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David O. Matson
Old Dominion University

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On a Multinational Assessment of Rotavirus Disease in Europe

David O. Matson

Graduate Program in Public Health, Eastern Virginia Medical School and Old Dominion University, Norfolk

Rotaviruses were discovered in the 1960s in animals and in the 1970s in humans; the latter discovery was made by an intrepid group who performed duodenal biopsies on children with acute gastroenteritis (AGE) [1]. By the late 1970s, data already clearly indicated that rotavirus was the cause of the annual winter peak of AGE affecting young children, as well as a frequent cause of severe gastroenteritis in various animal species (e.g., [2–5]). Use of the retrospectroscope clarified or left as tantalizing the suggestion that rotaviruses were the cause of the annual "winter vomiting syndrome" first described in children in 1910 in Japan [6] and in 1929 in the United States [7]. The recognition of that winter peak was a result of improved water and sewage handling that markedly reduced exposure to bacterial and parasitic pathogens but not to the common viral pathogens.

Many studies have been conducted to examine the burden of rotavirus disease. Most of these have been cross-sectional in design, have documented the high (usually 30%–60%) frequency of rotavirus detection among children hospitalized with AGE, and have found that the more intense the severity of illness, the more frequently rotavirus is detected. Longitudinal, cohort studies of rotavirus disease have been fewer in number, and most of these have suffered from study design issues, such as enrollment of subjects at an age later than birth, resulting in infections at an early age being missed, or assessment of rotavirus infection only by detection of virus excreted in stool, when a large fraction of rotavirus infections are detected not by routinely applied assays but by seroresponse. Population-based studies have been even less frequently undertaken, and most such studies have depended on indirect measures of rotavirus disease—namely, the assignment of International Classification of Diseases codes, along with occurrence of the codes within age, season, and list position (within a list of assigned International Classification of Diseases codes) distributions [8].

Direct, active surveillance always is preferred to indirect measures in attempts to identify cases of any disease. In the studies reported in this supplement to the *Journal of Infectious Diseases,* conducted by Pierre Van Damme and his colleagues in Europe [9–12], several laudable features were part of the study design: establishment of defined geographic surveillance regions with known populations, active surveillance at treatment sites for different acuities of AGE and for that fraction of cases caused by rotavirus, application of the same study protocol within different countries at the same time, and broad probing for factors affecting the cost of the illness and care for it.

Perhaps the authors expected that the cumulative results of this effort would lead to data enabling a unified, simplified extrapolation, to Europe or to western Europe, of the burden of the syndrome and that fraction caused by rotavirus. The surprise, for me, is the variance that was observed in the results: multifold differences among study regions in the incidence of AGE of all causes in the same age group, similar differences among regions in the incidence of AGE attributable to rotavirus, major differences in the prevalence of different rotavirus serotypes in study regions not too far apart, and striking differences in estimates of the cost of AGE as a syndrome and of AGE attributable to rotavirus. The least unexpected of these results are the differences in rotavirus serotype prevalence by region. We have known from prior studies that rotavirus serotype distribution changes every 1–2 years in some regions, but a single serotype also may be predominant for as many as 10 years in a region.

These differences in disease incidence were, perhaps, not unexpected, because we still have major differences within countries with well-developed infrastructure in water and sewage handling and in living conditions that affect exposure to enteric

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Reprints or correspondence: Dr. David O. Matson, Eastern Virginia Medical School, PO Box 1980, Norfolk, VA 23501-1980 (matsondo@evms.edu).

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pathogens. Particular differences that affect gastroenteritis disease burden include the presence and amount of sewage handling through septic tanks, practices for the pretreatment of sewage before discharge, types and degree of contamination of drinking source waters (lakes and rivers in comparison with aquifers accessed through deep or shallow wells and the soil and rock formations above them), differences in close exposures to animals that can be a source of human infections, and the degree of crowding in living conditions. For the latter, think only of differences in the "environmental quality" among and within child care centers, nursing homes, and hospitals: food handlers who do not wash their hands or wear mandated gloves; changing of soiled diapers and bed clothes and their disposal and cleaning at inappropriate locations, such as in kitchens; and the use of contaminated water for the washing of food. It also is possible that, just as physicians differ in the frequency of referral of patients from the office setting to the emergency department and/or hospital setting, parents are also likely to differ in their sense of a need for medical care for their child's gastroenteritis episode. There are hints that the study populations may have differed to large degrees; for example, the rate of parents speaking a language not native to the study region was 41% at one study site, whereas this rate was much lower (<10%) elsewhere.

The limitations of the studies perhaps are overemphasized by the authors. It is important to emphasize the positive aspects: large, predefined study populations; active surveillance at treatment sites intended to care for differing acuities of disease; and uniform definitions and analysis factors. The authors properly restate, on the basis of their work, that rotavirus is a significant cause of an expensive potentially vaccine-preventable disease in Europe. Their results provide useful information needed to design surveillance protocols for assessing vaccine effectiveness. It is worth noting that Europe now has 2 licensed rotavirus vaccines and that these 2 vaccines differ greatly in their approaches to the induction of protective immunity. One vaccine is monovalent, the other pentavalent. Although phase 3 studies [13, 14] have given similar overall efficacy results, differences were found in serotype-specific efficacy that would be expected from the differences in antigenic composition of the vaccines. The 2 vaccines also differ in the number of studied doses. I encourage the authors, in a follow-up report, to consider the fraction of vaccine-preventable disease by study region and to study the efficacy of the 2 licensed vaccines. It will be important, going forward, to continue to measure accurately the differences in effectiveness related to the number of vaccine doses and serotype-specific protection. In this regard, the variability in observed rates of illness, patterns of treatment related to physician referral practices, and serotype distribution in these studies with a common, robust study protocol suggest that ongoing surveillance will need careful design. Active surveillance is also likely to trump indirect surveillance in this undertaking.

The observation of significant differences among age distributions of prevailing serotypes in the different study regions deserves some comment. When examined over multiple years and/or over different regions, rotavirus serotypes do not show significant differences in age distribution among affected children; such findings have falsely led to the conclusion that rotavirus serotypes never differ in age distribution. What should we think when faced with the REVEAL Study findings of marked differences in serotype distribution by age? Distributions of rotavirus serotypes do differ within a single region, across ages from one season to the next, and among widely separated regions in the same rotavirus season [15, 16]. The patterns observed result from the introduction of serotypes that are new to a region; these serotypes first appear within cities and then spread over a 2- to 3-year period to the surrounding rural regions. Spread of the new serotype across broad geographic regions may take years, unlike influenza and more like cholera [17, 18]. When the epidemic serotype enters a population, its age distribution is broader than that of established, endemic serotypes, affecting a greater percentage of young infants whose mothers lack recent exposure to the serotypes and of older children and adults whose acquired immunity is insufficient to protect against illness caused by the epidemic type. These patterns have important implications for the design of appropriate disease and serotype surveillance after the introduction of mass immunization.

We can look forward to a reduced burden of rotavirus disease, now that we have new vaccines to prevent infection and illness. The success of that intervention strategy will be measured by the collection of accurate data. Van Damme and colleagues have provided a model from the prelicensure period for how to consider such studies now that mass vaccination has begun.

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