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No Evidence of Long-Term Immunosuppression after High-Titer Edmonstron-Zagreb Measles Vaccination in Senegal

Colleagues—In measles vaccine trials in Guinea-Bissau [1], Senegal [2], and Haiti [3], girls who received high-titer Edmonston-Zagreb (EZ; $>10^{4.7}$ infectious particles) or Schwarz measles vaccines at 4–6 months of age had a higher mortality than girls receiving standard measles vaccine at 9–10 months of age. An explanation of this surprising observation, which was not due to insufficient protection against measles [2, 4, 5], is important for the future development of measles vaccines and measles control. We and others [3] thought that high-titer measles vaccine could mimic natural measles, inducing immunosuppression with subsequent susceptibility to other infections. Thus, like others in Guinea-Bissau [6] and Peru [7], we undertook an immunologic examination of a subsample of 143 children who had received high-titer EZ or standard-titer Schwarz measles vaccines. Little is known about the best predictors of immunocompetence among children in developing countries, so we used several different tests with the objectives of finding immunologic differences between the vaccine groups and identifying possible defects that could be corrected through specific interventions (e.g., vitamin A supplementation or nutritional rehabilitation).

The study was carried out in Niakhar, Senegal, a rural area with a population of ~26,000 [2]. The trial of high-titer vaccine included all children born to resident mothers between February 1987 and January 1989 [2]. There were 73 children who had received EZ vaccine at 5 months and 70 children who had received placebo at 5 months and standard Schwarz vaccine at 10 months who were selected at random from the children residing in the study area in the fall of 1991 when the children were 36–44 months old. The children were visited at home three times. At the first visit, the children were examined anthropometrically, had a venous blood sample collected, and were vaccinated with diploid rabies vaccine lot E1227 (Institut Mérieux, Lyon, France). Rabies vaccine was selected as a potentially beneficial immunization that none of the participants were likely to have encountered already. During the first visit, skin tests with tuberculin purified protein derivative (PPD) and candida antigens were also applied; indurations of ≥2 mm at the reading 2 days later were considered positive [7]. The children received the second dose of rabies vaccine 4 weeks after the first visit. At the last visit, 2 months later, a fingerprick blood sample was obtained for the determination of rabies antibodies (Platelia ELISA, Diagnostic Pasteur, Marnes-la-Coquettes, France).

At enrollment at 5 months of age, there was no difference in maternal measles antibody levels or nutritional status between the 143 children in the immunologic study and the other 1436 children in the trial. At the time of the immunologic study in 1991, there were no differences between the EZ and Schwarz groups with respect to weight for age, height for age, or weight for height. Other results from the study are reported in table 1. Though there were no differences overall, more consultations at a health center or hospital were reported for girls who had received EZ (47%) than for those who had received standard Schwarz vaccine (24%; relative risk = 2.01; 95% confidence interval, 1.00–4.03). As expected [8], EZ recipients had lower levels of measles hemagglutinin-inhibiting antibodies than recipients of standard Schwarz vaccine. All children had been vaccinated against yellow fever in the past, and there was no difference in antibody levels between groups. Though there was no difference overall, girls in the EZ group had a significantly higher neutralization ($P = .012$) or ELISA ($P = .030$) antibody response to rabies vaccine than girls in the standard vaccine group. There was no significant difference, overall or by sex, between the EZ and Schwarz groups with respect to lymphocyte counts or T cell subsets (FACScan; Becton Dickinson, Mountain View, CA). None of the children had a total CD4 cell count $<800 \times 10^6$/L or a CD4:CD8 cell ratio of <0.5. There was no significant difference with respect to levels of neopterin (RIA; Henning, Berlin), serum albumin (standard colorimetric method), C-reactive protein (immunoturbidometric method; Hoffman La Roche, Basel, Switzerland), or retinol (high-performance liquid chromatography; Waters Associates, Milford, MA), delayed hypersensitivity to candida or PPD, or prevalence or density of malaria parasitemia. During the 2 years subsequent to the immunologic study, 2 children died, 1 in the EZ and 1 in the Schwarz group.

The subsample included in the immunologic study appears to be representative of the children enrolled in the trial. We examined antibody and cellular immune responses and found no meaningful differences. Apart from the expected difference in measles antibody levels [8], the only significant difference was a higher antibody response to the rabies vaccine among EZ girls. There was no sign that either boys or girls in the EZ group had

The study was approved by the Ministry of Health, Senegal, and the Scientific and Ethical Committees of Medical Research Council, The Gambia.

