Loss of maternal measles antibody in black South African infants in the first year of life — implications for age of vaccination

P. KIEPIELA, H. M. COOVADIA, W. E. K. LOENING,
P. COWARD, S. S. ABDOOL KARIM

Summary

In order to investigate the feasibility of measles vaccination before the age of 9 months the duration of passive immunity against measles was estimated by conducting a longitudinal study of measles antibody levels in 20 black neonates delivered at term. Measles serum antibody (IgG) was measured by enzyme-linked immunosorbent assay in the mother at childbirth and on consecutive samples taken from the infants from birth until 9 months of age. Protective measles antibody level was defined as > 200 mIU. Unprotective levels were found in 88% (95% confidence interval (CI) 81 - 99%) of 6-month-old infants, while at 9 months all were susceptible. The mean antibody level was 192 mIU (CI 104 - 348%) at 4 months; 34 mIU (CI 15 - 73%) at 6 months and 13 mIU (CI 6-24%) at 9 months of age. Our data support the recent World Health Organisation recommendation to immunise children in developing countries at 6 months with the 'high titre' Edmonston-Zagreb measles vaccine, since most infants in our study had lost passive immunity against measles by this age.

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Department of Paediatrics and Child Health, University of Natal, Durban
P. KIEPIELA, PH.D. (IMMUNOL.)
H. M. COOVADIA, M.D., F.C.P. (S.A.), M.SC. (IMMUNOL.)
W. E. K. LOENING, M.B. CH.B., F.C.P. (S.A.)
P. COWARD, A.M.I.L.T.
S. S. ABDOOL KARIM, M.B. CH.B., M.SC. (EPIDEMIOL.), DIP. DATA

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Measles remains one of the most important infectious diseases in children born in poor socio-economic conditions,[1] where it is well known to be a prominent cause of morbidity and mortality.[2-7] The high measles mortality among infants is partially attributable to early age at exposure to the virus and geographical differences in the duration of passive immunity.[8-15]

The age-specific incidence rate and other aspects of measles in developing countries are different from the pattern in developed countries. On the basis of serological evidence, children in the USA are vaccinated at 15 months, since the disease is uncommon in younger children.[16] In specific regions of South Africa 20 - 45% of cases of measles occur in black infants under the age of 8 months.[5] At this age, vaccination is hampered because circulating maternal antibodies neutralise the conventional Schwarz vaccine. It is therefore pertinent to establish, on the basis of serological evidence, the optimum age at which to immunise these infants against measles.

Data on measles IgG antibody levels measured by enzyme-linked immunosorbent assay (ELISA) in newborn black infants and the subsequent decline and disappearance of the maternally acquired specific antibodies over time are reported.

Subjects and methods

The study population comprised 20 normally delivered newborn infants (half of whom were male) from the black community of KwaMashu township, Durban. Serum samples were obtained during a trial using acellular pertussis vaccine (conducted by A. Ramkissoon, H. M. Coovadia and W. E. K. Loening). All babies were delivered at term. Serial blood

samples were obtained by venepuncture from these same infants at birth, 2, 4, 6 and 9 months of age.

Nutritional status, using the weight-for-age, height-for-age and weight-for-height criteria of the US National Center for Health Statistics (NCHS) standards, was assessed at each visit. The parity of the mother and type of feeding (breast or bottle) was also recorded. The age and vaccination status of the mother was not recorded.

The following common problems of infancy were detected in these babies during the period of follow-up: impetigo (10 infants), upper respiratory tract infection (5), otitis media (4), lower respiratory tract infection (3), diarrhoea (3), conjunctivitis (1), febrile convulsion (1) and post-vaccinial transient hypotonia (1).

