Practice Report

MEASLES VACCINATION: COMPARING TWO COHORTS WITH DIFFERENT IMMUNIZATION SCHEDULES

Mohamed Khalil[1*], Yagob Al-Mazrou[2], Annedore Tischer[3], Mohamed Al-Jeffri[4], Salah Tumsah[5], Ameen Mishkhas[6], Mostafa Eissa[7]

بالرغم من أن لقاح الحصبة قد بدأ استعماله منذ وقت طويل إلا أن الحصبة مازالت تتسبب في مشاكل صحية بالغة. إن القضاء على الحصبة هو هدف لن يتحقق دون فهم العملية المعقدة التي تعقب التلقيح والتي تطلق كلاً من الأجسام المضادة والأجسام المضادة الدائمة. إن الهدف من هذا البحث هو تقييم الحالة المناعية لأطفال في المدارس الابتدائية في المملكة العربية السعودية وتأثير سياسات التلقيح السابقة. لذلك فإنه وأثناء حملة التلقيح لطعوم كل من الحصبة والنكاف والحصبة الألمانية تم جمع عينات دم قبل وبعد شهر من إعطاء هذا اللقاح وذلك من أطفال الصف الأول والصف السادس وتم تقدير الأجسام المضادة للحصبة فيها. وأظهرت النتائج أن لدى أطفال الصف السادس أجسام مضادة أكثر معنوياً قبل الحملة بالمقارنة مع ما لدى أطفال الصف الأول. كما أن الأطفال الذين تم تلقيحهم مسبقاً بجرعة واحدة من الطعوم الثلاثة بعد سن 12 شهراً كان لديهم أعلى متوسط للأجسام المضادة للحصبة وذلك بالمقارنة مع الأطفال الذين تم تلقيحهم بجرعة واحدة مرتين (واحدة عند من هم أقل من 12 شهراً والثانية عند من هم أكثر من 12 شهراً) أو بجرعة واحدة لمن هم أقل من سن 12 شهراً. ويجب ألا يعتبر التحويل المصلي بعد التلقيح أنها الطرق الوحيدة لتقييم أي سياسة للتحصين ولكن يجب أن تكون المتابعة جزءاً لا يتجزأ من أي عملية تقييم.

Although measles vaccine was introduced long time ago, measles remains an important public health problem. Achieving the goal of measles elimination can not be done without understanding the complex process of post-vaccination elicited antibody and the persistence of antibody. The aim of this research is to evaluate the immune status of children in primary schools in Saudi Arabia and the effect of previous vaccination policies. During MMR (Measles Mumps, Rubella) campaign blood samples were collected before and one month after giving MMR from children in the 1st and 6th grades. Blood samples were assessed for measles antibody. Results showed that children in the 6th grade had a significant higher measles antibody before the campaign compared to children in the 1st grade. Also, children vaccinated previously with one dose of MMR after the age of 12 months showed the highest mean measles antibody compared to children vaccinated with two-dose (one <12 months & 2nd >12 months) or with one dose before the age of 12 months. Seroconversion after vaccination should not considered the main methods of evaluating any immunization policy but follow up should be a part of any evaluation.

[1] Consultant communicable diseases, Head of Research unit, Medical Education and Research Center (MERC) King Fahad Specialist Hospital, Buraidah, Saudi Arabia. [2] Assist Deputy Minister for preventive medicine, Riyadh, SA. [3] Director,MMR reference lab, Germany. [4] Director General of Infectious Diseases, MOH, Riyadh, SA. [5] EPI, MOH, Riyadh, SA. [6] Director infectious diseases, MOH, Riyadh, SA. [7] Virologist, Central Lab, Riyadh, SA

[*] To whom correspondence should be addressed.
E-.mail: statkhl@hotmail.com

Introduction

Life attenuated measles vaccines have dramatically reduced measles morbidity and mortality. In early years of introducing vaccination and with one measles injection and adequate coverage, some countries including Saudi Arabia, have reduced morbidity and mortality due to measles. In Saudi Arabia, the overall impact of one-dose schedule was not satisfactory. Although a substantial of cases were occurring in children younger than 9 months, measles infection was shifted to older age groups and a big proportion of cases occurred in vaccinated children (1). Follow-up study for 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% (2). Accordingly in 1991, measles immunization schedule was changed to two-dose schedule using standard dose of Edmonston-Zagreb (E-Z) at 6 months and MMR at 12 months of age. This change was supported by serological studies (3,4).

