

Seroepidemiological Study of Measles Virus among Young Adults: Response to Revaccination

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Abstract:

The 2011 Iraqi Measles Control Campaign had as its aim to improve immunization coverage among young adults' 17-24 years and, in the longer term, prevention of measles epidemics. The aim of the study is estimation measles vaccination and revaccination efficacy by evaluate the seroprevalence of antibody and response to reimmunization in young adults. A previously vaccinated 189 young adult medical students were tested for measles specific IgG & IgM pre and post catch-up revaccination by using commercially available ELISA. To assess the seroprevalence of antibody response pre measles reimmunization in previously vaccinated young adults; 45 were found to be seronegative. To differentiate between primary and secondary vaccine failure, anti-measles IgM and IgG titers were assessed again 2-4 weeks after revaccination in 189 seronegative participants [45 seronegative, 144 seropositive individuals: 29 seronegative participants responded to revaccination anamnesticly ($P < 0.001$) and developed immunity; 7 also showed IgM response (probably primary vaccine failure); 144 seropositive participants remained seroprotected without significant increase in antibody titer ($P=0.577$). Primary vaccine failure was found to be 3.7%; while secondary vaccine failure was 11.6%. After revaccination, 85.1% were seroprotected. This study demonstrates the waning measles immunity in young adults in Iraqi medical students, which poses the potential risk of transmission of measles. Periodic Serological surveillance and revaccination of susceptible young adults are recommended.

Key words: Measles, Seroprevalence, Revaccination

Introduction:

Measles is a highly contagious viral illness that has fortunately been fairly well-controlled through measles vaccination plans. Measles vaccine is inducing long-term and probably lifelong immunity in most individuals [1]. Although effective, measles vaccination with only one dose provides just 95% protection against measles. This led to the recommendation of a second dose for children between 5-19 years of age, to ensure protection for those who had not developed immunity from the first dose [2]. A second, booster dose helps

to improve the effectiveness of the measles vaccine to over 99%. The routine measles vaccination plan calls for kids to get the first MMR (Measles, Mumps, Rubella) vaccine when they are 12 to 15 months old and the MMR booster when they are 4 to 6 years old but didn't become routine until 1990 [3].

During 1980, it was reported 26542, measles cases in Iraq. This figure decreased to 3045 and 726, cases during 1990 and 2000, due to successful expanded program in immunization (EPI) in Iraq, but in

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2004, 2005 & 2006, there was some increase, then decline in measles cases (9082, 908 & 474), respectively [4]. Significant progress has been made in the Eastern Mediterranean Region (EMR) toward measles elimination, through increasing coverage with a routine Measles-containing vaccine (MCV) and implementation of catch-up and follow-up measles supplemental immunization activities (SIAs) in EMR countries. The number of confirmed measles cases has decreased dramatically from 89,518 in 1998 to 12,186 in 2008 (86% decrease), and the EMR achieved a 93% reduction in estimated measles mortality during 2000–2008—the largest percentage reduction among all WHO regions, accounting for 17% of the global reduction in measles mortality [5]. Despite these successes, in recent years, there has been a resurgence of measles virus circulation and outbreaks in a number of countries, including a nationwide epidemic in Iraq during 2008–2009 as a clear indication of serious problems in routine and (SIA). Due to lack of funding WHO could not support the requested support to conduct (SIA) & too weak health infrastructure [6]. Records indicate that around 27,000 Iraqi children were infected with measles between 2008 and 2010. As a result of ceaseless efforts the ministry made to fight this disease, which is pandemic in Iraq, the incidence of the disease was only one case recorded during 2012, which is a major accomplishment [7]. A low vaccine failure rate of 66.1% and effectiveness of 90.03% were estimated in Iraq for the years 2005 to 2010 in a study which concluded that measles continues to be an important cause of morbidity in Iraq. Improvements in vaccine coverage, proper vaccine handling, and prompt reporting of suspected cases are all necessary to

eliminate measles from Iraq [8]. The primary reason for continuing high childhood morbidity is the failure to deliver at least one dose of measles vaccine to all infants [9].

