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Immunogenicity of the AIK-C measles vaccine in infants aged <9 months in Vietnam

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ABSTRACT

Measles-associated deaths have been reported in infants <9 months during outbreaks. A cohort study was conducted on 210 infants aged 6–8 months to evaluate the immunogenicity and safety of the AIK-C measles vaccine containing $10^{4.21}$ plaque-forming units (PFU)/0.5 mL produced in Vietnam. Paired serum samples were obtained from 196 subjects. Seropositivity was defined as ≥120 mIU/mL. The seroresponse rate was 173/196 (88.27%, 95% confidence interval (CI): 83.77–92.77%) with geometric mean titer (GMT) of 511 mIU/mL (95% CI: 688–880 mIU/mL), and no significant differences were observed by different age groups. Among 196 paired sera, they were categorized into four groups: 122 subjects <14 IU/mL, 28 subjects 14–<60 mIU/mL, 30 subjects 60–<120 mIU/mL, and 16 subjects ≥ 120 mIU/mL. The seroresponse rate was 112/122 (91.8%, 95% CI: 86.94–96.67%) with GMT (597 mIU/mL, 95% CI: 749–1002 mIU/mL) in the <14 mIU/L group. In the 14–<60 mIU/mL group, the seroresponse rate was 18/28 (64.29%) with 184 mIU/L of GMT and was significantly lower ($p < 0.01$) than that in the <14 mIU/mL group. In the 16 seropositive group, all subjects showed seroconversion (4-fold higher than before) with a higher GMT of 1078 mIU/mL. Local pain and itching at the injection site were observed in 8 subjects (3.8%) within 7 days of the vaccination. Regarding systemic adverse reactions, febrile illness ≥37.5 °C was observed in 14 subjects (6.7%). These results indicate that the AIK-C measles vaccine is effective and safe for infants aged 6–8 months and will contribute to reducing the number of measles-associated deaths in future outbreaks.

1. Introduction

Measles is a highly contagious, life-threatening, and serious viral infectious disease. Most patients recover spontaneously within one week, developing serum-specific antibodies and cell-mediated immunity. The measles virus infects lymphocytes, macrophages, and antigen-presenting immunological cells, resulting in transient immune suppression and concomitant bacterial or other viral infections [1]. It was a leading cause of infant deaths and, thus, effective attenuated live vaccines were developed in the late 1960s. The World Health Organization (WHO) launched the Expanded Programme on Immunization (EPI), particularly against measles. Measles vaccine coverage was initially less than 20% but has now increased to approximately 85% worldwide [2]. The number of measles-associated deaths decreased to 110,000 in 2017. All six WHO regions claimed the goal of measles elimination by 2020, and two regions also set the goal of rubella elimination by the same year, with the expansion of the two-dose schedule of the measles-rubella combined vaccination [3]. Several countries in the WHO Western Pacific Region (WPR) implemented the two-dose immunization of the measles-containing vaccine: the first dose at 9 months and the second dose at 18 months or older [4]. However, measles outbreaks have been reported in several countries, mainly affecting unvaccinated infants, adolescents, and young adults [5].

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It is crucial to protect infants <9 months from measles infections and related deaths, and many clinical trials were conducted on this age group in highly endemic countries, mainly Africa, in the 1980–1990s [6–8]. The protective serological responses that occur after vaccination with measles vaccines were previously shown to be influenced by the presence of maternally conferred immunity as well as the vaccine strains and dosages used in clinical trials [9]. The high-titer Edmonston-Zagreb measles vaccine with a titer of more than $10^{4.7}$ plaque-forming units (PFU) was used in several countries. However, an adjusted higher mortality ratio was reported among females immunized with the high-titer Edmonston-Zagreb vaccine in Guinea-Bissau and Senegal: 1.86 for females and 0.91 for males [10,11]. Aaby et al. [12] summarized the findings of 9 clinical trials, and three conducted in Guinea-Bissau, Senegal, and Haiti showed an increased incidence of female mortality after the administration of the high titer Edmonston-Zagreb vaccine. Therefore, the WHO working group no longer recommends high-titer measles vaccines for use in immunization programs [13]. The reason for the increased mortality rate was attributed to transient immunosuppression by a measles vaccine component. A later study reported that high mortality in females immunized with high dose measles vaccines was noted with subsequent immunization with the pertussis combined with diphtheria and tetanus toxoid vaccine (DPT) [14].

