Sero-epidemiological study of measles after 15 years of compulsory vaccination in Alexandria, Egypt

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دراسة وبائية مصلية على الحصبة بعد خمسة عشر عاماً من التلقيح الإجباري في الإسكندرية، مصر

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خلاصة: تمت دراسة حالات الحصبة بين 165 من الأطفال الملقحين وغير الملقحين، وتم تحديد مستوى أضداد الحصبة لدى 230 من الأطفال الذين سبق تلقيحهم. كما تم بحث الارتباطات بين العوامل الديموغرافية والاستجابة المناعية للتلقيح. ووجد أن 80% تقريباً من الأطفال المصابين بالحصبة كانوا ملقحين. وكانت معدلات المضاعفات المصاحبة لحالاتهم منخفضة بدرجة ذات معنوية إحصائية. وتبين أن أكثرية الحالات غير الملقحة كانت توجد في المناطق الريفية. ولم تكن الحالة التلقيحية للأطفال مرتبطة بمكان التعرض ولا بمدة وجود البوادر ولا بدقة التشخيص الأولي. وبلغ معدل إيجابية المصل بين الأطفال الملقحين 86.1% من دون تباين إحصائي معنوي مع تقدم السن. ونحن نوصي بإعطاء الأطفال جرعة ثانية من لقاح الحصبة، مع الحفاظ على مستوى مرتفع للتغطية بالتطعيمات.

ABSTRACT Cases of measles among 165 vaccinated and unvaccinated children were studied and the level of measles antibody in 230 previously vaccinated children was determined. Associations between demographic factors and immunological response to vaccination were also investigated. Approximately 80% of the children with measles had been vaccinated; their cases had significantly lower rates of complication. Rural areas accounted for significantly higher numbers of unvaccinated cases. Vaccination status did not correspond to place of exposure, duration of prodrome or accuracy of preliminary diagnosis. The seropositivity rate among vaccinated children was 86.1% with no significant variation with age. We recommend a second dose of measles vaccine and maintaining high vaccine coverage.

Etude séro-épidémiologique de la rougeole quinze ans après l'introduction de la vaccination obligatoire à Alexandrie (Egypte)

RESUME Des cas de rougeole chez 165 enfants vaccinés et non vaccinés ont fait l'objet d'une étude et le taux d'anticorps antirougeoleux chez 230 enfants vaccinés auparavant a été déterminé. On a également examiné les associations entre les facteurs démographiques et la réponse immunitaire à la vaccination. Environ 80% des enfants atteints de rougeole avaient été vaccinés; leurs cas avaient des taux de complication considérablement plus faibles. On comptait un nombre beaucoup plus élevé de cas d'enfants non vaccinés dans les zones rurales. Le statut vaccinal ne correspondait pas au lieu de l'exposition à la maladie, à la durée du prodome ni à l'exactitude du diagnostic préliminaire. Le taux de séropositivité chez les enfants vaccinés était de 86,1% et il n'y avait aucune variation significative avec l'âge. Il est donc recommandé d'administrer une deuxième dose de vaccin antirougeoleux et de maintenir une couverture vaccinale élevée.

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Introduction

Measles is unquestionably one of the most important sources of morbidity and mortality throughout the world. Data gathered from several developing countries indicate that measles is not only a major cause of immediate mortality, but that its residual effects contribute to malnutrition and increased mortality from other diseases for many subsequent months [*1*].

The widespread use of measles vaccine in many developed countries has resulted in greater than 90% reduction from peak reporting [*2*]; in contrast, little success has been observed in many developing areas and measles continues to kill more than one million children each year [*3*]. Furthermore, measles transmission remains a problem in many African and Latin American countries despite high immunization coverage rates [*4*].

In Egypt, Sherif et al. [*5*] reported that the introduction of compulsory measles vaccination had reduced the average number of reported measles cases by approximately 57% and had markedly reduced measles deaths. However, this was still far below the Expanded Programme on Immunization (EPI) target reduction of 90% of measles cases and 95% of measles deaths by the year 1995 [*6,7*].

