

Sero-response to measles-mumps-rubella vaccine campaign in Saudi Arabia

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ABSTRACT

Objectives: To evaluate the measles-mumps-rubella vaccine campaign targeting primary school children in the Kingdom of Saudi Arabia during the months of January and February 2000.

Method: Pre and post measles-mumps-rubella vaccine blood samples were collected from 54 children from the first grade and 96 children from the 6th grade. Antibodies against measles, mumps and rubella were assayed using enzyme immunoassay and a backup test of plaque neutralization test. This assay was carried out at the Reference Center, Koch Institute, Berlin, Germany.

Results: When the backup test results were added, 96%-98% of children had protection level against measles before the campaign. It is interesting to notice that pre-vaccination measles mean titer and positivity rate with enzyme linked immunoassay in the first grade were significantly lower than the 6th grade. One hundred

percent and 96.8% were positive for rubella antibody before the campaign, in the first and 6th grades. Seventy-seven percent and 67% were positive for mumps before the campaign, in the first and 6th grade. After the measles-mumps-rubella vaccine campaign, protection rate reached 100% for the 3 antigens with a statistically significant boosting effect and increase in geometric mean of the titre.

Conclusion: Measles-mumps-rubella vaccine campaign was effective in increasing protective levels and boosting antibodies against the 3 targeted diseases which can prevent epidemics in the primary schools.

Keywords: Measles-mumps-rubella vaccine campaign, antibody.

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In the pre-vaccination era all children in developing countries were immune to measles, by the age of 5 years, due to high exposure to the measles infection.¹ In the early years of introducing vaccination, and with one measles injection and adequate coverage, some countries including the Kingdom of Saudi Arabia, (KSA) have reduced morbidity and mortality due to measles.² In KSA, the overall impact of the one-dose schedule was not satisfactory. Although a substantial amount of cases occurred in children younger than 9 months, measles infection shifted to

older age groups and a big proportion of cases occurred in vaccinated children.³ A follow-up study for the measles maternal antibody at that time, showed that 33% at 6 months and 36% at 9 months of age were negative for measles maternal antibody. Seroconversion after Schwartz measles vaccine at 9 months was only 65%.⁴ Accordingly the measles immunization schedule was changed to 2-dose schedule using standard dose of Edmonston-Zagreb (E-Z) at 6 months and measles-mumps-rubella vaccine (MMR) at 12 months of age. This change

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was supported by serological studies.^{5,6} It should be noted that, even with very high immunization coverage (95%), susceptibles will continue to accumulate fairly rapidly as measles vaccine is not 100% effective. Also, it is known that the disappearance of circulating wild measles virus can play an important role in decreasing post-vaccination protective levels.⁷

The impact of implementing the 2-dose schedule and maintaining a high coverage of >90% was reflected on the epidemiological pattern of measles in KSA. The percentage of cases among children over 15 years old increased from 10% in 1987 to more than 40% in 1997, while the percentage of cases among the one year - 4 year age group dropped by 20%.⁸ The same surveillance data showed that 50% of measles cases in the one year - 4 year age group were in vaccinated children compared to 20%-40% in the 5 years - 14 year age group and 13% above 15 years. The overall incidence reduced from 44/100,000 population in 1990 to 21/100,000 in 1997, but 54% of all measles cases occurred in primary school children (6 years -12 years) and 14% in intermediate and secondary schools (12-18 years of age). As a result, KSA decided to start a national program for measles elimination, which included mass vaccination campaign for school children. The main objective of the campaign was to prevent a predicted measles epidemic in school age children by vaccinating children who did not have vaccination, and those with primary or possible secondary vaccine failure.⁹ As a part of the evaluation of this campaign, safety and immunogenicity studies were carried out. In this paper the immune response to MMR will be presented.