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 disappearance of circulating wild measles virus can play an important role on decreasing post-vaccination protective levels (5). The impact of implementing the two-dose schedule and maintaining a high coverage of >90% was reflected on the epidemiological pattern of measles in Saudi Arabia. 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 1-4 years group dropped by 20% (6), The same surveillance data showed that 50% of measles cases in the 1-4 years group were in vaccinated children compared to 20-40% in 5-14 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 (6-12 years) and 14% in intermediate and secondary schools (12-18 years of age).

As a result, Saudi Arabia decided to start a national program for measles elimination, which includes mass vaccination campaign for school children. The main objective of the campaign was to prevent predicted measles epidemic in the school age children by vaccinating children who did not have vaccination and those with primary or possible secondary vaccine failure (7). Secondary vaccine failure may responsible for disease in sero-converted individuals, evidence suggests that many more vaccines who are protected against the disease may not be fully protected against virus infection (8).

As a part of the evaluation of this campaign, safety and immunogenicity studies were done. The aim of this paper is to evaluate the pre-campaign status of measles antibody according to previous measles vaccination history.

Methods

Overall design:

This is a follow up study to evaluate immunogenicity of MMR vaccine given to schoolchildren from 1st grade primary to 6th grade intermediate schools. This study was done during the second 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). In a multi-stage sampling technique, 8 cities were selected from the kingdom in the first stage, (Makkah and Madinah in the west, Buraidah and Oneza in the center, Algatif and Al-Hofof in the east, and Khamis Mushait and Belgurashi in the south). In the second stage, 20 primary schools (10 male and 10 female schools) were selected randomly from each of the 8 cities. In the third stage, 3 children from the 1st 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. 54 from the 1st grade and 96 from the 6th grade.. Children the 1st grade were previously vaccinated with Edmonston-Zagreb (E-Z) measles mono vaccine at 6 months and MMR at 12 months of age. While children in the 6th grade were vaccinated with different schedules, ranging from mono schwartz measles vaccine below one year , to two-dose schedule at different ages.

Serology:

A sub-sample of 150 children was selected randomly to send their sample to a reference lab in Germany (National Reference Center ,measles, mumps, rubella, Robert Koch Institute, Nordufer 20, 13353 Berlin) as a pre and post vaccination.

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 measles antibody. Plaque Neutralization Test (PNT) was used as a backup test for negative and equivocal samples. Table 1, shows the cut-off values and results interpretation.

Statistical analysis:

Data were entered directly in the lab in Excel format and was analyzed by SPSS V10. T-test and Analysis of Variance (ANOVA) were used to test the difference of means of antibody titer in different groups while Chi-square was used for qualitative comparison of data.

Results

Pre-campaign measles antibody is significantly higher in 6th grade children compared to 1st grade children, (p=0.0001) table 2. Also, Children with positive pre-campaign measles antibody by EIA is significantly higher in the 6th grade, 84.3%, compared to 1st grade, 40.7% , (p=0.0001). This was reflected on seroconversion or booster reaction rate, where after campaign 79.6% converted in 1st grade compared to only 31% in the 6th grade, (p=0.0001) table 3.

Different vaccination schedules in the 6th grade: children vaccinated with one MMR after the age of 12 months have the highest pre-campaign measles antibody, 3.69±4.95 IU/ml compared to children vaccinated with one dose <12 months or one less and the 2nd >12 months, 1.76±2.1 IU/ml (p=0.012)..

Discussion

High post vaccination and the persistence of antibody is the result of a complex process where age at vaccination, number of doses, strain of vaccine, prevalence of wild virus and coverage rate can contributes to the response and the persistence of post vaccination antibody.