Epidemiological phenomena are far from static. Updating knowledge of the status of measles is necessary in order to achieve better understanding and control of this childhood killer disease. This study was implemented to compare the natural history of measles among vaccinated and unvaccinated cases and to determine the levels of antibody against measles in previously vaccinated children, as well as to investigate possible associations between age, sex and residence and the immunological response to measles vaccine.

Subjects and methods

This study was carried out in Alexandria, Egypt. The fieldwork extended over a 1 year period from May 1993 to April 1994 (3 days randomly selected per week).

Subjects included all cases of measles (n = 165) attending the Alexandria Fever Hospital during the days of the fieldwork. Verification of diagnosis was in accordance with the WHO case definition of measles [*6*]. History of measles vaccination was ascertained by checking birth certificates.

Subjects of serological assessment were drawn from children attending Alexandria Main University Hospital, aged from 2 to 12 years and having a birth certificate-documented history of a single dose of live-attenuated measles vaccine (n = 230). The sample size was governed by the budget of the research and the cost and size of serological kits. The total group was classified into five equal age intervals of two years each. Children with a previous history of measles and children having any immunocompromising conditions were excluded. The collection of blood samples was carried out twice weekly from those fulfilling the selection criteria. It was necessary to approach a total of 290 children to recruit the pre-decided number of children (response rate = 79.3%).

A pre-designed questionnaire was used for children with measles or their parents whenever feasible. This questionnaire recorded the vaccination status of cases and items pertaining to the natural history of the disease: age, sex, circumstances of exposure (home index or secondary cases), duration of prodrome, clinical presentation and post-measles complications. In addition, the permanent residence of cases (urban or rural) was recorded.

Another questionnaire was used to record age, sex and residence of children subjected to serological analysis.

Blood samples were collected from vaccinated children. Sera were separated and kept frozen until subjected to the ELISA test for measuring the IgG antibody titre (Enzygnost anti-measles virus IgG packs from Hoechst-Behring laboratories, Germany). Chen et al. [8] considered an antibody (AB) level of 200 mIU (mIU = 1/1000 international units) as the cut-off optical density value that correlates well to protection. The following formula was applied to the optical density value of each test sample to deduce the corresponding AB level [8]:

$$\text{Log}_{10}\,(\text{in mIU/ml}) = \alpha\Delta A\beta$$

where:
α and β are batch dependent constants given in the table of values accompanying the analysis kit for quantitative evaluation; and ΔA is the absorbance antigen – absorbance control antigen, or the optical density of the test sample.

Analysis of data was performed using SPSS (version 6). The level of significance chosen was 5%.

Results

Natural history of measles

A total of 165 cases of measles were studied. Approximately four-fifths of these had been vaccinated before onset of measles (79.4%). The rest were either unvaccinated (15.8%) or were below the recommended age for vaccination (4.8%).

Ages ranged from 5 months to 26 years with a mean age of 7.4 ± 4.7 years (Table 1). Vaccinated cases had an insignificantly higher mean age compared to non-vaccinated ones (7.5 ± 4.1 and 7.0 ± 6.5 years respectively, $t = 0.6$). The highest proportion of cases was in the age group 5 to less than 15 years (69.1%). A significantly higher percentage of vaccinated cases was found in this age category (74.0% compared to 50.0%, $Z = 2.0$).

Table 1 **Distribution of measles cases according to characteristic and vaccination status**

Characteristic	Vaccinated cases		Unvaccinated cases		Total		Test of significance
	No.	%	No.	%	No.	%	
Age (years)							
< 1	1	0.8	8	23.5	9	5.5	$Z = 0.5$
1–	28	21.4	6	17.7	34	20.6	$Z = 0.2$
5–	97	74.0	17	50.0	114	69.1	$Z = 2.0$*
15–26	5	3.8	3	8.8	8	4.8	$Z = 0.3$
Sex							
Male	57	43.5	11	32.4	68	41.2	
Female	74	56.5	23	67.6	97	58.8	$\chi^2_1 = 1.4$
Residence							
Urban	112	85.5	19	55.9	131	79.4	
Rural	19	14.5	15	44.1	34	20.6	$\chi^2_1 = 14.5$*
Total	131	79.4	34	20.6	165	100	

*Significant at 5%

The male to female ratio in the total group was 0.7:1 (Table 1). A predominance of females was also found among unvaccinated cases. The variations, however, were statistically insignificant ($\chi^2_1 = 1.4$).

