

# Comparison of AIK-C measles vaccine in infants at 6 months with Schwarz vaccine at 9 months: a randomized controlled trial in Ghana\*

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*In a randomized controlled trial in a measles endemic area, standard-dose (4.0 log<sub>10</sub> pfu) AIK-C measles vaccine administered at 6 months of age was compared to standard-dose Schwarz vaccine (3.7 log<sub>10</sub> pfu) given at 9 months. Seroconversion rates at 3 and 6 months after immunization in the two groups were comparable and similar. The geometric mean titres achieved were, however, significantly higher in the Schwarz group (P < 0.05). No immediate serious side-effects were observed with either vaccine. We conclude that standard-dose AIK-C measles vaccine can be recommended for measles immunization in children below 9 months of age, especially in highly endemic and high-risk areas in developing countries.*

## Introduction

Despite the availability of safe and effective vaccines, the high morbidity and mortality of measles continue to be a major child health problem in developing countries. It is estimated that measles claims the lives of over 1 million children in the world every year. Among children who contract measles in the first year of life, mortality over the next 10–12 months after infection could range from 6% to 32% (1–3). Since measles case fatality is highest in young infants it is desirable to immunize as early in life as possible.

WHO currently recommends measles immunization at 9 months of age in endemic countries. The Schwarz strain measles vaccine, which is usually used for this schedule of immunization, is inadequately immunogenic below this age in the presence of pre-existing maternal antibodies (4–6). Many children in measles-endemic countries therefore contract the disease before 9 months of age (1, 7, 8). This limitation of the Schwarz vaccine, coupled with the severity of measles in infants who contract it before the recommended age of immunization, has necessitated a search for alternative measles vaccines which may be more immunogenic in younger infants.

Several workers have investigated the efficacy of alternative measles vaccines as well as different

routes of administration in infants aged 4–9 months (9–12). Prominent among these vaccines are the Edmonston–Zagreb (E–Z), CAM-70, Leningrad-16, and the AIK-C strains. The E–Z strain vaccines have received the most attention in field research (12–14), and WHO initially advocated the use of high-titre E–Z vaccines in highly endemic areas (15). However, considering the safety of this vaccine when administered in high-titre doses to infants below 9 months of age (16), WHO rescinded the initial recommendation for its use at titres above 4.7 log<sub>10</sub> plaque forming units (pfu) (17). Another potential candidate vaccine is the AIK-C strain measles vaccine which, in a limited trial in Japan, produced 100% seroconversion in children immunized at 8 months of age (18) and, in Togo, 96% seroconversion in seronegative infants immunized at age 4–5 months and 50% in infants who were seropositive before immunization (19). Despite these encouraging results, there are very few studies of infants below 9 months immunized with the AIK-C vaccine. Issues relating to the immunogenicity of this vaccine, especially in the presence of maternal antibodies, and the duration of immunity have not been fully documented. In this study, we compare the seroresponse of standard-dose heat-stable AIK-C measles vaccine administered to infants at 6 months of age with that of standard-dose Schwarz vaccine administered at 9 months in a measles-endemic area in West Africa.

## Methods

**Study area and population.** The study was conducted in Asamankese, the capital town of East Akim District in the Eastern Region of Ghana. Measles is

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endemic in the district (population, approximately 100 000), with cases reported throughout the year. About 10% of cases occur in infants <9 months of age. Curative health services are delivered through a district hospital at Asamankese and a number of satellite health centres located in smaller towns. Preventive health activities are centred around maternal and child health (MCH) clinics. Routine immunization is carried out as recommended by the Ghana Ministry of Health (MOH) and infants receive measles vaccine (Schwarz) at 9 months of age. Measles vaccine coverage in the district averaged 45% over the period of the study (February 1993 to January 1995).

