Measles Antibody in Mothers and Infants 0-2 Years and Response to Measles Vaccine at the Age of 9 and 18 Months

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Background: *Despite the declining trends in measles cases corresponding to an increase in routine measles immunization coverage, measles outbreaks occur in some isolated areas in Nan province, northern Thailand. The primary reason for these outbreaks is inadequate vaccine coverage. Another reason is primary vaccine failure.*
Objectives: *To study maternal and cord blood measles antibody, the kenetic change of infant measles antibody from 0-9 months and the response to measles vaccine at the age of 9 and 18 months.*
Material and Method: *A prospective cohort study for measles antibody of 1,010 mothers and infants 0-2 years was done between April 1999 and March 2001 at three hospitals in Nan province. Consecutive blood samples were drawn for measles antibody measurement by ELISA assays at Virus Research Institute, National Institute of Health, Thailand. The demographic data of mothers and infants were recorded at each visit.*
Results: *Maternal and cord blood measles antibody were high and the authors found a higher level in cord blood than in maternal level. Measles antibody level in infants declined significantly from the age of 4 months (246.4 $\pm$ 364.2 mIU/L) to their lowest level at the age of 9 months (17.7 $\pm$ 197.1 mIU/L).*
Conclusion: *After the first dose of 9-month measles vaccination, the authors found the seroconversion rate of 82.2 percent. The seroconversion rate was significantly higher to 99.6 percent after the second dose at 18 months old.*

Keywords: *Measles antibody, Maternal and infants 0-2 year, Response to measles vaccine*

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Measles is a ubiquitous, highly infectious disease affecting nearly every person in a given population by adolescence in the absence of immunization programs. Measles is transmitted from person to person by large respiratory droplets[1], but can also be spread by the airborne route as aerosolized droppler nuclei[2]. Measles virus is a member of the genous Morbillivirus in the family Paramyxoviridae[3]. An incubation period of measles is 10 to 12 days. The prodomal period begins with fever, malaise, conjunctivitis, coryza and tracheobronchitis. Koplik spots appear on the buccal mucosa 1 to 2 days before rash onset and may be noted for an additional 1 to 2 days after rash onset. The rash is an erythematous maculopapular eruption that usually appears 14 days after exposure and spreads from the head to the extremities over a 3 to 4 day period. Over the next 3 to 4 days, the rash fades, in severe cases desquamation may occur. Other constitutional signs and symptoms such as anorexia, photophobia, diarrhea, and generalized lymphadenopathy may be present. The most commonly cited complications associated with measles infection are otitis media, pneumonia, postinfection encephalitis, subacute sclerosing panencephalitis and death[4]. In developing countries, case-fatality rates (CFR) vary from 3 to 15 percent, vary depending on the age at infection, intensity of exposure, nutritional status, and availability of treatment[5].

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Routine vaccination of infants at the age of 9-12 month against measles since 1984 has resulted in declining measles cases in Thailand from 62.03 per 100,000 in 1984 to 4.80 in 2005[6]. The national surveillance for EPI program conducted by the Communicable Disease Control division, Ministry of Public Health found that measles vaccine coverage among children 1-2 years-old was 97.6 percent, and the coverage of the completeness at the age 9-12 months was 74.2 percent[7].

During 1994, a measles outbreak occurred in Nan province, the authors reported 212.40 per 100,000 population compared to 65.42 of the whole country report[8]. Outbreak investigation in 2 hill - tribes villages revealed only 50.9 and 71.7 percent of measles vaccine coverage and the authors found vaccine efficacy was only 39.9 and 35.2 in the two villages[9]. Another hospital based study for measles neutralization antibody in 312 patients who were admitted in a Nan Hospital with mild to moderate, not measles illness age between 0-14 years, the authors found only 9.1 percent of infants aged 6-8 months had protective level of measles antibody and among children 1-5 years-old who received 1 dose of measles vaccine at the aged of 9-12 months developed protective measles antibody in only 36.9 percent[10].

According to the local problems regarding measles as described above, the authors decided to conduct the study maternal and infants aged of 0-2 years to determine measles antibodies in the population of Nan province.

Objectives

1) To study maternal and cord blood measles antibody

2) To study the kenetic change of infant measles antibody from 0 -9 months.

3) To study the response to measles vaccine at the age of 9 and 18 months.

Material and Method

One thousand and ten healthy mothers and normal newborn infants were enrolled in the present study. Mothers were informed during antenatal visits and at the delivery room before informed consent were done. Maternal cord blood and consecutive venous blood samples of the newborn infants were used for measles antibody measurement and analysis.

