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MINISTRY OF HEALTH

NATIONAL INSITUTE OF HYGIENE AND EPIDEMIOLOGY

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ANTI-MEASLES IgG ANTIBODIES IN CHILDREN 2 - 9 MONTHS OLD AND THE SAFETY, IMMUNOGENICITY AFTER MVVAC MEASLES VACCINATION FOR CHILDREN 6 - 8 MONTHS OLD IN TU KY DISTRICT, HAI DUONG PROVINCE

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SUMMARY OF THESIS

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Có thể tìm hiểu luận án tại:

1. National Library
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LIST OF ABBREVIATIONS

- ELISA	Enzyme-linked ImmunoSorbent Assay (Kỹ thuật miễn dịch hấp phụ gắn enzyme)
- GMC	Geometric mean concentration (nồng độ kháng thể trung bình nhân)
- HI	Hemagglutination inhibition (Kỹ thuật ngăn ngưng kết hồng cầu)
- HT	Huyết thanh
- MR	Measles Rubella (vắc xin sởi - rubella)
- MMR	Measles Mump Rubella (vắc xin sởi - quay bị - rubela)
- MVVAC	Vắc xin sởi MVVAC do POLYVAC sản xuất
- OD	Mật độ quang học
- PRNT	Plaque reduction neutralization test (Kỹ thuật trung hòa giám đám hoại tử)
- POLYVAC	Trung tâm Nghiên cứu sản xuất vắc xin và Sinh phẩm y tế
- TCMR	Tiêm chủng mở rộng
- TNLS	Thử nghiệm lâm sàng
- TL	Tỉ lệ
- TP	Thành phố
- VSDTTƯ	Vệ sinh dịch tễ Trung ương
- NCV	Nghiên cứu viên
- ICF	Phiếu tình nguyện tham gia nghiên cứu
- AE	Biến cố bất lợi
- SAE	Biến cố bất lợi nghiêm trọng
- DC	Sổ theo dõi
- CRF	Hồ sơ nghiên cứu
- WHO	World Health Organization (Tổ chức y tế thế giới)

INTRODUCTION

Measles is an acute infectious disease caused by the measles virus, with a high transmission potential, leading to large-scale outbreaks and severe manifestations, especially in young children. Despite the widespread deployment and proven safety and efficacy of the measles vaccine, measles remains a leading cause of death among vaccine-preventable diseases.

In Vietnam, the measles vaccine was introduced into the Expanded Immunization Program in 1984 and achieved a coverage rate of 90% by 1992. However, large outbreaks still occurred nationwide. In 2014 at Hai Duong province, 434 cases of measles-like fever were recorded, with 97 out of 130 samples positive with measles in all 12 districts/cities. Among them, 16.7% were children under 9 months old, who had not yet reached the age for vaccination.

Studies on measles immunology, immune responses to the measles vaccine worldwide and in Vietnam, have been conducted on various scales. However, there has been no research on immunology, safety, and immune response evaluation in children aged 6-8 months after measles vaccination in Hai Duong. To address the questions: (1) Does maternal antibody transfer provide sufficient immunity to protect children from measles up to 9 months of age? (2) If the measles vaccine schedule is adjusted earlier for children, does it ensure safety and effectiveness? We conducted the study: "Status of measles IgG antibodies in children aged 2-9 months and safety, immune response after MVVAC measles vaccination for children aged 6-8 months in Tu Ky district, Hai Duong province" with the following objectives:

1. Evaluate the status of measles IgG antibodies in children aged 2-9 months in Tu Ky district, Hai Duong province in 2016.

2. Evaluate the safety and immune response after administering one dose of MVVAC measles vaccine produced by POLYVAC to children aged 6-8 months in Tu Ky district, Hai Duong province.

The new finding of the thesis

The study evaluated the level of measles IgG antibodies in infant under 9 months old, when infant have not yet been vaccinated, showed that only 13.1% of infants had a protective IgG antibody (at the threshold of >120 mIU/ml). This result indicates that the measles antibodies from the mother to the infant are not sufficient to provide protection against measles up to 9 months old of infants, reality of an increasing number of measles cases in the infants not vaccinated.

The results of the safety and immune response assessment when administering a single dose of measles vaccine to infant under 9 months old are considered satisfactory, with no recorded instances of serious adverse events to health in the 6-8 month-old group during the study period. Regarding immune response, the percentage of protection in infant aged 6-8 months before vaccination was 7.6%, and after receiving one dose of MVVAC measles vaccine, it increased to 88.3%. The findings of this study provides additional scientific evidence for the Ministry of Health to consider recommending vaccination for children under 9 months in high-risk areas of measles.

CONTENT OF THESIS

The thesis consists of 121 pages, excluding the references and supplementary, with 22 tables, 18 charts, 3 figures, and 1 diagram. The introduction spans 3 pages, the overview covers 40 pages, the methods section is 21 pages, the results section is 28 pages, the discussion section is 23 pages, and the conclusion, recommendation sections are 2 and 1 pages, respectively.

SECTION I. OVERVIEW

1.1. Measles epidemiology

The measles virus (MeV) is member of the Paramyxoviridae family, Morbillivirus genus. The virus has a single-stranded negative-sense RNA

genome, non-segmented, approximately 16 kb in length, encoding for 6 structural proteins and 2 non-structural proteins. While there are multiple genotypes, MeV has a single antigenic type. Consequently, individuals vaccinated remain protected, and vaccines produced from different MeV genotypes, administered in various regions worldwide, are highly effective in providing protection.

Humans are the only natural reservoir of the MeV and infected individuals being the sole source of transmission. Measles is primarily transmitted through respiratory droplets, mainly via direct contact with the secretions of the throat.

