In this issue of the Journal, the report by Banerjee et al. [1] on the postneonatal protective effect of a prior neonatal infection with G10P[11] rotavirus has important implications for rotavirus vaccinology. The protective efficacy of a neonatal rotavirus infection has been addressed previously by various investigators. In a 1983 Australian study, neonates with asymptomatic rotavirus shedding during the first 14 days of life developed fewer and less-severe rotavirus-positive diarrheal illnesses postneonatally than did control children [2]. The available strains causing neonatal infection had identical electrophoretic patterns (in addition, 1 strain was identified as an “M-like” [G3] strain [3, 4]), whereas the strains causing postneonatal infection had varying patterns. Although serotypic characterization was not readily available at the time, evidence now indicates that asymptomatic neonatal G3 infections protected against community rotavirus strains, including heterotypic serotype G1 and G2 strains, during the 3-year period of surveillance [5, 6].

Two groups set out to confirm this concept by comparing the incidence of postneonatal rotavirus illnesses in a cohort of infants infected during the neonatal period with a G9[P11] rotavirus strain 116E or with a G10P[11] strain I321 [7, 8], the latter strain being similar to the neonatal strain described by Banerjee et al. in this issue of the Journal [1]. These studies also found that a neonatal infection induced protection against postneonatal rotavirus illnesses. Data on protection against specific serotypes were not available; however, in the study on strain I321, the postneonatal strains had varying electrophoretic patterns, suggesting heterotypic protection.

A variety of other longitudinal studies of children, beginning at birth and extending up to 3 years of age, have examined the protective efficacy of a primary rotavirus infection against subsequent rotavirus exposure [9–13]. However, the degree of protection was found to be inconsistent, ranging from none to substantial. Substantial protection was exemplified by a Mexican study in which a single rotavirus infection induced 87% protection against moderate-to-severe rotavirus–positive diarrhea, and 2 infections induced 100% protection. When a second infection occurred, the serotype responsible tended to be different from the original infecting strain [13]. Moreover, high titers of serum anti-rotavirus antibodies, particularly IgA, were associated with protection against rotavirus infection and moderate-to-severe diarrhea [14].

The protective role of preexisting, naturally acquired homotypic and heterotypic rotavirus antibodies was addressed in a study in a home for infants in Japan [15]. A relatively high level of neutralizing antibodies against the infecting serotype was highly protective, whereas neutralizing antibodies against heterotypic strains provided much less or no protection, indicating that homotypic antibodies were a major correlate of protection in this study.

The protective effect of neonatal infection on postneonatal illness also has been addressed in vaccine studies in Finland, where (1) neonatal vaccination with a monovalent bovine Nebraska calf diarrhea virus vaccine (NCDV; G6P[1]) modified the severity of rotavirus illness [16] and (2) a single dose of tetravalent rhesus rotavirus–based tetravalent (RRV-TV) vaccine (a Rotashield precursor) given to neonates protected against fever associated with a second dose of RRV-TV vaccine at 2 months of age [17].

Furthermore, field trials of rotavirus vaccines given to infants and young children compared the protective efficacy of multivalent and monovalent rotavirus vaccines against homotypic and heterotypic rotavirus serotypes. Such trials included comparisons of (1) a tetravalent RRV-TV vaccine and one of its monovalent components [18–20], (2) a multi-
valent human-bovine (WC3) reassortant vaccine and one of its monovalent components [21], and (3) a monovalent Rotarix vaccine and a placebo [22]. Overall, these studies demonstrated that serotype-specific (homotypic [protein VP4 or VP7]) protection was not only an important correlate of resistance but also more effective than heterotypic protection; however, the advantage of homotypic protection was not absolute, given that heterotypic protection was also observed but at a lower level. Furthermore, a significant protective effect of prior natural infection against later rotavirus disease was documented in follow-up studies of placebo recipients from rotavirus-vaccine field trials [23–25].

Animal studies have failed to clarify the issue. For example, in cross-challenge studies of piglets and infant mice, serotype-specific protection against diarrhea was demonstrated [26, 27]. However, in challenge studies of adult mice, the involvement of neutralizing antibodies against infection was not observed [28].