A prospective cohort study was done from April 1999 to March 2001 at three hospitals located in the central, northern and southern part of Nan province, northern Thailand. Maternal cord blood samples and consecutive venous blood samples of the newborn until the age of 24 months were collected at well baby clinics under sterile technique and cold chain at the age of birth, 4, 6, 9, 10 (1 month after the first dose of measles vaccine), 18, 19 (1 month after the second dose of measles vaccine) and 24 months. Measles vaccines used in the present study were attenuated freeze-dried Schwarz strain vaccine, manufactured by the Pasteur M rieux Company and distributed by the Thai Government Pharmaceutical Organization, administered subcutaneously at the age 9 months and 18 months at each well baby clinic of the three hospitals. The blood samples were centrifuged and serum was separated in sterile test-tubes and frozen in the refrigerator at Nan Hospital. Frozen serum were collected and sent to Virus Research institute of Nontaburi province, Thailand. Measles antibodies were measured by ELISA assays using Enzynogst Anti-Measles Virus/IgG Test (Behring Germany. Cal No. OWLN 15) and semi-automate machine.

Maternal and infants data such as age, hill-tribe or non-hill tribe, gestational age, delivery type, medical illness, history of measles illness and vaccine, BW, and height were recorded at birth and each visit.

Statistical analysis

The results were analyzed using SPSS version 10.0 program, the percentage, mean, SD, 95% confidence interval, Chi-square and Student- t test were used to compare measles antibody level, Antibody level equal to or more than 255 mIU/L considered to be protective level. Correlation between maternal factors, infant factors and maternal antibody level, infant antibody level were also analyzed. A p-value of less than 0.05 was considered significant differences.

Results

One thousand and ten mothers and infants enrolled at the beginning. Many were lost to follow-up as time went on, and there were only 440 infants left at the end of the present study. Maternal and cord blood measles antibody level were quite high and cord bloods level were significantly higher than the maternal level ($p = 0.000$) (Table 1).

Measles antibody level declined significantly at the age of 4 months and was lost to the lowest level at the age of 9 months (Fig. 1).

After the first dose of measles vaccine at the age of 9 months antibody response rose significantly from 17.7 ± 197.1 mIU/L to 2292.7 ± 2052.5 mIU/L at 1

Table 1. Measles antibody levels in maternal and infants 0-24 months

Maternal and infant age	N	Measles antibody levels (mIU/L) Mean ± SD	CV* (%)	Percentage of antibody ≥ 255 mIU/L
Maternal	1010	3905.1 ± 2834.2	72.6	97.3
Cord blood	1013	4451.0 ± 3171.5	71.0	97.8
Infants aged 4 months	829	246.4 ± 364.2	147.8	35.9
Infants aged 6 months	839	19.4 ± 84.6	436.1	3.3
Infants aged 9 months (first dose of measle vaccine)	818	17.7 ± 197.1	1113.6	1.1
Infants aged 10 months	814	2292.7 ± 2052.5	89.5	82.2
Infants aged 18 months (second dose of measle vaccine)	723	3021.1 ± 3127.4	103.5	84.5
Infants aged 19 months	672	5360.4 ± 3371.8	62.9	99.6
Infants aged 24 months	440	3888.6 ± 2855.4	73.4	98.4