Since 2006, a two-dose strategy of measles immunization has been implemented in Vietnam at the age of 9–11 and 18 months. Despite improved vaccination coverage, the rapid resurgence of measles was observed in 2005–2010 [15,16]. A measles outbreak occurred in 2014 in Vietnam and 16,606 laboratory confirmed cases were reported among approximately 60,000 suspected cases [17,18]. Most of these cases were unvaccinated children younger than 5 years and infants aged 7–8 months who had not yet reached the age of vaccination and were complicated by bacterial or viral pneumonia possibly related to transient immunosuppression caused by measles [19]. In the present study, a cohort study was conducted on healthy 6–8-month-old infants to assess the immunogenicity and safety of the AIK-C strain vaccine produced in Vietnam.

2. Materials and methods

2.1. Study design

In our preliminary serological surveillance in Tu Ky district, Hai Duong City, Vietnam, 86.9% of subjects aged 6–8 months were seronegative for the measles virus in 2015, indicating that this age population will be susceptible to measles in the next outbreak. Therefore, an observational cohort study was conducted between March and December 2017 in Tu Ky district, targeting infants aged 6–8 months.

The acute vaccine adverse event of allergic reactions was monitored for 30 min after immunization, and the occurrence of local reactions was checked in a diary of individual health cards. Solicited adverse events were also checked every day for 30 days: local adverse events (redness, pain, itching, and swelling) and systemic adverse events (fever, irritability, crying, and measles-like eruptions). These events were confirmed by commune health staff members visiting the homes of vaccinated infants every day during the first 7 days and then once a week until the second visit. Individual health cards were collected and confirmed by investigators. The study design and clinical trial were approved by the Ethics Committee of Vietnam.

2.2. Subjects

A total of 262 inhabitants aged 6–8 months were recruited when they visited the regional health centers for health check and approached by health workers to explain the protocol, purpose, and significance of the study. Fifty-two infants were excluded due to health reasons, not providing consent, or for other reasons; therefore, 210 infants were ultimately enrolled with written informed consent by their parents or legal guardians. Inclusion criteria were as follows: healthy infants aged 6–8 months, living in Tu Ky district, free of infectious diseases, no history of measles vaccination, no immunosuppressive conditions, and no medical treatment with blood products.

2.3. Vaccine

Subjects were immunized subcutaneously with the standard potency measles AIK-C vaccine containing $10^{4.21}$ PFU/0.5 mL, produced by POLYVAC (MVVAC, Lot No. M-1116). The AIK-C strain was technically transferred from Kitasato Institute, Japan, and was licensed in 2010 in Vietnam [20].

2.4. Serological assay

Serum samples were obtained immediately before and 30–35 days after immunization. Peripheral blood was obtained through venipuncture, and serum samples were separated in the laboratory of the Provincial Preventive Medicine Center and then transported to the National Institute of Hygiene and Epidemiology (NIHE) in cold ice boxes at 4–8 °C. They were stocked at −20 °C until assayed.

Serum samples were inactivated at 56 °C for 30 min. Two-fold serial dilutions were mixed with the challenge virus (AIK-C) containing 100 PFU at 37 °C for 1 h. The mixture was placed on a monolayer of Vero cells in a 96-well plate. The plaque reduction neutralization (PRNT) antibody was calculated as 50% reduction. PRNT titers were calculated using the WHO reference serum 3rd version (cat. No: 97/648). The WHO working group reported that the protective level is estimated to be 120 mIU/ml of PRNT against the measles virus [21].

2.5. Statistical analysis

Measles PRNT was defined by referring to WHO reference serum and the lowest detection limit was 14 mIU/mL. PRNT < 14 mIU/mL was assumed to be 7 mIU/mL and geometrical mean titers (GMT) were calculated. The seroresponse rate was defined as a seropositive rate ≥120 mIU/mL and the 95% confidence interval (CI) was analyzed using STAT I software.

3. Results

3.1. Enrolled subjects

A total of 210 healthy subjects were enrolled in the present study, consisting of 103 male and 107 female infants, and the proportion of females was slightly higher in the 7 months group. The age distribution of subjects is shown in Table 1; 69 aged 6 months, 71 aged 7 months, and 70 aged 8 months. Safety profiles were analyzed in all subjects, and serological responses in 64 subjects aged 6 months, 66 aged 7 months, and 66 aged 8 months. Serum samples were not obtained from 14 subjects because of the refusal of blood sampling of post-vaccination sera.

