

# Sero-surveillance of Measles in Iranian Army Students after Nationwide Revaccination in 2004

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## ABSTRACT

**Background:** Decay of vaccine-induced antibody titres without boosting of the wild measles virus has been well documented. Revaccination against measles has reduced the prevalence of the disease worldwide. Revaccination may cause IgE induced anaphylaxis. **Objective:** To study measles IgG antibody in revaccinated populations and its relation to IgE induced hypersensitivity. **Methods:** Blood samples were taken from 800 volunteer army students aging from 18-22 years after one month of nationwide revaccination in Tehran in the year 2004. Sera were collected and kept frozen until used. Anti-measles IgG antibody and total IgE antibody were measured by ELISA assay. **Results:** Data indicated that only 2.37% of subjects were negative for measles antibody (titre less than 500) after a single dose of booster vaccination. From those individuals with positive IgG, 200 cases (25%) had antibody titres over 5000 IU/ml. The results showed a maximum IgE antibody titre of 1000 IU/ml ( $p < 0.02$ ) in which thirty cases (3.75%) had IgE titres over 1000 IU/ml ( $p < 0.02$ ). **Conclusion:** Single vaccination against measles during childhood is not sufficient for protecting against measles virus and revaccination is needed to recall specific immunity, although like other viral infections it may trigger IgE antibody responses in a small percentage of the population.

**Keywords:** IgG, IgE, Measles, Revaccination

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## INTRODUCTION

Seroepidemiology is a powerful tool in monitoring the effectiveness of immunization programs (1). Previous serological studies have shown that post vaccination measles antibody titre declines in the absence of natural reinfection (2) and age at vaccination has an influence on the immune response (3). Vaccination programs have resulted in a major reduction in measles incidence; nonetheless occurrence of measles in individuals with documented seroconversion indicates that the current vaccines occasionally do not provide lifelong protection (4). It has also been reported that vaccination at 9 and 15 months of age is unable to induce long lasting protection and booster immunization later in life is suggested (5-11). Dayan et al (9), in a seroepidemiological study demonstrated that by single vaccination in childhood, approximately 15% of women aging 15-29 years were immune to measles. It has also been demonstrated that single dose vaccination in childhood, in addition to having higher primary vaccination failure rates, is likely to cause secondary vaccination failure (1).

It has been observed that without boosting of the wild type measles virus, vaccine-induced antibody titres will be reduced (6, 12, 13). Single dose measles, mumps and rubella vaccine (MMR) at the age of 15 months had been changed to vaccination at 15 months and 11 years since 1995 in Spain (14). Since then, the incidence rate for measles and rubella has declined to one case per 100000 and for mumps to 23 cases per 100000. In a seroepidemiological survey on a population aging from 2-39 years, it was shown that vaccine efficacy was 96.7% for measles and the immunity was lowest in the 6-9 years age group (90.8%). Due to the low anti-measles antibody titres reported above, the Iranian Ministry of Health and Medical Education launched the national expanded program on immunization for individuals aged between 5-25 years in the Islamic Republic of Iran in the year 2004. The aim of this study was to evaluate the anti-measles IgG antibody after nation wide revaccination in army students. On the other hand, revaccination may result in anaphylaxis via IgE antibody. Increasing evidence suggests that viral infections are associated with induction and exacerbation of asthma. Asthma in humans is associated with an increase in the levels of circulating IgE (7). Therefore, to determine whether revaccination can also induce IgE class switching, total IgE antibody as well as measles specific IgG was measured in 800 revaccinated army student volunteers.

