A Comparison Study of Measles Antibody between Two Doses Vaccination at 9, 18 Months and Single Dose at 9 Months in Children 4-6 Years Old

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Background: *The authors have added the second dose of measles vaccine to children aged 18 months since 1997 because of the measles outbreaks in Nan province in 1993-1994.*
Objective: *To compare measles antibody level between two doses vaccination at 9, 18 months and single dose at 9 months in children at the age of 4 to 6 years old.*
Material and Method: *A cross sectional serological study in children 4 to 6 years old was performed between August 2008 and August 2009 at three hospitals in Nan and Phrae provinces. The subjects were divided into two groups, 1) 100 children in Nan provincial hospital received two doses of measles vaccination at the age of 9 and 18 months and 2) 91 children received single dose measles vaccination at the age of 9 months, 41 from Phrae provincial hospital and 50 from Weingsa district hospital. Blood samples were drawn for measles antibody measurement by ELISA assays at Virus Research Institute, National Institute of Health, Thailand.*
Results: *The mean measles antibody level in children 4 to 6 years old in both groups was a satisfactory high level, 1,887.67 and 1,621.02 mIU/ml in single and two doses vaccination respectively, which were not statistically significant ($p = 0.431$). The higher level in single dose group could be explained by the average age being younger than the two doses group by one year (4 years 2 months vs. 5 years 4 months). Therefore, the waning immunity in younger age group is suspected to be less than the older age group. The rate of protective measles antibody level ($\geq$ 255 mIU/ml) was significantly higher in the two doses group than the single dose, 87% compared to 76% ($p = 0.046$), which represented primary vaccine failure at the age 4 to 6 years of 13% and 24%, respectively.*
Conclusion: *The authors suggest that a second dose of measles vaccine at the age of 18 months be administered to decrease the number of primary vaccine failure from 24% to 13%. Further studies in the same age group and in different areas are required to confirm these findings.*

Keywords: *Comparison study, Measles antibody, Single or two-dose measles vaccination*

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Measles is a ubiquitous and a 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 airborne route as aerosolized droppler nuclei[2]. Measles virus is a member of the genus *Morbillivirus* in the family *Paramyxoviridae*[3]. The 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 and in severe cases, desquamation may occur. Other constitutional signs

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and symptoms, such as anorexia, photophobia, diarrhea and generalized lymphadenopathy may also be present. The most commonly cited complications associated with measles infection are otitis media, pneumonia, post infection encephalitis and subacute sclerosing panencephalitis[4]. In developing countries, case fatality rates (CFR), vary from 3% to 15%, depending on the age at infection, intensity of exposure, nutritional status, and availability of treatment[5].

Routine vaccination of infants at the age of 9 to 12 months against measles since 1984 has resulted in declining measles cases in Thailand from 62 per 100,000 in 1984 to 6.9 per 100,000 population in 2007[6] but measles outbreaks still occurred in Nan province and some places in Thailand. There were reported outbreaks of college students at Nan, Phrae, Chiang Rai, and Chiang Mai Provinces in 2006 and 2007[7]. Additionally, the authors found the age group of measles was high in teenagers. Therefore, the authors questioned the cause of waning immunity. Was it because of a primary or secondary vaccine failure?

Primary vaccine failure is defined as the failure of the initial vaccination to elicit an immune response. It is believed to be caused by 1) interference by maternal antibody when vaccination occurs at a young age[8], 2) technical problems such as improper vaccine storage or administration (suboptimal vaccine handling practices)[9], or 3) other unknown reasons.

Secondary vaccine failure is defined as a waning immunity after successful immunization. The most convincing evidence of secondary vaccine failure would be provided by confirmed measles disease in a person who had a documented seroconversion after vaccination. Similarly, the best estimates of the risk of secondary vaccine failure would come from follow-up of successful immunization cohorts after exposure to measles. However, such data are difficult to obtain. Other types of studies have been designed to investigate different issues. Those are[10] 1) clinical and serologic studies of measles disease in vaccinated persons, 2) studies of persistence of antibody after vaccination, 3) studies of the serologic response to revaccination and 4) studies of duration of protection after vaccination.