Method. Overall design. This is a follow up study to evaluate immunogenicity of MMR vaccine given to schoolchildren from first grade primary to first grade intermediate schools. In a multi-stage sampling technique, 8 cities were selected from KSA in the first stage, (Mekkah and Medina in the West, Buraidah and Oneiza in the center, Algatif and Al-Hofof in the East, and Khamis Mushait and Belgurashi in the South). In the 2nd stage, 20 primary schools (10 male and 10 female schools) were selected randomly from each of the 8 cities. In the 3rd stage, 3 children from the first grade and 3 from the 6th grade primary schools were recruited randomly after taking parent consent. So, 120 children were recruited from each city making a total of 960 children. Sub samples of 150 children (pre and post vaccination) were selected randomly to send their sample to a reference laboratory in Germany, 54 from the first grade and 96 from the 6th grade. The results of the reference laboratory, have been used to study the overall positivity and antibody level and then to standardize the laboratory work to be carried

out in Riyadh, KSA for the whole samples (960) which will allow the inclusion of more variables. The serological assay carried out in the reference lab will be presented in this paper.

Serology. Blood sample were collected before and one month after giving MMR vaccine in the campaign. Enzyme Immuno Assay (EIA) was used to assess the level of MMR antibody. Plaque Neutralization Test (PNT) was used as a backup test for negative and equivocal samples. **Table 1** shows the cut-off values for measles, mumps and rubella and the interpretation of laboratory tests.

Statistical analysis. Data was entered directly in the laboratory in Excel and was analyzed by statistical package of social sciences Version 10. T-test was used to compare means of different groups and results were expressed as Geometric Mean of the Titre (GMT), mean optical density or mean titre. Chi-square was used for qualitative comparison of data.

Results. This study was carried out during the 2nd phase of MMR campaign conducted during January-February 2000 and targeted primary school children and the first grade of intermediate school (2,496,613 children). Campaign coverage was 96.4%. All first grade children in our sample were vaccinated with Edmonston-Zagreb measles vaccine at 6 months and MMR at 12 months while 6th grade children were vaccinated with one or 2 doses of measles vaccine. **Table 2** shows that when the back up test results were added, 98% of children in the first grade and 96.7% in the 6th grade had protection level against measles before the campaign. It is interesting to notice that pre-vaccination positivity rate with enzyme linked immunoassay (ELISA) and GMT in the first grade was significantly lower than the 6th grade. [p=0.001] After the MMR campaign, 98% with ELISA and 100% after backup test were positive to measles in both first and 6th grade. Mean measles antibody significantly increased from 167m IU/ml to 2040 m IU/ml in the first grade, after immunization (p=0.0001) and from 1071 to 2773 mIU/ml in the 6th grade (p=0.001). This was reflected on proportion of seroconverted (negative to positive or 4-fold rise) children after the MMR campaign, 75.9% (41/54) in the first grade compared to only 26% (25/95) in the 6th grade. (p=0.0001). If we use the an increase of EIA by factor 2 as an indicator of boosting effect, 79.5% in first grade compared to 31% in 6th grade were boosted, p=0.001. For Rubella, even before giving MMR in the campaign, 100% (54/54) were positive for rubella antibody in the first grade and 96.8% (93/96) in the 6th grade. One hundred percent in the 6th grade became positive after vaccination. No significant difference was found also in the mean optical density (OD) before immunization. After immunization,

Table 1 - Interpretation of laboratory tests.

Methods for antibody detection	Enzyme Immuno Assay (EIA)	Plaque Neutralization Test (PNT)
Producer/product	Behring/Enzygnost	In-house assay
Standardization by International Standard	Measles - IS Rubella - IS	Measles-IS Rubella-IS
Sera (IS) or Internal Reference sera (SR)	Mumps RS	Mumps-RS
Evaluation Negative ab value Positive ab value	OD<0.100 OD>0.200 Measles > 0.35 IU/ml Rubella > 7 IU/ml Mumps titre > 500	Titre ≤1:1.0 Titre ≥1:2.0 Measles ≥ 0.04 IU/ml Rubella ≥ 4 IU
Seroconversion	Change from negative positive ab value	
Booster reaction	A significant increase of the pre-vaccination ab for EIA value by factor 2	
OD - optical density 0.100-0.200-retest-equivocal results, ab - abnormal		

Table 2 - Proportion of children with positive measles antibody.