## SUBJECTS AND METHODS

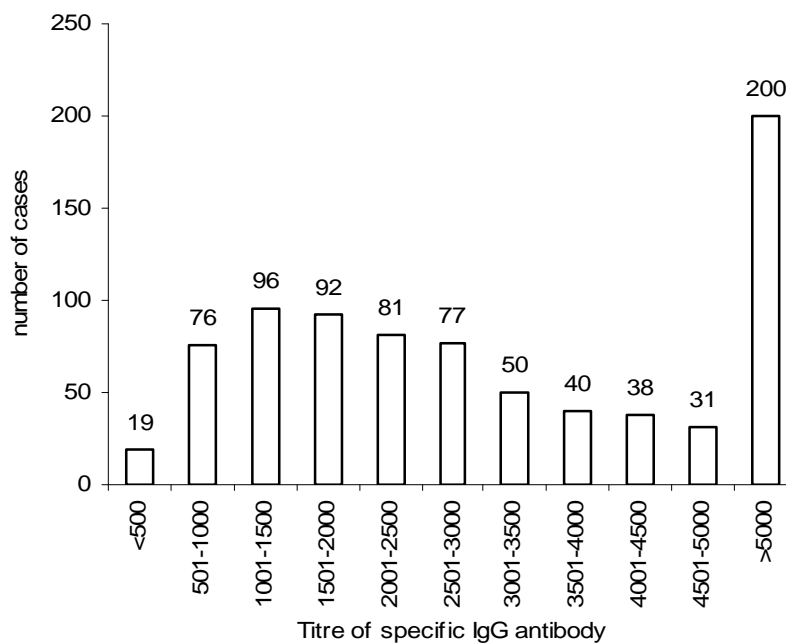
This cross-sectional study was performed on 800 male army student volunteers 18-22 years old ( $19.16 \pm 1$ ). The study was approved by the research ethical committee of Baqiyatallah University of Medical Sciences. Five ml of blood sample was taken from the subjects after a month from the nationwide revaccination in Tehran in 2004. All the sera were refrigerated at  $4^{\circ}\text{C}$  and transported to the molecular immunology laboratory. The sera were kept at  $-20^{\circ}\text{C}$  until the assay time. All the tests were carried out in molecular immunology laboratory of Baqiyatallah University of Medical Sciences. Using the ELISA method, samples were assayed for specific IgG antibody against the measles virus (Date Behring, Enzygnost, Germany), and total IgE antibody (Radim, ELISA, Italy). The OD value was read at 450 nm by the Multi Scan system. All the results were calculated, and the data were converted to titers as de-

scribed by the kit manufacturer. Total IgE antibody was measured, and the data were reported in IU.

**Statistical Analysis.** The results were expressed as descriptive study regarding the prevalence of IgG and IgE antibody. In case of IgG seronegative prevalence, the values were analysed by Student's t-test.

## RESULTS

A total of 800 revaccinated individuals participated in our study. IgG titres less than 500 were stated as negative. Nineteen subjects (2.38%) were seronegative for measles specific IgG antibody (Table 1 and Figure 1). A significant difference was seen between IgG<sup>-</sup> and IgG<sup>+</sup> individuals ( $P < 0.001$ ) (2.38% IgG<sup>-</sup> and 97.62% IgG<sup>+</sup>). In IgG<sup>+</sup> group, 200 individuals had anti-measles antibody titres over 5000 (Figure 1). Also in this group, no significant differences were noted regarding positive or negative response to the history of primary vaccination, having measles individually or in family members, and having contact with patients with measles.



**Figure 1.** The frequency distribution of specific IgG antibody against measles one month after revaccination

**Table 1. The prevalence of IgG antibody against measles after nationwide revaccination**

		No. of cases 800	IgG <sup>-</sup> (%) *a 19 (2.375%)	IgG <sup>+</sup> (%)*a 781 (97.625%)
History of primary vaccine	Yes	546 (68.25%)	11 (1.375%)*b	535 (66.875%)
	No	212 (26.5%)	8 (1%)	204 (25.5%)
	Un-known	42 (5.25%)	0	42 (5.25%)
History of having measles patients	Yes	23 (2.875%)	0	23 (2.875%)
	No	776 (97%)	19 (2.375%)	757 (94.625%)
	Un-known	1(0.125%)	0	1(0.125%)
Being in family with measles disease	Yes	30 (3.75%)	3 (0.375%)**	27 (3.375%)
	No	761(95.125%)	15 (1.875%)	746 (93.25%)
	Un-known	9 (1.125%)	1 (0.125%)	8 (1%)
Having contact with someone with measles	Yes	28 (3.5%)	1 (0.125%)***	27 (3.375%)
	No	762 (95.25%)	16 (2%)	746 (93.25%)
	Un-known	10 (1.25%)	2 (0.25%)	8 (1%)

\*a. A significant difference was observed between IgG<sup>+</sup> and IgG<sup>-</sup> individuals (P<0.001).

\*b. A significant difference was seen in IgG<sup>-</sup> individuals between those with a history of primary vaccine and those having no primary vaccine (p<0.001).

