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Follow-up of infants given measles vaccine at 6 months of age: antibody and CMI responses to MMRII® at 15 months of age and antibody levels at 27 months of age

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Abstract

The worldwide elimination of measles is an important target. In developed countries, to control measles outbreaks, immunization from 6 months of age is recommended. In this study, infants ($n = 290$) who were (1) born to mothers with natural immunity or to vaccinated mothers and (2) previously immunized with Connaught (CLL) or AIK-C measles vaccine at 6 months of age, were evaluated for measles immunity before and after measles–mumps–rubella (MMRII®) at 15 months of age. Eight weeks after MMRII®, 98.9% of infants were seropositive by enzyme immunoassay (EIA) and 70% demonstrated measles specific cellular immunity by blast transformation (BT) of lymphocytes. At 27 months of age, 98.4% of infants had protective antibody levels by plaque reduction neutralization (PRN) test. These results suggest that AIK-C and CLL vaccines elicit durable protective immunity in young infants when used in early immunization programs.
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1. Introduction

Over the past 5 years, the incidence of measles in North America has declined to an all-time low. In 2001, the number of reported cases fell to 116 in the US [1] and 34 in Canada [2] largely due to concerted efforts by government and health agencies at all levels to vaccinate and re-vaccinate, identify measles cases and reduce spread to susceptibles immediately upon diagnosis. This success is remarkable, as measles virus is a most highly contagious organism and easily transmitted by aerosol [3,4].

Simultaneously, these measures to control measles have minimized the circulation of wild-type measles virus and therefore have also limited boosting of specific measles immunity in the general population. Nowadays in North American newborns, passive maternal measles antibodies are almost exclusively dependent on the vaccination experience of the mother [5,6]. Consequently, because antibody levels after vaccination are lower than those seen after natural infection, infants born today have less measles antibody than during the pre-vaccine era. In view of the observed shift in maternal measles antibody levels leading to susceptibility in infants at earlier ages, vaccination at $\geq$6 months is recommended for infants traveling to measles endemic areas [7] or during measles outbreaks [8]. Outbreaks linked to imported cases [1,9–11] will occur as long as endemic measles persists in some countries, spreading measles in well-immunized societies to susceptible infants and to previously vaccinated indi-

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viduals whose immunity may not be complete [12]. We previously demonstrated that measles vaccination after 6 months of age was successful in immunized populations [13,14] and further that routine measles vaccination at 6 months would be convenient and cost-effective because it could be given with other regularly scheduled pediatric vaccines [15]. This shift in age for primary measles vaccination would reduce the high rate of complications associated with measles in infants less than 1 year of age [16], which continues to be a risk during outbreaks.

This study extends our evaluation of an early two-dose measles vaccination schedule for infants born to mothers with natural immunity or to vaccinated mothers. Previously [13,14], we observed high seroconversion rates in 6-month old infants immunized with either of two standard titer monovalent measles vaccines: AIK-C, which has been shown to have good immunogenic potential in areas with endemic measles [17–19] or Connaught monovalent (CLL) measles vaccine, which has not been extensively evaluated but has been used in the Caribbean and during outbreaks in Canada [20]. The present study is a follow-up of infants previously vaccinated at 6 months of age with AIK-C or CLL and whose maternal vaccination history is documented [14]. We now report the persistence of measles antibody in these children and their measles-specific immune response to measles, mumps, rubella vaccine (MMRII®) at 15 months of age, with serologic follow-up until 27 months.