Serology

Measles IgG antibody was detected by ELISA, which was supplied in a kit form by Behring (West Germany). Measles antigen-coated plates were all supplied from the same batch (OSOK 02103 lot No. 406446A) as was the anti-human IgG-alkaline phosphatase conjugate (OSDH 04/05 lot No. 410955A) and supplementary agents (lot 19604). Results are expressed as mIU/ml with reference to the World Health Organisation standard anti-measles serum (obtained as a gift from the WHO). An optical density (OD) of $< 0{,}2$ (equivalent to < 34 mIU) was considered negative. Each child's and the respective mother's serum was processed in duplicate and always included in the same tests. All sera specimens were tested on the same day in the same tests. All sera specimens were tested on the same day in order to avoid any bias in sample testing due to the intrinsic variability of ELISA to either the environment or technical variation. International and local standards were included as controls (2 of which were kindly donated by Dr Roger Glass, Centers for Disease Control, Atlanta, Georgia, USA). Seropositivity was defined according to the persistence of antibody.[17] For this reason, seropositivity was defined as $>$ 200 mIU/ml at any time after birth. (Dr N. Halsey — personal communication; based on unpublished data from Dr P. Albrecht's laboratory.)

Ethical approval

The acellular pertussis vaccine trial was approved by the Ethics Committee of the Faculty of Medicine, University of Natal. Informed consent was obtained from the parent(s) or guardian who voluntarily consented to their child being entered into study after due explanation of the object of the trial and the number of blood specimens required.

Statistical methods

1. Polynomial regression was used to determine the relationship between mIU and OD readings obtained from the WHO reference serum. It was found that the parabola, given by $\sqrt{\text{mIU}} = -3{,}1161 + 27{,}5328\ (\text{OD}) + 9{,}3737\ (\text{OD})^2$, described the relationship that existed between mIU and OD readings. The adjusted coefficient of determination was $r^2 = 0{,}99$, i.e. 99% of the variation in mIU is explained by the variation in OD.

The utility of the above equation is limited to the observed range in OD values, i.e. from 0 to 1,6, since the latter OD reading was the maximum reading obtained for the patient sera tested.

Results are reported to the nearest whole number.

2. The data comprised a classic repeated measures set in that each of the 20 children was measured on 5 occasions. The purpose of the statistical analysis was to determine an average curve relating changes in antibody level to age and to demonstrate the changing proportions of children (whose antibody level remained above 200 mIU). In both analyses the reliability of predictions, in terms of confidence limits, must be made in relation to 'between-child' variability. Naturally, any extrapolation of these results to a wider population of children assumes the sample of 20 to represent that wider population.

(a) *The mean curve comparing antibody levels with age.* We took the log (OD) value for each child and fitted a cubic equation through the 5 points. While a sigmoid curve may represent the underlying relationship better, the data were insufficient to allow the necessary parameter estimation. As a means of interpolation, however, the cubic polynomial seemed satisfactory. The means and standard error of the predicted values for all 20 children were calculated for each of the 5 points. The t-distribution was used to calculate the 95% confidence limits. Finally, the predicted values and confidence limits were transformed back to mIU. The results appear in Table I and Fig. 1. Note that the crosses on the graphs are observed median values.[18]

TABLE I. PROPORTION OF CHILDREN WITH > 200 mIU IgG MEASLES ANTIBODY

Age (mo.)	Predicted value (%)	95% confidence limits Lower	Upper
0,0	100	100	100
0,5	100	99	100
1,0	99	97	100
1,5	97	91	100
2,0	92	83	99
2,5	85	72	97
3,0	75	59	93
3,5	62	49	83
4,0	49	35	69
4,5	36	23	49
5,0	26	10	36
5,5	18	4	26
6,0	12	1	19
6,5	8	0,5	15
7,0	5	0,1	11
7,5	3	0	7
8,0	2	0	5
8,5	1	0	3
9,0	1	0	2

The predicted values were obtained from the central distribution function of a normal distribution on the log data. Confidence limits were calculated using the bootstrap method.

(b) *The proportion of children with antibody level above 200 mIU.* For each age the mean log (OD) predicted value and standard error were calculated. Assuming a normal distribution in the log transformed data, the probability of an individual log (OD) value exceeding the equivalent of 200 mIU was estimated. Confidence limits were calculated using the bootstrap method. The probability predictions and confidence limits are shown in Table II and Fig. 2.[19]

Mother's antibody, height and weight were included as covariates in a multivariate analysis.