3.2. Serological study

A total of 210 serum samples were obtained before vaccination and serological backgrounds are shown in Table 1. There were 180 out of 210 (85.71%) initially seronegative samples, with a similar

Table 1
Age distribution and serological background of subjects.

	6 months	7 months	8 months	Total
Number of subjects [male/female]	69 [40/29]	71 [29/42]	70 [34/36]	210 [103/107]
Initially seronegative (%) [male/female]	57/69 (82.61%) [33/24]	63/71 (88.73%) [26/37]	60/70 (85.71%) [27/33]	180/210 (85.71%) [86/94]
Serological examination [male/female]	64 [37/27]	66 [27/39]	66 [30/36]	196 [94/102]

ratio being observed among the 6, 7, and 8 months age groups. Number of females was higher than male in subjects aged 7 months. Paired sera were collected from 196 subjects and the results of immune responses are shown in Table 2. Seronegative subjects initially accounted for 180/196 subjects (91.84%, 95% CI: 88.01–95.67%) and, in the different age groups, 57/64 (89.06%) at 6 months, 63/66 (95.45%) at 7 months, and 60/66 (90.90%) at 8 months. GMT before immunization ranged between 12.29 and 20.77 mIU/mL, with no significant differences being noted among the 6, 7, and 8 months groups.

Seropositivity was defined as ≥120 mIU/mL and seroresponse rates with GMT in the different age groups are shown in Table 2. The seroresponse rate was 173/196 (88.27%, 95% CI: 83.77–92.77%) with 511.11 mIU/mL (95% CI: 687.69–879.90 mIU/mL). It was 56/64 (87.5%, 95% CI: 79.40–95.60%) at 6 months, 58/66 (87.87%, 95% CI: 79.99–96.75%) at 7 months, and 59/66 (89.39%, 95% CI: 81.96–96.82%) at 8 months.

Among 64 subjects aged 6 months, GMT increased to 532.81 mIU/mL (95% CI; 623.93–962.46 mIU/mL). GMT post-vaccination was 504.12 mIU/mL (95% CI; 608.75–942.96 mIU/mL) at 7 months and 497.71 mIU/mL (95% CI: 610.71–954.51 mIU/mL) at 8 months. No significant differences were observed in seroresponse rates or GMT among the different age groups. When seroconversion was defined as >200 mIU/mL, the seroconversion rate was 55/64 (85.94%) at 6 months, 55/66 (83.33%) at 7 months, and 52/66 (78.79%) at 8 months.

Sixteen out of 196 paired serum samples were seropositive before vaccination, immune responses were investigated in different pre-immune serological statuses, and the results obtained are shown in Table 3. They were categorized into four groups: <14 IU/mL, 14–<60 mIU/mL, 60–<120 mIU/mL, and ≥120 mIU/mL. The seroresponse rate was 112/122 (91.8%, 95% CI: 86.94–96.67%) with GMT (597.05 mIU/mL, 95% CI: 748.84–1002.43 mIU/mL) in the <14 mIU/L group. In the 14–<60 mIU/mL group, the seroresponse rate was 18/28 (64.29%) with 184.18 mIU/L of GMT, which was significantly lower ($p < 0.01$) than that in the <14 mIU/mL group. GMT in the 60–<120 mIU/mL group was also significantly lower ($p < 0.05$) than that in <14 mIU/mL group. In the seropositive group, all subjects showed seroconversion (4-fold higher than before) with a higher GMT of 1077.51 mIU/mL. Correlationship of measles NT titers between pre- and post-immunization is shown as scatter plotting in Fig. 1. The lower serological responses were supposed in subjects having NT levels of ≥120 mIU/mL before immunization. But, however, they demonstrated the sufficient serological responses.

No significant differences were observed in seroconversion rates between 86 male and 94 female subjects or among the different age groups (data not shown).

3.3. Adverse reactions

A diary of health cards was collected from 210 subjects, and the results obtained from 173 subjects with a positive seroresponse and 23 subjects without a seroresponse were analyzed and shown in Table 4. Local pain and itching at the injection site were observed in 8/173 subjects positive for seroresponse (4.62%) and redness and swelling in 3/173 (1.73%) within 7 days of the vaccination. Regarding systemic adverse reactions, febrile illness ≥37.5 °C was observed in 12/173 (6.94%) in seroresponse + group and 2/23 (8.70%) in subjects without a seroresponse. Crying, loss of appetite, diarrhea, cough or running nose, and vomiting were observed in 5–8 subjects each (2.90–4.62%).

