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MEASLES VACCINATION: INFLUENCE OF AGE ON ITS EFFICACY

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SUMMARY

The authors compare the serologic efficacy and the clinical protection afforded by three different measles vaccination schemes in adequately nourished children in São Paulo city, Brazil.

Two hundred forty two children were divided into three groups. Group A, comprising 117 children who had received the vaccine before 12 months of age and a second dose at 12 months of age or more. Group B, comprising 46 children who had received only one dose, before 12 months of age. Group C, comprising 79 children who had received only one dose, at 12 months of age or more.

The geometric mean titer of antibodies in Group A was 790.1; in Group B, 251.1; and in Group C, 550.3. There was no statistically significant difference between Groups A and C.

The exposure to the measles virus was probably similar in all groups, and the children in Groups A and C had similar chances of acquiring the disease after vaccination whereas in Group B the chances were higher when compared to the other two groups.

The results obtained in this study favor the use, in developing countries, of a vaccination program against measles that includes an early first dose at eight months of age and revaccination after 12 months of age.

KEY WORDS: Measles vaccine; Measles; Children immunization.

INTRODUCTION

In developing countries, measles causes high rates of morbidity and mortality in children [9, 16, 21, 22, 24, 26, 29], so that local health authorities have sugested vaccination beginning at the first year of age[4, 5, 6, 7, 8, 9, 12, 18, 20, 34]. The presence of maternal antibodies, in some cases up to 12 months after birth[2], has led to difficulties in using this strategy. These antibodies, even in a low titer, can interfere with the child's immunologic response to the vaccine[1, 2, 11, 13, 14, 27, 28, 30, 31, 38]. In Brazil, the use of only one dose of the measles vaccine, given before 12 months of

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age, has produced different results in the different geographic areas studied. In São Paulo, the seroconversion rate is approximately 80%[19, 23] showing that there are still a great number of children susceptible after vaccination. The use of a second dose, for children above one year old, could solve this problem. However it has been suggested by some authors[15, 37] that a percentage of the children vaccinated before 12 months of age do not respond adequately to a later second dose. If this is confirmed, then a vaccination program that included two doses, the first one given before one year of age, would have to be immediately dropped.

All these facts demonstrate deep controversies as to the ideal age for vaccination against measles in developing countries[35], and show that there are still few field studies on this subject.

The object of this study is to compare the serologic efficacy and the clinical protection afforded by three different measles vaccination schemes in adequately nourished children in São Paulo.

MATERIAL AND METHODS

From October 1979 to November 1981, all the children who had initiated their vaccination program from 1975 to 1979 in the Hospital do Servidor Público Estadual de São Paulo (São Paulo city, Brazil) were called by letter together with their parents for an interview.

Two hundred forty two children responded and their parents were questioned as to the history of previous vaccination, contact with known cases of measles (brothers and sisters, cousins, neighbors, children at school or day-care centers) and previous history of measles based on the norms established by the Centers for Disease Control, i. e., fever, cough, typical rash, Koplik spots and catarrhal symptoms). The precise dates of vaccination were obtained from the hospital files. The parents were also asked to consent to the drawing of a blood sample from the child.

The 242 children were divided into three groups according to the ages at which they had received measles vaccination.

Group A — comprising 117 children who had received the vaccine before 12 months of age and a second dose at 12 months of age or more. There were 75 serum samples obtained in this group.

Group B — comprising 46 children who had received only one dose, before 12 months of age. There were 32 serum samples obtained.

Group C — comprising 79 children who had received only one dose, at 12 months of age or more. There were 61 serum samples obtained.

The total number of serum samples was 168, drawn by venopuncture. The blood was centrifuged immediately and the serum was stored at a temperature of -20°C. Later they were tested for antibodies against the measles virus by Enhanced Neutralization[3] done by one of the authors (P. A.).