* CV = Coefficient of variation = $\frac{SD}{\bar{x}} \times 100$

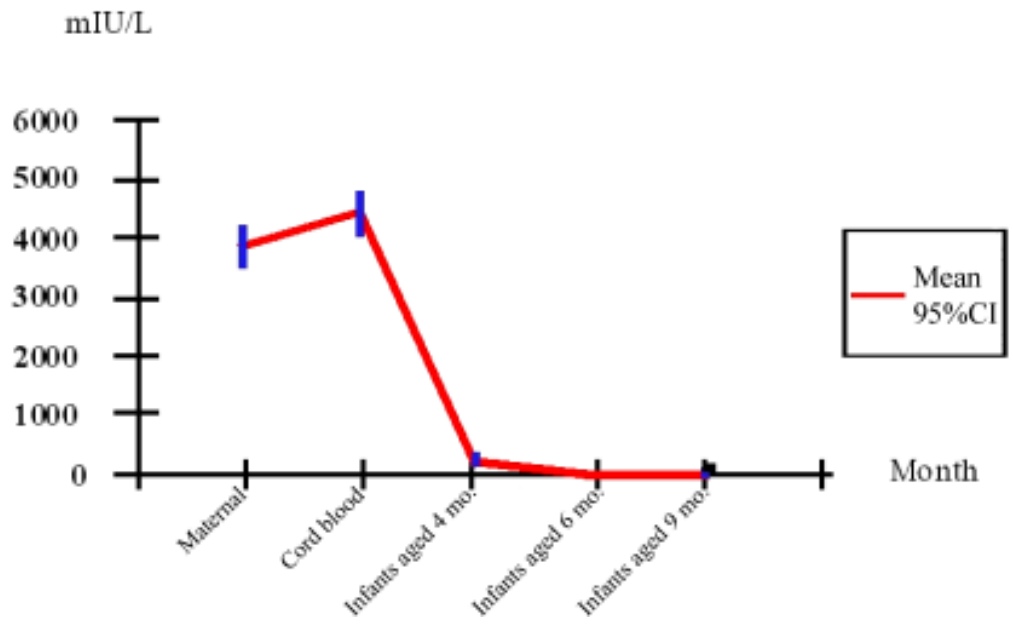

Fig.1 Mean and 95% CI measles antibody in maternal and infants 0-9 months

month after vaccination and continued rising until the age of 18 months when the authors found the antibody level of 3021.1 ± 3127.4 mIU/L. The seroconversion rates were 82.2 at the age of 10 months and 84.5 percent at the age of 18 months, and after the second dose of measles vaccine at the age of 18 months antibody response stepped up to the level higher than cord blood (5360.4 ± 3371.8 vs 4451.0 ± 3171.5 mIU/L) and then slowly declined to the same maternal level at the age of 24 months (3888.6 ± 2855.4 vs 3905.1 ± 2834.2 mIU/L). After the second dose of measles vaccine at the age of 18 months the seroconversion rates were 99.6 and 98.4 percent at the age of 19 and 24 months, the authors found a significantly higher seroconversion rate after the second dose of measles vaccine compared to after the first dose at 9 months (99.6% vs 82.2%) (Fig. 2).

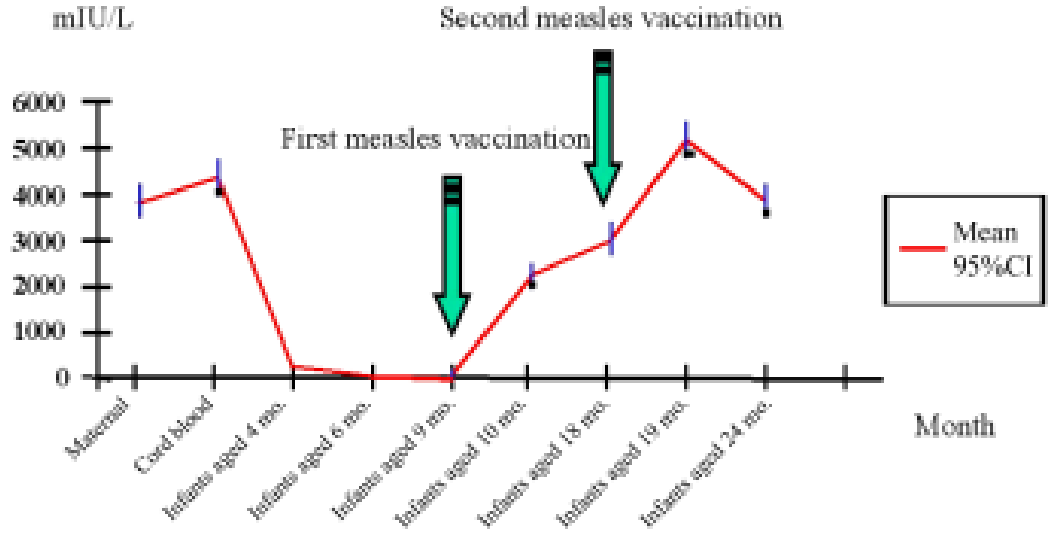

Fig. 2 Mean and 95%CI of measles antibody in maternal and infants 0-24 months

The correlation study of various maternal factors such as age, hill-tribe or non hill-tribe, gestational age, delivery type, weight, height, BMI, maternal illness and history of maternal measles vaccine, the authors found only maternal age less than 20 years and maternal antibody levels less than 255 mIU/L had significant correlation to non-protective level of cord blood ($p < 0.001$), and a correlation study in infant factors such as birth weight, apgar score, term or preterm, medical illness during the time of blood sample collection failed to detect the correlation to infant antibody except birth weight less than 2,500 gm. had significant correlation to cord blood antibody level ($p = 0.046$).