A higher proportion of cases (63.0%) was described as home index cases, i.e. exposure occurred outside the home (Table 2). The rest were home secondary cases (37.0%). The differences according to vaccination status were insignificant where $\chi^2_1 = 0.3$.

The overall mean duration of prodrome of measles was 3.5 ± 1.4 days (Table 2). The majority of both vaccinated and unvaccinated groups had a duration of prodrome within the usual range of 4 days or less (78.6% and 76.5% respectively, $\chi^2_1 = 0.1$).

About three-fifths of the sample had nonclassical clinical presentation and were first misdiagnosed as having other diseases (61.2%). There was no significant association between vaccination status and the nature of clinical presentation ($\chi^2_1 = 1.6$).

Slightly more than half of the sample (51.5%) had complications (Table 2). A significantly higher percentage of unvaccinated cases (82.4%) suffered complications as

Table 2 **Distribution of measles cases according to characteristics of measles attack and vaccination status**

Characteristic	Vaccinated cases		Unvaccinated cases		Total		Test of significance
	No.	%	No.	%	No.	%	
Exposure							
Home-index 84 64.1	20	58.8	104	63.0			
Home-secondary 47	35.9	14	41.2	61	37.0	$\chi^2_1 = 0.3$	
Duration of prodrome (days)							
≤ 4	103	78.6	26	76.5	129	78.2	
5–7	28	21.4	8	23.5	36	21.8	$\chi^2_1 = 0.1$
Clinical presentation							
Classical	54	41.2	10	29.4	64	38.8	
Non-classical[a]	77	58.8	24	70.6	101	61.2	$\chi^2_1 = 1.6$
Complications							
None	74	56.5	6	17.6	80	48.5	
Respiratory	40	70.2	22	78.6	62	72.9	
Gastrointestinal	15	26.3	6	21.4	2	24.7	$\chi^2_2 = 1.3$
Other	2	3.5	0	0.0	2	2.4	
Subtotal	57	43.5	28	82.4	85	51.5	$\chi^2_1 = 16.3$*
Season							
Winter	16	12.2	3	8.8	19	11.5	
Spring	92	70.2	25	73.5	11	70.9	
Summer	19	14.5	6	17.7	25	15.2	
Autumn	4	3.1	0	0.0	4	2.4	
Total	131	79.4	34	20.6	165	100	

*Significant at 5%

[a]Non-classical presentation includes unrecognized prodrome, unusual distribution or morphology of rash

compared to vaccinated cases (43.5%; $\chi_1^2 = 16.3$). The most commonly reported types of complication were respiratory (72.9%), followed by gastrointestinal ailments (24.7%). There was no significant difference regarding the type of complications between vaccinated and unvaccinated cases ($\chi_2^2 = 1.3$).

There were no deaths associated with measles in the present series of cases (vaccinated or unvaccinated).

About four-fifths of the cases were residents of urban areas (79.4%) (Table 1). The remaining fifth were residents of rural areas of Alexandria and other governorates (20.6%). A significantly higher proportion of unvaccinated cases came from rural areas than did those previously vaccinated (44.1% and 14.5% respectively, $\chi_1^2 = 14.5$).

The seasonal distribution of interviewed cases was spring, 70.9%; summer, 15.2%; winter, 11.5%; and autumn, 2.4% (Table 2). The distribution of both vaccinated and unvaccinated groups by season of occurrence was in accordance with the distribution of the total cases.

Serological analysis

The percentage of seropositivity among vaccinated children was 86.1%, denoting a vaccination failure rate of 13.9% (Table 3). Age had no significant relationship to the rate of seropositivity ($\chi_4^2 = 8.9$). There was a decreasing mean AB level with increasing age until 8 years followed by increasing mean AB level among the oldest age intervals. The differences, however, were statistically insignificant ($F = 0.9$).