Test	Vaccination Pre	Vaccination Post	p-value
First grade			
Enzyme Immunoassay			
Positive	22/54	53/54	0.0001
Negative	22/54	1/54	
?	10/54		
Final*			0.5
Positive	53/54	54/54	
Negative	1/54	-	
6th Grade			
Enzyme Immunoassay			
Positive	81/96	95/96	0.001
Negative	13/96	1/96	
?	2/96		
Final			0.364
Positive	94/96	96/96	
Negative	1	-	
?	1	-	
* - Final positivity after adding the backup test (plaque neutralization test) to enzyme immunoassay results ? - equivocal			

mean OD increased from 1.4274 to 2.1665 in first grade, ($p=0.0001$) and from 1.3939 to 2.0415 in the 6th grade ($p=0.0001$).

Surprisingly enough, the proportion of children with positive antibody against mumps 77%, (42/54) was lower than expected in children in the first grade who were vaccinated previously with MMR at 12 months, compared to 67% (65/96) in the 6th grade. After the campaign, 100% in both grades were positive. After MMR campaign, 75.9% in the first grade and 72.9% the 6th grade were boosted (an increase of EIA by a factor of 2); no significant difference was found between the 2 grades. Geometric mean of the titre increased from 684 to 2538 IU in first grade, ($p=0.002$) and from 674 to 2471 IU in the 6th grade. ($P=0.0001$).

Discussion. Measles. Lower pre-vaccination measles antibody in first grade children is an interesting phenomenon as they were vaccinated with 2 measles doses, measles at 6 months and MMR at 12 months. Immunogenicity studies were carried out and showed a 100% protection after MMR at 12 months.¹⁰ Seroassay for that study was carried out in the same reference laboratory for this study. Although there is no difference in the proportion of children with protective level, lower GMT in children in the first grade was reflected, as expected, on the higher seroconversion rate. Surveillance study shows that although the overall incidence of measles is markedly decreasing, a proportion of cases is more

in pre-school age, one year - 5 years.⁸ Comparing children in 1st and 6th grade is difficult as they are 2 different cohorts, exposing 2 different groups of factors. Different vaccination schedule was not the only important factor but exposure to circulating natural infection is more important in our opinion. Sixth grade children were exposed more to natural infection, which boosted their measles antibody. This phenomena of natural exposure was noticed in age-stratified seroprevalence study for MMR, where antibodies against 3 viruses increased during adolescence due to wild virus circulation.⁷ Another important fact is that early measles vaccination; although needed for certain epidemiological situations can result in a lower post-immunization antibody even after revaccination.^{11,12}

Rubella. Although the 2nd objective of the campaign was to reduce to risk of rubella infection especially in older age, 96.8% of children were already protected before immunization. Children in the 6th grade and although MMR was not compulsory, 80% were given MMR and it was recorded in their vaccination certificate. Others may have unrecorded vaccination or exposed to natural infection. In KSA, which implements post partum vaccination as well as childhood MMR vaccination, only 9% of 10824 women attending antenatal clinics in 1992-1993 were seronegative.¹³ There was an increase in congenital rubella syndrome cases.¹⁴

Mumps. It is known that children in the 1st grade were vaccinated previously with mumps vaccine as

MMR at the age of 12 months. In a previous study, 92.9% reached the protection level measured at 14 months of age by EIA in the same reference laboratory and even reached 100% when measured by Indirect Fluorescent technique (IFT).¹⁰ The low proportion of children with pre-campaign positive mumps antibody in both grades may be caused by the absence of a circulating wild virus before or at the time of the campaign.⁷ Our results showed that there was a crucial need for mumps revaccination to prevent expected epidemics in the schools.

Long-term effects and the extent of success of this campaign can be proved mainly through surveillance of the targeted diseases. Serological evaluation shows that one campaign was able to protect children in primary schools and prevent a predicted measles epidemic at that age group.

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