Discussion

Maternal Ig G transfer across placenta by active transportation, the authors could detect maternal Ig G as early as fetal age 13-15 week gestation, fetal Ig G subclass 1-4 has the same level as maternal at 38 weeks gestation after that fetal level exceeds maternal level until delivery[11,12].The present study also showed this phenomenon. The authors found a significant decline in maternal antibodies in the present cohort infant group starting from 4 months and lost almost completely at the age of 9 months compared to 12 months in a study in the USA[13], and 6 months in the developing countries such as Kenya[14]. A previous serological survey conducted in Bangkok also found a rapid loss of measles antibodies to the lowest levels at the age of 6-7 months and to undetectable levels at 8-9 months[15] and another immunoglobulin level study in Thai children also found the lowest level at the age of 4-6 months[16]. It is clear that in the developing countries, including Thailand, the passive maternal antibody loss rapidly starting from 4-6 months and lost almost completely at 8-9 months, the major reason is due to excessive use of passive antibody to combat frequent infections and loss by GI tract from diarrhea diseases, and also less Ig G transfer capacity from maternal to the fetus[13]. The studies in developing countries[17-19] revealed the seroconversion rate after measles vaccine at the age of 9 months was 80-90 percent; vaccine efficacy was 85 percent in the USA and European countries; the seroconversion rate after a single dose of measles vaccine at 15 months was 95 percent and vaccine efficacy was 98 percent[20]. A previous study in Thailand[21] found a seroconversion rate after a single dose at 7-8 months, and at 9 months were 67 and 91 percent. In the present study, the seroconversion rate after the 1st measles vaccine was 82.8 and 84.5 percent at 1 and 9 months after vaccination.

In 1989, the USA used 2-dose schedules in measles vaccination to reduce susceptibility to those who had non-protective antibody levels after the first dose, and another reason for the booster effect on the ones who had low or undetectable levels[20]. In Nan, even the measles coverage figure is higher than 90 percent, but there are many mountainous, isolated areas and 18 percent of the hill-tribe people experience frequent migration and have crowded communities of

young children due to lack of good birth control. This results in low vaccine coverage and measles outbreaks periodically[9].

According to the present study, the authors found the seroconversion rate after the first dose, about 82-85 percent. The authors decided to add a second dose of measles vaccine at the age of 18 months, additional with regard to the national recommendation to improve vaccine coverage and to provide boosters to the children who have low antibody levels after the first dose. The present study showed a satisfactory outcome, the seroconversion rate of 99.6 percent after the second dose compared to 82-85 percent after the first dose.

In the correlation study between maternal factors and protective measles antibodies in infants, the authors found only maternal antibody levels. Maternal age had significant correlation, as described elsewhere maternal antibody and was actively transported via the placenta to the fetus during 13-15 weeks gestation. This increased to the same maternal levels at 38 weeks gestation. All of the study groups were full term so they had corresponding correlation to their mothers. Maternal age of less than 20 years were related to mothers who were born after 1981 and suspected to have received measles vaccination, which started in 1984. The immunity after measles vaccine has a lower level and does not persist as long as after natural infection; it lasts only 4-5 years without a booster effect by natural measles infection[22].

In the correlation study in infant factors, the authors found only birth weight less than 2,500 gm related to lower cord blood antibodies ($p = 0.046$), which is different from the previous study[23] that showed a correlation of maternal Ig G and gestational age but not the birth weight. Thus, the present study was conducted in full-term infants so the authors could not express the effect of pre-term infants on measles antibodies.

Conclusion

A prospective cohort measles antibody study of 1, 010 mothers and infants 0-2 years in Nan province was performed from April 1999 to March 2001, the authors found:

1. Higher cord blood antibody levels than maternal with the mean $4,454.0 \pm 3,171.5$ mIU/L compared to $3,905.1 \pm 2,834.2$ mIU/L

2. Significantly less maternal measles antibodies starting with infants the age of 4 months to the lowest level at the age of 9 months

3. The seroconversion rate was 82.2 percent after the first dose of 9 months measles vaccination and it stepped up to 99.6 percent after the 18-month second vaccination.

The authors suggest increasing herd immunity in isolated areas as the first priority; the authors must increase vaccine coverage in every village. Additional second dose measles vaccine is also an important strategy to improve coverage and increase antibody levels in those who do not have protective level. In the near future, the authors would like to study the weaning effect in this cohort group when they are 5-10 years-old.

