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Immunity to Measles in Young Adults in Israel*

Summary: The likelihood of an epidemic of measles in 1990–92 in Israel prompted us to study the immune status against measles in a random sample of 454 recruits aged 18–19 years in order to obtain data that might be used in determining vaccination policy. This cohort had received one dose of measles vaccine at 12 months of age. The measles immunity status was studied by determination of antibody values that were measured by means of an enzyme-linked immunosorbent (ELISA) IgG antibody test. Of the recruits, 84.6% were found to have positive sera for anti-measles IgG antibodies, while 13.7% had negative sera. Eight (1.7%) subjects had borderline results. The results of this study indicate the need to administer a second dose of measles vaccine at an older age in addition to the MMR (measles, mumps, rubella) vaccine that is now given in Israel at 12 months of age. This step will help achieve the World Health Organization's target of complete eradication of measles.

Zusammenfassung: *Immunität gegen Masern bei jungen Erwachsenen in Israel.* Die Möglichkeit einer Masernepidemie in Israel in den Jahren 1990–92 veranlaßte eine Stichprobenuntersuchung, wobei 454 18- bis 19jährige Rekruten auf ihren Masernimmunstatus untersucht wurden. Die Daten sind für die weiteren Impfstrategien von grundlegender Bedeutung. Die untersuchte Gruppe hatte im Alter von 12 Monaten eine Dosis Masernimpfstoff erhalten. Der Masernimmunstatus wurde durch IgG-Antikörper mittels ELISA bestimmt. Bei 84,6% der Seren fanden sich positive, bei 13,7% negative und bei acht Fällen (1,7%) grenzwertige Testergebnisse. Aus diesen Ergebnissen ist abzuleiten, daß zusätzlich zu der nun in Israel eingesetzten MMR-Vakzine (Masern, Mumps, Röteln), die im Alter von 12 Monaten appliziert wird, eine Auffrischimpfung gegen Masern zu einem späteren Zeitpunkt erforderlich ist. Das Ziel der WHO, die Masern vollständig auszurotten, dürfte damit erreichbarer werden.

Introduction

Routine measles immunization was introduced in Israel in 1967 with the Schwartz strain live attenuated vaccine administered at 9 months of age. Relatively low coverage of the population was achieved. In addition, no vaccination program for susceptible adults has been undertaken [1]. In 1971, because of a high percentage of vaccine failure, immunization was given to children at 12 months of age. The age of vaccination was raised to 15 months in 1973, using the Edmonston strain live attenuated vaccine [2,3]. Coverage with measles immunization was 82–90% in 1970–75 and 88% by 1988–89 [2,3]. The immunization program resulted in a dramatic decline in measles morbidity and mortality, disappearance of massive epidemics and a change in the age distribution of measles cases [3]. In 1950 the rate of measles in Israel was 1,112/100,000, while the incidence reported for 1989 is 0.57/100,000 [1]. Nevertheless, measles outbreaks are reported in Israel every 5–7 years. The 1982 and 1985–86 epidemics involved some 7,800 and 5,000 reported cases, respectively [3]. Significantly higher rates of illness were reported among those with higher education and socioeconomic classes, indicating a higher exposure rate at an earlier age in less educated lower socioeconomic groups [4]. The likelihood of another epidemic of measles in 1990–92 prompted us to study the immune status against measles in a representative sample of young adults in Israel in order to obtain data that might be used in determining vaccination policy.

Materials and Methods

Study population: During 1989–90, blood samples were drawn from a random sample of Israeli young adult male and female military recruits to the Israel Defence Force for routine surveillance of immunity to infectious diseases. Since army service is compulsory in Israel, the sample can be regarded as representative of the male, and much of the female, Jewish population in this age group. It is assumed that 82–90% of this cohort received the measles vaccine (Schwartz strain) at 12 months of age, according to the reported percentage of the Israeli population covered by the routine measles immunization program in the early 1970s when this cohort was born [2,3]. Demographic data including age, sex, country of birth, ethnic origin and number of years of education as well as history of cigarette smoking were obtained from all subjects in the sample. Ethnic origin was classified according to the father's birthplace (or, if this was Israel, the paternal grandfather's birthplace). Two broad areas of origin, East and West, were defined. West included Europe (excluding Turkey), the Americas, Australia and South Africa. All other countries (mainly in the Middle East and North Africa) were classified as East.

Received: 17 September 1992/Revision accepted: 27 January 1993

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*Part of M. D. thesis (*S. R. M.*) submitted to the Hebrew University, Jerusalem.