The samples were analyzed on the following dates: May 26th. and 27th., 1983 and June 2 nd., 1983. All tests were repeated on June 21st., 1983.

The vaccine used was that of live further attenuated measles virus. When given before 12 months it was not combined with any other vaccine and was furnished by the Health Authorities of the State of São Paulo[25]. When given to children of 12 months of age or more, the vaccine was combined with the mumps and rubella live attenuated virus vaccines (from Merck, Sharp & Dohme).

RESULTS

The mean age of the children at the time of vaccination and at the time of the interview, and the average interval between vaccination and collection of blood samples are shown in Table 1.

All the serum samples from Group A were positive for measles antibodies. Only one serum sample in Group B was negative and only one in Group C too. The geometric mean titer of antibodies in Group A was 790.1; in Group B, 251.1; and in Group C, 550.3 (Table 1). Possibly low (≤250) titers of antibodies measured by Enhanced Neutralization do not mean protection, and of 75 children in Group A, 13 (17.33%) had titers

TABLE 1
Schedule of subject enrollment and geometric mean titer (GMT) of anti-measles serum antibodies.

Group	Total number of cases interviewed	Number of blood samples	Mean age at time of interview (months)	Mean age at time of vaccination (months) 1st dose	2nd dose	Average interval between vaccination and blood collection (months)	GMT
A	117	75	48.48	8.21	16.86	32.58	790.1
B	46	32	51.75	8.40	—	44.21	251.1
C	79	61	51.94	16.06	—	35.96	550.3
	—	—					
	242	168					

below 250. Also in Group B, 13 children (40.62%) and in Group C, 8 (13.11%) had antibody titers below 250. Of these 34 children with low titers, eight later had contact with clinical measles and did not develop the disease.

Comparing the antibody log titers of the three groups, using the Kruskall Wallis multiple comparisons test and the Neuman Kluls technique, we noticed that there was no statistically significant difference between Groups A and C and that Group B is different from the other two groups ($p = 0.05$).

Within Group B, there was no significant difference in antibody titers between the children vaccinated early (7 or 8 months old), and those vaccinated later (9, 10 or 11 months old) using Student's t test ($t = 0.34$). Thus the mean titer of antibodies detected in Group B children was not significantly different whether the vaccination had taken place before or after nine months of age.

In Table 2 we have the number of children in each group exposed to measles after vaccination and the number of children who developed the disease. Diagnosis was confirmed by a doctor in three Group A cases, four Group B cases and two Group C cases. Using the Chi-square test, children in Groups A and C had similar chances of acquiring the disease after vaccination where as in Group B the chances were higher when compared to the other two groups ($p = 0.05$).

DISCUSSION

The results obtained in this study agree with those of other reports[9, 17, 32] confirming the efficacy of revaccination after an early first dose of the measles vaccine. In our study, along with demonstrated serologic results, we present clinical evidence of its usefulness.

Levels of serum antibodies measured in 168 of 242 children, after an average 38.96 months after vaccination were relatively high in the three groups studied. However the mean titer of the children vaccinated before 12 months of age (Group B) was significantly lower even though in this group there were more cases of naturally acquired measles (15.21%), a fact that would normally raise the mean because the levels of antibodies after natural disease are known to be higher than those obtained by vaccination[36].

The mean titer of antibodies in children vaccinated with one dose given at 12 months of age or more (Group C) was similar to that obtained from children who had received an early dose and were revaccinated at 12 months of age or more (Group A). This shows that there seems to be no negative serologic effect of an early dose (given before 12 months of age) on the efficacy

TABLE 2
Group of children with clinical measles.

	Total number of children	Number of children with a history of contact with clinical measles (%)	Number of children who developed clinical measles (%)
Group A	117	32 (27.3%)	5 (4.3%)
Group B	46	13 (28.3%)	7 (15.2%)
Group C	79	21 (26.6%)	7 (8.9%)

of a second dose (administered at 12 months of age or more).