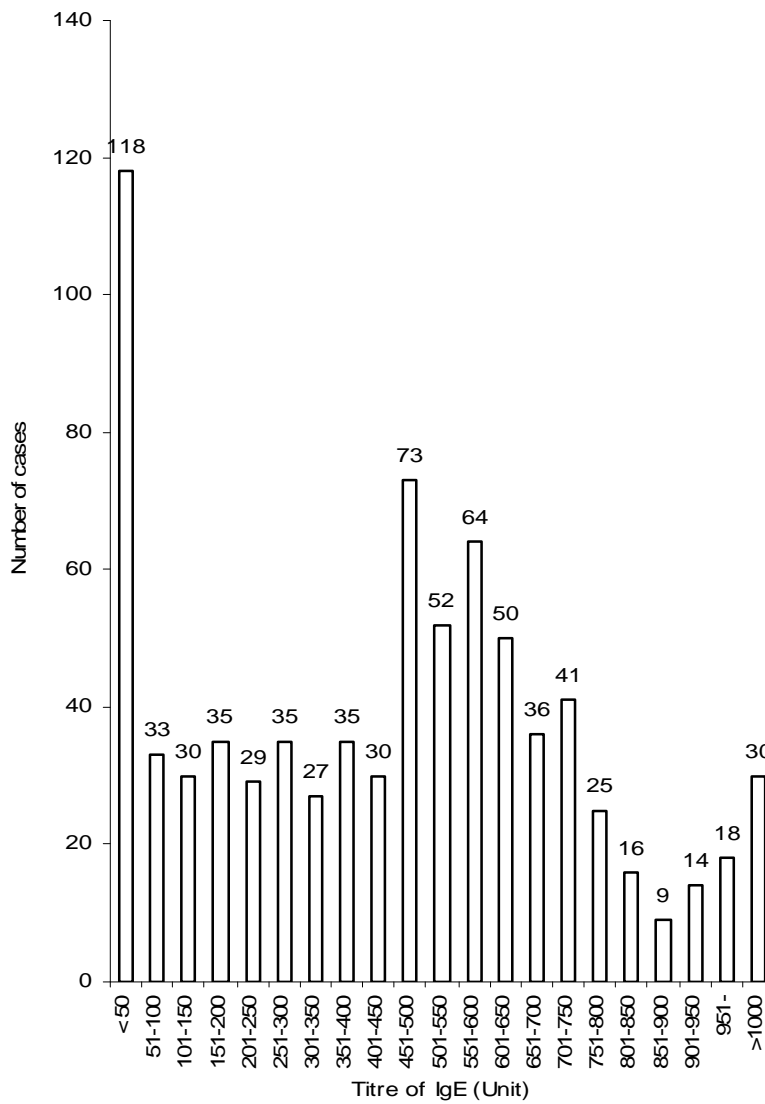
\*\* A significant difference was seen in IgG<sup>-</sup> individuals being in a family with measles disease and those being in a family with no measles disease (p<0.005).

\*\*\* A significant difference was seen in IgG<sup>-</sup> individuals having contact with somebody with measles disease and those having no contact with somebody with measles disease (p<0.01).

In case of IgG<sup>+</sup> subjects, no significant difference was seen between those individuals that said yes or no to the 4 above situations.

The results also showed that from those individuals (68.25%) who had primary vaccination against measles virus during childhood, 1.375% and 66.875% were found to be negative and positive for specific anti-measles IgG antibody, respectively (table1). Table 1 shows that having a history of primary vaccination in childhood will induce a significant difference in IgG negative individuals compared to those who did not receive primary vaccines (p<0.001). Among individuals who had history of measles disease (2.875%), none of them were found to be negative for IgG. A significant difference existed between IgG<sup>-</sup> individuals who had a history of primary vaccination and those who did not (p<0.001).

The results in figure 2 and table 2 show that 181 (22.625%) individuals have IgE antibody levels less than 200 units and 619 (77.375%) have IgE levels over 200 units.



**Figure 2.** The frequency distribution of total IgE antibody in revaccinated individuals

**Table 2.** The Relative frequency of IgE titers in 800 individuals one month after nationwide revaccination

Titer	%	Titer	%	Titer	%
<50	14.75	351-400	4.37	701-750	5.12
51-100	4.12	401-450	3.75	751-800	3.12
101-150	3.75	451-500	9.12	801-850	2
151-200	4.38	501-550	6.5	851-900	1.12
201-250	3.63	551-600	8	901-950	1.75
251-300	4.37	601-650	6.25	951-1000	2.25
301-350	3.38	651-700	4.5	>1000	3.75

## DISCUSSION

Our previous study before nationwide revaccination indicated that primary measles vaccination in childhood does not induce lifelong protection against measles (8). In our previous study, it was found that only 41.94% of individuals were positive for specific anti-measles IgG antibody (8). Supporting this, Emami-Naeini and his colleagues demonstrated that 40.7% of medical students were IgG positive before nationwide revaccination against measles (7). Dayan et al. also demonstrated that measles seroprevalence tended to increase with age and almost 15% of women at child-bearing age (15-49 years) were not immune to measles (9). Therefore, the occurrence of measles in individuals with documented seroconversion indicates that current vaccines occasionally fail to provide lifelong protection (4,8). As a result, booster vaccination has been accepted.