Infection 21 (1993) No. 3

Serology: The sera were stored at -20°C until tested for IgG antibodies to measles virus. The antibody levels were measured by means of an enzyme-linked immunosorbent (ELISA) IgG antibody test, using a commercial kit (Human, Taunusstein, Germany). Briefly, microtiter wells as a solid phase were coated with measles virus antigens. Sera at a dilution of 1:100 were added to the wells. Corresponding specific antibodies that were present in the specimens were bound to the antigen at the solid phase. After a washing step to remove unbound material, anti-human IgG conjugated to peroxidase was added. After a second washing step to remove unbound conjugate, the enzyme-linked complexes were detected by incubation with a substrate (3,5,5-tetra-methyl-benzidine) and development of a blue colour that changed into yellow after stopping the enzymatic reaction with sulphuric acid. The optical density, which is directly proportional to the amount of anti-measles IgG antibodies in the specimen, was measured by an ELISA microtiter plate reader (EL 340, Biotek Instruments Inc., Winooski, USA). Each serum was tested in duplicate and the average result was compared with a cut-off value that was based on positive and negative controls. Specimens with absorbance values greater than or equal to the cut-off value were considered positive for anti-measles IgG antibodies. Specimens with absorbance values less than the cut-off value were considered negative for anti-measles IgG antibodies.

The Chi-square test for differences between percentages was used to evaluate statistical significance in the univariate analyses. Multiple logistic regression analysis was used to determine correlates of anti-measles antibodies while controlling for other potentially confounding factors.

Results

Four hundred fifty-four subjects were included in the study. Of these, 53.9% were males and 46.1% females. Overall, 98.4% were born in 1970–72 and were therefore very likely to have received measles vaccination at the age of 12 months. The serological data of the study population is presented in Table 1. Of the 454 subjects examined, 84.6% were found to have positive serum for anti-measles IgG antibodies, while 13.7% were found to be negative. Eight (1.7%) subjects had borderline results: these subjects were excluded from further analysis. Of the female recruits, 88.2% were found to have positive sera, compared with 84.5% of the males ($p = 0.26$).

Table 1: Presence of anti-measles IgG antibodies among young adults in Israel by sociodemographic and smoking variables.

Variable	Positive for anti-measles IgG antibodies	
	No.	%
Study population	384	84.6
Females	180	88.2
Males	202	84.5
p value		0.26
Western origin	168	89.4
Eastern origin	170	82.9
p value		0.07
> 11 years of schooling	322	86.6
≤ 11 years of schooling	60	84.5
p value		0.65
Smokers ≥ 20 cigarettes/day	84	88.4
Smokers < 20 cigarettes/day	16	64.0
p value		0.007

A borderline-significant difference was found between subjects from different ethnic origins. Whereas 89.4% of subjects of western origin had positive sera, only 82.9% of the subjects of eastern origin had antibody levels above the cut-off point ($p = 0.07$). Of the male subjects of western origin, 91.2% were positive, compared with 80.0% of male subjects of eastern origin ($p = 0.02$). No statistically significant difference in the percentage of females with positive sera was found between those of western and those of eastern origin (87.2% vs. 86.3%, $p = 0.86$).

No significant association was found between education and immunity level. Among subjects with 12 or more years of education, 86.6% had positive sera, compared with 84.5% of subjects with less than 12 years of education ($p = 0.65$). However, among subjects with a higher level of education (12 years of schooling or more), a greater percentage of positive sera was detected among those of western origin compared with those of eastern origin (90.0% vs. 82.1%, $p = 0.04$). Of the smokers, 83.3% had positive sera compared with 87.1% of the non-smokers ($p = 0.31$). However, the percentage of positive sera among heavy smokers (20 cigarettes or more per day) was significantly lower compared with the percentage among subjects who smoked less than 20 cigarettes per day (64.0% vs. 88.4%, $p = 0.007$). Of all the variables examined (sex, education, ethnic origin, smoking), only smoking (number of cigarettes smoked per day) retained a significant association with the level of immunity within a multiple logistic regression analysis model ($p = 0.03$).

Discussion

Measles outbreaks have been reported in schools and colleges in which 98% or more of the population had valid immunization records [5]. Epidemiologic data from several measles outbreaks showed that even a level of 94% immunity does not confer herd protection where large groups of persons gather together [5]. *Anderson* and *May* [6] suggested that a level of 95% immunity is needed to bring the disease under control by interrupting transmission. According to the data presented in this report, no more than 85% of the young adult population in Israel has adequate immunity against measles, a proportion which is well under the level required for herd immunity.