In this study 13 children (17.33%) who had been vaccinated before one year of age and later revaccinated presented low antibody titers against the measles virus (< 250), which was similar to the percentage obtained in the group of children who had received only one dose, at 12 months of age or more (13.11%), and significantly lower than the 40.62% obtained in the group of children vaccinated before 12 months of age. The clinical significance of these low titers has not yet been sufficiently established[33]. It is interesting however to note that eight of these 34 children with low titers had contact with measles without acquiring the disease.

Most important in this study is the evidence that revaccination after an early first dose of measles vaccine gave good serologic results, similar to those obtained in children receiving only one dose after 12 months of age, and also offered similar clinical protection against the disease. The children in this study all live in the same geographic area (São Paulo city) where measles is an endemic disease and thus exposure to the measles virus was probably similar in all groups (Table 2). As is to be expected the risk of having the clinical disease after exposure to the virus was found to be higher in the group of children receiving their only dose of vaccine before 12 months of age.

In countries like Brazil, where in many large areas measles is a cause of illness and death to a high number of children below one year of age, the encouraging results of this study, obtained with a vaccination scheme against measles that included an early first dose at eight months of age and revaccination after 12 months of age, must be emphasized.

RESUMO

Vacinação contra o sarampo: influência da idade em sua eficácia.

Os autores comparam a eficácia sorológica e a proteção clínica obtidas com três esquemas diferentes de vacinação contra o sarampo, em crianças eutróficas, na cidade de São Paulo, Brasil.

Duzentas e quarenta e duas crianças foram divididas em três grupos. Grupo A, compreendendo 117 crianças primovacinadas antes dos 12 meses de idade e revacinadas com 12 ou mais meses de idade. Grupo B, compreendendo 46 crianças vacinadas com dose única, antes dos 12 meses de idade. Grupo C, compreendendo 79 crianças vacinadas com dose única, aos 12 ou mais meses de idade.

A média geométrica do título de anticorpos no grupo A foi 790,1; no grupo B, 251,1; e no grupo C, 550,3. Não houve diferença estatisticamente significante entre os grupos A e C.

A exposição ao vírus do sarampo foi provavelmente semelhante em todos os grupos. As crianças dos grupos A e C apresentaram risco de adoecimento semelhante após vacinação, enquanto que tal risco foi maior no grupo B quando comparado aos outros dois grupos.

Os resultados obtidos neste estudo falam a favor do uso, em países em desenvolvimento, de um programa de vacinação contra o sarampo que inclua uma primeira dose aos oito meses de idade e revacinação após os 12 meses de idade.

REFERENCES

1. ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES OF THE U. S. PUBLIC HEALTH SERVICE — Measles vaccines. **Ann. intern. Med., 67**: 1055 1058, 1967.

2. ALBRECHT, P.; ENNIS, F. A.; SALTZMAN, E. J. & KRUGMAN, S. — Persistence of maternal antibody in infants beyond 12 months: mechanism of measles vaccine failure. **J. Pediat., 91**: 715-718, 1977.

3. ALBRECHT, P.; HERRMAN, K. & BURNS, G. R. — Role of virus strain in conventional and enhanced measles plaque neutralization test. **J. virol. Meth., 3**: 251-260, 1981.

4. BORGONO, J. M. & GREIBER, R. — Sarampion. Cinco anos de experiencia con el programa de vacunación en Chile. **Rev. méd. Chile, 99**: 502-506, 1971.

5. BURROWES, J. & CRUICKSHANK, J. G. — At what age should measles vaccine be given? **Cent. Afr. J. Med., 22**: 45-47, 1976.

6. COLLABORATIVE STUDY BY THE MINISTRY OF HEALTH OF KENYA AND THE WORLD HEALTH ORGANIZATION — Measles immunity in the first year after birth and the optimum age for vaccination in Kenyan children. **Bull. Wld. Hlth. Org., 55**: 21 30, 1977.