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Table 1. Clinical visits, mean immunologic and hematologic values, number of positive skin tests, and malaria parasitemia among recipients of high-titer EZ or standard-titer Schwarz measles vaccine, Niakhar, Senegal, 1991.

	High-titer EZ			Standard		
	Total (n = 69)	Girls (n = 32)	Boys (n = 37)	Total (n = 67)	Girls (n = 31)	Boys (n = 36)
Consultation, no. (%)*	30/73 (41)	17/36 (47)†	13/37 (35)	22/70 (31)	8/34 (24)	14/36 (39)
Antibodies						
Measles HAI‡	5.0 (2.39)†	5.3 (2.46)†	4.6 (2.31)†	6.3 (2.07)†	6.6 (2.22)†	5.9 (1.91)†
Yellow fever§	1.4 (0.14)	1.6 (1.15)	1.3 (1.17)	1.4 (0.14)	1.8 (1.23)	1.0 (0.89)
Rabies NT‖	2.8 (0.34)	3.0 (0.25)†	2.7 (0.34)	2.8 (0.34)	2.8 (0.30)†	2.8 (0.37)
Rabies ELISA, OD	4.0 (1.75)	4.6 (1.48)†	3.4 (1.78)	3.9 (1.83)	3.6 (1.71)†	4.0 (1.94)
Lymphocytes × 10^6/L						
Total CD3	4703 (2203)	5074 (2642)	4365 (1682)	4483 (2296)	4192 (1712)	4752 (2734)
Total CD4	2673 (1364)	2939 (1584)	2453 (1125)	2435 (1178)	2345 (877)	2513 (1393)
Total CD8	2006 (1156)	2133 (1466)	1900 (823)	1857 (1119)	1751 (909)	1948 (1277)
CD4:CD8	1.4 (0.6)	1.5 (0.5)	1.4 (0.6)	1.5 (0.5)	1.5 (0.5)	1.4 (0.5)
Other hematologic values						
Neopterin, $\log_{10}$ nmol/L	1.21 (0.32)	1.23 (0.32)	1.19 (0.33)	1.20 (0.28)	1.22 (0.30)	1.17 (0.27)
Albumin, g/L	40.4 (4.9)	40.9 (5.7)	39.9 (4.0)	39.8 (4.9)	39.5 (5.3)	40.1 (4.5)
C-reactive protein						
≥5 mg/L, no.	11.38	3/15	8/23	9/39	3/15	6/24
Retinol, nmol/L	0.58 (0.20)	0.60 (0.17)	0.56 (0.22)	0.60 (0.23)	0.59 (0.22)	0.60 (0.23)
Skin tests						
Candida ≥2 mm, no.	15/73	6/36	9/37	16/70	8/34	8/36
PPD ≥2 mm, no.	5/73	4/36	1/37	2/70	1/34	1/36
Malaria						
Parasitemia, no. (%)¶	28/70 (40)	11/34 (32)	17/36 (47)	24/69 (35)	14/33 (42)	10/36 (28)
Density, $\log_{10}/\mu$L	3.8 (0.15)	4.0 (0.59)	3.8 (0.88)	3.7 (0.22)	3.8 (0.97)	3.6 (1.23)

NOTE. Data are mean (SD) unless stated otherwise.

* Children who had at least 1 consultation since age 10 months at health center or hospital.

† $P < .05$.

‡ Log_2 measles hemagglutinin-inhibiting (HAI) antibodies [8].

§ Log_2 yellow fever neutralization antibodies.

‖ Log_{10} rabies antibodies by reduction neutralization (NT) method.

¶ Children with malaria parasites at time of first visit.

worse nutritional status, vitamin A deficiency, antibody response, or cellular immunity than those in the standard vaccine group. Thus, we have little evidence for long-term immunosuppression. On the basis of data from Niakhar, it has been suggested that a persistently high mortality rate was associated with high-titer measles vaccine [5]. However, given the data from this and a similar study in Guinea-Bissau [6], it is unlikely that there is an important immunosuppression persisting beyond 3 years of age among recipients of high-titer vaccines. Our study provided no clues for specific interventions that could correct a defined defect for girls in the EZ group.