4. Discussion

In the present study, the initially seronegative population was180/210 (85.71%), similar to the preliminary serological study (86.9%) performed in 2015. The seroresponse rate was 180/196 (88.27%) with GMT of 511.11 mIU/mL in PRNT, and no significant differences were observed among different age groups. These were consistent with the other reports [9]. Among 122 subjects in the initially seronegative group <14 mIU/mL, 112 (91.8%) became seropositive with GMT of 597.05 mIU/mL. Subjects in the14–<60 mIU/mL group showed significantly lower seroresponse rates and GMT than those in the group <14 mIU/mL. However, subjects in the initially seropositive groups showed a sufficient booster response. In our previous clinical trial using AIK-C produced in Vietnam, the seroresponse rate was 92.59–98.3% in an enzyme-linked immunoassay (EIA), showing a higher serological response; however, it is important to note that different serological assay methods were employed [20]. The sensitivity of EIA is higher but does not correlate with protective activity.

Table 2
Immune responses in different age groups.

	Immunized at			
	6 months (n = 64)	7 months (n = 66)	8 months (n = 66)	Total (n = 196)
Initially seronegative (%)	57/64 (89.06%)	63/66 (95.45%)	60/66 (90.90%)	180/196 (91.84%)
[95% CI: %]	[81.46–96.74]	[90.42–100]	[83.96–97.84]	[88.01–95.67]
GMT Pre	19.87 mIU/mL	12.29 mIU/mL	20.77 mIU/mL	17.15 mIU/mL
[95% CI: mIU/mL]	[30.59–73.79]	[13.45–39.65]	[33.95–70.55]	[33.26–53.89]
Post seroresponse +	56/64 (87.50%)	58/66 (87.87%)	59/66 (89.39%)	173/196 (88.27%)
[95% CI: %]	[79.40–95.60]	[79.99–96.75]	[81.96–96.82]	[83.77–92.77]
GMT Post	532.81 mIU/mL	504.12 mIU/mL	497.71 mIU/mL	511.11 mIU/mL
[95% CI: mIU/mL]	[623.93–962.46]	[608.75–942.96]	[610.71–954.51]	[687.69–879.90]

GMT: geometric mean titer, CI: confidence interval.

Table 3
Immune responses in groups with different PRNT titers before vaccination.

	Serological status before vaccination			
	<14 mIU/mL	14–<60 mIU/mL	60–<120 mIU/mL	≥120 mIU/mL
Number of subjects	122	28	30	16
Seroresponse rate (%)	112/122 (91.8%)	18/28 (64.29%)**	27/30 (90%)	16/16 (100%)
[95% CI:%]	[86.94–96.67]	[46.54–82.04]	[79.26–100.74]	[100–100]
GMT post	597.05 mIU/mL	184.18 mIU/mL**	473.16 mIU/mL*	1077.51 mIU/mL
[95% CI: mIU/mL]	[748.84–1002.43]	[156.60–339.60]	[478.78–835.87]	[869.43–1665.45]

* Significantly different from the < 14 mIU/mL group ($p < 0.05$).
** Significantly different from the < 14 mIU/mL group ($p < 0.01$).

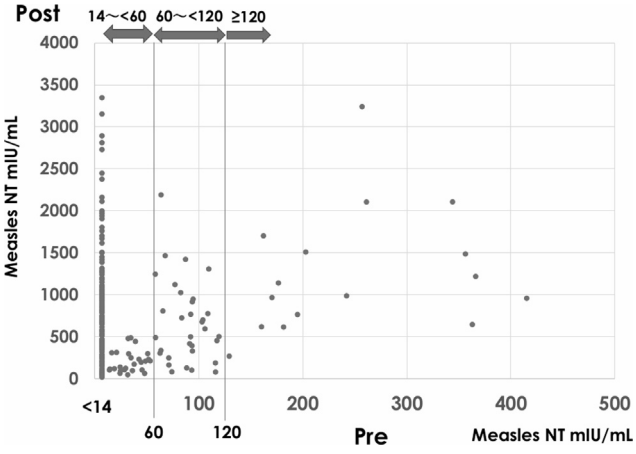

Fig. 1. Correlationship of measles NT titers between pre- and post-immunization. They were categorized into four groups: <14 IU/mL, 14–<60 mIU/mL, 60–<120 mIU/mL, and ≥120 mIU/mL.