7. DICK, B.; SMITH, T. & KIPPS, A. — A minimum age for measles vaccine administration to coloured children. **S. Afr. med. J., 49**: 1951 1954, 1975.

8. FUNDAÇÃO SESP, MINISTÉRIO DA SAUDE — Investigação sobre a vacina anti sarampo. **Bol. epidem. (Rio de J.), 11**: 129 131, 1979.

9. HALSEY, N. A.; BOULOS, R.; MODE, F.; ANDRE, J.; BOWMAN, L.; YAEGER, R. G.; TOUREAU, S.; ROHDE, J. & BOULOS, C. — Response to measles vaccine in Haitian infants 6 to 12 months old. **New Engl. J. Med., 313**: 544 549, 1985.

10. HAYDEN, R. I. — The epidemiology and nature of measles in Nairobi before the impact of measles immunization. **East Afr. med. J., 51**: 199, 1974.

11. KRUGMAN, R. D.; ROSENBERG, R.; McINTOSH, K.; HERRMAN, K.; WITTE, J. J.; ENNIS, F. A. & MEYER, B. C. — Further attenuated live measles vaccines: the need for revised recommendations. **J. Pediat., 91**: 766 767, 1977.

12. LEE, Y. L.; BLACK, F. L.; CHEN, C. L.; WU, C. L. & BERMAN, L. L. — The optimal age for vaccination against measles in an Asiatic city, Taipei, Taiwan: reduction of vaccine induced title by residual transplacental antibody. **Int. J. Epidem., 12**: 340 343, 1983.

13. LINNEMAN JR., C. C.; ROTTE, T. C.; SCHIFF, G. M. & YOUTSEY, J. L. — A seroepidemiologic study of a measles epidemic in a highly immunized population. **Amer. J. Epidem., 95**: 238 246, 1972.

14. LINNEMAN JR., C. C. — Measles vaccine: Immunity, reinfection and revaccination. **Amer. J. Epidem., 97**: 365 371, 1973.

15. LINNEMAN JR., C. C.; DINE, M. S.; ROSELLE, G. A. & ASKEY, P. A. — Measles immunity after revaccination: results in children vaccinated before 10 months of age. **Pediatrics, 69**: 332 335, 1982.

16. LOENING, W. E. K. & COOVADIA, H. M. — Age specific occurrence rates of measles in urban, peri-urban, and rural environments: implications for time of vaccination. **Lancet, 2**: 324 326, 1983.

17. MACGRAW, T. T. — Reimmunization following early immunization with measles vaccine: a prospective study. **Pediatrics, 22**: 45 48, 1986.

18. MEYER, H. M. — Response of Volta children to live attenuated measles virus vaccine. **Bull. Wld. Hlth. Org., 30**: 769 781, 1964.

19. MINISTRIES OF HEALTH OF BRAZIL, CHILE, COSTA RICA, AND ECUADOR AND THE PAN AMERICAN HEALTH ORGANIZATION — Seroconversion rates and measles antibody titers induced by measles vaccination in Latin American children six to 12 months of age. **Rev. infect. Dis., 5**: 596 605, 1983.

20. MIRCHAMSY, J. — Measles immunization in Iran. **Rev. infect. Dis., 5**: 491 494, 1983.

21. MORLEY, D. — Severe measles in the Tropics. Part I. **Brit. med. J., 1**: 297 300, 1969.

22. MORLEY, D. — Severe measles in the Tropics. Part II. **Brit. med. J., 1**: 363 365, 1969.

23. PANNUTI, C. S.; SOUZA, V. A. U. F.; TAKAOKA, N.; LEME, S. T. S.; PEREIRA, C. R.; CARVALHO, R. P. S. & AMATO NETO, V. — Interferência entre as vacinas anti sarampo e anti poliomielite. **Bol. Ofic. sanit. panamer., 103**: 227 232, 1987.