Vaccine failure remains a major obstacle that must be overcome before measles can be controlled [10]. Primary vaccine failure (PVF) is failure of immediate seroconversion, with a documented lack of detectable specific antibody. Administration of a second dose of vaccine results in a high proportion undergoing a primary antibody response, with an initial IgM response followed by IgG seroconversion. Secondary vaccine failure (SVF) results when there is initial documented seroconversion in response to vaccination followed by loss of protection, usually linked to waning serum antibody levels [11]. On exposure to measles virus, an individual may contract the virus and only show anamnestic type of antibody response, or may become ill. Following a second dose of vaccination, a large boost in IgG antibody levels generally occurs, with little or no IgM response [11]. Around 95%–98% of individuals who receive a single dose of measles vaccine after 12 months of age develop measles antibodies [12]. The measles vaccine is, however, less immunogenic in the presence of maternal antibodies before 12 months of age [11]. The Immunization policy in Iraq follows the World Health Organization's recommendation for developing countries, and includes monocomponent vaccine against measles at 9 months of age [13]. In addition, vaccination against measles has been recommended for children aged 12–15 months in Iraq which was started in 1986 as a single measles antigen vaccine, then at 1988 MMR was introduced [14]. Excellent seroconversion rate (96.8%) was

obtained among children in response to MMR vaccination, who's received mono-valent measles vaccine during their first year of age, in contrast moderate seroconversion rate was obtained after measles live vaccine, and approximately quarter remained seronegative which represents PVF to measles vaccine [15]. After implementing the 2-dose vaccination schedule with high levels of coverage (> 95%), between 1988 and 1998 the incidence of measles decreased markedly in Iraq. During recent years, however, the incidence of the disease has been increasing, with some incidences in previously vaccinated individuals among all age groups, mainly adolescents and young adults [16].

This study was designed to evaluate the IgM and IgG antibody responses to reimmunization with measles-containing vaccine (MCV) to differentiate PVF from SVF especially in young adults who had been vaccinated against measles according to the vaccination schedule in Iraq [On the basis of WHO recommendations, MCV has been administered in the EMR to children at 9 months of age in countries with high measles incidence and to children 12 months of age in countries with low measles incidence and a low risk of measles infection among infants [17].

Materials and Methods:

Study subject;

This study was carried out from September 2011 to February 2012. Healthy volunteers [with no history of medical problems (e.g. acute respiratory infection, febrile illnesses, and skin rash), physician-diagnosed measles or chronic illness] between 17 and 24 years of age were recruited from the student population at Al-Mustansiriyah University/Medical College. Written informed consent was

obtained from all participants with vaccine histories. The protocol was reviewed and approved by the Medical Ethics Committee of the university.

Blood sampling;

for initial screening, 5 mL of venous blood was drawn from each participant by the researcher. Samples were taken during September 2011–October 2011 and for the second phase during January 2012–February 2012. Sera were stored at -20°C until assayed. Measles Catch-up campaign vaccination programme in Iraq (October 2011), all individuals (17-24) years of age were vaccinated with measles virus-containing vaccine (Rouvax brand Sanofi Pasteur-MSD in Lyon, France), i.e. all those in the study sample were revaccinated after the first blood sampling. Sera were obtained 2–4 weeks after revaccination to determine the IgM and IgG antibody responses to revaccination.

Serologic assay

Measles IgG and IgM antibodies were detected by enzyme-linked immunosorbent assay (Measles IgM-ELISA and measles IgG-ELISA, IBL, Hamburg). The tests were performed in the Virology Lab. /Al-Yarmook Teaching Hospital, Ministry of Health according to the manufacturer's instructions. Quantitative antibody titers < 10 IU/mL were reported as negative and ≥ 10 IU/mL as positive. All sera (samples obtained before and after revaccination) were tested for IgG measles-specific antibodies; IgM was measured only in blood samples taken after revaccination to differentiate primary and secondary response types.

Statistical analysis

Data were analyzed as ordinal and continuous variables. Antibody levels were log-transformed for calculation of geometric mean antibody

concentrations. The student t-test was used to compare the mean values in the pre- and post-vaccination groups and Pearson Chi-square test at 0.05 level to test the significances. All statistical analysis was performed using SPSS, version 11.

