

# Sero-response to measles vaccination at 12 months of age in Saudi infants in Qassim Province

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## ABSTRACT

**الأهداف:** تقييم الاستجابة المصلية لتطعيم الحصبة (MMR) الذي يعطى ضمن تطعيم ثلاثي الحصبة، والنكاف، والحصبة الألمانية، عند سن 12 شهر من خلال قياس أضداد الحصبة قبل وبعد شهر من التطعيم.

**الطريقة:** أجريت دراسة تتبعية شملت 57 طفلاً في سن 12 شهر، والذين تم اختيارهم بشكل عشوائي من مراكز الرعاية الصحية الأولية - القصيم - المملكة العربية السعودية، من خلال عينة متعددة المراحل. تم تنفيذ العمل الحقلية في الفترة من أكتوبر 2006م وحتى ديسمبر 2006م. جمعت عينات الدم لقياس أضداد الحصبة (IgG) قبل وبعد شهر من إعطاء تطعيم الحصبة (MMR)، وذلك باستخدام مقياس الـ ELISA، وتم مقارنة متوسط أضداد الحصبة والانقلاب المصلي قبل وبعد التطعيم.

**النتائج:** في السبعة وخمسون طفلاً، ازدادت الايجابية ضد التطعيم من 3.5% (57/2) إلى 100% خلال شهر بعد التطعيم ( $p=0.0001$ ) وبلغ الانقلاب المصلي 96.5% (57/55). كما ازداد متوسط أضداد الحصبة (GMT) من 0.014IU/ML وحدة دولية قبل التطعيم إلى 2.172IU/ML بعد التطعيم بدلالة إحصائية ( $p=0.0001$ ).

**خاتمة:** سجل الانقلاب المصلي وأضداد الحصبة (GMT)، ارتفاعاً ذو دلالة إحصائية وذلك بعد تطعيم الحصبة عند 12 شهر.

**Objective:** To evaluate the sero-response to measles component of the first measles, mumps and rubella (MMR) dose given at 12 months by measuring measles antibody before and one month after the vaccination.

**Methods:** A follow-up study where, 57 children at the age of 12 months were recruited randomly from the Primary Health Care Centers in Qassim, Saudi Arabia using a multistage sampling techniques. Fieldwork was conducted from October until December 2006. Blood samples were collected to measure measles IgG

antibody before, and one month after giving MMR using enzyme linked immunosorbent assay. Data were compared before and after vaccination using geometric mean titer (GMT) and seroconversion.

**Results:** In the 57 infants, positivity rate increased significantly from 3.5% (2/57) pre-vaccination to 100% one month after ( $p=0.0001$ ), and with a seroconversion of 96.5% (55/57). Also, GMT increased significantly from 0.014-2.172 IU/ML, after vaccination ( $p=0.0001$ ).

**Conclusion:** Sero conversion and GMT are significantly high after the first MMR given at 12 months and this is supported by the surveillance data in Qassim.

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Measles is a highly communicable disease that is a significant cause of illness and death worldwide. Measles vaccinations have been routinely applied over the past 40 years, but measles is still persistent worldwide, and it occurs in vaccinated persons.<sup>1</sup> Measles vaccination in Saudi Arabia has passed through many phases since the 1970s. Measles vaccination was giving as mono dose vaccination in the 1970s and 1980s, shifting to a 2-dose schedule, mono dose at 6

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months and measles, mumps, and rubella (MMR) at 12 months in the 1990s. In 1998-2000, a national MMR campaign was conducted targeting all school age children. A detailed description of different stages of measles immunization strategies was published.<sup>2-4</sup> In 2001, measles vaccination schedule was changed to MMR at 12 months and a second one before school entry. Although this was based on epidemiological and serological studies, no sero-response study was carried out to evaluate the new schedule. Furthermore, in the last 2-3 years, outbreaks started to occur in certain parts of Saudi Arabia.<sup>5</sup> Evaluation and monitoring of an immunization program should depend on serosurvey, sero-response studies in addition to surveillance data. This can help in optimizing immunization activities and in predicting outbreaks. The aim of this study is to measure measles antibody before vaccination at 12 months, and sero response to the first measles vaccination.