**Study design.** Infants aged 6 months (24–27 weeks) who had been attending the Asamankese MCH clinic regularly and had received all the required immunizations (BCG at birth, oral poliovirus vaccine  $\times$  3, and diphtheria-pertussis-tetanus  $\times$  3) were identified when they came for their routine clinic visits. The study was explained to the parents and their verbal consent obtained to participate in the study. The child was then randomly allocated to either group A (to receive AIK-C measles vaccine at 6 months) or B (to receive Schwarz measles vaccine at 9 months), using computer-generated random numbers. To blind the study, infants receiving the Schwarz vaccine at 9 months of age received yellow fever vaccine at 6 months, and infants in the AIK-C group received yellow fever vaccine at 9 months of age. A child was excluded from the study if he or she was febrile (temperature  $\geq 38^\circ\text{C}$ ), or had a previous history of measles (according to mother's report), or was malnourished (<80% of expected weight-for-age).

Infants were immunized subcutaneously with 0.5 ml of reconstituted vaccine. Venous blood samples (1 ml) were obtained immediately prior to immunization and at 3 months and 6 months after immunization. The blood samples were transported under cold conditions to the Noguchi Institute on the same day, centrifuged, separated, and the serum stored at  $-20^\circ\text{C}$  until used. Mothers were requested to note any reactions in the child and return to the clinic with their infants on day 10 after immunization. At these visits, the infants were examined, axillary temperature was measured, and information on adverse reactions obtained with the aid of a questionnaire. Those defaulting were visited at home on day 11–12. Health care providers did not know to which vaccine group the infants belonged.

**Sample size.** It was assumed that seroconversion 3 months after immunization with Schwarz measles vaccine would be 85% and the study would have

80% power to detect a difference of 15% in the seroconversion rates between infants given AIK-C and Schwarz measles vaccine with 95% confidence. Allowing for a drop-out rate of 30% the number required per group was approximately 175.

**Vaccine details and schedule of immunization.** Standard-dose ( $4.0 \log_{10}$  pfu) heat-stable AIK-C strain vaccine, supplied by the Kitasato Institute of Japan, was used according to the manufacturer's recommendations. Standard-dose Schwarz vaccine ( $3.7 \log_{10}$  pfu), provided by UNICEF for routine immunization, was obtained from the national EPI programme in Ghana. Potencies of the two vaccines were pre-tested by titration in parallel with international reference measles vaccine. In addition, vials of vaccines from the cold storage as well as left-overs from the field were randomly tested for potency throughout the study.

**Measles serology.** The haemagglutination inhibition (HI) assay, as recommended by WHO, was used for the detection of measles antibodies (20). The test sera were run in parallel with an in-house reference serum whose agglutination inhibition titre had been determined in international units (IU) by calibration with the international antimeasles reference serum, containing 10 IU. The in-house reference serum contained 1250 mIU by this calibration. Test results were expressed in mIU using the formula:

$$(a/b) \times 1250$$

where  $a$  is the reciprocal of the highest dilution at which the test serum inhibits haemagglutination, and  $b$  is the reciprocal of the highest dilution at which the reference serum inhibits haemagglutination.

**Definitions.** *Seropositivity* of HI was defined as antibody detectable at a dilution of  $\geq 1:4$  (equivalent to approximately 40 mIU).

*Seroconversion* for infants with no detectable pre-existing antibodies was defined as a change from seronegative status to seropositive status. For infants with detectable pre-existing antibodies before immunization, an individual was considered to have seroconverted when the measured antibody level equalled or exceeded fourfold the computed residual maternal antibodies. The decay of maternal antibodies was assumed to follow first-order kinetics with a half-life of 30 days. The level of antibodies measured at 6 months of age (recruitment) was used to calculate the expected antibody levels at 3 and 6 months after immunization for the AIK-C group according to the following formula:

$$C_t = C_0^{-x}$$

where  $C_t$  = antibody level at time  $t$ ,  $C_0$  = antibody level at time 0,  $t$  = time, and  $x$  = a constant.

For the Schwarz group, the antibody level measured at 9 months was used to calculate the expected values at 3 and 6 months after immunization.