It is possible that those most affected had already died and that we were therefore not able to detect any important immunologic differences between the groups. However, the idea of a clinically important immunosuppression associated with high-titer vaccine [3, 7] finds little support in the fact that EZ vaccine is not associated with excess mortality in areas with low mortality rates [7–9] and that in areas of high mortality [1–3], excess mortality is found only in comparison with standard Schwarz vaccination but not in comparison with unvaccinated children [1, 2, 10]. Studies of Peruvian children 2 years after immunization with high-titer EZ revealed a lower percentage of CD4 cells and reduced mitogen-induced lymphoproliferation responses than in children receiving low-titer vaccine [7]. In Guinea-Bissau [6], recipients of high-titer vaccine had no difference in CD4 cell percentages or total CD4 cell counts but tended to have lower CD4:CD8 cell ratios than recipients of standard vaccine. These differences, though small in magnitude and within the range of normal values, were most consistently observed in girls [6, 7]. In Senegal, we did not observe a reduction in CD4 cell percentage, in total CD4 lymphocyte count, or in CD4:CD8 cell ratio. It is unclear whether these observations are meaningfully related to the sex-specific differential mortality observed in several studies [1–3]. Hence, we may need to look for other mechanisms to explain the differential mortality for girls receiving different measles vaccines.

Studies have suggested that Schwarz standard vaccine has a beneficial impact on survival that cannot be explained by control of acute and long-term consequences of measles infection, and this effect may be particularly strong for girls [10]. In this perspective, the reduced survival associated with high-titer EZ measles vaccine may be due not to a damaging effect of the vaccine but more to high-titer vaccine not having the same beneficial impact as standard Schwarz measles vaccine.

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Disseminated Acyclovir-Resistant Herpes Simplex Virus Type 2 Treated Successfully with Foscarnet

Colleagues—We describe a case of disseminated herpes simplex virus (HSV) type 2 infection in which a 22-year-old man developed multiple cutaneous lesions, organomegaly, hepatitis, and renal insufficiency. He was initially treated with intravenous (iv) acyclovir, but cultures of skin lesions demonstrated resistance to acyclovir. After he was switched to trisodium phosphonoformate (foscarnet), his condition improved. We believe this to be the first reported case of acyclovir-resistant disseminated HSV infection with acute hepatitis treated successfully with foscarnet in a patient without AIDS or organ transplantation.

Dissemination of an HSV infection is rare and usually occurs in organ (heart, liver, or kidney) [1, 2] transplant patients and in those receiving medical treatment with steroids [3]. It also occurs in pregnant women [3], infants [4], and those with hematologic malignancies [5], chronic alcoholic liver disease [6], leukopenia [1], and thymic abnormalities [7], all of which depress cell-mediated immunity. Patients with compromised cell-mediated immunity have more frequent and more severe infections with HSV [8].

Dissemination may be a complication of acute infection or reactivation of latent HSV [2]. Clinical presentations include fever and an early viral prodrome. The development of abdominal pain, mucocutaneous vesicular eruptions, and lethargy often follows the prodrome. Laboratory data show a left shift, fulminant hepatic necrosis with elevation of aminotransferase, and a coagulopathy that may progress to disseminated intravascular coagulation [5]. Autopsy studies of subjects with disseminated HSV infections have shown organ involvement of the skin, liver, kidneys, adrenal glands, and respiratory and gastrointestinal tracts [2]. The mortality rate of those with HSV involvement of the liver is >80% [1].

The use of acyclovir prophylaxis in patients with recurrent local HSV infections or with more immunosuppressed conditions (e.g., AIDS and medical immunosuppression) are contributing to the emergence of acyclovir-resistant strains of HSV [9]. These acyclovir-resistant strains can cause disseminated disease in immunosuppressed or immunocompetent patients. Acyclovir is dependent on viral thymidine kinase for phosphorylation and cellular enzymes for additional phosphorylation to its triphosphorylated form, which inhibits viral DNA polymerase and therefore inhibits viral replication. Thymidine kinase–deficient or –defective HSV strains have become more frequent in immunocompromised patients and in those previously treated with acyclovir [9]. This resistance is due to selection of thymidine kinase–deficient or –defective virus strains that are unable to phosphorylate acyclovir. Foscarnet also inhibits viral DNA polymerase, but it is not dependent on viral thymidine kinase or phosphorylation and is therefore effective against acyclovir-resistant HSV strains.

We describe a 22-year-old patient who initially presented to his local emergency department with a 1- or 2-day history of dysuria and urethral discharge and increasing abdominal pain accompanied by anorexia and fatigue. He was found to have elevated serum aminotransferase levels. He was transferred to our institution for further evaluation. The patient had persistent fever following a viral prodrome and developed cutaneous lesions (scalp, face, nares, palms, fingers, buttocks, perineum, and soles; figure 1).

His medical history included aplastic anemia diagnosed in 1988 and untreated myelodysplasia diagnosed in 1991. Al-

Informed consent was obtained from the patient for photography of the lesion.

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