Results:

A total of 189 young adults, mean age 22.3 ± 3.3 years (range 17-24 years), were enrolled in a measles seroprevalence study underwent serological screening for measles specific IgG antibody. All of these individuals had previously received measles vaccine, 2 doses (at 9 months and 15 months) in 110 participants (age range 17-21 years) and one dose (after 12 months) in 79 participants (aged 22 years and older) as part of the routine measles vaccination schedule in Iraq.

The study revealed that 45 (23.8%) participants were serologically negative for measles antibody, geometric mean concentration 4.1 ± 2.6 IU/ml (mean age 20.3 ± 2.8 years) and 144 (76.2%) were seropositive, geometric mean concentration 23.9 ± 37.2 (mean age 21.0 ± 2.6 years) (Table 1).

All the 189 individuals were revaccinated (as part of catch-up program, October 2011) and the follow up for their measles seroprevalence post vaccination showed 45 seronegative and 144 seropositive individuals (Table 1). Twenty-nine of revaccinated seronegative individuals (64.4%) responded to revaccination and showed significant increase in the levels of measles antibody ($P < 0.001$) (Table 2); 7 (15.6%) also showed IgM response (Probably primary vaccine failure). The revaccinated

seroprotected individuals; remained seropositive with no statistically significant increase in IgG measles antibody ($p=0.577$). No IgM response was detected in them.

As shown in Table 1 comparison of the seropositivity rates and responses to revaccination in two age groups; 17-21 years (previously received 2 doses of measles vaccine) and 21 years and older (previously received 1 dose of measles vaccine) were found to be; 28 (25.45%) of 110 individuals in the younger group and 17 (21.5%) of 79 in older age group were seronegative. Table 3 showed 51.7% of the revaccinated participants enrolled in younger (2 dose) group responded to revaccination compared to 87.5% in the older (single dose) group with significant difference ($p=0.016$).

Based on our results, extrapolations can be made regarding PVF, SVF and efficacy of initial vaccination and revaccination programs [18]. Thereafter PVF was estimated at 3.7% ($(45 \times 100 \times 7) / (189 \times 45)$) and SVF at 11.6% ($(45 \times 22 \times 100) / (189 \times 45)$) and total vaccination and revaccination efficacy was estimated at 85.1% [$144 + (45 \times 29) / (189 \times 9)$], so community immunity on 95% vaccination coverage would be 80.9% [$(85.1 \times 95) / 100$], where 189 = total no. participants in primary screening, 45 = no. seronegative in primary screening, 9 = no. seronegative after revaccination, 29 = no. responding to revaccination (IgM and IgG), 22 = no. seronegative responding with IgG response only (probably SVF), 7 = no. seronegative responding with IgM (probably PVF) and 144 = no. immune in primary screening.

Table1: The seroprevalence status of young adults before measles revaccination.

Measles seroprevalence	Total (n=189)		17-21 years (n=110)		22 years & older (n=79)	
	No.	%	No.	%	No.	%
Antibody positive*	144	76.2	82	74.55	62	78.5
Antibody negative**	45	23.8	28	25.45	17	21.5
GMC±SD (IU/mL)	23.9±37.2		22.4±37.2		26.4±37.3	
GMC=Geometric mean antibody concentration SD=standard deviation * antibody titers ≥ 10 IU/mL ** antibody titers < 10 IU/mL						

Table 2: The comparison of response to revaccination between seronegative and seroprotected individuals.

	Seronegative (n=45)
IgG response	22(48.8%)
IgM response	7(15.6%)
IgG & IgM response	29(64.4%)
GMC Pre vaccination (Mean±SD)	4.1±2.6
GMC Post vaccination (Mean±SD)	37.9±42.3
GMC=Geometric mean antibody concentration ±SD (Standard deviation)	

Table 3: Comparison of response to revaccination in seronegative individuals according to number of doses of measles vaccine originally given.