**Statistical analyses.** These were performed using SPSSPC+, version 6 (SPSS Inc, Chicago, IL, USA) and Epi Info version 6.0 (Centers for Disease Control, Atlanta, GA, USA). Proportions were compared using the  $\chi^2$ -test and continuous variables with the Student's  $t$ -test after log transformation of non-normally distributed data. Statistical significance was set at  $P \leq 0.05$ . HI titres were converted to IU and analysed using geometric mean titres. Means are reported with 95% confidence intervals.

## Results

A total of 184 infants were randomized into the AIK-C group and vaccinated at 6 months of age; 37 (20.1%) were seropositive (titre  $\geq 1:4$ ) before immunization. In the Schwarz group, 220 infants were initially recruited at 6 months of age; 40 (18.2%) of them were seropositive. Of these 220 infants, 193 (87.7%) were immunized at 9 months of age. There were no important differences between the two groups at pre-immunization (Table 1). In the Schwarz group, pre-immunization serology repeated at 9 months showed that 45 were seropositive; 28 were seroconversions from seronegative status at 6 months to seropositive status at 9 months, and an-

other 12 demonstrated a fourfold or greater increase in titre between the ages of 6 and 9 months. These 40 infants were subsequently excluded from further comparative analysis of the data, since it was assumed that they had been exposed to wild measles virus in the intervening 3 months. In the Schwarz group, therefore, only 5 infants had pre-existing maternal antibodies at 9 months of age. Three of the infants randomized to receive Schwarz vaccine developed clinical measles before they were due for immunization at 9 months of age; one of them died of measles-associated complications.

**Adverse reactions** (Table 2). No immediate severe adverse reactions were reported during the 10-day follow-up period after immunization in either group. Fever was reported by mothers more often in infants immunized with the AIK-C vaccine (21.7%) than in the Schwarz group (11.4%) (odds ratio (OR) = 2.16 (95% confidence interval (CI) = 1.18, 3.95);  $P = 0.01$ ). There was, however, no significant difference in recorded temperatures above 37.5°C in those reporting fever at the time of visit. Mild rash was also more frequently reported by mothers in the AIK-C group (4.9%) compared with the Schwarz group (1.3%), but the difference was not statistically significant (OR = 3.26 (95% CI = 0.79, 15.43);  $P = 0.10$ ).

**Seroconversion and post-immunization geometric mean titres (GMT)** (Table 3). A total of 164 out of the 184 infants who received the AIK-C vaccine at 6 months of age were seen and evaluated 3 months after immunization; 126 out of 130 (96.9%) infants who at pre-immunization were seronegative had seroconverted. Their geometric mean titre (GMT) was 338.9 mIU (95% CI = 279.8, 398.3). Of the re-

Table 1: Pre-immunization characteristics of study infants at enrolment in the two vaccine groups

|  | Vaccine group                  |                               |
|--|--------------------------------|-------------------------------|
|  | AIK-C                          | Schwarz                       |
| No. recruited  | 184                            | 220                           |
| Age at recruitment   | 6 months                       | 6 months                      |
| Age at immunization  | 6 months                       | 9 months                      |
| Median weight (kg) at recruitment  | 7.4; 6.5–8.00 <sup>a</sup>     | 7.0; 6.5–8.0 <sup>a</sup>     |
| No. of infants with detectable antibody at recruitment                           | 37 (20) <sup>b</sup>           | 40; (18.2) <sup>b</sup>       |
| Geometric mean titre of infants with detectable antibody at recruitment (mIU/ml) | 129.6; 86.1–193.1 <sup>c</sup> | 91.3; 67.1–124.2 <sup>c</sup> |

<sup>a</sup> 25th and 75th percentiles of weight.

<sup>b</sup> Figures in parentheses are percentages.

<sup>c</sup> Figures in italics are 95% confidence intervals.