The secondary vaccine failure rate is rare compared to primary vaccine failure. It was found in only 2% to 5%[11]. The longest follow-up period for a seroconversion study is 16 years. In that study, Krugman followed institutionalized children longitudinally and found that 9 of 70 vaccinees (13%) had undetectable HI antibody 16 year after receipt of Schwarz vaccine, compared with none of 47 children with a history of natural measles[12]. Krugman also studies children living at home who had exposure to wild virus 14 years after vaccination. The GMT and seropositivity rate were higher in these children than in institutionalized children. This suggested a more rapid decline in antibody in a population that does not have boosts from re-exposure to wild virus[13]. The serologic studies of antibody persistence after vaccination is difficult because of the varying degree of exposure to wild measles virus, causing subclinical boosting of antibody titres and to the different sensitivity of the assay used to measure antibody.

Because of the measles outbreaks in Nan Province in 1993 and 1994[14], the authors have added the second dose of measles vaccine to children age 18 months since 1997. The previous study in measles antibody in Nan province[15] found the seroconversion rate was 82.2% and antibody level was $2,292.7 \pm 2,052.5$ mIU/ml after the first measles vaccination dose that was given at 9 months. The seroconversion rate stepped up to 99.6% and antibody level was $5,360.4 \pm 3,371.8$ mIU/ml after the second dose at the age of 18 months.

Objective

To compare measles antibody level between two doses vaccination at 9 and 18 months and a single dose at 9 months in children at the age 4 to 6 years old.

Material and Method

A cross-sectional serological study in children age 4 to 6 years old were performed at baby clinics in Nan provincial hospital, Phrae provincial hospital, and Weingsa district hospital in Nan province. These three hospitals are located in the northern part of Thailand. The children were divided into two groups.

1) 100 children in Nan provincial Hospital received two doses vaccination at 9 and 18 months and

2) 91 children received single dose vaccination at 9 months, in this group 41 from Phrae provincial Hospital and 50 from Weingsa district Hospital.

The data recorded for each subject were age, sex, body weight, height, the date and place where measles vaccine were done and the history of measles illness or contract with measles. Written consent forms were needed for enrollment.

The study was done between August 13, 2008 and August 12, 2009 with the approval from the Ethical Review Committee for Research in Human Subjects,

Ministry of Public Health, Thailand, Document No.95/2008. Measles vaccines used in the present study were attenuated freeze-dried Schwarz strain vaccine, manufactured by the Pasteur Merieux Company and distributed by the Thai Government Pharmaceutical Organization. The venous blood samples, 3 to 5 ml, were collected under sterile technique and centrifuged at speed 1,500 rpm for 15 minutes by the KOKUSAN machine 220 V. MFG NO. 139516, made in Korea, which was calibrated once a year. The serum were separated in sterile test tubes and frozen in Ultralow temperature freezer, serial NO. 61121617, made by Sanyo electric company limited, Japan. They remain frozen for two months before they were collected in ice packed foam containers and sent to Virus Research Institute at Nontaburi province, Thailand under the cold chain system. Measles antibodies were measured by ELISA assays using Enzynogst® Anti-Measles virus/IgG Test (Behring Germany. Cal no. OWLN 15) and semi-automate machine.

Statistical analysis

The results were analyzed using SPSS version 11.0 program. The percentage, mean, SD, 95% confidence interval, Chi-square and student-t test were used to compare measles antibody level. A p-value of less than 0.05 was considered significant. Antibody level equal to or more than 255 mIU/ml was considered an adequate protective level.

Results

One hundred children from Nan Hospital and 91 children from Phrae and Weingsa Hospital were enrolled in the present study. The average age in group 1 was 5 years 4 months and in group 2 was 4 years and 2 months, which was significant different ($p = 0.00$ Table 1). The two groups were comparable according to gender, history of measles illness, and nutritional status (Table 1).

The percentage of the protective measles antibody level (≥ 255 mIU/ml) was significantly different between the two groups. The authors found 87% in the two dose group and 76% in the single dose group ($p = 0.046$ Table 2). Mean measles antibody level in single dose was higher than the two doses group, but with no significant difference ($p = 0.431$ Table 2).

Measles antibody level distribution in the two-dose group was more than single dose group in the range of 255-1,999 mIU/ml and less than single dose group at the level less than 255 mIU/ml (13% vs. 24% Fig. 1). Measles antibody level more than 6,000 mIU/ml was found in single dose group more than in the two-dose group (10% vs. 3% Fig. 1).