Doses	Total (n=45)	Responded No.(%)
One Measles dose	16	14 (87.5%*)
Two Measles doses	29	15 (51.7%)
P value=0.016* (Significant using Pearson Chi-square test at 0.05 level)		

Discussion:

This was the first attempt to our knowledge of mass catch-up campaign of young adults in Iraq which were at October 2011. Serological surveys should be conducted to characterize measles seroepidemiology prior and post to that mass vaccination. The increase of vaccination rates means that fewer children will be vulnerable to vaccine preventable diseases such as measles, which will invariably result in a drop in the infant mortality and morbidity rates [19].

The presenting results showed measurement of anti-measles IgG antibody titers 17 to 24 years after 1 or 2 doses of measles vaccination to determine the proportion of seropositivity. Of the studied population 23.8% were seronegative, and there was no difference between those who had 1 dose of vaccine and those who had 2 doses (Table-1). Reinfection and disease seem to

occur in individuals who have previously had a measles immunization and when the titer has fallen below a critical level [16, 20]. Our results in Table- 3 were found to be consistent with previous results; children vaccinated twice have better protection than single dose recipients [11, 13] and inconsistent with others elsewhere; additional doses of vaccine could not boost the antibodies to a satisfactory level, and that any boosting that did take place was only short-lived [11, 13].

Although the waning immunity after immunization may be a factor in previously immunized children seem to occur in people in whom response to the vaccine was inadequate [i.e. Primary vaccine failures (PVF)] [21]. Seronegativity or vaccine failure may occur either because the immune response never developed or because it waned over time [22]. Changes in the age of vaccination and type of vaccine

used over past decades may impact on future epidemiology of measles through differing rates of waning immunity [23]. It had been found that 40% of children who had received 2 doses of measles vaccine (first dose before 12 months of age) were seronegative, and 33% of the seronegative ones did not respond to a third dose of vaccine [13]. While seroconversion rates in children after the first and second doses of measles vaccination at 9 and 15 months of seroconversion rates of 77.6% and 69.9% after the first dose and 81.9% and 90.3% after the second dose of measles vaccine [24]. The SVF phenomenon due to waning immunity may become apparent only after the passage of years. It was suggested that vaccine-induced measles antibodies decline with time, and fall below protective levels [25].

In our study, after revaccination, 64.4% of 45 participants who were seronegative showed IgG & IgM antibody response to revaccination. However there was no significant increase in antibody level post-revaccination in the 144 seropositive participants we examined ($P=0.577$). These results were comparable with the finding of others elsewhere: Cohen and his colleagues found that 12% of seronegative individuals 10-30 years of age never developed a positive measles specific IgG titer after revaccination, while 58% did that remained positive for at least one year after vaccination [26]. Other study showed that 19.2% of people vaccinated were seronegative 4-11 years after the primary series of vaccination and 18.5% of seronegative individuals remained seronegative after revaccination [27]. Other studies showed that people with protective levels of antibodies did not respond to revaccination anamnesticly, but seronegative individuals did [18, 28]. To determine whether the

seronegativity had been induced by PVF or SVF, the IgM antibody responses were assayed. Seven of 45 (15.6%) seronegative individuals showed IgM antibody response after revaccination, the results suggested that they probably were a result of PVF. The lack of an IgM response in other responders suggests the previous response to vaccination had been lost over time as have been suggested previously [29].

Recent successes in interrupting measles transmission in the World Health Organization Region of the Americas, most other countries in Europe and selected countries in other regions provide evidence for the feasibility of global eradication [30]. The World Health Organization has developed a global plan for accelerated measles control which calls for implementation of a strategy based on that used to successfully control measles in the Pan American Health Organization (PAHO): a catch-up campaign providing measles vaccine to all children regardless of prior history of immunization or disease, followed by high levels of routine coverage with measles immunization (keep-up) and periodic Mass "catch up" measles immunization campaigns are recommended by the WHO as one of the main strategies to control or eliminate measles [31]. To prevent measles outbreaks we have to have at least a coverage rate of 95% with measles vaccine [32]. To interrupt virus transmission in a community, > 95% of a population must be protected. It seems impossible to reach a sufficiently high level of protection by routine vaccination. In this study among young adults in Iraq 17-24 years after scheduled measles vaccination, PVF and SVF were found to be 3.7% and 11.6% respectively. After revaccination, 85.1% of those vaccinated developed immunity.