ELISA, which was used in our study to determine immunity against measles, was reported to be as sensitive a test as the hemagglutination inhibition test [7] and more sensitive than the complement fixation test [8]; it was also shown to have good reproducibility [8]. However, ELISA may also detect antibodies to internal virus proteins, which play a small role in immunity to measles [9]. Thus, it may

be possible that the 84% immunity reported by us is an overestimate of the true prevalence of subjects who are protected against measles. It has been suggested that in enzyme immunoassay, physiologic variations in virus antibody levels, including antibodies against measles, occur [10]. The large number of controls and individuals tested in this study overcomes the possibility of such minor fluctuations.

The results presented, which are pertinent to a cohort born in Israel in 1970–71, are not surprising in view of the relatively low immunization coverage (82% in 1970), the rate of immunization vaccine failure, which is estimated to be 5–8%, and the exposure to disease throughout all the years until sera were drawn [3]. Since immunization coverage has been 85% for most of the 1980s, it is unlikely that any age group in the 0–20 year range would have higher immunized protective antibody levels, even though epidemic disease exposure may have boosted immunity levels [3]. Serosurveys of small non-random samples done among Israeli schoolchildren during 1981–85 suggested that about 90% of Israeli adolescents had adequate levels of protective circulating antibodies [11]. Highly immunogenic, safe and effective attenuated measles virus vaccines are now available and confer protection as measured by persistent antibody for at least 15 years [12], enabling control of measles.

Current immunity levels according to the data presented in this report indicate that large numbers (15%) of children and young persons are susceptible to the disease and its transmission. Thus, despite the long-standing childhood immunization program, the goal of complete control over and elimination of the disease as defined by the World Health Organization [13] will not be achieved in the near future.

From the findings of the present study it appears that immunity against measles is higher among individuals of western origin compared with those of eastern origin. A higher infectivity rate or a higher rate of compliance with the immunization program among the western population in Israel can explain this difference. Since in the early 1970s the western population in Israel constituted the higher socioeconomic levels, and since previous studies indicated possible higher rates of exposure in early childhood in less educated populations [4], we can assume that the ethnic difference in the level of immunity to measles is due to greater compliance with the vaccination program among this group. Data from another study that evaluated immunity against diphtheria among a similar random sample of recruits aged 18–19 in 1987 also showed a higher, albeit not significant, level of immunity among subjects of western origin compared with subjects of eastern origin [14].

It is of interest to note that the number of cigarettes smoked was associated with the level of immunity against measles. A variety of alterations in the immune system have been observed that are presumably due to cigarette smoking. Two studies suggested that smoking produces a more rapid decline in influenza antibody titers after natural infection or vaccination with influenza virus [15,16]. Thus, the results presented by us may be related to the effect of smoking on the immunity against measles.

In conclusion, the level of immunity to measles found in the sample examined in the present study indicates the need to reconsider the immunization policy against measles in Israel. These data were presented to the Ministry of Health and to the Israeli Advisory Committee on Immunization Practices, which decided, based on recommendations in the medical literature [17,18], to adopt a "two-dose policy." This involves giving a second dose of measles vaccine to all children at the age of 6 years in addition to the MMR vaccine (measles, mumps, rubella) that is given at 15 months of age.

