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Rotavirus G9 Severity Data Revisited

To the editor. Linhares et al. [1] and the accompanying editorial commentary by Kang [2] describe an association between rotavirus serotype G9 (hereafter referred to as G9) infection and severity of diarrhea among infants from Brazil, Mexico, and Venezuela in 2001–2002. Such a finding is important when >100 million rotavirus infections and 440,000 deaths occur yearly among children <5 years of age [3]. G9 has emerged as the fifth most common rotavirus serotype; however, specific coverage of G9 strains is not included in 2 well-studied, currently available vaccines [4–6].

Several issues warrant additional comment. Linhares et al. [1] used data collected from 454 infants in the placebo group of a rotavirus vaccine study [7] who met criteria for the primary efficacy analysis; these were "subjects who received 2 doses of study vaccine or placebo [and] who had no rotavirus other than vaccine strain in stool samples collected from the first dose until 2 months after the second dose" (p. 809). Because the second placebo dose was administered at a mean of 18.1 weeks, the primary efficacy analysis data only include subjects between 5–12 months of age.

Sixteen additional placebo recipients developed rotavirus infection (all due to the G1 serotype) between receipt of the first and second placebo doses; one-half of the infections were severe [7]. The primary efficacy analysis data excluded these recipients, thereby artificially elevating G9 prevalence to 29% (15 of 51; from 22% [15 of 67]). Eight of the excluded G1 episodes were severe, potentially impacting calculations and comparisons with G9.

Two recipients of placebo each experienced 2 separate episodes of rotavirus gastroenteritis: 1 patient experienced 2 G1 infections, and the other experienced a G9 infection followed by a G1 infection [7]; however, it appears that these recipients were included in the primary efficacy analysis. Prior infection with rotavirus reduces subsequent infection severity [8], which is also important in vaccine protection against severe disease [5–7]. Inclusion of these 2 subjects who experienced second G1 infections in the severity analysis would, therefore, decrease G1 infection severity calculations.

Data are provided regarding the age at hospitalization and not at infection [1]; however, data suggest that G1 disease might occur earlier. If all episodes of rotavirus are considered, it is likely that G1 infections occurred earlier than G9 infections—a fact that is difficult to attribute to maternal antibodies. Another possibility, as alluded to by Kang [2], is that a G9 epidemic occurred, as serotype data in Venezuela, Mexico, and Brazil are sparse and vary regionally [9–11]. The natural incidence of severe rotavirus gastroenteritis peaks among patients aged 9–11 months [12]; a G9 infection epidemic in 2002 would have encountered many infants in this age range. Although introduction of a new strain of rotavirus into a new population should result in disease across all age groups, as Kang argues [2], the failure to document cases of adult disease does not provide evidence against an epidemic. Adults are rarely tested for rotavirus, and serotype data are lacking, with few exceptions [11, 13, 14]. Thus, failure to appreciate an epidemic among adults does not exclude a late G9 epidemic, which could account for excess G9 infection severity.

These important issues complicate the G9 infection severity calculations that have global implications for the development of several rotavirus vaccines (for which G9 efficacy data are limited) [5–7]. Voluntary ingestion of G1 versus G9 in a randomized, blinded trial [13], although unpalatable, is necessary to completely clarify the relationship between serotype and severity of diarrhea.

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Reply to Anderson

To the Editor—In response to the letter by Anderson [1] entitled "Rotavirus G9 Severity Data Revisited," I would like to take this opportunity to address his comments. I agree that it is scientifically valid to consider the entire intention-to-treat cohort when assessing the disease severity associated with infection with individual rotavirus strains. Accordingly, a preliminary reanalysis of the intention-to-treat data from placebo recipients has been conducted. This analysis includes all cases of rotavirus gastroenteritis in our study that occurred between the first and second dose of placebo, cases of rotavirus gastroenteritis that occurred within the first 2 weeks after receipt of dose 2, and all cases that occurred from 2 weeks after administration of dose 2 up to 1 year of the patient's age, but it excludes the 2 second episodes in the 2 infants who experienced them, as previously documented [2]. The median severity of illness (according to the Vesikari severity score) was 11 for rotavirus serotype G1 (hereafter referred to as G1) infection and 14 for rotavirus serotype G9 (hereafter, G9) infection, the difference between which was found to be statistically significant ($P = .009$). This reanalysis supports our original observations [2, 3]: that more-severe disease is associated with infection with G9.

Recent data support the growing epidemiological importance of G9 in rotavirus disease [4], and experience with human rotavirus vaccine clinical trials has also shown a high incidence of circulating G9 (e.g., up to 60% in Brazil) [2, 5]. Thus, rotavirus vaccines will need to demonstrate efficacy against this serotype. Results of clinical trials for the human rotavirus vaccine have shown high efficacy against G9 in Latin America (90% efficacy against severe disease due to G9); these findings have also recently been confirmed in a trial conducted in a European setting (95% efficacy against severe disease due to G9) [5].

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Pandemic Influenza Outbreak Planning in Seattle

To the Editor—The News section of the 1 August 2006 issue of *Clinical Infectious Diseases* [1] includes a reprinted *Reuters* article dated 7 June 2006 and entitled "U.S. States Plan How to Handle Pandemic Flu Threat" that contains inaccurate information regarding recommendations reportedly being made by Public Health–Seattle and King County (Seattle, WA). Specifically, the article states that, "And in Washington State, the King County public health department in Seattle has warned people that if body bags and refrigerated trucks are in short supply, influenza victims should be buried in backyards, provided that the graves are far from septic systems" [1, pg. iv].

This is not a recommendation Public Health–Seattle and King County has made or will make during a pandemic influenza outbreak or during any other mass-fatality incident. We do not and will not recommend or condone burying of the deceased on private property (e.g., a backyard). This violates current Washington state law [2]. Furthermore, it is essential that every death be recorded and that a death certificate be filed with the county. Private, unauthorized disposition would preclude both of the above.

Public Health–Seattle and King County is currently planning how to properly manage the increased number of deaths that might occur during a pandemic influenza outbreak. In all of our fatality-management planning for pandemic influenza and other multiple-fatality events,