1.2. The measles in the world and Vietnam

In the world, approximately 100 million people contracted measles annually, resulting in about 6 million deaths before the introduction of vaccination. In countries such as England and the United States, measles outbreaks occur in cycles of 2-3 years, with the peak usually occurring in late winter or early spring. About 95% of cases involve children, and the highest risk of mortality is observed in the age group under 1 year. In developing countries, nearly 100% of children contract measles before the age of 4, and malnutrition coupled with the loss of maternal antibodies from an early age can lead to severe complications, and even death in young children.

The measles vaccine has been developed since 1963, and widespread vaccination has reduced the incidence and mortality of measles worldwide, altering the epidemiological characteristics of the disease over the past 50 years. Globally, estimates indicate that the measles cases and deaths decreased from 100 million cases and 5.8 million deaths in 1980 to 44 million cases and 1.1 million deaths in 1995. However, measles remains the fifth leading cause of death in children under 5 among vaccine-preventable diseases. The World Health Organization (WHO) estimates 777,000 measles-related deaths globally, with 452,000 cases (52%) occurring in Africa. Regions such as Europe, the Middle

East, and the Asia-Pacific continue to report measles outbreaks, and the incidence of measles remains high in these areas.

In Vietnam, from 1979 to 1984, the incidence of measles ranged from 69.4 to 137.7 per 100,000 people. In 1985, the measles vaccine was introduced in the EPI program for infant aged 9-11 months, and by 1993, the vaccination coverage had reached and maintained over 90%. However, measles remained the ninth leading cause of death in the period from 1996 to 2000. Supplementary measles vaccination campaigns were organized, and in 2002-2003, a nationwide campaign was conducted for children aged 9 months to 10 years. After the campaign, the number of measles cases in 2004 decreased to 217 compared to 6,755 cases in 2002. The measles incidence one year after completing the nationwide campaign decreased by 39 times compared to the year before the campaign.

In the 2013-2014 outbreak, 17,000 measles cases were recorded, with outbreaks occurring in all 63 provinces/cities nationwide. Among measles cases in infant under 1 year old, the group under 9 months old accounted for 9.6% of total cases. The majority of cases (88.2%) were either not vaccinated or had an unclear vaccination history. In 2014, a series of catch-up vaccination activities, supplementary measles vaccination campaigns were strengthened, with the first dose achieving > 95% and the second dose > 90%. As a result, measles outbreaks were brought under control by the end of 2014.

1.2. Immune response to measles

1.2.1. Immune response

Immunity to measles consists of active and passive components. Passive immunity is a state of immunity not produced by the body itself. There are two types of passive immunity: natural passive immunity acquired from maternal transfer and artificial passive immunity such as the administration of measles immune serum.

Active immunity includes natural immunity when the body comes into contact with the measles virus, becomes ill, and recovers. After being infected with the measles virus, the body produces antibodies against the

virus, aiding in recovery and establishing long-term immunity. Active immunity through vaccination involves introducing a vaccine into the body to create disease-preventing immunity. Antibodies can persist for 26 to 33 years after natural measles infection, providing long-lasting protection.

Several factors influence the immune response to vaccination, including the age at vaccination, passive antibodies received from the mother, the maturity of the immune system, and the presence of immuno-compromising conditions.

1.2.2. The measles antibodies and immune response after measles vaccination

In the world and Vietnam

There is a certain proportion of pregnant women, and subsequently newborns, who lack measles antibodies. Studies indicate that several factors influencing the transfer of measles IgG antibodies from mother to child, such as the mother's history of measles or vaccination, gestational age, and birth weight. A study by Hayley A. Gans in the United States revealed that the persistence rates of measles antibodies in infants at 6, 9, and 12 months of age were 52%, 35%, and 0%, respectively. In Vietnam, the National Expanded Immunization Program in 2016 conducted a study involving 272 pregnant women, and the test results showed that only 71.7% (196 pregnant women) had sufficient antibodies to protect against measles. Further research on 196 mother-child pairs indicated that 147/196 children born were protected against measles, accounting for 75%. Children born to mothers aged ≥30 had the highest measles protection rate (90.5%), while the lowest was observed in the group born to mothers aged 18-19 (53.8%).

Immune response in children after measles vaccination

Most studies indicate that the immune response rate and antibody concentration in children vaccinated early for measles are generally lower than those in children vaccinated for measles at 9-12 months of

age. Although the immune response rate in children before the vaccination age is lower than in older children, this vaccination schedule effectively reduces the incidence and mortality rates due to measles. A study (Peter Aaby et, al.) on children aged 4.5 to 36 months showed that children receiving two doses of measles vaccine at 4.5 and 9 months of age had a mortality rate only 0.74 times that of the group of children receiving one dose of vaccine at 9 months of age.

In Vietnam, according to a study by Dang Thi Thanh Huyen involving 160 baseline serum samples from vaccinated children, only 120 samples had sufficient IgG measles antibodies for protection. After vaccination for this group, 100% of the children had protective antibodies after 1 month. A study on immune response after the first dose of AIK-C measles vaccine produced in Vietnam: 154 children vaccinated with Measles I, 118 children with Measles II from POLYVAC, and 128 children with a control vaccine (Rouvac). Serum samples were taken before and after vaccination, using ELISA asay. All children had negative serum before vaccination. After vaccination, the conversion rate (>4 times) of serum samples for Polyvac I, Polyvac II, and Rouvac vaccines were 100%, 100%, and 94.7%, respectively.

1.2.3. Laboratory diagnosis methods

The laboratory methods to diagnosed MeV include serological assays to identify specific antibodies, molecular biology (RT-PCR, realtime RT-PCR, RT-LAMP) to detect genetic of MeV and virus isolation assay.