Although the weight of evidence shows that naturally occurring or vaccine-induced infections confer a high degree of protection against a subsequent rotavirus illness, consensus on whether serotype-specific immunity is the key to this protection still has not been reached. Therefore, 2 points of view have emerged: one supports the concept that serotype-specific immunity is vital to achieving a high level of protection and, hence, the development and evaluation of multivalent vaccines (based on rhesus and bovine rotavirus [WC3 or UK]) [29–31]. The other supports the concept that a single rotavirus infection of any serotype will induce protection against all relevant rotavirus serotypes, leading to the development and evaluation of monovalent vaccines, such as Rotarix [22]; lamb rotavirus, a G10 strain [32]; neonatal strains 116E[G9], I321[G10] [33, 34], and RV3[G3] [5, 6]; and, in earlier studies, other monovalent strains such as NCDV (G6) [35], RRV (G3) [36], and M37 [37].

In this issue of the Journal, Banerjee et al. [1] examine whether a naturally occurring, monovalent neonatal rotavirus infection will protect against postneonatal illnesses caused by prevailing rotavirus serotypes. They studied a cohort of children from 3 overcrowded urban slums in Vellore, India, who were recruited at birth and screened during the first 28 days of life (the neonatal period) for evidence of infection specifically with a G10P[11] rotavirus strain, a criterion for inclusion in the study group. They compared the incidence of rotavirus illness in this neonatally infected group (called the “exposed group”) over a 2-year period with that in a control group of infants not infected neonatally with any rotavirus (called the “unexposed group”). The G10P[11] strain had particular relevance because neonatal infection with I321, a G10P[11] strain, had been shown previously (as described above) to protect against postneonatal rotavirus-confirmed diarrhea and, in addition, had been considered as a vaccine candidate [8, 33, 34]. This work by Banerjee et al. involved a comprehensive clinical and laboratory-based epidemiological study: infants were visited routinely twice a week by a field-worker, and stool specimens were collected routinely every 2 weeks and, in addition, during periods of illness. The exposed and unexposed groups were unequal in size, with 33 children in the exposed group and 300 children in the unexposed group. The authors found that, in the exposed group, neonatal G10P[11] infection did not protect against subsequent postneonatal rotavirus diarrhea (of any severity) caused by prevailing serotypes, when compared with the occurrence of rotavirus diarrhea in the unexposed group. Critical to understanding this failure was an analysis of the prevailing rotavirus serotypes. In short, was there any heterotypic protection; if not, was there homotypic protection?

Advoates of the view that serotype-specific immunity is the key to protection may now be thinking that, in the study by Banerjee et al. [1], neonatal G10P[11] infection failed to provide protection, because most of the postneonatal illnesses were caused by non-G10P[11] rotavirus serotypes. Although illness caused by heterotypic non-G10P[11] rotavirus serotypes occurred, postneonatal illness caused by homotypic G10 serotypes also occurred. To our surprise, Banerjee et al. found that the rates of all postneonatal episodes of illness caused by G10 serotypes, regardless of severity, were not significantly different between the exposed and unexposed groups. Thus, there was neither homotypic nor heterotypic protection induced by neonatal G10 infection, an unanticipated finding.

Among children <5 years old, rotavirus causes ~610,000 deaths annually worldwide but predominantly in developing countries [32]; with the urgent need to introduce rotavirus vaccines in developing countries, this type of study takes on special importance. It is critical to know whether protection will be induced in a developing country through the use of vaccines that have been shown to be highly effective in developed countries. The failure of certain vaccines in developing countries is well known [38]. Banerjee et al. [1] have performed a comprehensive study to examine the protective role of neonatal infection in the setting of a poor developing country: a total of 69,264 scheduled routine visits were done, and 19,503 stool samples were collected from the 333 children during 15,964 child-fortnights of observation. Studies of this type are undertaken too infrequently because they are expensive, unglamorous, and time consuming; are not considered by some to be “cutting edge”; and usually are not published in journals of the broadest interest. However, these studies are essential for the evaluation of licensed and candidate vaccines before widespread introduction into any immunization program. In addition to the monovalent Rotarix and pentavalent RotaTeq vaccines, which are now licensed by regulatory authorities for use in various countries, other vaccine candidates including neonatal rotavirus strains 116E and RV3 are under devel-
opment in India and Indonesia, respectively, and a bovine (UK) rotavirus–based vaccine is under development in China, India, Brazil, and the United States; in addition, a licensed lamb G10 rotavirus–based vaccine is already in use in China [32, 39]. These vaccines need to undergo comprehensive evaluation in the setting of a developing country.