In this study, the results of specific IgG antibody against measles one month after nationwide revaccination showed that 97.625% of individuals were IgG positive with 200 (25.6%) of them have antibody titres over 5000. This demonstrates that nationwide revaccination against measles in the year 2004 was successful. This finding also confirms the previous studies by Gans (15) and Redd et al. (16) who demonstrated that current vaccination scheduled should change into a two times vaccination program; one in childhood and the other in adulthood, in order to refresh the immune response memory after the primary vaccination.

Baer et al. demonstrated that a great majority of medical students had an immunization gap after booster vaccination and seroprevalence for IgG antibody against measles was 85% in 149 students (17). Therefore, they suggested implementing a systemic immunization program for medical students. In this study, we found that only 2.375% of revaccinated individuals were IgG seronegative, supporting our data and the data of Davidkin and Valle (6), Kukino et al. (18) which showed that in a serological survey, 2.2% were seronegative for measles. Seronegative subjects in their study were revaccinated against measles and a high seroconversion rate of 100% was obtained, demonstrating that primary vaccination does not induce long term protection against measles and booster reimmunization was suggested. In this regard, Panut et al. (19) suggested that understanding the role of primary vaccine failure (failure to seroconvert after vaccination) and secondary vaccine failure (waning immunity after seroconversion) in measles epidemic is important for the evaluation of measles control programs in developing countries. Comparing to our results, Rager-Zisman et al. in a study in Beer-Sheva, Palestine, in primary school children, showed that 24% of children were seronegative for measles prior to reimmunization and after reimmunization 92% seroconversion was noted (20). In contrast to Rager-Zisman, in our study, 97.625% of reimmunized individuals were IgG seropositive demonstrating that nationwide reimmunization against measles was needed and effective in Iran.

However, there is the possibility of IgE release after revaccination, and it has been postulated that vaccination may contribute to the development of allergic diseases by reducing clinical infections in infancy or through the direct IgE-inducing effects of the vaccines (21,22). In a recent study, Roost and Colleagues (21) reported that exposure to MMR-vaccines or natural MMR-infections in childhood did not increase the risk of sensitization to common allergens. In our study, it was found that in revaccinated individuals, 44.375% had IgE antibody titres over 500 units, while using the same kit in normal subjects i.e. individuals with no reimmunization against measles, about 25%

had IgE titres over 500 units. This shows that after a booster vaccination against measles, a smaller percentage of individuals will show higher IgE antibody levels. Pool et al. have also reported the prevalence of anti-gelatine IgE antibodies in sera of people with anaphylaxis after vaccination with MMR vaccine (23).

Imani et al, (24) have also demonstrated that measles virus infection synergizes with IL-4 in IgE class switching. Not only did Imani et al. showed that circulating IgE levels were elevated during the early phase of measles infection but they also reported that in addition to IL-4 enhancement, another mechanism by which viral infection could increase IgE levels was the induction of IgE class switching through the activation of antiviral protein kinases (24).

In contrast to our study, data presented by Imani (24) and Gruber et al. (25) reported that measles vaccination have been proposed as suppressors of allergy because of their Th1-fostering properties. They proposed that vaccination programs do not explain the increasing prevalence of allergic disease, but children may uncommonly develop an allergic reaction to vaccines. In support of our findings and in contrast to Gruber et al. findings (25), Kelso et al (26), demonstrated an anaphylaxis to measles vaccine which was mediated by production of IgE against the gelatine component in the vaccine used. Supporting our findings, Griffin et al. (27) and Shalit et al. (28), demonstrated a high level of plasma or serum IgE levels in patients with acute measles virus infections. Therefore, it is possible to suggest that revaccination may induce IgE enhancement in some individuals, but vaccination remains an essential part of health programs and should not be withheld, even from those individuals predisposed to allergy.

In conclusion, our results consistent with those reported by others, show that IgG is enhanced after revaccination, demonstrating the necessity and success of nation wide revaccination. It also indicates that IgE levels could increase in a small percentage of the population, which may be related to susceptibility to allergic diseases.

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