Considering the vaccine coverage of 95% and efficacy of 85%, only 80.9% of individuals would be immune, a rate which may not prevent measles outbreaks. Un-immunized young children are at highest risk for measles and its complications, including death. However, any person who has not been immunized with vaccine or through experiencing the disease can become infected [21]. Measles can be particularly deadly in countries experiencing or recovering from war, civil strife or a natural disaster. Infection rates increase because damage to infrastructure and health services interrupts routine immunization and overcrowding in camps for refugees and internally displaced people greatly increases the risk of infection [16]. The geopolitical situation of the Region is complex: several countries are in a state of crisis and conflict or have experienced natural disasters, including Afghanistan, Iraq, and Pakistan. According to UNICEF, about 332 cases of measles have been reported since December 2012 in the Domiz refugee camp in Iraq [33]; so AMMAN/GENEVA, 30 April 2013 – UNICEF and partners have stepped up vaccination campaigns in Syria, Jordan, Lebanon, Iraq and Turkey amid a number of measles outbreaks in a region already struggling to provide humanitarian assistance to millions of people affected by the Syrian crisis. Meanwhile, in Iraq's Domiz camp, about 19,300 refugees from the age of six months to 30 years were vaccinated with the support of UNICEF [34]. It is imperative to evaluate the vaccine with reduced potency because of poor storage and transportation, facilitated by the adverse effect of tropical climate on the vaccine [35]. Mulholland stated that; a generation of young adults with waning vaccine-derived immunity may

become susceptible to some extent to wild measles infections, although the role of such "secondary vaccine failures" in measles epidemiology is unclear. The longer a community goes without circulating measles virus, the more vigilant public health officials must be to maintain immunity levels in the community [36]. We concluded that; basing on the results of this and previous studies on measles epidemiology in Iraq [30, 37], and also taking into account experiences on measles control in other parts of the world [30, 31, 32, 38], we advise the implementation of World Health Organization-recommended strategies to reduce and interrupt indigenous measles virus transmission in Iraq. Mass vaccination with a keep-up phase and follow-up cyclic campaigns would reduce the number of susceptible individuals and to prevent new outbreaks. Additional SIAs are likely required to eliminate measles in Iraq.

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دراسة مصلية وبائية لفيروس الحصبة بين اليافعين: الاستجابة لإعادة التطعيم

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الخلاصة:

قام الباحث بتقييم معدل الانتشار المصلي لمستضدات الحصبة والاستجابة لإعادة التمنيع (الحملة الوطنية الشاملة لوزارة الصحة في الفترة من 9-20 تشرين الاول 2011) ضد الحصبة لدى 189 يافعاً (17-24 سنة) سبق تطعيمهم؛ فثبت أن 45 منهم سلبي المصل. وللتفرقة بين فشل اللقاح الأولي والثانوي، تم تقييم عيار الغلوبولين المناعي G والغلوبولين المناعي M (وذلك باستعمال اختبار قياس الامتصاص المناعي المرتبط بالانزيم) بعد مضي 2-4 أسابيع من إعادة التطعيم لدى كل الافراد، وقد استجاب 29 من سلبِيِّ المصل لإعادة التطعيم الإذكاري ($P < 0.001$) حيث ظهرت لديهم المناعة، بينما أظهر 7 اشخاص استجابة للغلوبولين المناعي M (مما يشير غالباً إلى فشل اللقاح الأولي)؛ بينما ظلت الحماية المصلية متوافرة لنحو 144 من المشاركين إيجابياً المصل دون زيادة ملموسة في عيار المستضد ($P=0.577$). وقد كان معدل الإخفاق الأولي 3.7%، و11.6% الثانوي؛ وبعد إعادة التطعيم أصبح 85.1% محميين مصلياً. قد اوضحت الدراسة الحاجة الى المزيد من الحملات الوطنية لإعادة التطعيم من اجل تقليل نسبة الاخفاق وزيادة الحماية المصلية ضد فايروس الحصبة.