Discussion

The purpose of the present study was to compare measles antibody level between two doses vaccination at the age 9 and 18 months and single dose vaccination at 9 months in children at the age 4 to 6 years old. The authors found that mean antibody level in the single dose group was higher than the two doses group but it was not statistically different ($p = 0.431$). The explanation for this finding was the average age in the single dose group was younger than in the two doses group with significant difference ($p = 0.000$ Table 1), which show waning immunity in the advancing age. The authors suggest further studies in the same age group to confirm this finding. In the

Table 1. Demographic data

	Group 1 Vaccine 2 dose	Group 2 Vaccine 1 dose	
Number	100	91	
Average age (y)	5 years 4 months	4 years 2 months	p-value = 0.000
Age range	4 years 2 months–6 years 9 months	3 years 5 months-5 years 4 months	
Male	50	46	
Female	50	45	
History of measles			
Yes	0 (0%)	1 (1.1%)	
No	100	90	
Weight for height			
Normal	53 (53.0%)	45 (55.6%)	
Malnutrition	32 (32.0%)	22 (27.2%)	p-value = 0.759
Overweight	15 (15.0%)	14 (17.3%)	

Table 2. Percentage of protective, mean (SD) and range of measles antibody level

	Group 1 vaccine 2 dose n = 100	Group 2 vaccine 1 dose n = 91	
Protective (%)	87 (87.0%)	69 (75.8%)	p-value = 0.046
Nonprotective (%)	13 (13.0%)	22 (24.2%)	
Mean (SD) mIU/ml	1,621.0 (2,238.6)	1,887.7 (2,427.0)	p-value = 0.431
Median mIU/ml	877.5	876.0	
Range mIU/ml	34-17,387	0-10,338	
95% confidence interval	176.8-2,065.2	1,382.2-2,393.1	

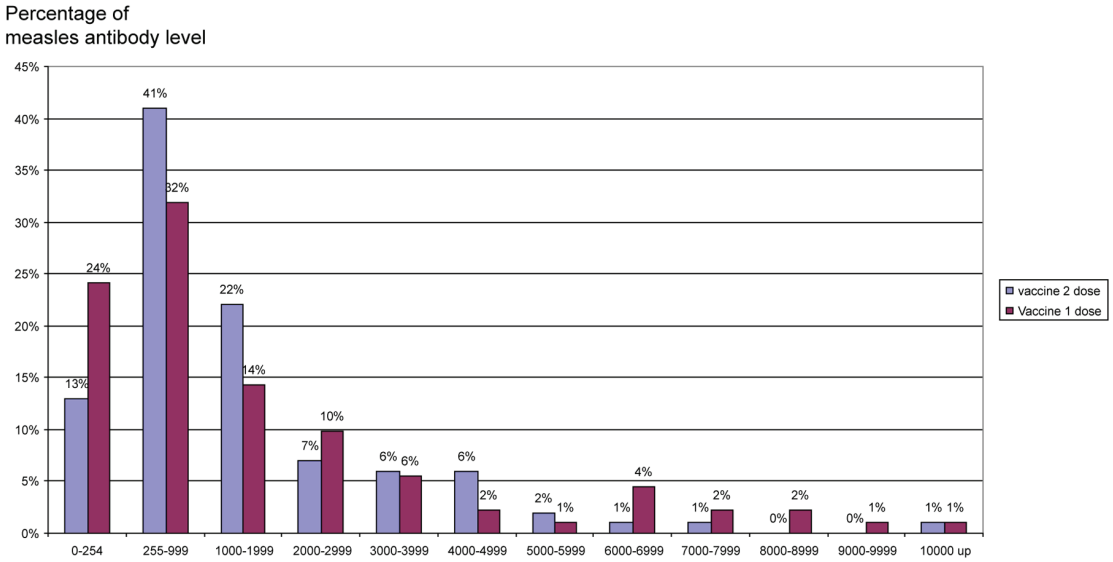

Fig. 1 Percentage of measles antibody level in the two doses and single dose of measles vaccine

present study, measles antibody level at the age of 4 to 6 years was higher than the protective level (≥ 255 mIU/ml) in both groups, 1,621.02 mIU/ml in two doses and 1,887.67 mIU/ml in single dose. This means that once the antibody level was successfully established, it will persist for a long time 8 to 16 years, which corresponded to the studies in China[16,17]. The studies of measles antibody in Thailand[18,19] also showed that after single dose of measles vaccine at the age 9 months, the antibody level dropped to the lowest level by the age of 4 to 5 years old.