Although there was nosignificant difference in the rate of seropositivity between the two sexes ($\chi_1^2 = 0.3$), the female mean AB level was significantly higher than that of males (4850 ± 5550 mIU/ml compared

Table 3 **Distribution of children subjected to serological analysis for measles antibody**

Characteristic	Test result: Seropositive No.	%	Seronegative No.	%	Total (n = 230) No.	%	Mean antibody level[a] Mean ± s	Test of significance
Age (years)								
2–	39	84.8	7	15.2	46	100.00	5120 ± 6580	
4–	40	87.0	6	13.0	46	100.00	3950 ± 3960	
6–	34	73.9	12	26.1	46	100.00	2970 ± 3800	$F = 0.9$
8–	42	91.3	4	8.7	46	100.00	4150 ± 4490	
10–12	43	93.5	3	6.5	46	100.00	4080 ± 4640	
Sex								
Male	113	85.0	20	15.0	133	100.00	3420 ± 4080	
Female	85	87.6	12	12.4	97	100.00	4850 ± 5550	$t = 2.1$*
Residence								
Urban	169	87.6	24	12.4	193	100.00	4200 ± 5010	
Rural	29	78.4	8	21.6	37	100.00	3120 ± 3360	$t = 1.5$
Total	198	86.1	32	13.9	230	100	4040 ± 4810	

*Significant at 5%

[a]Seronegative subjects were excluded from calculation of the mean

s = standard deviation

to 3420 ± 4080 mIU/ml respectively, $t = 2.1$).

The rate of seropositivity among residents of urban areas was found to be insignificantly higher than that among residents of rural areas (4200 ± 5010 mIU/ml and 3120 ± 3360 mIU/ml respectively, $t = 1.5$). This was also the case for mean AB level (87.6% and 78.4% respectively, where $\chi_1^2 = 2.2$).

Discussion

Measles vaccine became compulsory in Egypt only in 1977 [*1*]. Vaccination coverage was as low as 41% in 1984 [*9*]. However, after accelerated immunization activities, the 1990 survey showed that measles vaccination coverage had reached 86%. Further increases in coverage occurred until it reached 92% in 1994 [*10*].

Despite the high coverage rate, measles cases are reported every year in Egypt. The present study revealed that the majority of cases had histories of measles vaccination (79.4%), 15.8% were unvaccinated and 4.8% were below the age of vaccination. Orenstein and Hanman stated that

> *persistent measles transmission in a community is attributed to the accumulation of susceptible persons who include immunized children who are not protected due to primary vaccine failure or waning immunity, unimmunized persons or children too young to be immunized* [11].

Our findings raise concern about vaccination failure. Reports of large numbers of cases of measles among vaccinated children risk loss of confidence in the programme and may lead to a lack of community motivation seeking and supporting vaccination programmes.

The large number of cases of measles occurring in immunized individuals is related to the level of coverage achieved. As immunization coverage increases, a higher proportion of cases will occur among immunized children [*12*]. The role of vaccine failure in developing countries, however, is often difficult to assess due to poor documentation of immunization [*7*].

The vaccination failure rate derived from the serological results of the present study is approximately 14%. In another serologic study in Egypt, Fathy et al. [*13*] demonstrated a seropositivity rate of only 77% among vaccinated children aged 4 to 6 years. In Alexandria, Aref et al. [*14*] found a serologic vaccine failure rate of 36.36% among children vaccinated at 9 months of age 1 year after vaccination and 45.45% failure rate among those tested after 2 years. Variation in sample size, method of verification of vaccination status, cut-off points for detection of immunity or real changes in vaccine failure rate may explain the differences between various reports.

Whatever the reasons for these differences, the vaccination failure rate is clearly higher than that accepted for measles vaccine. The accepted failure rate is in the range of 2% to 10% [*15*].

Vaccination failure may be due to immunization at less than 1 year of age or administration of nonviable, low potency vaccine that may have been improperly stored or handled [*16*].

The WHO/EPI recommendation for developing countries is routine administration of a single dose measles vaccine to infants at age 9 months [*17*].