24. PAREDES, J. A. — El impacto del sarampion en Centro America. **Bol. Ofic. sanit. panamer., 76**: 503 511, 1974.

25. PRAL, M. M.; WOE FANG, F. L. & DE RIZZO, E. — Potency control of live, attenuated vaccines against measles used in children vaccinations in the State of São Paulo, Brazil (1976 1980). **Rev. Inst. Med. trop. S. Paulo, 24**: 1 5, 1982.

26. PUFFER, R. R. & SERRANO, C. V. — Caracteristicas de la mortalidad en la ninez. Washington, Organización Panamericana de la Salud, Organización Mundial de la Salud, 1973. **(Publicación Científica no. 262).**

27. RECOMMENDATION OF THE PUBLIC HEALTH SERVICE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES — Measles vaccine. **MMWR, 25**: 359 360, 1976.

28. REYNOLDS, D. W. & START, A. — Immunity to measles in children vaccinated before and after 1 year of age. **Amer. J. Dis. Child., 124**: 848 850, 1972.

29. RISI JR., J. B. — Control of measles in Brazil. **Rev. infect. Dis., 5**: 583 587, 1983.

30. SCHLUEDERBERG, A.; LAMM, S. H.; LANDRIGAN, P. J. & BLACK, F. L. — Measles immunity in children vaccinated before one year of age. **Amer. J. Epidem., 97**: 402 409, 1973.

31. SHELTON, J. D.; JACOBSEN, J. E.; ORENSTEIN, W. A.; SCHULZ, K. F. & DONNEL Jr., H. D. — Measles vaccine efficacy: influence of age at vaccination vs. duration of time since vaccination. **Pediatrics, 62**: 961 964, 1978.

32. SOERENSEN, B.; TAKEDA, A. K.; NAKANDAKARE, I. K.; CURI, L. C.; UMERITA, L. F.; ZUCCAS, W. A.; GUIDONI, R.; MAGALHÃES, E.; BRITTO, S. S. & FEIJÓ, I. C. — Sarampo: Idade ótima e número de doses recomendadas para a vacinação no Brasil. **Rev. Inst. Med. trop. S. Paulo, 27**: 55 65, 1985.

33. STETLER, H. C.; ORENSTEIN, W. A.; BERNIER, R. H.; HERRMANN, K. L.; SIROTKIN, B.; HOPFENSPERGER, D.; SCHUH, R.; ALBRECHT, P.; LIEVENS, A. W. & BRUNELL, P. A. — Impact of revaccinating children who initially received measles vaccine before 10 months of age. **Pediatrics, 22**: 471 476, 1986.

34. VERONESI, R.; SCHMID, A. W.; MOURA, R. A.; CARVALHO, R. P. S.; ZUCCAS, W. A. & CAMARGO, M. — Revisão de dados da epidemiologia e etiologia do sarampo e subsídios para a vacinação contra a doença. **Arq. Fac. Hig. S. Paulo, 17**: 135 204, 1963.

35. WALSH, J. A. — Selective primary health care: Strategies for control of disease in developing world. IV. Measles. **Rev. infect Dis., 5**: 330-340, 1983.

36. WEIBEL, R. E.; BUYNAK, E. B. & McLEAN, A. A. — Persistence of antibody in human subjects for 7 to 10 years following administration of combined live attenuated measles, mumps, and rubella virus vaccines. **Proc. Soc. exp. Biol. (N. Y.), 165**: 260-263, 1980.

37. WILKINS, J. & WEHRLE, P. F. — Additional evidence against measles vaccine administration to infants less than 12 months of age: Altered immune response following active/passive immunization. **J. Pediat., 94**: 865-869, 1979.

38. YEAGER, A. S.; DAVIS, J. H.; ROSS, L. A. & HARVEY, B. — Measles immunization. Successes and failures. **J. Amer. med. Ass., 237**: 347-351, 1977.

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