The rate of protective measles antibody level (≥ 255 mIU/ml) was significantly higher in two doses at 9 and 18 months measles vaccine than single dose at 9 months, 87% compared to 76% (p = 0.046). The reason for this figure is primary vaccine failure. Studies in developing countries[20,21] revealed the seroconversion rate after measles vaccine at the age of 9 months was 80% to 90%, whereas the study in Nan province, Thailand found 82% of seroconversion rate after 1 dose Schwarz strain measles vaccine at the age 9 months[15]. It is known that primary vaccine failure occurred 10% to 20% or more depending on the setting of immunization practices. Those who do not have protective measles antibody are at risk of developing measles illness in the places where circulating wild measles viruses exists. Such populations are the children aged 6 to 9 months whose maternal passive immunity was lost and children after 9 months who failed measles vaccination, at least 10% to 20%. However, this depends on the rate of primary vaccine failure and the children who missed the opportunity to receive measles vaccine. The second dose of measles vaccine is very useful in developing countries

including Thailand because it decrease the number of primary vaccine failure that occurred after single dose vaccination. Furthermore, it boosts the immune response and provides a second opportunity to immunize children who missed the first dose. The authors found waning immunity was evidenced by the percentage of antibody levels more than 255 mIU/ml dropped from 99.6% at the age of 24 months in the previous study[15] to 87% and antibody level dropped from 3,888.60 to 1,621.02 mIU/ml when the child grew up to the age of 4 to 6 years old. The reported cases of measles in Thailand are still high in the age group 0 to 4 years and 10 to 14 years[22]. Therefore, the recommendation of the second dose should be at 18 to 24 months rather than 4 to 6 years. It will decrease the population at risk from 24.2% to13%, according to the present study. In the environment where circulating wild virus still exist, the small number of non protected populations, 13% and 24% (as shown in Fig. 1), will have natural booster effect. This will turn them to protected populations. The present study showed this phenomenon in the children who had high level (> 6,000 mIU/ml) of antibody. The authors believe the number of measles cases in teenagers and the outbreaks of measles in school or college students will decrease. Therefore, a measles elimination program in Thailand will successfully be established. The authors suggest further studies in the same age group and in different area to confirm the findings of the present study.

Conclusion

A cross-sectional serological studies in children 4 to 6 years old to compared measles antibody level between 100 children who receive two doses measles vaccination at 9 and 18 months and 91 children who received single dose measles vaccine at the age 9 months. The present study was performed between August 2008 and August 2009. The authors found three main outcomes:

1) Mean measles antibody level in children 4 to 6 years old in both groups was at a satisfactory high level (1,887.67 vs. 1,621.02 mIU/ml), which was not statistically different (p = 0.431). This means that waning immunity is not a problem in children in this age group.

2) The rate of protective measles antibody level (≥ 255 mIU/ml) was significantly higher in the two doses group than the single dose group, 87% vs. 76% (p = 0.046). The difference was because of primary vaccine failure.

3) Distribution of measles antibody level was in the range of 255-1,999 mIU/ml in both groups. However, levels less than 255 mIU/ml was found more in the single dose group (24% vs. 13%). Furthermore, levels of more than 6,000 mIU/ml were also found more in the single dose group than the two doses group (10% vs. 3%).

The authors suggest further studies in the same age group and in different area to confirm these findings and suggest second dose measles vaccine at the age of 18 months aiming to decrease the number of primary vaccine failure from 24.2% to 13%.