**Methods.** This is a follow up study where blood samples were collected from 57 children at the age of 12 months before receiving MMR, and another sample one month later. Paired sera were sent for measles IgG assay using enzyme linked immunosorbent assay (ELISA). Sero-response was measured as proportion of children with protection level and proportion sero-converted after vaccination. The study was conducted through primary health care centers (PHCCs) in Qassim areas, Saudi Arabia, during the vaccination visits at 12 months of age. Saudi children at the age of 12 months  $\pm$  2 weeks, whose guardian agreed to participate and signed the written informed consent, without history of fever or rash and who were available at the study period were recruited for the study. Children with chronic illness, on corticosteroids, or with recent history of blood transfusion were excluded. The fieldwork was conducted from October to December 2006. The study was approved by the Ministry of Health Research and Ethical Committee and by King Abdul-Aziz City for Science and Technology (KACST) by grant number LGP-10-13. The planned sample size (50 children), was calculated with 95% confidence and 80% power assuming proportion of 40% positivity rate before vaccination compared to 95% after vaccination. Using a multistage sampling techniques, 10 PHCCs were selected randomly, using computer generated random number depending on the weight of the catchment population of each center from a sample frame containing a list of PHCCs, 2 centers from Auneza, one from each of Bekeria and Mednab and the remaining 6 were from Buraida. Fifteen children from each center were recruited randomly from the MMR vaccination appointment list. Assuming 30% of the

150 children will refuse to participate, and a 50% drop from the remaining 100 in the second visit due to blood collection to end with 50 children. Three-five ml of blood was collected by phlebotomy. Blood samples were centrifuged and sera were divided into 2 cryo tubes, one ml each. Both tubes were stored at -20°C until shipment to the reference lab. One tube for each child was sent to Germany and the retention tube was kept at the research site. Blood samples were sent in dry ice to the reference lab (MMR Reference Center, Robert Koch Institute, Berlin, Germany Annette Mankertz, PhD). Serological assay was carried out in Berlin in February 2007. A commercial enzyme (EIA, Dade Behring, Germany) was used to detect the virus specific IgG against measles virus according to the instructions of manufacturers as described previously.<sup>6</sup> The quantitative antibody values for measles were expressed in international units (IU). Equivocal results were repeated. The cut off values for the Dade Behring assay are: positive:  $>0.200$  OD (optic density) (300 mIU/ml), negative:  $<0.100$  OD (150 mIU/ml), and equivocal:  $0.100- <0.200$  OD (values between 150-300 mIU/ml). Study definitions: positive antibody "positive by ELISA" where seroconversion was defined as "negative to positive or more than double the ELISA titer comparing pre and post-vaccination titer."

The SPSSPC version 13 was used for data entry and analysis. Data are presented as mean antibody, geometric mean titer (GMT), and proportion of children with positive or seroconverted with 95% confidence intervals.

**Results.** One hundred and fifty children were invited for the study, but as the recruitment was gradual and drop out was not as expected, 75 were included in the first visit and a total of 57 children completed the study with visit one and 2, where 2 blood samples, pre and post vaccination were collected, see enrolment flow chart (Figure 1). One hundred and fourteen samples (57 X 2) were assayed, and only 8 samples were repeated. They were repeated as they were equivocal or to confirm positivity in pre-vaccination sample or negativity in post vaccination samples. Although the statistical analysis plan was decided before, the data were explored to see whether it fits the analysis plan. Figure 2 shows the histogram distribution data of post vaccination titers.

**Measles antibody.** All children except 2 were negative for IgG before vaccination. Paired-t test shows a significant increase after vaccination ( $p=0.0001$ ). The GMT increased from 0.0142 IU/ML prevaccination to 2.172 IU/ML 4 weeks after vaccination ( $p=0.0001$ ). The 2 children with positive titer before vaccination did not have history of measles infection and did not show any increase of measles antibody titer after vaccination. Table 1 shows that using both definitions