2. Materials and methods

The study design is summarized in Fig. 1. The response of 300 infants to early measles vaccination has been described in a prior report in which infants attending public health clinics in Edmonton, Alberta, Canada were enrolled according to the source of maternal measles immunity [14]. Group 1 included 61 infants whose mothers were born before 1958 and are assumed to have natural measles immunity. The mothers of the 239 infants in Group 2 were born after 1964 and had documentation of vaccination with live attenuated measles vaccine after 12 months of age. All infants in Group 1 and 119 infants in Group 2 received AIK-C [21] measles vaccine (Pasteur–Merieux–Connaught, minimum potency 3.7 $\log_{10}$ $TCID_{50}$) at 6 months of age. The remaining 120 infants in Group 2 received CLL [21] measles vaccine (Pasteur–Merieux–Connaught, minimum potency 3.3 $\log_{10}$ $TCID_{50}$) at 6 months of age. Screening methods, recruitment, vaccines, laboratory methods, blinding and the serological and cell-mediated responses of the study group infants to 6-month measles vaccination have been previously detailed [14]. An outbreak of measles occurred in Alberta with 92 confirmed cases in Edmonton between 11 February and 13 May 1997 [22]. Although no study infants were reported by the Edmonton Board of Health to have been exposed, data have been examined for possible confounding effects of measles cases in the community.

Fig. 1 also presents the protocol for follow-up of 290 of the original 300 study infants after subsequent immunization with MMRII® (Merck-Frosst, Canada) and the fourth PENTA™ [DPT-IPV-PRP-T, Pasteur–Merieux–Connaught, Canada (now Aventis Pasteur)]. All study infants received MMRII® (0.5 cm^3, subcutaneous, left deltoid) at 15–17 months of age (15 months, $n = 275$; 16 months, $n = 14$, 17 months, $n = 1$). Approximately half ($n = 148$) of the infants received the fourth PENTA™ (1.0 cm^3, intramuscular, left thigh) at 18 months (Subgroup A) and the remainder ($n = 142$) received the fourth PENTA™ at the 15-month clinic visit for MMRII® (Subgroup B). Infants were alternately assigned to Subgroup A or B during the recruitment process. MMRII® was scheduled at 15 months of age to fall within recommended ranges for administration of both MMRII® (12–15 months) and the fourth dose of PENTA™ (15–18 months) [23]. Vaccines were administered by public health nurses in clinics operated by the Edmonton Board of Health. Research team members responsible for laboratory testing and reporting were blinded with respect to infant subgroup but parents and research team members involved with recruitment and administration of vaccines were not.

As for the earlier blood samples taken from study infants at 6 (Sample A) and 8 (Sample B) months of age [14], pre- and post-MMR vaccination blood samples were taken in the child's home in 3 ml sodium heparin vacuum tubes. Most pre-MMR samples (Sample C) were taken during the week before MMRII® ($\leq$7 days, $n = 245$; >7 days, $n = 39$; sample not available, $n = 6$) and most post-MMR samples (Sample D) were taken 8 weeks after vaccination (6–7 weeks, $n = 20$; 8 weeks, $n = 236$; 9–10 weeks, $n = 29$; sample not available, $n = 5$). A fifth blood sample (Sample E) was taken 1 year after MMRII® (27–28 months of age, $n = 275$; 29–31 months of age, $n = 3$; sample not available, $n = 22$) in 3 ml serum vacuum tubes for serology only. Samples C and D were treated to obtain plasma for antibody studies and lymphocytes for blast transformation (BT) studies as previously described [14]. Samples were obtained between 27 September 1995 and 8 June 1998.

Samples C–E were assayed by enzyme immunoassay (EIA) for measles specific antibody using the Behring Enzygost ELISA kit as used for routine measles antibody screening previously described [14]. An O.D. value $\geq$0.200 was considered seropositive. Additionally, 250 Sample E sera were tested by the plaque reduction neutralization (PRN) test for measles antibodies [13], in order to assess the persistence of measles antibody in a functional assay that has been correlated with protection [24]. Seroconversion was defined as a fourfold increase in PRN titer and titers $\geq$120 mIU were interpreted as being protective [25]. Cell mediated immunity (CMI) was evaluated by routine methods [26,27] for blast transformation (BT) of peripheral blood mononuclear cells (PBMC) cultured in the presence and absence of measles hemagglutinating antigen (HA) [13]. BT results are expressed as raw counts per minute (CPM) of H^3 thymidine in stimulated samples minus CPM of the same sample without HA.