Measles surveillance data in Vietnam showed a marked reduction in the number of measles cases following a nationwide measles immunization campaign with a second dose for children aged 9 months to 9 years in 2002 and 2003 [15,16]. In 2005, the WHO WPR set the regional goal of the termination of measles transmission by 2012, and Vietnam adopted this action plan. However, large outbreaks occurred between 2008 and 2010 among children aged 1–4 years and adults aged 20–24 years [22]. The measles vaccine has been supplied through EPI; however, large numbers of doses are needed to control unexpected outbreaks. A domestic production project started in Vietnam through the technical transfer of the production of AIK-C. The outbreak in 2014 was controlled by the urgent supply of 5 million doses. The WHO has launched an action plan for the elimination of measles and rubella and recommended the use of the measles and rubella (MR) combined vaccine [3]. A clinical trial on the MR vaccine containing AIK-C measles and rubella Takahashi strain produced by POLYVAC was conducted using 733 subjects aged 1–45 years in 2016, and data were compared with the MR vaccine produced by the Serum Institute of India containing Edmonston-Zagreb and RA27/3. The findings obtained showed that the MR vaccine produced by POLYVAC was highly immunogenic and safe for all generations and was licensed in 2017 [23].

Tidjani et al. [24] reported that vaccination with the standard potency of AIK-C strain at 4–5 months was as effective as that with the AIK-C strain at 8–10 months and superior to that with the high dose Schwarz strain at 8–10 months in 1989. Good serological responses were confirmed in other trials [25–27]. Cell-mediated immunity was induced in infants immunized with the AIK-C strain at 6 months, as assayed by lymphocyte blastogenesis and interferon-gamma and interleukin-10 production [28]. The higher immunogenicity of AIK-C than the Schwarz strain was reported in 9-month-old infants in Taiwan [29]. The AIK-C strain was established by passages through sheep kidney and chick embryogenic cells at 32.5 °C, not through human cells [30].

Pan American Health Organization (PAHO) had achieved measles elimination and strategic guidelines highlight how to limit measles transmission in elimination settings [31]. First-dose measles-containing vaccines are generally administered at 1 year in developed countries and at 9 months in developing countries. If there are many measles cases in infants younger than 12 months during an outbreak, the vaccination of those aged 6–12 months is recommended in order to control and prevent young infant deaths. The safety profile of the early measles-mumps-rubella (MMR) vaccination was examined in a measles outbreak in the Netherlands in 2013–2014 and the incidence of adverse events was lower in infants aged 6–8 months than in those aged 9–11 and 12–14 months [32].

The limitation of the present study was that it was a non-comparative observational study and only 210 subjects were used for the safety profile. The measles outbreak in Vietnam in 2018 involved unvaccinated young infants, and early measles vaccination represents an effective measure to prevent infant deaths in future outbreaks. The low incidence of adverse events needs to be confirmed in future large-scale studies.

Table 4
Adverse events of local and systemic symptoms following vaccination.

	Local reactions			Systemic reactions	
	Seroresponse + (n = 173)	Seroresponse – (n = 23)		Seroresponse + (n = 173)	Seroresponse – (n = 23)
Pain	8	0	Fever	12	2
Itching	8	0	Irritability	13	1
Redness	3	1	Crying	8	1
Swelling	4	0	Loss of appetite	6	1
			Diarrhea	7	0
			Cough, running nose	7	0
			Vomiting	5	0

Adverse reactions were analyzed in 173 subjects with a positive seroresponse and in 23 subjects without a seroresponse.

5. In summary

The AIK-C measles vaccine produced in Vietnam induced sufficient immune responses in infants <9 months. Therefore, early vaccination with the AIK-C strain appears to be acceptable for young infants and will contribute toward reducing the number of measles-associated deaths by providing a prompt domestic supply in future outbreaks.

Conflict of interest

Nguyen Dang Hien and Pham Thi Phuong Thao are employees of POLYVAC. The corresponding author Nakayama T received a research fund from Daiichi Sankyo Pharmaceutical and Daiichi Sankyo Vaccine.

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