Fathy et al. [*13*] found that 10% of Egyptian infants still have maternal antibody by the age of 9 months. Lower seroconversion rates were reported when vaccinating at 9 months (80% to 90%) [*18,30*] than when vaccinating after the

first year of life (95% to 98%) [*23*]. However, if immunization is withheld until most children have lost maternal antibodies, a substantial proportion of children will have already contracted measles, especially in densely populated areas [*19*]. In our series of measles cases about 5% were below the recommended age of vaccination. This is similar to the findings of Kamel et al. and Hegazy et al. (8.31% and 8.2%, respectively) [*20,21*]. These rates are the consequences of behavioural and demographic factors such as high birth rates and overcrowding which create a large pool of susceptible children [*1*]. Development of measles vaccines that are safe and effective before 6 months of age in the presence of maternal antibodies is currently at the centre of measles immunological research.

Poor maintenance of the cold chain has been implicated as another cause of low vaccine efficacy. In the latter part of 1989, a joint Egyptian Ministry of Health/WHO/UNICEF cold chain survey was conducted to examine 289 cold chains by tracing the vaccine's progress from the airport to peripheral level health units. It was found that despite Egypt's high immunization coverage levels, 50% of the cold chains surveyed had a break of one type or another [*9*].

Several prospective serologic studies found a gradual progressive decline in measles antibody titres during several years of observation after vaccination with live-attenuated measles virus vaccine. Shasby et al. [*22*] observed a non-significant increase in the rate of seronegativity with increasing years since vaccination. The present study revealed that there was a trend of decreasing mean antibody levels with increasing age among children below the age of 8 years. The lowest level of seropositivity and lowest mean antibody levels were observed among children in the age group of 6 to less than 8 years. Since antibody titres immediately after vaccination are not known for the children in the present study, the initial response to measles vaccine is not known and so it is possible that the vaccines never achieved protective immune responses and were primary vaccine failures. Alternatively, antibodies may have responded adequately to the initial vaccination and experienced a subsequent decline in antibody titre over time (a secondary vaccine failure) [*8*].

In fact, most epidemiological evidence suggests that waning vaccine-induced immunity and the proportion of secondary vaccine failure do not play a significant role in measles outbreaks [*23*]. The high level of susceptibility and vaccine failure noted in the present study justify the need for an increase in vaccination coverage and necessitate a two-dose measles vaccine schedule. Khashaba et al. [*24*] recognized that there was a significant increase in antibody titre in the ages of 5 to 7 years among Egyptian children after revaccination.

The present study revealed persistence of measles antibody titre in children more than 10 years after vaccination. In addition, children vaccinated several years ago were found to have even higher rates of seropositivity and higher mean antibody levels than those vaccinated more recently (children in the oldest age group of 10 to 12 years versus those in the 4 to less than 8 years age categories). Elevation of antibody titre after vaccination is most likely due to boosting effect from repeated exposure to circulating wild virus resulting in inapparent infection [*23*].

The majority of measles cases in the present study were in the age group of 5 to less than 15 years (69.1%). This is consistent with that reported by Kamel et al. [*20*] in which 68.61% of the reported cases of measles in Saudi Arabia were in the same age group. Despite the fact that school-aged

children are less prone to the occurrence of complications and death from measles, as demonstrated by several investigators, outbreaks among school-aged children are of great concern. School-aged children may act as important source of infection for younger siblings who are more vulnerable to complications and mortality [*7*].

In the present study, the most commonly reported circumstance of infection was of contraction outside the home. The control of measles outbreaks necessitates the increase of vaccination coverage among school-aged children and further justifies the need for two doses of measles vaccine with the second dose given on school entry [*12*].

In this study, 4.8% of cases were 15 years of age or more. In Saudi Arabia, 2.29% of cases were above 15 years [*20*]. Hasab [*25*] recognized that a substantial number of individuals are now entering their adult life without having encountered the measles virus either in its wild or vaccine form.

Young adults may be susceptible because perhaps at the start of immunization programmes they were too old to have been immunized or they received vaccine of low potency and less heat-stability. They escaped measles due to the general decline in incidence rate in the community [*2,7*].

The results of the present study revealed that the mean age of measles cases was 7.4 ± 4.7 years. This finding is similar to that reported by Kamel et al. [*20*] in Saudi Arabia (6.77 ± 4.38 years). It is higher than that among the reported cases in Egypt in 1971 before the start of the immunization programme (3.57 years) [*5*]. The shift in the age distribution of measles cases towards older children is one of the major effects of immunization programmes on measles epidemiology due to lowering of exposure rate in the community [*12*].