Table 2: Distribution of adverse reactions following immunization with AIK-C and Schwarz measles vaccines

|                                       | Vaccine group          |                        |
|---------------------------------------|------------------------|------------------------|
|                                       | AIK-C (n = 184)        | Schwarz (n = 193)      |
| <i>Systemic reactions:</i>            |                        |                        |
| History of fever                      | 40 (21.7) <sup>a</sup> | 22 (11.4) <sup>b</sup> |
| Temperature $\geq 37.5^\circ\text{C}$ | 12 (6.5)               | 8 (4.1)                |
| Diarrhoea                             | 2 (1.1)                | 0                      |
| Running nose                          | 19 (10.3)              | 19 (9.8)               |
| Cough                                 | 18 (9.8)               | 17 (8.8)               |
| Rash                                  | 9 (4.9)                | 3 (1.6)                |
| Conjunctivitis                        | 1 (0.5)                | 0                      |
| <i>Local reactions:</i>               |                        |                        |
| Redness of injection site             | 1 (0.5)                | 0                      |
| Swelling of injection site            | 0                      | 0                      |

<sup>a</sup> Figures in parentheses are percentages.

<sup>b</sup>  $P = 0.01$ .

maining 34 infants with pre-existing antibodies at 6 months of age, 27 (79.4%) seroconverted with a GMT of 564.0 mIU (95% CI = 313.4, 1015.1). The difference in seroconversion rates between infants with and without pre-existing antibodies was statistically significant ( $P < 0.05$ ), but the difference in GMTs was not.

In the Schwarz group, 118 infants were assessed 3 months after immunization. Of 114 infants who were seronegative at immunization 112 (98.2%) seroconverted; their GMT was 690.1 mIU (95% CI = 579.8, 821.3). Four infants who were seropositive prior to immunization also seroconverted after im-

munization; they all had very low levels of pre-existing antibody (1:4).

Seroconversion rates 3 months after immunization with the AIK-C vaccine (immunized at 6 months) were not statistically different from the rates in the Schwarz group immunized at 9 month of age. The Schwarz group, however, exhibited significantly higher GMTs ( $P < 0.05$ ).

A total of 143 infants who received AIK-C vaccine were reassessed 6 months after immunization. Seroconversion rates in those who were seronegative at the time of immunization ( $n = 113$ ) or had pre-existing antibodies ( $n = 30$ ) were 97.3%

Table 3: Seroconversion rates 3 and 6 months after immunization with AIK-C and Schwarz measles vaccines

|                                  | 3 months after seroconversion |                                 | 6 months after seroconversion |                    |
|----------------------------------|-------------------------------|---------------------------------|-------------------------------|--------------------|
|                                  | n                             | GMT <sup>a</sup>                | n                             | GMT <sup>a</sup>   |
| <i>AIK-C vaccine:</i>            |                               |                                 |                               |                    |
| Seronegative before immunization | 130 (96.9) <sup>b</sup>       | 333.8; 279.8–398.3 <sup>c</sup> | 113 (97.3)                    | 389.6; 327.2–464.0 |
| Seropositive before immunization | 34 (79.4)                     | 564.0; 313.4–1015.1             | 30 (100)                      | 531.7; 346.5–815.8 |
| Total                            | 164 (93.3)                    | 366.2; 306.5–437.5              | 143 (97.9)                    | 416.5; 353.5–490.6 |
| <i>Schwarz vaccine:</i>          |                               |                                 |                               |                    |
| Seronegative before immunization | 114 (98.2)                    | 690.1; 579.8–821.3              | 111 (99.1)                    | 691.3; 572.1–835.4 |
| Seropositive before immunization | 4 (100)                       | 156.3; 25.8–946.3               | 5 (80.0)                      | 262.8; 40.0–1728.5 |
| Total                            | 118 (98.3)                    | 655.6; 549.4–782.3              | 116 (98.3)                    | 668.2; 554.7–805.0 |

<sup>a</sup> GMT = geometric mean titre of HI antibody.

<sup>b</sup> Figures in parentheses are percentages.