1.3. The measles vaccines and vaccination schedules worldwide and in Vietnam

Measles vaccines currently used worldwide are live attenuated vaccines that have been developed since 1965. The majority of these vaccines are produced from the Edmonston A or B strains. Clinical trials of measles vaccine strains AIK-C, Edmonston-Zagreb, Leningrad-16, and Schwartz were conducted on 1,202 infants at 6 months and 1,250 infants at 9 months in Tashkent, Uzbekistan. The results showed no

severe reactions within 6 weeks after vaccination, and the reaction rate after vaccination, such as fever, rash, conjunctivitis, and mild sore throat, was low (6-14). No deaths occurred in the study population one year after vaccination. In Vietnam, clinical trials of the MVVAC vaccine producted by POLYVAC in Phases I and III met safety requirements in adults and infants aged 9-11 months. The seroconversion rate (log2 ≥ 2 EIA units) after vaccination reached 100.0%. The MVVAC vaccine has been used in Vietnam's expanded immunization program for over 10 years and has been noted safety.

1.3.3. The measles vaccine use in worldwide and Vietnam

In the updated 2021 WHO recommendations on routine immunization, children should receive at least two doses of measles-containing vaccines. In countries with measles transmission, the first dose of measles vaccine is administered to children from 9 months of age. The second dose is recommended at the age of 15 - 18 months. WHO advises administering the measles vaccine to children under 9 months of age as a supplementary dose in response to one of the following epidemiological factors: emergency vaccination during an outbreak, supplementary measles vaccine in high-risk areas, children traveling to countries with measles outbreaks, or exposure or confirmed diagnosis of HIV infection.

SECTION II. RESEARCH METHEDOLOGY

2.1. Methedology for objective 1:

2.1.1. Study population: Healthy children aged 2 to 9 months, meeting all the research criteria.

2.1.2. Location: Tu Ky district, Hai Duong province

2.1.3. Time of study: The study period is from August 2015 to April 2016.

2.1.4. Definitions and concepts

IgG antibody concentration: the quantitative value of IgG measles antibody, measured in international units per milliliter (IU/ml).

Geometric mean concentration (GMC): The GMC of antibody from serum samples calculated using the formula:

$$GMC = \sqrt[n]{x_1.x_2 \dots x_n}$$

2.1.5. Study design

The study is a cross-sectional descriptive design.

2.1.6. Sample size and Sampling method

- Sample size: Applying the formula for estimating the minimum sample size based on the proportion in the population, after calculation and rounding, the sample size is 400, evenly distributed among 8 groups, from the 2-month to the 9-month age groups.

- Sampling method: Based on the immunization record book, the required number of children for each age group was randomly selected.

2.1.7. Collecting, Preserving, and Transporting Samples

In accordance of Serum specified in no. 43/2011/BYT dated December 5, 2011, by the Ministry of Health.

2.1.8. IgG antibody testing

Indirect ELISA assay using Enzygnost® Anti-Measles Virus/IgG reagents, conducted at the Respiratory Virus Laboratory, National Institute of Hygiene and Epidemiology according to standard technical procedures.

2.1.9. Variables and indices in the study

Age, gender, quantitative measurement of measles antibody concentration *(mIU/ml).*

2.2. Methedology for objective 2:

2.2.1. Study population: Healthy children aged 6 to 8 months, meeting all the research criteria.

2.2.2. Location: Tu Ky district, Hai Duong province

2.2.3. Definitions and concepts

- Measles vaccine dose 0: Children receive one dose of measles vaccine before 9 months of age.

- Measles vaccine dose 1: Children receive the first dose of measles vaccine at 9 months of age.
- Protective antibody concentration: > 120 mIU/ml.
- Serum conversion: Serum sample 2 has an antibody efficacy at least 4 times higher than the initial value in serum sample 1, or serum sample 1 is negative and becomes positive in serum sample 2

2.2.4. Study design

Employing a cross-sectional, open-label, non-controlled design (according to Decision no. 2292/QD-BYT assigned by the Ministry of Health).

2.2.5. Sample size and Sampling method

- Sample size: The sample size is 210 children divided into 03 groups (6 months, 7 months, 8 months), with each group consisting of 70 children.

- Sampling Method: Simple random sampling.

2.2.6. Methodology

- Subject recruitment examination

Communication about participation in the study, signing the ICF. Screening health examination to select subjects until each age group reaches the required 70 children. Health examination, evaluation of selection according to the study criteria, blood collection 1, and administration of the research vaccine. After 30 - 35 days of the first examination, blood collection 2.

- Subject management process

Communication, counseling for the parents/legal guardians of the study subjects about the content, purpose, and benefits of the study. Implementation of the subject selection examination according to the criteria. Purchase insurance to ensure the rights and benefits of the study subjects in case of adverse events.

2.2.7. Vaccine used in the study

Measles vaccine (MVVAC), live attenuated, freeze-dried, produced by POLYVAC.

2.2.8. Detection and quantification of IgG antibodies

The neutralization assay is used to detect and quantify measles-specific IgG antibodies in serum samples.

2.2.9. Evaluation indices

a) Safety evaluation indices

- *Adverse events are classified into the following levels:*

+ Normal (0): No signs or symptoms.

+ Mild (1): Occurs but the subject can easily tolerate, causing minor discomfort and not affecting daily activities.

+ Moderate (2): Causes discomfort and affects daily activities.

+ Severe (3): Occurs and hinders normal daily activities (e.g., not going to work/school and requires treatment for these adverse events).

+ Life-threatening (4): Requires emergency room or hospitalization.

- Serious Adverse Event (SAE): Any unexpected medical event occurring after vaccination that leads to the following incidents:

+ Resulting in death
+ Threatening life
+ Leading to substantial disability/loss of major function
+ Prolonging hospitalization
+ Resulting in a congenital anomaly/birth defect

b) Immunogenicity evaluation indices

- Measles-specific IgG antibody before measles vaccine dose 0: Serum antibody concentration 1, proportion of serum samples with protective antibodies, proportion of serum samples without protective antibodies, geometric mean antibody concentration (GMT).