Acknowledgement

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Potential conflicts of interest

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การศึกษาเปรียบเทียบภูมิต้านทานโรคหัดในเด็กอายุ 4-6 ปี ที่เคยได้รับวัคซีนหัด 2 ครั้ง เมื่ออายุ 9 และ 18 เดือนกับ 1 ครั้ง เมื่ออายุ 9 เดือน

วราภรณ์ เตชะเสนา, พงศ์เทพ วงศ์วัชรไพบูลย์, สุวรรณา ตีระวณิชย์, ศิริมา ปัทมดิลก

ภูมิหลัง: *สืบเนื่องจากปัญหาการระบาดของโรคหัดในจังหวัดน่าน ในปี พ.ศ. 2536, 2537 โรงพยาบาลน่านได้เพิ่มการฉีดวัคซีนหัด ครั้งที่ 2 ให้แก่เด็กอายุ 18 เดือน ตั้งแต่ ปี พ.ศ. 2540 เป็นต้นมา*

วัตถุประสงค์: *เพื่อเปรียบเทียบระดับภูมิต้านทานโรคหัด ระหว่างเด็กอายุ 4-6 ปี ที่เคยได้รับวัคซีน 2 ครั้ง ที่อายุ 9, 18 เดือน กับได้วัคซีน 1 ครั้ง เมื่ออายุ 9 เดือน*

วัสดุและวิธีการ: *เป็นการศึกษาภาคตัดขวาง ที่ทำขึ้นในช่วงเดือนสิงหาคม พ.ศ. 2551 ถึง สิงหาคม พ.ศ. 2552 ณ โรงพยาบาลน่าน, โรงพยาบาลแพร่ จังหวัดแพร่ และโรงพยาบาลเวียงสา จังหวัดน่าน โดยแบ่งกลุ่มศึกษาเป็น 2 กลุ่ม 1) 100 คน จากโรงพยาบาลน่าน เป็นกลุ่มที่ได้รับวัคซีน 2 ครั้ง เมื่ออายุ 9 และ 18 เดือน 2) 91 คน จากโรงพยาบาลแพร่ 41 คน โรงพยาบาลเวียงสา 50 คน เป็นกลุ่มที่ได้วัคซีน 1 ครั้ง เมื่ออายุ 9 เดือน เก็บตัวอย่างเลือดจากหลอดเลือดดำไปตรวจวัดระดับภูมิต้านทานโรคหัด ณ สถาบันวิจัยไวรัส, สถาบันวิจัยวิทยาศาสตร์สาธารณสุข จังหวัดนนทบุรี*

ผลการศึกษา: *ค่าเฉลี่ยของระดับภูมิต้านทานโรคหัดของทั้งสองกลุ่ม ยังคงมีระดับสูงโดยที่กลุ่มได้รับวัคซีน 1 ครั้ง มีค่าสูงกว่าเล็กน้อย ไม่มีความแตกต่างกันทางสถิติ โดยมีค่าเฉลี่ย 1,887.67 และ 1,621.02 mIU/ml ตามลำดับ ($p = 0.431$) ทั้งนี้อาจเกิดจากค่าเฉลี่ยอายุของกลุ่มที่ได้วัคซีน 1 ครั้ง ต่ำกว่าประมาณ 1 ปี (4 ปี 2 เดือน เปรียบเทียบกับ 5 ปี 4 เดือน) จึงยังมีผลของ waning immunity ไม่มากเท่ากลุ่มที่อายุมากกว่า อัตราการมีระดับภูมิต้านทานโรคหัดในระดับป้องกันโรคได้ (≥ 255 mIU/ml) ในกลุ่มที่ได้รับวัคซีน 2 ครั้ง สูงกว่ากลุ่มที่ได้รับวัคซีน 1 ครั้ง อย่างมีนัยสำคัญทางสถิติ 87% และ 75.8% ตามลำดับ ($p = 0.046$) แสดงว่า ที่อายุ 4-6 ปี เด็กที่ได้รับวัคซีนครั้งเดียว มีความล้มเหลวจากวัคซีนถึง ร้อยละ 24.2 ในขณะที่กลุ่มที่ได้วัคซีน 2 ครั้ง มีความล้มเหลวร้อยละ 13*

สรุป: *จากผลการศึกษานี้ผู้นิพนธ์เสนอว่าควรมีการศึกษาแบบนี้ในกลุ่มเด็กที่มีอายุเท่ากัน และในพื้นที่อื่น ๆ ถ้าพบว่าผลลัพธ์ใกล้เคียงกัน ควรฉีดวัคซีนหัดครั้งที่ 2 แก่เด็กไทยเมื่ออายุ 18 เดือน เพื่อลดจำนวนผู้ป่วยเด็กที่ล้มเหลวจากการฉีดวัคซีนครั้งแรกจากร้อยละ 24.2 ให้เหลือร้อยละ 13 ตามผลการศึกษานี้*