<sup>c</sup> Figures in italics are 95% confidence intervals.

and 100% respectively; corresponding GMTs were 389.6 mIU (95% CI = 327.2, 464.0) and 531.7 mIU (95% CI = 346.5, 815.8). Differences in the seroconversion rates and GMTs were not statistically significant.

In the Schwarz group, 116 infants were reassessed 6 months after immunization. The seroconversion rate in those who were seronegative at the time of vaccination was 99.1%, with a GMT of 691.3 mIU (95% CI = 572.1, 835.4). No significant differences were observed in seroconversion rates between the AIK-C and Schwarz groups at 6 months post-immunization. GMTs were again significantly higher in the group that received the Schwarz vaccine compared to the AIK-C group ( $P < 0.05$ ). There was a significant positive correlation between pre-immunization antibody levels and those 3 months after immunization ( $r = 0.49$ ,  $n = 32$ ,  $P = 0.014$ ), but not between pre-immunization antibody levels and those 6 months after immunization ( $r = 0.13$ ,  $n = 28$ ,  $P > 0.5$ ) in the AIK-C group. In the Schwarz group, although pre-immunization antibody levels correlated with antibody levels at 3 and 6 months after immunization, there was a wide variation in the antibody levels and none of the correlations was statistically significant.

The 40 children in the Schwarz group who demonstrated serological evidence of natural seroconversion by 9 months were also assessed at 3 and 6 months post-immunization. This group achieved the highest GMTs at both 3 months (983.4 mIU (95% CI = 541.0, 1787.4)) and 6 months (906.0 mIU (95% CI = 503.5, 1630.1)) after immunization.

## Discussion

WHO's recommendation for the administration of measles vaccine to infants at the age of 9 months in endemic countries represents a compromise between age-dependent vaccine efficacy and disease burden. In highly endemic countries with high measles-associated morbidity and mortality, such as sub-Saharan Africa (21, 22), immunization with standard-dose Schwarz vaccine at 9 months, even at relatively high coverage rates, has so far had only a modest impact on measles transmission, and major epidemics still occur (23, 24). During these epidemics many of the affected children in whom morbidity is particularly severe and mortality high are aged <9 months (8). There is therefore a need for alternative measles vaccines that are immunogenic in young infants under such epidemiological situations. The administration of such a vaccine at a younger age may more easily be incorporated into current EPI sched-

ules, thereby reducing drop-out rates and increasing coverage.

In the present clinical trial the seroresponse to standard-dose AIK-C measles vaccine administered at 6 months of age was comparable to that of standard-dose Schwarz vaccine administered at 9 months. Moreover, the AIK-C vaccine provided 3 months extra protection at the most vulnerable time of the child's life. The study showed no serious immediate adverse reactions in both vaccine groups. It may therefore be concluded that immunization with AIK-C vaccine at 6 months of age is as safe as Schwarz vaccine at 9 months. Even in the presence of pre-existing maternal antibodies, seroconversion rates of close to 80% at 3 months and 100% at 6 months after immunization were achieved in infants receiving the AIK-C vaccine. Antibody responses, as measured by GMTs, were equally high and above the frequently cited protective level of 200 mIU (21). Our results compare well with previous findings, which suggest that, at 6 months and possibly earlier, immunization with AIK-C measles vaccine induces satisfactory and acceptable levels of protection (12, 19).

An appreciable proportion of the infants (20.7%) who were randomized to receive the Schwarz vaccine seroconverted between 6 and 9 months of age, indicating exposure to circulating wild measles virus in the study community. Similar observations have been made in Togo (19). These findings suggest that in measles-endemic areas the interpretation of seroresponses after measles immunization should take into consideration possible silent seroconversions resulting from exposure to circulating wild measles virus. The fact that three infants randomized to receive the Schwarz vaccine developed severe clinical measles before they were due for immunization at the age of 9 months underscores the need to immunize infants earlier than this recommended age in highly measles-endemic areas.

