We thank Dr. VanderWeele for his thoughtful addition (1) to our analysis of the interactions between coinfecting enteric pathogens (2). We appreciate the generalizability of his framework that allows the relaxation of the assumption of monotonicity. Here, we consider the importance of the biology to the monotonicity assumption, causal inference, and the scale on which mechanistic interaction is assessed. Furthermore, we highlight the public health impact of our findings on the additive scale.

“Monotonicity” refers to the condition in which the exposure never prevents the outcome. The importance of assuming monotonicity depends on the threshold to which the relative excess risk due to interaction (RERI) is compared (referred to as the “interaction contrast ratio” by Bhavnani et al. (2)). In his invited commentary, Dr. VanderWeele points out that our inferences about rotavirus-Giardia and rotavirus-Escherichia coli interactions do not require assumptions of monotonicity because our estimated RERI exceeds the most stringent of these thresholds (RERI > 2) (1). However, in some applications, such as our study, monotonicity is not implausible. Like many other infectious agents, rotavirus, Giardia, E. coli, and Shigella are widely accepted as being pathogenic and not protective for diarrheal disease. Hypothesized pathways through which these agents might confer protective effects may themselves be less plausible than monotonicity. Thus, given our biologic understanding of these pathogens, our finding that RERI is greater than zero may be sufficient to signal mechanistic interactions between rotavirus and other enteric pathogens. To move beyond reporting statistical interaction to making causal interpretations however, it is important to consider the biology underlying the mechanism of interaction. Evidence for statistical interaction on a population level does not necessarily correspond to mechanistic interaction at the individual level.

The underlying biology may also guide the decision of the scale on which to assess interaction. Dr. Weinberg describes in a recent commentary (3) that we should focus on the construction of causal models (additive or multiplicative) that best describe the data, such that we may gain better insight into the disease process. Although it is common to use multiplicative models to make inferences about additive interactions, there may be systems in which multiplicative interaction is of greater interest. For example, molecular research has shown that antiretroviral drugs and drug-resistant reverse transcriptase may have multiplicative effects on the replication of human immunodeficiency virus type 1 (HIV-1) mutants (4). In contrast, there are systems in which there is biologic basis for additive interactions (e.g., refer to the report by Lee et al. (5)). In our efforts to further understand the etiology and pathogenesis of diarrhea, we present results that strongly support synergistic interactions between rotavirus and Giardia on both scales; future molecular studies are needed to confirm the biologic plausibility of these inferences.

As addressed by Dr. VanderWeele, estimates of multiplicative interaction are reported with greater frequency than those of additive interaction. Although it is often more convenient to assess multiplicative interaction by using the regression models typically found in epidemiology, reporting on additive interaction may be more relevant for a public health audience. For instance, Dr. VanderWeele shows that, in those exposed to both pathogens, the proportion of the risk of diarrhea attributable to the interaction between...
rotavirus and Giardia is 74.2%. Similarly, for rotavirus and E. coli coinfections, the attributable proportion is 75.2%. This suggests that, in areas with high rates of coinfecting pathogens, such as Giardia and E. coli, vaccination efforts that reduce exposure to rotavirus may prevent more cases of diarrhea than originally estimated. Furthermore, although Giardia on its own may not be considered highly pathogenic, our evidence for synergistic interactions between rotavirus and Giardia highlights its pathogenic potential in populations where rotavirus is also circulating.

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