**Table 4** Serum Anti-Vi IgG Response in Children Two to Five Years Old Receiving Two Injections of Vi-rEPA at Various Dosages

| Dosage (μg) of Vi as Vi-rEPA | Number of children, IgG anti-Vi (N, GM of ELISA units/mL) | | |
|---|---|---|---|
| 5.0 | 80, 0.17 | 80, 43.0 | 75, 6.43 |
| 12.5 | 80, 0.14 | 80, 74.7 | 79, 11.3 |
| 25.0 | 78, 0.13 | 77, 102 | 77, 13.3 |

11.3 and 13.3 versus 6.43, $p < 0.001$; 13.3 versus 11.3, $p > 0.5$.

immune response. At one year's time, the anti-Vi IgG levels were 13.3, 11.3, and 6.43, respectively (13.3 and 11.3 vs. 6.43, $p < 0.001$; 13.3 vs. 11.3, NS). The anti-Vi IgG levels in all three dosages declined about sevenfold from the 10 weeks levels, but remained significantly higher than the preimmune levels ($p < 0.0001$); 96% of children still had levels eightfold or greater over their baseline. Based on these data, we recommend a dosage of 25 μg for all ages. This study also confirmed the safety and consistent immunogenicity of the four lots of Vi-rEPA used in this and previous trials (10,33,34).

*Infant Study*

To complete the full course of clinical studies of the Vi conjugate vaccine, a safety and immunogenicity study of Vi-rEPA administered to infants concurrently with routine immunizations (DPT, polio, and hepatitis B) is currently under study in Phu Tho province, Vietnam. In this study, 308 infants were randomly divided into three groups, each receiving four injections of Vi-rEPA or Hib conjugate vaccine or none, in addition to the routine vaccines at 2, 4, 6, and 12 months. Safety data compared among groups showed that Vi-rEPA was safe in infants. Cord blood at birth will be used for estimation of preimmune anti-Vi levels. Blood samples taken at 7, 12, and 13 months will be analyzed and compared for their DPT, Vi, or Hib IgG levels, whenever applicable. The level of anti-Vi IgG will be compared with the estimated protective level from our phase III efficacy trial for assessment of the protection against typhoid fever.

## Vi as a Probe to Investigate the Effect of Birth Weight on Antibody Responses in Adulthood

There is evidence that links low birth weight to susceptibility to chronic disease in adulthood. Evidence is also emerging that some components of immune function may be programmed in early life. The relation between size at birth (full term) and response to Vi vaccination in a cohort of 257 adults (mean age: 29.4 year; 146 men) born in an urban slum in Lahore, Pakistan, during 1964 to 1978 was studied. A single dose of Vi polysaccharide vaccine or two doses of rabies vaccine, representing T-independent and T-dependent antigens, respectively, were given to the volunteers. Antibody titers were measured in pre- and postvaccination serum samples. Response to typhoid vaccination was positively related to birth weight (IgG anti-Vi; $r = 0.138$, $p = 0.031$; IgM anti-Vi, $r = 0.197$, $p = 0.034$) but no correlation was found with the rabies vaccine (35).

Reinjection of Vi three years later was compared with another T-dependent antigen, the Hib conjugate. The results showed the same birth weight dependence for Vi but not for Hib conjugate (36). These findings add to a growing body of evidence suggesting that components of the immune system may be permanently programmed by events in early life. The contrasting effects on responses to typhoid and rabies or Hib conjugate vaccines suggest that antibody generation to polysaccharide antigens is compromised by fetal growth retardation. Since this birth weight phenomenon was not observed with a polysaccharide conjugate vaccine, the early-life programming is probably targeted mainly at B-cell immunity. It still remains the case that the molecular basis of immune responses to polysaccharide antigens is the least well understood of all antibody responses yet clinically deficient responses have the most profound consequences for humans.

We plan to use the Vi vaccine as a probe to assess functional immunity in a cohort of children five years old in Gambia, which might help us to understand conditions in infancy that affect the immune response in childhood. This particular group is well characterized with detailed information available on maternal nutritional status, fetal growth (by serial ultrasonography), birth size, infant feeding status, growth and morbidity in infancy, and thymic development. The study will link the correlation of birth weight to immune response in early ages.

## VACCINES AGAINST *SALMONELLA PARATYPHI* A AND NONTYPHOIDAL *SALMONELLA*

For many years in South and Southeast Asia, the second most common cause of enteric fever has been *Salmonella paratyphi* A (37,38). Since 1999 after implementing Vi vaccination, more *S. paratyphi* A than *S. typhi* strains have been isolated in the province of Guangxi, southeastern China (39). There has also been an increase in *S. paratyphi* A infections in the Indian subcontinent (40).

In developed countries, the most common causes of *Salmonella* outbreaks are *S. typhimurium* (group B) and *S. enteritidis* (group D) (41). These *Salmonella* are zoonotic, and the infections are generally foodborne. *S. typhimurium* and *S. enteritidis* are also important causes of bacterimia in African children (42). The emergence of multidrug-resistant Typhimurium phage type DT104 in United Kingdom in the 1980s raised alarm over the usage of antibiotics in animal feed. DT104 infection is common in a broad range of food animals, such as poultry, pigs, and sheep (43). DT104 spread to other parts of the world in the 1990s, and it is now a common *Salmonella* type in as many as 30 countries, mostly industrialized, including the United States, the United Kingdom, Germany, Denmark, and France (43,44). This phage type has become a matter of concern because of its rapid international dissemination and its ability to readily acquire additional resistance traits to other, clinically important antimicrobial drug classes, such as fluoroquinolones, trimethoprim, and cephalosporins (44).

There are no licensed vaccines for nontyphoidal *Salmonella*. The killed whole-cell parenteral TAB vaccine, composed of inactivated *S. typhi*, *S. paratyphi* A and B, was discontinued from manufacture in the United States and other countries because of the high rates of adverse reactions and lack of efficacies for the Paratyphi components (45). The major challenges in development of new *S. paratyphi* A and *S. typhimurium* vaccines are to reduce adverse reactions and improve immunogenicity.

The O-SP of groups A, B, and D *Salmonella* share the same backbone structure:

2-αD-Man*p*-(1→4)-αL-Rha*p*-(1→3)-αD-Gal*p*(1→
3
↑
1
R