- Measles-specific IgG antibody response after measles vaccine dose 0 with MVVAC measles vaccine: Serum antibody concentration 2 (HT2), proportion of HT2 with protective antibodies, proportion of HT2 without

protective antibodies, GMT, proportion of serum conversion samples (antibody concentration increased > 4 times).

2.3. Data analysis

The data are entered, cleaned, and processed using specialized software. Statistical tests such as χ^2, Fisher's exact test are used to assess the difference in proportions, and the Mann-Whitney test is used to assess the difference in GMT between characteristic groups.

2.4. Measures to Limit Errors

The research staff is trained in monitoring, sampling, and vaccine administration. The data collection is objective and honest. Diagnostic specimens comply with WHO recommendations.

2.5. Ethics in study

This study has been approved by the Institutional Review Board In Biomedical Research, National Institute of Hygiene and Epidemiology and the Evaluation Board for Biomedical Research Ethics, Ministry of Health before implementation.

SECTION 3. RESULTS

3.1. Measles IgG Antibodies in Children Aged 2-9 in Tu Ky District, Hai Duong Province

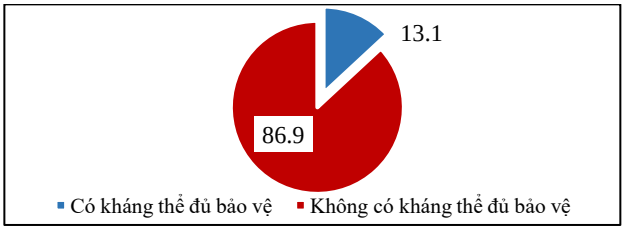


Chart 3.1. The rate of children with protective measles IgG antibodies (n=405)

Only 13.1% (53 samples) had a sufficient protective concentration of measles IgG antibodies at the threshold of >120mIU/ml (protected).

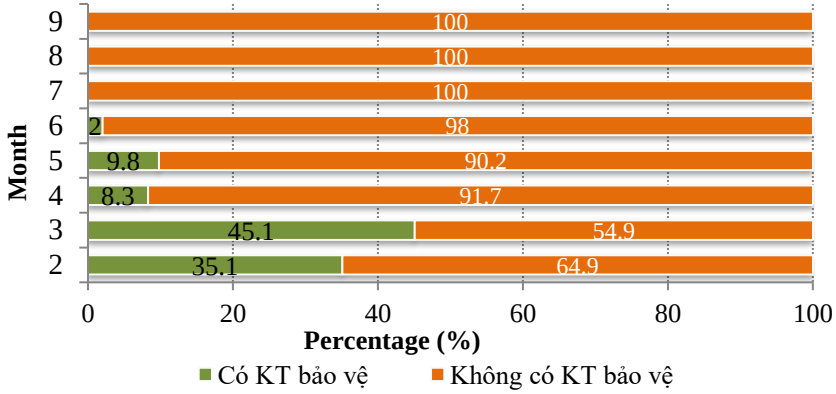


Chart 3.2. The rate of children with protective measles IgG antibodies following age group

The 3-month-old group had the highest protection rate (45.1%), followed by the 2-month-old group (35.1%). The protection rate in the 4-month-old group was 8.3%, 5-month-old group was 9.8%, and 6-month-old group was 20%. None of the children aged 7-9 months were protected.

Table 3.5. Proportion of children with anti-measles IgG antibodies according to gestational age

Gestational age	Protected		Non-protected		Total	
	Number	Percent (%)	Number	Percent (%)	Number	Percent (%)
< 37 weeks	0	0	11	83.3	11	100
≥ 37 weeks	53	13.5	341	87.3	394	100
Total	53	13.1	352	86.9	405	100
OR=0.6 (0.02-3.5), p=0.51 (Fisher)						

There were 11 child born before 37 weeks of gestation, all of whom did not have sufficient protective antibodies. The group born at or after 37 weeks of gestation had a protection rate of 13.5%. However, the difference in the protection rate between the two groups was not significant with p>0.05.

Table 3.6. The rate of children with specific IgG antibodies according to maternal age groups

Maternal age group	Protected		Non-protected		Total		OR (95%CI)
	Count	%	Count	%	Count	%	
17 - 19 years old	0	-	12	100.0	12	100	-
20 - 24 years old	12	11.8	90	88.2	102	100	1.0
25 - 29 years old	25	14.9	143	85.1	168	100	0.8 (0.4 – 1.6)
≥30 years old	16	13.0	107	87.0	123	100	0.9 (0.4 – 2.0)
Cộng	**53**	**13.1**	**352**	**86.9**	**405**	**100**	

Among the 404 mothers with available age information, the average maternal age was 27.6 years. The youngest mother was 17 years old, while the oldest was 44 years old. Of the 12 children with mothers aged 17-19, none of them were protected.

Table 3.7. The rate of children with specific IgG antibodies according to the maternal history of measles

Maternal history of measles	Protected		Non-protected		Total	
	Count	%	Count	%	Count	%
Yes	18	22.8	61	77.2	79	100
No	35	10.7	291	89.3	326	100
Total	53	13.1	352	86.9	405	100
OR=2.5 (95%CI: 1.3-4.6); p=0.004 (χ^2)						

The protected children in the group of mothers with a history of measles (22.8%) was 2.5 times higher than the group of mothers without a history of measles (10.7%).

Bảng 3.8. The rate of children with specific IgG antibodies according to the maternal history of measles vaccination

maternal history of measles vaccination	Protected		Non-protected		Total	
	Count	%	Count	%	Count	%
Yes	7	11.5	54	88.5	61	100
No	28	10.6	237	89.4	265	100
Total	35	10.7	291	89.3	326	100
OR=1.1 (95%CI: 0.5-2.6); p=0.8 (χ^2)						

The protected children in the group with mothers who have received measles vaccination was 11.5%, higher than the group with mothers who have never received measles vaccination (10.6%).