Higher prevaccination titer at 6th grade (12 years of age) ,in our study, compared to prevaccination titer in the 1st grade at the age of 6 years is an interesting phenomena which needs an explanations although they are two different cohort. Immunogenicity studies were done for children vaccinated with E-Z at 6 months and MMR at 12 months and showed a 100% protection after MMR at 12 months (9).

Table 1. The cut-off values for measles and the 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 Sera (IS)		
Evaluation		
Negative ab value	OD <0.100#	Titre <1:1.0
Positive ab value	OD >0.200 Measles ≥ 0.35 IU/ml	Titre ≥ 1:2.0 Measles ≥ 0.04 IU/ml
Seroconversion	Change from negative to positive ab value	
Booster reaction	A significant increase of the pre-vaccination ab for EIA-value by factor 2	

OD :optical density ; ab: antibodies
0.100-0.200= retest-equivocal results

Table 2. Qualitative and quantitative comparison of measles antibody by Grade.

	TEST	Vaccination		p-value
		PRE	POST	
1st GRADE	EIA			
	+	22/54	53/54	0.0001
	-	22/54	1/54	
	?	10/54		
	GMT	167 m IU/ml	2040 m IU/ml	0.0001
	Final*			
	+	53/54	54/54	0.5
	-	1/54		
6th GRADE	EIA			
	+	81/96	95/96	0.001
	-	13/96	1/96	
	?	2/96		
	GMT	1071 m IU/ml	2773 m IU/ml	0.001
	Final			
	+	94/96	96/96	0.364
	-	1		
	?	1		

Table 3. Proportion of children with seroconversion after MMR campaign (by EIA).

Conversion	Grade 1ST	Grade 6th	Total
Total			
% Converted	79.6%	31%*	48.6%
Number	43	30	73
Total	54	96	150

P=0.0001

Seroassay for that study was done in the same reference lab for this study. In fact there is no contradiction about the proportion of children with protective level. It is the lower GMT , but not the proportion of children with protective level. Surveillance study shows that although the overall incidence of measles is markedly decreasing, proportion of cases is more in pre-school age , 1-5 years which supports our serological data (6). Comparing children in 1st and 6th grade is difficult because they are two different cohorts, exposed two 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. 6the grade children were exposed more to natural infection, which boosted their measles antibody. This phenomenon of natural exposure was noticed in age-stratified seroprevalence study for measles, mumps and rubella, where antibodies against the three viruses increased during adolescence due to wild virus circulation (5). Sites with higher vaccination rate sometimes shows a lower seroprevalence rate than sites with lower vaccination rate and this may be explained also by the decrease exposure to the wild virus (10).

Regarding the immunogenic response, two-dose schedule is not always superior to mono-dose measles schedule. In fact , some studies showed that the reverse is true where one dose schedule may produce higher GMT than two dose schedule. One measles vaccine at the age of 9 months produced higher GMT than children vaccinated with two-doses at the age of 6 and 9 months. The second dose may result even in a lower post vaccination titer (11). In turkey, one dose of MMR at the age of 12 months was more immunogenic and efficacious than two-doses of measles given at 9 months and 15 months (12). This is also evident in our study where the 6th grade children vaccinated with one MMR after the age of 12 months showed the highest level of persistent antibody level at the age of 12 years before the campaign compared children previously vaccinated with one monovalent measles vaccine followed by one MMR vaccine. Age at first dose should be taken in consideration as induction of vaccine-mediated infant protection is directly correlated with the progressive maturation of their immune system. IgG and IgA responses to viral infection remain weak in the first 12 months of age (13). Age dependent increase in seroconversion after measles immunization was documented in many studies (14). Another limitation of antibody elicited in response to vaccines below 12 months of age, is its short duration. Secondary vaccine failure occurs significantly in teenagers immunized before the age of 15 months (15).

Although our study showed that single dose given > 12 months of age may be superior to other vaccination schedules, this does not mean that we should go back to single dose schedule. Shifting the first immunization dose to higher age and to increase the interval between the first and second dose may be the logic policy in the next few years.