Results

Of the 6-month-old infants 88% (confidence interval (CI) 81 - 93%) and of 9-month-old infants 100% (CI 99 - 100%) had reached unprotective levels ($<$ 200 mIU) of measles IgG

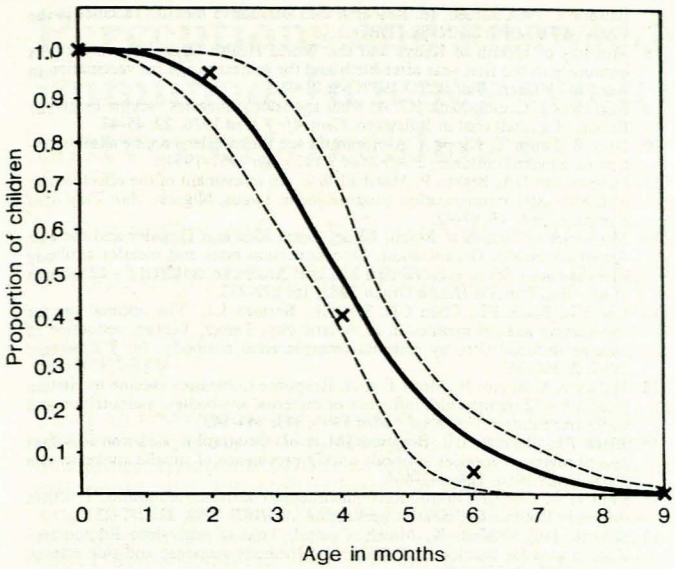

Fig. 1. Proportion of children with antibody level > 200 mIU.

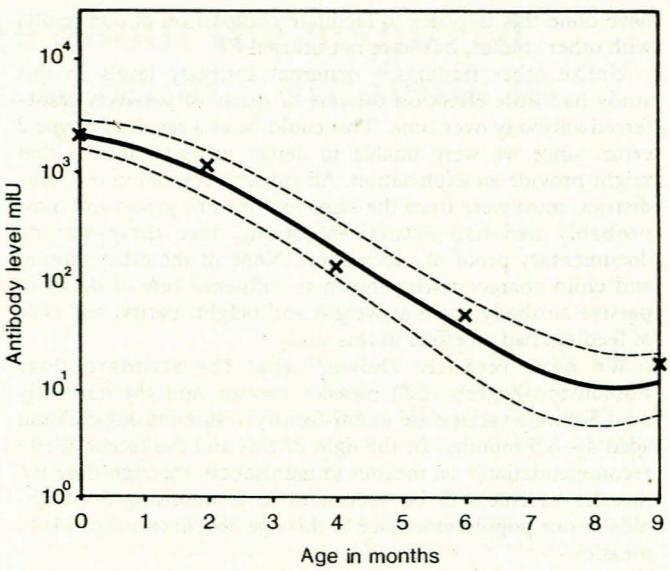

Fig. 2. Mean antibody level by age.

TABLE II. CHANGES IN ANTIBODY LEVEL (mIU) WITH AGE

Age (mo.)	Mean predicted value	95% confidence limits Lower	Upper
0,0	**2 148,2**	**1 607,2**	**2 877,7**
0,5	**1 930,4**	**1 368,7**	**2 730,6**
1,0	**1 604,2**	**1 065,1**	**2 424,6**
1,5	**1 247,7**	**785,0**	**1 989,7**
2,0	**919,0**	**555,8**	**1 522,2**
2,5	**647,9**	**380,7**	**1 101,6**
3,0	**441,7**	**253,3**	**766,2**
3,5	**293,7**	**164,2**	**519,5**
4,0	**192,1**	**104,1**	**347,7**
4,5	**124,4**	**64,7**	**232,0**
5,0	**80,5**	**39,7**	**155,6**
5,5	**52,4**	**24,3**	**105,5**
6,0	**34,7**	**15,1**	**72,7**
6,5	**23,7**	**9,7**	**51,4**
7,0	**17,0**	**6,7**	**37,6**
7,5	**13,2**	**5,2**	**28,8**
8,0	**11,4**	**4,7**	**23,7**
8,5	**11,2**	**5,2**	**21,7**
9,0	**12,8**	**6,3**	**23,6**