3.1.2. The measles-specific IgG antibodies concentration in children aged 2 - 9 months

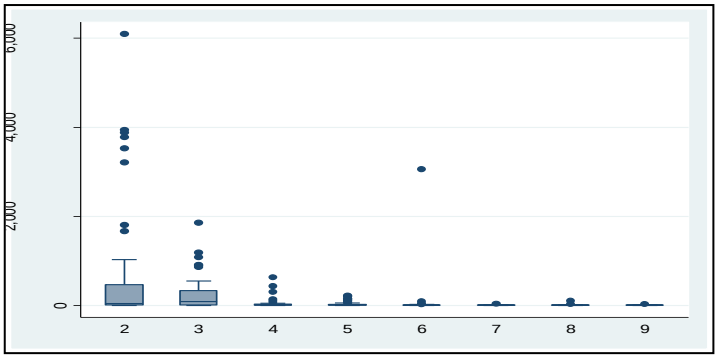


Chart 3.4. Distribution of IgG measles antibody concentration

The antibody concentration in 2-month-old children ranged from 1 to 6,096.1 mIU/ml, covering the entire study sample. As children grow older, antibody concentrations tended to cluster around the value of 0, with a decreasing fluctuation amplitude. The highest antibody concentration each group decreased with age.

Table 3.9. GMC of measles-specific IgG antibodies in children aged 2-9 months

Factor	Count	GMC (95%CI) (mIU/ml)	p
Mother had measles			
- No	326	15.3 (13.0 - 18.1)	0.11
- Yes	79	30.1 (18.7 - 48.6)	
Mother had measles vaccination			0.50
- No	326	17.1 (14.2 - 20.7)	
- Yes	79	18.7 (13.3 - 26.4)	
Preterm birth			
- Yes	11	8.6 (3.8 - 19.2)	0.26
- No	394	17.8 (15.1 - 21.1)	

Children age				
-	2 months	394	17.8 (15.1 - 21.1)	**0.0001***
-	3-5 months	11	8.6 (3.8 - 19.2)	
-	6-9 months	11	8.6 (3.8 - 19.2)	
Gender				
-	Male	213	17.6 (14.3 - 21.8)	0.59
-	Female	192	17.3 (13.4 - 22.3)	
Does the child breastfeed?				
-	No	326	21.7 (8.3 - 56.7)	0.98
-	Yes	79	17.3 (14.7 - 20.5)	
Is the child still breastfeeding?				
-	No	3	6.9 (0.1 - 636.6)	0.41
-	Yes	389	17.5 (14.8 - 20.7)	

Table 3.9 showed that the group with mothers who had measles previously, had a GMC of 30.1 (18.7-48.6) mIU/ml, higher than the group with mothers who have never had measles, with a GMC of 15.3 (13.0-18.1) mIU/ml. The GMC of mothers received measles vaccination was higher than the mothers not been vaccinated group. The preterm birth group had a lower GMC than the full-term group. The GMCs of breastfeeding group and the partially breastfeeding group were higher than the non-breastfeeding group and the no longer breastfeeding group, respectively.

3.2. Safety and immune response of MVVAC measles vaccination after a single dose for children aged 6 - 8 months

3.2.1. Assessment of the MVVAC measles vaccine safety for children aged 06 - 08 months.

Adverse events within 30 minutes after receiving the MVVAC measles vaccine dose 0

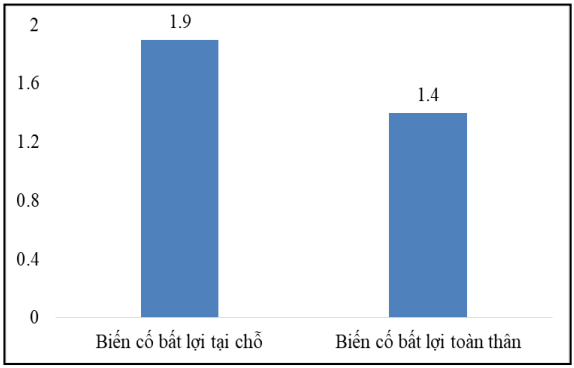


Chart 3.5. Local adverse events in children within 30 minutes after receiving the MVVAC measles vaccine dose 0 (n=210)

Four cases of children (1.9%) were observed with mild redness at the injection site, and there were three cases (1.4%) with mild fever. No systemic adverse events were recorded. The study also did not observe any local reaction signs from day 1-7 and 8-30 after vaccination.

Adverse events after MVVAC measles vaccination

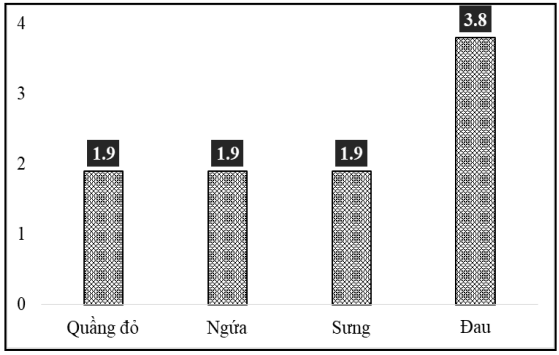


Chart 3.6. Local adverse events in children within the first 7 days after receiving the MVVAC measles vaccine dose 0 (n=210)

4 cases (1.9%) of children were observed with mild redness at the injection site on the first day after vaccination, and 4 cases (1.9%) experienced simultaneous swelling and pain at the injection site. No adverse systemic events of severity 2, 3, or 4 were recorded.