In vaccine trials, the seroconversion rate is considered as the criterion of efficacy but post vaccination level of antibody and low responder rate should be also considered when evaluating or comparing vaccination policy. Vaccinees that are protected against the disease may not be fully protected against viral infection or even they can develop a secondary vaccine failure. A booster is necessary for an adequate immunization either through re-immunization or to natural exposure and this supports the need for campaigns.

References

1. Abanamy A, Khalil M, Salman H, Abdulazeem M. Measles vaccine failure. Annals of Saudi Medicine. 1991;11:311-4.
2. Abanamy A, Khalil M, Salman H, Abdulazeem M. Follow-up study for measles maternal antibodies and seroconversion after measles vaccination. Annals of Saudi Medicine. 1991; 11:51-53.
3. Khalil M. The use of standard dose 3.0$\log_{10}$ of Edmonston-Zagreb measles vaccine_in solving the problem of measles vaccine failure. Annual Scientific meeting of Egyptian Medical Syndicate(EMS). Cairo. 2-4 February 1993. No. 3
4. Khalil M. Follow-up study of children vaccinated against measles at the age of six months with 3.0 $\log_{10}$ Edmonston-Zagreb measles vaccine. Saudi Medical Journal. 1993; 14(1): 44-45
5. Matter L, Germann D, Bally F, Schopfer K. Age-stratified seroprevalence of measles, mumps and rubella (MMR) virus infections in Switzerland after the introduction of MMR mass vaccination. Eur J Epidemiol 1997; 13(1):61-6.
6. Al-Mazrou YY, Al-Jeffri M, Ahmed OM, Aziz MS, Mishkhas AH. Measles immunization: Early two-doses experience. Journal of tropical Pediatrics. 1999; 45:98-104
7. Mansour O, Blakely T, Bajer M, Bloomfield A. A measles epidemic controlled by immunization. N Z Med J 1998; 111(1079):467-71.
8. Muller CP. Measles elimination: old and new challenge. Vaccine . 2001; 19(17-19):2258-2261
9. Khalil M, Poltera AA, Al-Howasi M, Herzog C, Gerik E, Wegmuller B, Gluck R. Response to measles revaccination among toddlers in Saudi Arabia by the use of two different trivalent measles-mumps-rubella vaccine. Transaction of the

Royal Society of Tropical Medicine and Hygiene. 1999; 214-219

10. Stohrer-Draxl P; Amstad H; Grizel L; Gassner M; Takken-Sahli K; Bourquin C; Braun-Fahrlander C. Measles, mumps and rubella: vaccination rate and seroprevalence in 8th grade students of 8 different sites in Switzerland in 1995/96. Schweiz Runsch Med Prax 1999 Jun 10;88(24):1069-77.
11. Garly ML, Bale C, Martins CL, Monterio M, George E, Kidd M. *et al.* Measles antibody responses after early two dose trials in Guinea-Bissau with Edmonston-Zagreb and Schwartz standard-titre measles vaccine: better antibody increase from booster dose of the Edomnston-Zagreb vaccine. Vaccine 2001;19(15-16):1951-1959.
12. Ceyhan M, Kanra G, Erden G, Kanra B. I mmunogenicity and efficacy of one dose measles-mumps-rubella (MMR) vaccinae at twelve months of age as compared to monovalent measles vaccination at nine months folloed by MMR revaccination at fifteen months of age. Vaccine 2001 Aug 14;19(31):4473-8
13. Brandenberg AH, Groen J, Van Steensel-Moll HA et al. Respiratory syncytial virus specific serum antibodies in infants under six months of age: limited serological response upon infection. J Med Virol 1997; 52(1):97-104.
14. Johnson CE, Nalin DR, Chui LW, Whittle J, Marusyk RG, Kumar ML. Measles vaccine immunogenicity in 6 versus 15 months old infants born to mothers in the measles vaccine era. Pediatrics. 1994;93(part 1):939-44
15. Paunio M, Hedman K, Davidkin I, *et al.* Secondary measles vaccines failures identified by measurements of IgG avidity: high occurrence among teenagers vaccinated at a young age. Epidemiol Infect 2000;124(2):263-71.