The predicted antibody levels are mean values from 20 children, with the value for each child being predicted by an equation determined by the method of least squares on log-transformed data. Calculations of confidence limits assume that the log-transformed data have a normal distribution.

antibody (Table I, Fig. 1). It appeared that the decline of maternal antibody began after 2 months of age, thereafter this decline was rapid, reaching a plateau at about 6 months.

Six-month-old infants had measles IgG antibody levels of 35 mIU (CI 15 - 73%), while in 9-month-olds this level was 13 mIU (CI 6 - 24%) (Table II, Fig. 2).

Neither the mother's antibody level nor height and weight, parity, and type of feeding had any influence on loss of passive immunity against measles.

Discussion

In the black population investigated, passively transferred measles antibody of maternal origin seems to wane earlier during infancy than was shown by initial studies on which vaccination policy was based in Africa.[8,20,21] This may have been partly influenced by the common infections seen in these infants. Furthermore, the level of maternal antibody was not an important factor in determining seropositivity levels over time. Anthropometric measurements (height and weight), parity and type of feeding had little, if any, effect on the loss of measles maternal antibody.

The reasons for the early loss of natural protection against measles are not clear. Several factors have been shown to play a role in the decrease over time of protection against measles by maternal antibody.[15,21,22]

Geographical differences may partly account for the durability of passive immunity. Results have varied in different parts of Africa. The proportion of seronegative children reached 90% by the end of 4 months of age in Gabon;[23] 7 months in Congo[20] and 8 months in rural Kenya[8] and in Lagos, Nigeria.[15] Outside Africa most of the available data come from the Americas.[12,14] Halsey *et al.*[14] in Haiti, found that 8 - 9 months was the age at which maternally transferred antibody was no longer present in more than 80% of the population, and satisfactory seroconversion rates to measles vaccination were obtained. In Bristol, UK, although limited by small sample size, Jenks *et al.*[22] found that maternal protection is lost in the majority of children by 8 months; and Bhaskaram *et al.*[6] in India found that it was lost by 9 months of age. These variations can be explained by epidemiological and demographic differences among communities (for example rate of decay of maternally derived antibody; age-specific mortality; rate of infection; and the net birth rate), which are important in the transmission of measles virus.[24]

An important consideration, which makes comparisons difficult, is the techniques used in different studies. The haemagglutination inhibition test is known to have poor sensitivity and does not give meaningful quantitative results, particularly for low-antibody titres. The ELISA is similarly not a good measure of maternal measles antibody because it measures the existence of antibody to viral nucleocapsids and other non-infectious viral components as well as to infectious viral particles,[25] whereas the plaque inhibition (PI) technique has been shown to yield results 4 times more sensitive and precise than the HI test, but it is a complex and difficult technique for routine use. Because of these differing sensitivities, serological data should be reported in comparison with data derived using the International Standard for human anti-measles serum. We

have done this in order to facilitate comparison of our results with other studies, but have not utilised PI.

Unlike other findings,[26] maternal antibody levels in this study had little effect on the rate of decay of passively transferred antibody over time. This could be as a result of a type 2 error, since we were unable to detect maternal factors that might provide an explanation. All subjects resided in the same district, most were from the same low-income group and most probably had had natural infection, since there was no documentary proof of vaccination. None of the other mother and child characteristics shown to influence rate of decay of passive antibody, such as weight and height, parity, and type of feeding, had an effect in this study.[21]

We have recently shown[27] that the standard dose Edmonston-Zagreb (EZ) measles vaccine and the currently used Schwarz vaccine are unsatisfactory in immunising children aged 4 - 8,5 months. In the light of this and the recent WHO recommendation[28] on measles immunisation, the high-dose EZ measles vaccine will be successful in immunising 6-month-olds in our population, since at this age 88% are susceptible to measles.

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