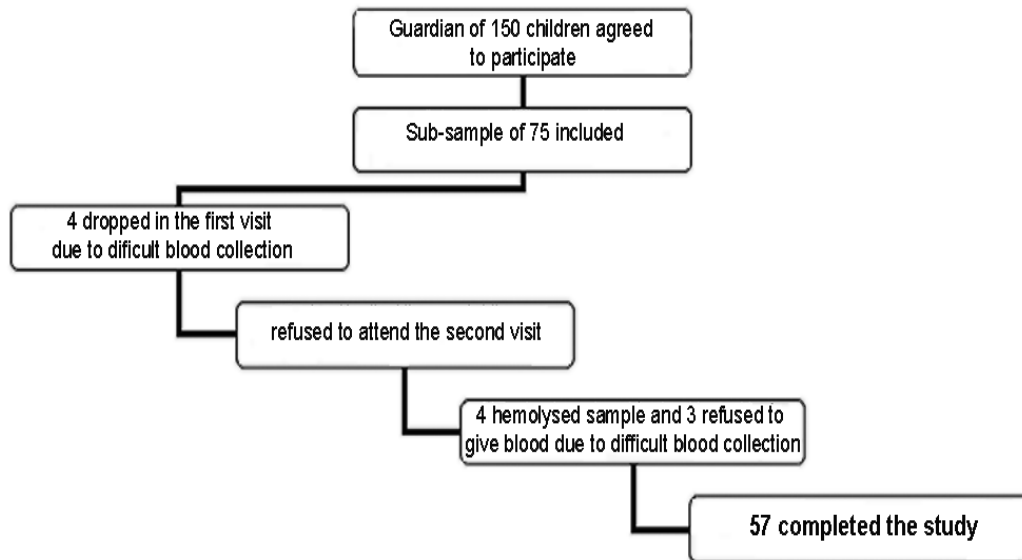


Figure 1 - Enrollment flow chart.

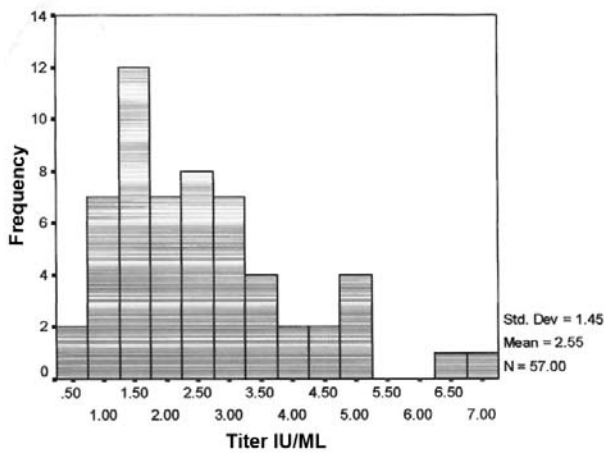


Figure 2 - Histogram distribution of post vaccination titer

Table 1 - Seroconversion after giving MMR at 12 months of age.

Sero-conversion definition	n (%)	95% CI
Negative to positive	55/57 (96.49%)	99.39-96.85
Post-vaccination OD is double the pre-vaccination	55/57 (96.49%)	99.39-96.85

CI - confidence interval, OD - optic density  
MMR - measles, mumps, and rubella

of seroconversion, 96.5% seroconverted, and 89.5% are positive with a titre of 1000 m IU/ml or more (Table 2).

**Discussion.** The sample size of our study was calculated assuming that the positivity rate at 12 months before vaccination was 40%. This proportion was extrapolated from published studies on maternal antibodies at 6 months before vaccination.<sup>7</sup> However, after lab work it was found that this was 3.5%. This means that even a smaller sample size can be enough to generate seroconversion rate after vaccination with the first MMR dose. This study measured measles antibody before giving the first MMR dose at 12 months of age. This new 2-MMR schedule was implemented in 2001. Although this study was conducted in Qassim province, results can be generalized in similar areas with similar conditions and in areas where people depend mainly on PHCCs for vaccinations. In our study, only 2 children were positive for measles IgG before vaccination, and as no measles outbreak was reported during the study period, this may represent persistent measles maternal antibody. Also, according to the study criteria of inclusion and exclusion, infants with a history of measles or fever with rash should be excluded from the study. According to our study sample, 96.5% are susceptible to measles infection before taking the first MMR dose at 12 months. However, antibodies may be detected by plaque neutralization (PNT) in negative sera assayed by ELISA. The cut off point for PNT is 50 m IU/ML. The cut off point for ELISA is 300 m IU/ml, while the protection level is >200 mIU/ml.<sup>8</sup> Seroconversion of all

