EDMONSTON-ZAGREB MEASLES VACCINE PROJECT

BACKGROUND

In the first few months of life, maternally derived measles antibody serves to protect the infant against measles infection; however, it also may be responsible for the failure of that infant to respond to live measles vaccine. Therefore, measles vaccination must occur after the infant's maternal antibody titer has subsided. Since 1963, when measles vaccine was introduced in the US, the recommended age for vaccination increased from 9 months to 12 months in 1965, and then to 15 months in 1976 (although in some areas, including LAC, the recommended age has been changed back to 12 months). These changes were implemented because of higher seroconversion rates at older ages, and because younger infants are considered to be protected by maternal antibodies. Most women of childbearing age in the US now have measles immunity from vaccination, rather than natural infection. Because vaccination results in lower antibody titer than does natural infection, these mothers are likely to pass lower levels of antibody to their infants. Recently, outbreaks in unvaccinated preschool-aged children, including children under 15 months (the recommended age for measles immunization in most parts of the US), have raised concerns that infants may be losing protection from passively acquired antibody at a younger age than in the past.

Studies comparing Edmonston-Zagreb (EZ) measles vaccine with Schwartz measles vaccine in young infants (four to nine months of age) have been conducted in several developing countries, including Guinea-Bissau, Senegal, Haiti, Gambia, Togo, and the Philippines. These studies revealed high seroconversion rates with EZ vaccine even in the presence of high maternal measles antibody. Several of these studies that used high-dose (4.84 In TCID50) EZ measles vaccine found increased mortality predominantly or exclusively among African female infants immunized with high-dose EZ measles vaccine. In these cases, death occurred approximately one year after vaccination. The causes of these deaths are common causes of infant and child mortality in Third World settings, e.g., respiratory infections, diarrhea and dehydration. Data from these, as well as other studies which did not find higher mortality post-vaccination, were reviewed during a two-day meeting organized by the Expanded Programme on Immunization (EPI), World Health Organization (WHO), in February 1991. Principal investigators of the major clinical trials of EZ vaccine and an international panel of experts attended the meeting and reviewed the data. The panel felt that the probability that the higher mortality was due to the vaccine was very low. Among the reasons cited was the lack of biologic plausibility, particularly in reference to the sex-specific findings.

A vaccine that would induce long-lasting immunity in young infants despite elevated maternal measles antibody levels is of particular interest because of the 1991 measles epidemic in LAC and other parts of the US. Many of the cases in these epidemics were infants less than 15 months of age (30%-40% in LAC). Until this project, no studies comparing the EZ measles vaccine with Moraten measles vaccine (the only measles vaccine currently licensed for use in the US) had been done in an industrialized nation.

Since 1990, the Acute Communicable Disease Control Unit has collaborated with Southern California Kaiser Permanente in a Centers for Disease Control and Prevention (CDC) funded clinical trial among Kaiser enrollees comparing immunologic and clinical differences among infants vaccinated with high- or standard-titer Edmonston-Zagreb (EZ) measles vaccine and infants vaccinated with the standard Moraten vaccine.

The study was originally initiated to evaluate the immunogenicity of the Edmonston-Zagreb measles vaccine in an effort to find a vaccine that would induce long-lasting immunity in young infants in the presence of maternal antibodies. Since then, the study has progressed through three phases: the Original, the Follow-Up, and the Extension. The study designs of each of these phases are presented in previous LAC DHS ACD annual reports (1992 and 1993). Data collection and analysis from the original study was completed by Centers for Disease Control and Prevention in 1993 and is presented in the LAC DHS ACD 1993 Annual Report.

FOLLOW-UP STUDY

The purpose of the Follow-up study was to monitor the health status of the cohort until four years of age. This study consisted of three parts: a clinical follow-up and medical record review (Part I); a serologic assessment of measles antibody persistence at three years of age (Part II); and an immunologic work-up (Part III).

Part I of the follow-up study, completed in March 1995, monitored all Kaiser outpatient visits for the 1,313 study participants up to their fourth birthday. Part II (measles antibody persistence) and Part III (immunologic work-up) concluded in April of 1994. Data analysis is in progress.

EXTENSION STUDY

The objectives of the Extension study, begun in September 1994 and ended July 1996, was to evaluate the immunologic status of original enrollees three to four years after receipt of the initial measles vaccine and to examine the effect of initial vaccine dose and child=s age at time of initial vaccination with respect to boosted antibody titers. Some children in the study received vaccine at six or nine months of age and were therefore revaccinated at 12 months of age.

Two blood draws were involved in this study, one between 48 and 72 months of age immediately prior to the child=s >school entry= MMR, and one at least six weeks later. By the end of 1995, 400 of the projected 500 subjects had enrolled, and 317 subjects had completed the study. The enrollment distribution was 1.8% Asian, 44% Black, 47.8% Hispanic, and 6.5% White. Data analysis is expected to be completed in 1997.