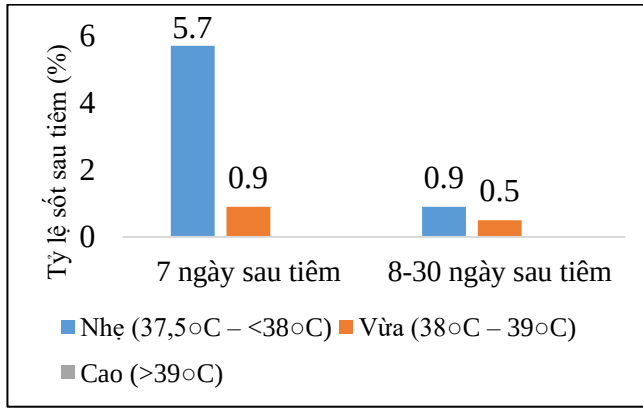


Chart 3.7: The fever rate in children within the first 7 days after receiving the MVVAC measles vaccine dose 0 (n=210)

Recorded 14 cases (6.6%) of children with fever, including 12 cases (5.7%) with mild fever ranging from 37.5 - 38.0°C and 2 cases (0.9%) with moderate fever ranging from 38.0°C - 39.0°C.

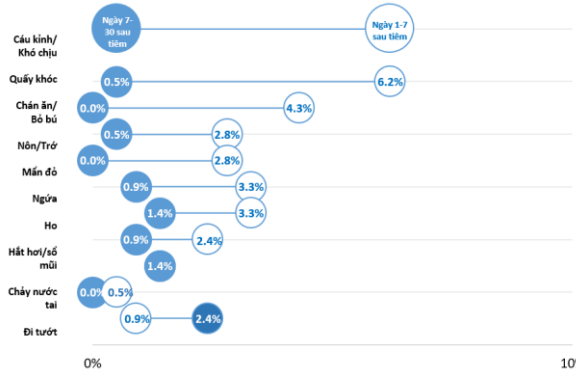


Chart 3.8. Systemic adverse events in children within 7 days and from 7 - 30 days after receiving MVVAC vaccine dose 0

The rate of adverse events within the first 7 days ranged from 0.5 - 6.2. All were recorded as mild, usually lasting from 1 - 3 days. There were no serious adverse events.

Table 3.11: Summarizing other adverse events in children within 30 days after receiving the MVVAC measles vaccine (n=210)

Systemic adverse events	Level 1 (low)	Level 2 (mid)	Level 3 (severity)	Level 4 (serious)
Anticipated local adverse events				
Areola	8 (3.8%)	0	0	0
Painful	8 (3.8%)	0	0	0
Itchy	4 (1.9%)	0	0	0
Swelling	4 (1.9%)	0	0	0
Anticipated systemic adverse events				
Irritability/irritation	14 (6.7%)	0	0	0
Lethargic	0	0	0	0
Crying	9 (4.3%)	0	0	0
Loss of appetite/stop breastfeeding	7 (3.3%)	0	0	0
Reflux/vomiting	6 (2.9%)	0	0	0
Redness	9 (4.3%)	0	0	0
Itchy	9 (4.3%)	0	0	0
Biến cố bất lợi toàn thân ngoài dự kiến				
Cough. sore throat	7 (3.3%)	0	0	0
Sneezing, runny nose	6 (2.9%)	0	0	0
Ear discharge	1 (0.5%)	0	0	0
Diarrhea	7 (3.3%)	0	0	0

Serious adverse events

There were no serious adverse events leading to incidents such as death, life-threatening, or prolonged hospitalization.

3.2.2. Evaluation of the MVVAC measles vaccine immunogenicity

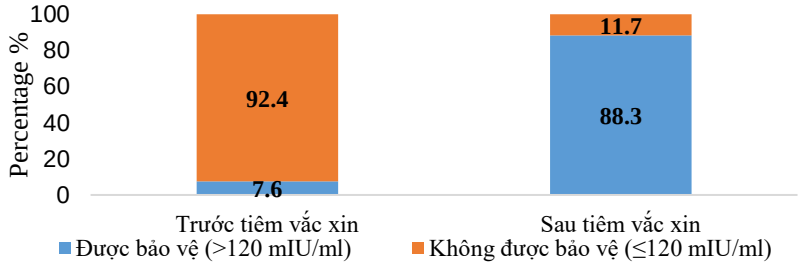


Chart 3.9. The rate of protected children before and after measles vaccination

Before vaccination, only 7.6% (16 children) had a sufficient neutralizing antibody concentration for measles protection. One month after vaccination, the rate of protected children increased by 11.6 times compared to before vaccination.

Table 3.13: The rate of protected children by age before vaccination (n=210)

Month of age measles vaccine dose 0	**Protected antibody**		**Non-protected antibody**		**Cộng**	
	Count	%	Count	%	Count	%
6 months	7	10.1	62	89.9	69	100
7 months	3	4.2	68	95.8	71	100
8 months	6	8.6	64	91.4	70	100
Total	**16**	7.6	**194**	**92.4**	**210**	**100**
p = 0.39 (χ^2)						

The rate of children aged 6-8 months with sufficient protective antibodies before receiving the measles vaccine dose 0 was 7.6%.

Table 3.15. The seroconversion after MVVAC measles vaccination dose 0 (n=196)

Seroconversion	**Frequency**	**%**
Seroconversion		
- Negative to positive	123	62.8
- GMC increased ≥ 4 times	50	25.5
No seroconversion	23	11.7
Total	**196**	**100**

Recorded 173/196 children (88.3%) with seroconversion, among them 123/210 children (62.8%) seroconverted from negative to positive, and 50/210 children had a measles neutralizing antibody concentration increased by 4 times or more.