**Table 2** - Frequency distribution of post vaccination quantitative measles antibody titer.

Titer m IU/ML	n (%)
< 350	0
351-500	2 (3.5)
501-999	7 (4)
≥ 1000	51 (89.5)
Total	57 (100)

M IU/ml: Milli international unit per milliliter

negative samples by ELISA is evident that all samples were either negative or had very low titer. Disappearance of maternal antibody before giving the first measles dose is an advantage for seroconversion after the first dose. This is evident in our study with the high GMT after vaccination. However, if the vaccination coverage is not high, outbreaks in young infants can occur where children younger than 12 months are at greater risk of complications from measles.<sup>9</sup> Herd immunity levels greater than 95% are required to prevent outbreaks as measles is highly contagious.<sup>10</sup> The half-life of measles maternal antibody ranged from 40-60 days.<sup>11,12</sup> Waning of measles maternal antibody varies in different communities. Decay of passively acquired measles antibody can occur faster than expected in certain areas. This may be attributed to transfer efficiency, which seemed to be more effective in certain populations. For example, it is higher in German mothers compared to Nigerian. This may be due to a healthy placenta in the German mothers.<sup>13,14</sup> Also, measles maternal antibody are higher in infants borne to mothers who gained their immunity from natural infection rather than from vaccination.<sup>15</sup>

A high sero-conversion of 96.5% is expected and comparable to other studies at the same age.<sup>10</sup> This 3.5% seroconversion failure is considered as primary vaccine failure due to persistent measles antibody before vaccination. This failure occurred specifically in the 2 children with positive measles antibody before vaccination. The high GMT after vaccination in our study, reflected as 2.17 IU/ML, and as almost 90% had a titer of more than 1000 mIU/ml represents the situation 4 weeks after vaccination. Longitudinal studies show that measles antibody levels reach the peak at 1-2 months post vaccination then decreased 4-8 folds within one year post vaccination and continue to decline with a half-life of approximately 2-4 years during 1-10 years post vaccination.<sup>16</sup> Also, measles-vaccine induced antibody titers will decrease with time post vaccination

when no wild measles virus circulates to boost antibody titers.<sup>17</sup> In the western region in Saudi Arabia and in vaccinated children, percentage of seropositivity obtained, using ELISA, according to age groups of 4-6 years for measles was 73.7%.<sup>5</sup> This means that evaluation of the first dose should take in consideration persistence of antibody until the second dose. Even if we use a simpler calculation of 90% coverage and assumption of 90% efficacy, only 81% will be protected from the target population, leaving almost 20% of every cohort susceptible to infection. This can lead to outbreaks before school entry or before receiving the second measles dose. If we increase coverage to 95% and assume that efficacy is 95%, only 90% will be protected and 10% will accumulate every cohort until school entry or taking the second dose. Measles can still occur in vaccinated persons. In a residential survey in Brazil, in Sao Paulo, showed that 31.9% of measles cases occurred in persons who had received one or more doses of the vaccine.<sup>1</sup> Measles can still occur although it may be mild. Measles IgG avidity can be used to differentiate between primary and secondary immune response occurring in primary and secondary vaccine failure.<sup>18,19</sup> From the public health perspective, subjects with low vaccine immunity can develop mild infection and can transfer it to non-immune. Accordingly, boosting immunity by vaccination is required.

In conclusion, we should not lose confidence in measles vaccination programs, as measles can still occur in a highly vaccinated population and in a community with herd immunity of 90%.<sup>20,21</sup> Further research is needed to evaluate all measles doses given in measles immunization schedules, including MMR given at school entry. This should include also, decay measles antibody after vaccination, avidity, and genotyping.<sup>22</sup> Even with high seroconversion rate after the first measles dose in our study, outbreaks still can occur under the age of 12 months if the vaccination coverage is not high in older age groups. This may explain partially the outbreaks, which occurred over the last years.

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### Related topics

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