Geometric mean titres at 3 and 6 months after immunization were consistently higher in the Schwarz group compared with the AIK-C group, although the seroconversion rates were similar. A likely explanation is that the Schwarz group of infants at 9 months were immunologically more mature and therefore had a better qualitative seroresponse than the AIK-C group who were immunized at 6 months of age. Our study population is currently being followed clinically and serologically on a long-term basis to compare antibody persistence over time and also assess possible late adverse effects.

The often cited interference by pre-existing maternally transferred antibodies on seroconversion after measles immunization could not be confirmed

in the Schwarz group owing to the small number of infants with antibodies at pre-immunization. In the AIK-C group good seroconversion rates were obtained in infants with pre-existing antibodies, suggesting that the strain of vaccine was adequately immunogenic in the presence of maternal antibodies. By 6 months of age, 80% of the study infants had lost their maternally derived measles antibodies and were susceptible to infection. Effective immunization against measles at this age or even earlier would greatly enhance control of measles in highly endemic countries, especially among very young children, or in high-risk densely populated urban areas and refugee camps. However, before the current WHO recommendations on measles immunization schedules and vaccine strains can be modified in the light of results like ours, issues concerning vaccine supply and cost will need to be carefully considered and addressed.

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### Résumé

#### Comparaison du vaccin antirougeoleux AIK-C administré à 6 mois et du vaccin Schwarz administré à 9 mois: essai contrôlé randomisé au Ghana

L'âge recommandé pour la vaccination antirougeoleuse avec le vaccin Schwarz dans les pays d'endémie est actuellement de 9 mois. Dans la plupart des secteurs d'endémie rougeoleuse, un nombre considérable d'enfants contractent la rougeole avant 9 mois, alors que c'est dans cette classe d'âge que la mortalité et la morbidité sont les plus élevées. Un vaccin antirougeoleux ayant une efficacité et une innocuité démontrées administré avant 9 mois serait particulièrement bienvenu dans les programmes de lutte des pays en développement. Nous avons par conséquent comparé les réponses sérologiques au vaccin Schwarz et au vaccin antirougeoleux AIK-C, lequel serait immunogène avant l'âge de 9 mois. On a comparé au cours d'un essai randomisé contrôlé réalisé dans un secteur d'endémie rougeoleuse au Ghana les réponses sérologiques, mesurées par inhibition

de l'hémagglutination (IH), vis-à-vis du vaccin antirougeoleux AIK-C administré à 6 mois à dose normale, soit  $4,0 \log_{10}$  UFP (unités formant plaque), et le vaccin antirougeoleux Schwarz administré à 9 mois à dose normale, soit  $3,7 \log_{10}$  UFP.

Trois et 6 mois après la vaccination, le taux de conversion était de 93,3% et 97,9% respectivement dans le groupe AIK-C, et de 98,3% et 98,3% respectivement dans le groupe Schwarz. Le titre géométrique moyen en mUI était cependant supérieur dans le groupe Schwarz respectivement 3 mois (655,6 avec intervalle de confiance à 95% ( $IC_{95\%}$ ): 549,4-782,3; contre 366,2 avec  $IC_{95\%}$ : 306,5-437,5;  $p < 0,05$ ) et 6 mois (668,0 avec  $IC_{95\%}$ : 554,7-805,0; contre 416,5 avec  $IC_{95\%}$ : 353,5-490,6;  $p < 0,05$ ) après la vaccination. Aucun effet indésirable grave immédiat n'a été observé avec aucun des vaccins.

La séroconversion après vaccination par le vaccin antirougeoleux AIK-C administré à 6 mois était comparable à celle obtenue avec le vaccin Schwarz administré à 9 mois. Si les titres moyens étaient plus faibles dans le groupe AIK-C, ils se situaient néanmoins bien au-dessus de 200 mUI, titre considéré en général comme protecteur. Nous en concluons que le vaccin AIK-C pourrait être recommandé pour la vaccination antirougeoleuse avant 9 mois, notamment en secteur de forte endémie et à risque élevé des pays en développement.

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