Table 3.16. The seroconversion after MVVAC measles vaccination dose 0 following the gender and seroprotection in serum 1 (n=196)

Variables	**seroconversion (n,%)**	**No seroconversion (n,%)**	**OR (95%CI)**
Gender			
- Female (n=102)	93 (91.2%)	9 (8.8%)	1.0

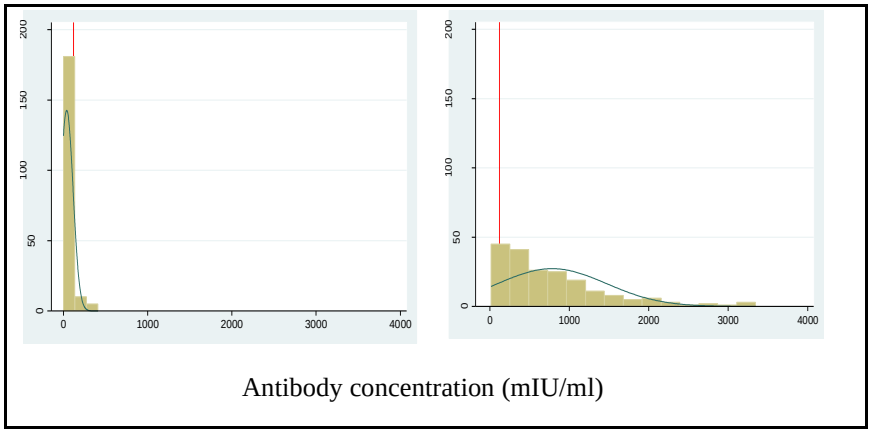
- Male (n=94)	80 (85.11%)	14 (14.89%)	0.55 (0.23-1.35)
seroprotection in serum 1			
- No (180)	164 (91.1%)	16 (8.9%)	1.0
- Yes (n=16)	9 (56.3%)	7** (43.7%)	0.13 (0.04-0.4)*
Total	**173 (88.3%)**	**23 (11.7%)**	

The seroconversion was observed in both genders after the administration of the measles vaccine dose 0.

Table 3.17. The antibody geometric mean titer (GMT) before and after administration of the MVVAC measles vaccine dose 0 (n=196)

Indicators	Before vaccination	After vaccination
The antibody geometric mean titer - GMT (mIU/ml)	75.2	511.1
Confidence interval (95%CI) of GMT (mIU/ml)	62.3 - 90.8	441.9 - 591.2
p = 0.0001 (Wilcoxon signed-rank test)		

The comparing antibody titers in 196 serum pairs showed that the GMT of antibodies after receiving the MVVAC measles vaccine dose 0 (75.2 (95% CI: 62.3 - 90.76) mIU/ml) increased 6.8 times, compared to before vaccination (511.1 (95% CI: 441.91-591.15) mIU/ml). This difference was significant with p < 0.001.



a) Before vaccination dose 0 (n=196) *b) After vaccination dose 0 (n=196)*

Chart 3.13. Distribution of neutralizing antibody concentrations before and after MVVAC measles vaccination dose 0 (n=196)

Before the measles vaccine dose 0 administration, the distribution of neutralizing antibody concentrations tended to skew left and be sharp. After receiving dose 0, the distribution of antibody concentrations tended to be less skewed to the right and less sharp. The frequency of samples with low antibody concentrations was decreased, conversely the frequency of samples with high neutralizing concentrations was increased ($p<0.05$, Skewness-Kurtosis test).

SECTION 4. DISCUSSION

4.1. The measles IgG antibodies in children aged 2-9 months in Tu Ky district, Hai Duong province.

The rate of measles IgG antibodies in children aged 2-9 months: The results showed that only 13.1% of children aged 2-9 months had measles IgG antibodies with a protective titer. This rate is lower than the Nguyen Thi Minh Hang's study (2013-2014) in cohort of children under 1 year old, which age of many children not yet vaccinated due to not reaching the vaccination age. However, this result is concordance to a study in Uganda. The 4-6 month age group has a low protection rate of 16%, and the remaining 84% of children have serum concentrations below the protective threshold.

In children aged 2-9 months with protective antibodies in Tu Ky district, Hai Duong province, the rate in females (15.6%) is higher than males (10.8%). In the study, all 8/8 malnourished children did not have protective antibodies. All preterm children did not have protective antibodies. The Susana Scott and colleagues research affirm that preterm children have a lower measles IgG antibody concentration below the protective threshold (14.7%), which is 1.96 times higher than the full-term group (7%). It is observed that the rate of children born to mothers

aged 25 and older with protective antibodies is higher than the group with mothers aged 20-24. The study has indicated that most mothers aged 25 and older were born during a period of low vaccination rates, and measles was circulating, so many mothers may have had measles and developed natural measles antibodies after contracting the disease.

Antibody concentration by age: At different ages, antibody concentrations is vary. The older the child, the lower the GMC value. It is noted that the GMC value in breastfed children is lower than in non-breastfed children, although the difference is not statistically significant.

Antibody concentration based on vaccination history and maternal measles: The group with mothers who had measles, had a significantly higher GMC than the group with mothers who had never had measles. The Jenks P. J., Caul E.O., and colleagues study also revealed that children with mothers who had measles had higher antibody concentrations than children whose mothers had been vaccinated.

4.2. Safety of children aged 6-8 months after receiving the MVVAC measles vaccine in Tu Ky district, Hai Duong province

The adverse events rate within 30 minutes in this study is lower than the results of the measles-rubella (MR) vaccine TNLS in children aged 1-14 in Ha Nam province produced by the Serum Institute of India (SII). Systemic reactions: the fever rate is 4.4%, irritability/crying 0.7% in the group of children ≤ 5 years old; rash 0.7%; itching 0.7%. AIK-C is currently considered the safest strain among those producing measles vaccines. No serious adverse events were recorded within 30 minutes after vaccination.

Adverse events within 7 days after vaccination

14 cases (6.6%) of fever were recorded, of which 12 cases (5.7%) were mild ranging from 37.5 - 38.0°C, and 2 cases (0.9%) were moderate ranging from 38.0°C - 39.0°C. Fever mostly occurred from day 1 to day 3 and lasted for 1-2 days. The fever rate within the first 7 days in this study

(6.6%) is lower than the results of the MR vaccine TNLS in Hà Nam province for children aged 1-14 produced by the Serum Institute of India.

