation of protective titres. J Infect Dis 1990; **162**: 1036–42.
26. Burgess W, Garelick H, Mann GF, Tomkins A. Measurement of prevaccination antibody levels using a plaque inhibition assay to predict the optimum age for measles immunization: 12th International Congress for tropical medicine and malaria; abstract. Kager PA, Polderman AM, eds. Amsterdam: Exerpta medica 1988. (Excerpta Medica International Congress Series 810).
27. Wolynetz MS. Maximum likelihood estimation in a liners model from confined and censored normal data. Appl Stat 1979; **28**: 195–206.
28. Ramsay M, Gay N, Miller E, Rush M, White J, Morgan-Capner P, Brown D. The epidemiology of measles in England and Wales: rationale for the 1994 national vaccination campaign. Commun Dis Rep 1994; **4**: R141–6.
29. Markowitz LE, Orenstein WA. Measles vaccines. Pediatr Clin N Am 1990; **37**: 603–25.
30. Christenson B, Böttiger M. Measles antibody: comparison of long-term vaccination titres, early vaccination titres and naturally acquired immunity to and booster effects on the measles virus. Vaccine 1994; **12**: 129–33.
31. Shasby DM, Shope TC, Downs H, et al. Epidemic measles in a highly vaccinated population. N Engl J Med 1977; **296**: 585.
32. Davis RM, Whitman ED, Orenstein WA, et al. A persistent outbreak of measles despite appropriate control measures. Am J Epidemiol 1987; **126**: 438.
33. Department of Health Statistics Division. 1995; Form SBL 607, 1966–86; Form KC51, 1987–94.
34. Miller E. The new measles campaign. BMJ 1994; **309**: 1102–3.