References

1. **Berger, S. A.:** The infectious diseases of Israel. Isr. Soc. Inf. Dis, Gefen, Jerusalem, 1991.
2. **Swartz, T. A.:** Prevention of measles in Israel: implications of a long-term partial immunization program. Public Health Rep. 99 (1984) 272–277.
3. **Tulchinsky, T. H.:** Prevention of measles in Israel: short- and long-term intervention strategies. Isr. J. Med. Sci. 27 (1991) 22–29.
4. **Matzkin, H., Regev, S., Nili, E.:** A measles outbreak in the Israel Defence Forces during 1982 epidemic. Isr. J. Med. Sci. 21 (1985) 351–355.
5. **Black, F. L.:** Measles active and passive immunity in a worldwide perspective. In: *Melnick, J. L.* (ed.): Prog. Med. Virol. Basel, Karger 1989, 36 pp. 1–33.
6. **Anderson, R. M., May, R. M.:** Vaccination and herd immunity to infectious diseases. Nature 318 (1985) 323–329.
7. **Murphy, M. D., Brunell, P. A., Lievens, A. W., Shehab, Z. M.:** Effect of early immunization on antibody response to reimmunization with measles vaccine as demonstrated by enzyme-linked immunosorbent assay (ELISA). Pediatrics 74 (1984) 90–93.
8. **Salmi, A. A.:** Measles virus. In: *Balows, A., Hausler, W. J., Hermann, K. L., Isenberg, H. D., Shadomy, H. J.* (eds.): Manual of clinical microbiology. American Society for Microbiology, Washington DC 1991, pp. 904–911.
9. **Norrby, E., Orvell, C., Vandvik, B., Cherry, J. D.:** Antibodies against measles virus polypeptides in different disease conditions. Infect. Immun. 34 (1981) 714–724.
10. **Meurman, O., Lehtonen, O. P.:** Fluctuation of virus antibody levels in healthy adults. Eur. J. Clin. Microbiol. Infect. Dis. 7 (1988) 656–658.
11. **Tulchinsky, T. H., Abed, Y., Ginsberg, G., Shaheen, S., Friedman, J. B., Schoenbaum, M. L., Slater, P. E.:** Measles in Israel, the West Bank, and Gaza: continuing incidence and the case for a new eradication strategy. Rev. Infect. Dis. 12 (1990) 951–958.
12. **Weidel, R. E., Buynak, E. B., McLean, A. A., Roehin, R., Hilleman, M. R.:** 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. Med. 165 (1980) 260–263.
13. **World Health Organization:** Targets for health for all: targets in support of the regional strategy for health for all. WHO, Geneva 1986.

14. **Cohen, D., Katzenelson, E., Green, M., Slepon, R., Bercovier, H., Danon, Y.:** Prevalence and correlates of diphtheria toxin antibodies among young adults in Israel. J. Infect. 23 (1991) 117–121.
15. **Finklea, J. F., Hasselblad, V., Riggan, W. B., Nelson, W. C., Hammwer, D. I., Newill, V. A.:** Cigarette smoking and hemagglutination inhibition response to influenza after natural infection and immunization. Am. Rev. Resp. Dis. 104 (1971) 368–376.
16. **MacKanzie, J. S., MacKanzie, I. H., Holt, P. G.:** The effect of cigarette smoking on susceptibility to epidemic influenza and on serological response to live attenuated and killed subunit influenza vaccines. J. Hyg. 77 (1977) 409–417.
17. **Centers for Disease Control:** Measles prevention: recommendations of the Immunization Practices Advisory Comittee. MMWR 38 (1989) 4.
18. **Committee on Infectious Diseases, American Academy of Pediatrics:** Measles: reassessment of the current immunization policy. Pediatrics 84 (1989) 1110–1113.

Book Review

D. L. Wiedbrauk, S. L. G. Johnston
Manual of Clinical Virology
380 pages, 74 figures
Raven Press, New York 1992
Price: $ 81.50

The authors present a handy manual which describes the classical procedures of viral cultures (CPE) as well as the use of immunofluorescence for the antigen detection in infected cells. Each chapter starts with a description of the disease which is caused by the virus and the ordinary immunological response. The choice and preparation of the clinical specimen, the isolation procedure itself as well as the performance of appropriate controls are depicted in great detail and the results are illustrated with instructive figures. As a special piece of information an "at-a-glance" summary gives the answers to frequent questions on the topic, including the most important clinical and sero-epidemiological data.

The detailed appendices on reagent resources and reagent formulations focus on the market in the United States, but may also be of some help in Europe due to the fact that most of the companies listed are international. The glossary, which leaves no abbreviation unexplained, should appear before the text; in its present location it is difficult to follow.

The authors made a special effort to provide complete information on cell culture and virus cultivation in a didactic style that leads even an inexperienced reader step by step toward the successful management of clinical virology. Thus, regarding classical virology this book is a real state-of-the-art manual.

However, immunologic methods of antigen detection have been developed and have entered the market that are not adequately covered in this book. For example, immunologic RSV antigen-detection systems are quoted as lacking "perfect sensitivity or specificity." As a rule sensitivity of these methods is superior to virus culture, which is an important characteristic of a test on which infection control measures are based. Of course, virus culture remains the gold standard when looking for specificity. Focussing on virus culture techniques, the authors omitted two viruses which call for diagnostic virology every day: hepatitis B and C. Serological tests for these two viruses should be mentioned at least in an "at-a-glance" section.

In the era of molecular virology, perhaps the next edition will contain more of the modern technology. Nevertheless, this "old-fashioned" manual is a good buy, as it condenses the virus culture experience of half a century in a reasonable, handy paperback.

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