The implications of changes in the age at infection depend on age-related changes in the outcome of infection [*12*]. The severity of measles is well documented among young children; among older children, the disease exhibits a lesser degree of severity. Thus, the shift from younger to older children reduces the overall measles mortality and is a positive impact of immunization programmes. However, the serious consequences of infection among adults should be considered after attaining high coverage rates.

In the present study, the mean age of unvaccinated cases was nearly as high as that for the vaccinated cases (7.0 ± 6.5 and 7.5 ± 4.1 years, respectively). Mclean and Anderson [*26*] found that when a high proportion of a community is immunized, a reduction in the transmission rate of the infectious agent will occur, making it less likely that persons—including unvaccinated ones—will be exposed to the agent at a young age.

The present study demonstrated a predominance of females among cases of measles (58.8%) over males (41.2%). Hegazy et al. attributed this to lower vaccination rates among females as a reflection of the sociocultural attitudes [*21*]. In fact, sex does not affect susceptibility to measles [*3*]. On the contrary, the findings of serological analysis in this research documented a significantly higher mean AB titre among females. This is in agreement with the general concept that measles antibody titres in women are marginally higher than that in men [*3*].

About four-fifths of studied measles cases were from urban areas. Despite the methodological limitation of the present work as a hospital-based study, it has been repeatedly reported that measles is a more common health problem in urban dwellings [*21*]. A significantly higher percentage of

unvaccinated cases in this study, however, were from rural areas than were vaccinated cases ($\chi^2_1 = 14.5$). It is possible that rural areas have lower measles vaccination coverage rates.

Urban children were also more fortunate in their immunological responses. The present study revealed a higher percentage of seropositivity and higher mean antibody levels in children from urban areas than those from rural ones.

The variation in serologic profile between urban and rural locality might have been the result of inadequate health care in rural areas, so that children might have received vaccine of low potency due to interruption of the cold chain. Alternatively, variations in frequency of contact with active measles infections between rural and urban areas may reflect frequent boosters of natural measles in urban areas with high population densities [*27*].

The present work found that complications were encountered among more than half of the total cases interviewed (51.5%). Encouragingly, vaccinated cases had a significantly lower proportion of complications than unvaccinated ones.

The most frequently encountered complication in the present study was respiratory illness (72.9%). In Harare, Zimbabwe, Kambarami et al. [*4*] also found that pneumonia was the most frequent complication associated with death.

In the present work, gastrointestinal complications and diarrhoea occurred in about one-fourth of the complicated cases (24.7%). Diarrhoea was doubtlessly due to invasion of the gastrointestinal mucosa by measles virus [*28*]. In addition, damage of the gastrointestinal epithelium might also have increased susceptibility to some microbes which cause diarrhoea. This may be the cause of chronicity and relapses over several weeks and months [*29*].

There were no measles-associated deaths among studied cases during the year of study. Sherif et al. [*5*] reported marked reduction (69%) in reported measles deaths in Egypt during the post-vaccination period.

The present study found that the peak incidence of measles cases occurred during spring while the lowest proportion occurred during autumn. A similar pattern was observed among vaccinated and unvaccinated cases. This is in accordance with the findings of Hinman [*30*] who reported that the seasonal trends of measles incidence in the US continue as in the prevaccination era with the highest recorded incidence occurring in spring and the lowest occurring in late summer and early autumn.

Seasonal variation in measles incidence probably relates to social and human habits more than any effect of climate on the virus. In winter people crowd together indoors and allow the short-lived virus a much better chance to spread than when they remain outdoors on summer evenings [*28*].

Recommendations

The following are addressed to health policy makers and field researchers:

- The introduction of second-dose measles vaccination at the age of utmost susceptibility as indicated by follow-up serological studies should be considered.
- Vaccination coverage with special focus on rural areas should be enhanced. These efforts should incorporate health education messages to mothers to promote vaccine-seeking behaviour.

- The role of vaccine spoilage and efficacy in causing primary vaccination failures should be investigated.
- Periodic sero-epidemiological studies on cases of measles and vaccinated children should be conducted to update information on the measles situation in response to higher vaccination coverage.

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Note from the Editor

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