It has been suggested recently that rotavirus vaccines be given neonatally at 0–4 weeks of age, followed by a second dose at 4–8 weeks of age, to avoid vaccination during the period of 3 or 4 to 9 months of age, when intussusception reaches its peak under natural conditions [40, 41]. This suggestion has been prompted by the observation that ~80% of the cases of intussusception after the first dose of Rotashield occurred in infants vaccinated at ≥90 days of age [40, 41]. Would a rotavirus vaccine be effective if given in this schedule in a poor developing country [42]? A study similar to that of Banerjee et al. [1] would be critical to answering this question in areas of the world where a rotavirus vaccine is needed most.

Is there any explanation for the absolute failure of neonatal infection to induce protection postneonatally, a finding not consistent with previous studies? Banerjee et al. [1] note that they obtained blood specimens from the cohort of infants; however, serologic data are not presented. This is a critical piece of information that may shed light on why neonatal infection failed to induce any protection. Did the neonates develop antibodies to the infecting neonatal strain? If not, could the shedding of virus represent carriage of rotavirus, at least in some of the neonates [43, 44]?

Was the I321 strain poorly immunogenic in these neonates, as described recently in a phase I trial of the I321 vaccine candidate among infants [34]? Did presumed high levels of maternal antibodies inhibit the seroresponse [45]? What was the nutritional status of the newborns? Did it influence their ability to mount an antibody response [42]? Did the large difference in the size of the exposed and unexposed groups (33 vs. 300 children), along with the wide confidence intervals for severe rotavirus–confirmed diarrhea and serotype–specific rotavirus–confirmed diarrhea, affect the outcome of the study?

In response to the title of our article, we support the concept that serotype–specific antibodies to epidemiologically important serotypes are the major component of and are essential for optimal protection, especially in unprimed infants, who characteristically develop only homotypic responses [46]. Serotyping of circulating strains should be an integral part of all field trials. In addition, if feasible, blood specimens should be obtained at least from a sample of vaccine recipients and control children, to determine not only whether the vaccine was acceptably immunogenic overall but also whether it induced antibodies against individual serotypes. Perhaps the question of the relation and importance of serotype–specific immunity in humans, a subject that has been examined carefully by numerous investigators [47], will finally be resolved conclusively only after large-scale use of the multivalent and monovalent rotavirus vaccines, both licensed and under development, and after analysis of their respective protective efficacies against a variety of serotypes (current or emerging).

However, caution must be observed in the interpretation of data regarding homotypic and heterotypic immune responses and protection in clinical trials. After rotavirus infection, infants (<6 months old) were found to mount significantly fewer heterotypic responses, compared with adults (1.2% vs. 59%, respectively), whereas the number of homotypic responses, although fewer, was not significantly different (66% vs. 83%, respectively) [46]. Moreover, in prevalence studies in Ecuador, a significantly greater percentage of infants (6–12 months old) had naturally acquired neutralizing antibodies to only 1 rotavirus serotype, compared with older children, whereas a significantly greater number of older children had such antibodies to each of 4 serotypes (G1–G4), compared with the infants [48]. In addition, immunity after primary infections in naive animal models is almost exclusively homotypic [49–51]. To further confound matters, asymptomatic rotavirus infections are not uncommon during the first 2 years of life [43, 44]. Thus, if infants develop heterotypic immunity after vaccination, it will be difficult to determine whether it was due strictly to the antigenic composition of the vaccine or it reflects prior rotavirus exposure [43, 44]. Nevertheless, regardless of the complexities in resolution of the role and importance of serotype–specific immunity, serotyping should remain a vital element in all rotavirus-vaccine trials.

References