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ระดับภูมิต้านทานโรคหัดในมารดา และทารก 0-2 ปี และการตอบสนองต่อวัคซีนโรคหัดที่อายุ 9 และ 18 เดือน

วราภรณ์ เตชะเสนา, พิศิษฐ์ ศรีประเสริฐ, ศิริมา ปัทมดิลก, พงษ์เทพ วงศ์วัชระไพบูลย์

วัตถุประสงค์: *เพื่อศึกษาระดับภูมิต้านทานโรคหัดในมารดาและทารกแรกเกิด และการเปลี่ยนแปลงระดับภูมิต้านทานโรคหัด เมื่อทารกอายุ 0-9 เดือน และศึกษาการตอบสนองต่อวัคซีน โรคหัดที่ฉีดเมื่ออายุ 9 และ 18 เดือน*

วัสดุและวิธีการ: *ศึกษาแบบไปข้างหน้าในกลุ่มมารดา และทารกปกติ จำนวน 1,010 คน ในจังหวัดน่าน ตั้งแต่ เมษายน พ.ศ. 2542 - มีนาคม พ.ศ. 2544 โดยติดตามระดับภูมิต้านทาน โรคหัดในเลือดของมารดา และทารกที่อายุแรกเกิด, 4, 6, 9, 10, 11, 18, 19 และ 24 เดือน และเก็บข้อมูลทั่วไป, ข้อมูลการเจ็บป่วย ทุกครั้งที่เจาะเลือด ตรวจหาระดับภูมิต้านทานโรคหัด โดยวิธี ELISA ที่สถาบันวิจัยไวรัส นนทบุรี*

ผลการศึกษา: *พบว่าระดับภูมิต้านทานโรคหัดในมารดา และทารกแรกเกิด มีระดับสูง โดยที่ทารกมีระดับสูงกว่ามารดาอย่างมีนัยสำคัญ และระดับภูมิต้านทานโรคหัดลดระดับลงอย่างรวดเร็ว เริ่มตั้งแต่ทารกอายุ 4 เดือน จนลดต่ำสุดเมื่ออายุ 9 เดือน, ภายหลังฉีดวัคซีนหัดเข็มแรกเมื่ออายุ 9 เดือน ระดับภูมิต้านทานเพิ่มขึ้น แต่ไม่เท่าตอนแรกเกิด พบการตอบสนองต่อวัคซีนเข็มแรก ร้อยละ 82.2 ระดับภูมิต้านทานสูงขึ้นมากกว่าตอนแรกเกิด และผลการตอบสนองต่อวัคซีนโรคหัดเพิ่มขึ้น เป็นร้อยละ 99.6 หลังฉีดวัคซีนหัดเข็มที่ 2 ที่อายุ 18 เดือน ต่อมาเมื่อทารกอายุ 24 เดือน ภูมิต้านทานโรคหัดลดลงระดับลงใกล้เคียงกับตอนแรกเกิด ปัจจัยต่าง ๆ ในมารดา ยกเว้น ระดับภูมิต้านทานที่ต่ำกว่า 255 mIU/L และอายุน้อยกว่า 20 ปี ไม่มีความสัมพันธ์ต่อระดับภูมิต้านทานของทารกแรกเกิด, ปัจจัยต่าง ๆ ในทารก ยกเว้น น้ำหนักแรกเกิดน้อยกว่า 2,500 กรัม ไม่มีผลต่อระดับภูมิต้านทานโรคหัดของทารก*

สรุป: *ระดับภูมิต้านทานโรคหัดในมารดา และทารกแรกเกิด มีระดับสูง โดยทารกแรกเกิดสูงกว่ามารดา และลดระดับลงอย่างรวดเร็วเมื่ออายุ 4-9 เดือน ภายหลังฉีดวัคซีนหัดเข็มแรกที่อายุ 9 เดือน ระดับภูมิต้านทานเพิ่มระดับขึ้น แต่ยังไม่เท่าแรกเกิด ต่อเมื่อฉีดเข็มที่สองที่อายุ 18 เดือน ระดับภูมิต้านทานโรคหัดเพิ่มสูงกว่าตอนแรกเกิด และค่อย ๆ ลดระดับลงเท่าแรกเกิด เมื่ออายุ 2 ปี seroconversion rate หลังวัคซีนเข็มที่ 1, 2 เท่ากับร้อยละ 82.2 และ 99.6*