Adverse events recorded include: irritability/discomfort, crying, loss of appetite/refusal to breastfeed, vomiting, regurgitation, itching, redness, cough, sneezing, runny nose, diarrhea. The adverse events rate within 7 days ranged from 0.5% - 6.2%, which is higher than the results of the MR vaccine TNLS for children aged 1-14 in Ha Nam province produced by the Serum Institute of India. No serious adverse events were recorded within 7 days after vaccination.

Adverse events within 8 - 30 days after vaccination

The rate of events during the 8 - 30 day period is low. Symptoms such as drowsiness, crying, vomiting were not recorded during this period. Some events requiring medication, such as cough, sneezing, or itching, were reported; however, the rate of spontaneous recovery in children was high, and all events were recorded as mild. No serious adverse events were reported. This result is consistent with the MVVAC vaccine TNLS results from Polyvac for the group of children aged 9-11 months.

Serious adverse events: No serious adverse events were recorded within 30 days after vaccination.

4.3. Evaluation of the immunogenicity after receiving the MVVAC measles vaccine

Immune status against measles in children aged 6-8 months before receiving the MVVAC measles vaccine (serum 1):

Among the 210 serum samples of children, only 16 samples had sufficient neutralizing antibodies against measles (protected), accounting for 7.6%. The remaining children lacked neutralizing antibodies against measles, constituting 92.4% (194 samples). This rate is higher than the study conducted by the Military Medical Academy in children aged 9-11 months (3.3%), possibly due to a gradual decline in immune antibodies transmitted from mothers in children aged 9-11 months compared to those aged 6-8 months..

The GMC before receiving the MVVAC measles vaccine (dose 0) in children aged 6-8 months in this study was 71.6 (95% CI: 58.1 - 88.3) mIU/ml, higher than the clinical trial results by author Hayley A. Gans in the United States, but lower than the research by author Nkrumah F.K in Ghana. In the US, the GMC in 6-month-old children before receiving the measles vaccine (dose 0) was 10 (95% CI: 4 - 26) mIU/ml, and in Ghana, it was 129.6 mIU/ml.

Immune response to measles in children aged 6-8 months after receiving the MVVAC vaccine (serum 2)

The proportion of children aged 6-8 months, who were protected after receiving the MVVAC measles vaccine dose 0 (88.3%), was 11.6 times higher than before vaccination (7.6%). In the group of non-protected children before vaccination, 87.2% of them were protected against measles after receiving the MVVAC measles vaccine. All children who were protected against measles before receiving dose 0 continued to be protected. The proportion of protected children after receiving the MVVAC measles vaccine dose 0 is higher than the clinical trial conducted by Hayley A. Gans (United States) in 6-month-old children (65%).

It was observed that 173/196 children (88.3%) had seroconversion, including 123/210 children (62.8%) converted from negative to positive, and 50/210 children had a fourfold or more increase in neutralizing antibody titers against measles (25.5%). The remaining 23/210 children (11.7%) did not show seroconversion. The seroconversion rate in children aged 6-8 months after receiving dose 0 in this study is higher than the clinical trial conducted by Hayley A. Gans.

CONCLUSION

1. Anti-measles IgG antibodies in children 2 - 9 months in Tu Ky district, Hai Duong province.

- Only 13.1% of children had a protective IgG measles antibody titer above 120 mIU/ml. The highest protection rate was observed in the 2-

month-old group (35.1%), while the lowest was in the 6-9 month-old group (0.5%). All children aged 7-9 months (100%) were not protected.

- The group of children whose mothers had a history of measles showed a protection rate of 22.8%, which was 2.5 times higher (95% OR: 1.3 - 4.6) compared to the group of mothers without a history of measles and no measles vaccination (10.6%; 15.3 mIU/ml; $p<0.05$).

- The group of children whose mothers had a history of measles, had a GMC of 30.1 (95% CI: 18.7 - 48.6) mIU/ml, which was higher than the group with mothers who had no history of measles and no measles vaccination, with a GMC of 15.3 (95% CI: 13.0-18.1) mIU/ml; $p<0.05$.

2. Safety and Immune response after a single dose of MVVAC measles vaccine manufactured by POLYVAC for children aged 6-8 months in Tu Ky district, Hai Duong province.

Administering a single dose of MVVAC measles vaccine to children aged 6-8 months is observed to be safe:

No serious health-related events were recorded in the group of children aged 6-8 months during the study.

Local adverse events were mild or moderate: 3.8% of children experienced redness at the injection site, and 1.9% had itching and swelling simultaneously.

Systemic adverse events were mild to moderate:

- The fever rate within 30 days after vaccination was 9.0%, with a duration not exceeding 3 days, and 70% resolved spontaneously.

- The rates of irritability/discomfort were 6.7%, crying 4.3%, and feeding refusal 3.3%. All these symptoms were mild.

- Itching and redness occurred in 4.3%, hoarseness in 3.3%, sneezing in 2.9%, runny nose in 3.3%, and diarrhea in 3.3% of children.

Immune response:

- The protection rate before vaccination was 7.6%. The protection rate after MVVAC measles vaccine at month 0 increased to 88.3% (95% CI: 97.2 - 100).

- The geometric mean titer of neutralizing antibodies after MVVAC measles vaccine increased by 6.8 times compared to before vaccination, from 75.2 (95% CI: 62.3 - 90.8) mIU/ml to 511.1 (95% CI: 441.9 - 591.2) mIU/ml.

- The seroconversion rate after MVVAC measles vaccine in children aged 6-8 months was 88.3%.

RECOMMENDATIONS

1. The Ministry of Health should consider approving a single-dose measles vaccination schedule for children aged 6-8 months in high-risk areas
2. The National Expanded Immunization Program continues to research the measles vaccination schedule for children to effectively prevent, moving towards the goal of measles elimination in Vietnam
3. Further studies are neccesory on the persistence of measles immunity in older children after completing the measles vaccine series and vaccinating women of childbearing age before pregnancy.

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