registry in Basrah and to prepare a design for a case-control study on childhood leukemia. This endeavor is still under way. ■

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Contributors

Both authors jointly wrote and amended this letter to the editor.

Reference

1. Hagopian A, Lafta R, Hassan J, Davis S, Mirick D, Takaro T. Trends in childhood leukaemia in Basrah, Iraq, 1993–2007. *Am J Public Health.* 2010;100(6):1081–1087.

HAGOPIAN ET AL. RESPOND

We thank our German colleagues for their interest in our work to measure the changing rates of pediatric leukemia in Basrah, Iraq, over the last 15 years. We appreciate their efforts before ours to measure cancer rates in the region, and their work to support the development of an Iraqi cancer registry, including valuable training for Iraqi epidemiologists. We would be interested in hearing more about their efforts to design a case–control study on childhood leukemia.

We agree with our German colleagues that to calculate accurate rates one must have both complete and accurate counts of the number of new cases (numerator) in a defined period of time as well as accurate counts of the population from which the cases arose (denominator) over the same period of time. In war zones, accurate population figures can be difficult to obtain. We were fortunate to have official population figures from Iraq's Central Organization for Statistics and Information Technology in 1997, and for other years we relied on population figures from other published work. The sources of our population numbers are carefully detailed in Table 1 of our paper.[1] We note the population increase over the 15-year period reported in our paper is 41.15%.[1] If that increase is overstated, then the increase in rates we report is actually underestimated; of course, the reverse is also true.

It is curious that the authors open their letter with a discussion about depleted uranium. We mention depleted uranium only once, and that is in the context of a list of possible exposures that could potentially be related to the rise in leukemia rates. We made no claims as to the likelihood that any of these exposures caused the rise in rates we observed.

Although we agree with the authors that it is important to be cautious in calculating rates, we maintain that, in the absence of certainty of the accuracy of the population data, it is incumbent upon us as scientists to report the information that *is* available, with full disclosure regarding the data sources used and appropriate caution in interpreting the results. ■

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Contributors

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Reference

1. Hagopian A, Lafta R, Hassan J, Davis S, Mirick D, Takaro T. Trends in childhood leukemia in Basrah, Iraq, 1993–2007. *Am J Public Health.* 2010;100(6):1081–1087.

APPARENT BENEFIT OF WATER FILTERS MAY BE AN ARTIFACT OF STUDY DESIGN

Colford et al. should be congratulated on an excellently conducted and presented study of the potential impact of filtering drinking water on gastrointestinal illness in older adults.[1] There is, however, one issue that deserves further consideration. The study basically compared self-reported illness rates among people who were given an active and a sham water filter. The study was a crossover design in that people were randomized to have an active or sham filter for 6 months and then were swapped to receive the alternate filter. Although crossover designed studies are frequently used in randomized controlled studies and have a number of advantages, they have serious problems when intervention in phase 1 influences the outcome in phase 2.[2]

Relative risk (RR) of illness associated with active filter use was very different in phase 1 compared with phase 2. From the mean episodes of highly credible gastrointestinal illness (HCGI) presented and person-years at risk from HCGI given in Colford et al.'s table 2, it is possible to calculate the crude RR for phase 1 and 2 independently. In phase 1 the crude RR of illness in people with the active filter was 1.030 (95% confidence interval [CI]=0.905, 1.172) whereas in phase 2 this was 0.740 (95% CI=0.622, 0.879). In other words all of the excess risk associated with the sham filter was seen among people who had previously used the active filter and then reverted to drinking unfiltered water. In people who had not previously used the active filter there was no excess risk and indeed the illness rate was slightly higher in the active group.

Although the authors included cycle number as a possible confounder in their models, this would be inadequate to identify any interaction with the order of filter use (active–sham versus sham–active). Simply including cycle phase in the model will be confounded by the decline in reporting of self reported symptoms with time since recruitment that is usually seen in prospective studies of self-reported symptoms.[3]

This issue will have important implications for the conclusions. As currently presented the conclusion is that if you are an older person drinking water from such a supply, then installing a filter will reduce your illness by around 12%. When taking into account the interaction with order of filter use, the conclusion may be that, if you are an elderly person drinking from the supply, installing a filter will not affect your risk of gastrointestinal illness. However, if you do install a filter and then stop using it after 6 months your risk of illness over the following 6 months will then increase by around 35%. Such an observation would be consistent with the theory that repeat exposure to pathogens in drinking water can influence immunity and that immunity to many enteric pathogens is relatively short lived, lasting for only a few months.[4,5]

This observation should not be taken as implying that the drinking water at the study area was not a risk to public health. Indeed, those people who have not built up their immunity through drinking unfiltered Sonoma water for a long time, especially visitors and young children, could be at a substantially increased risk, much greater than the 12% excess risk suggested by the initial analyses. ■

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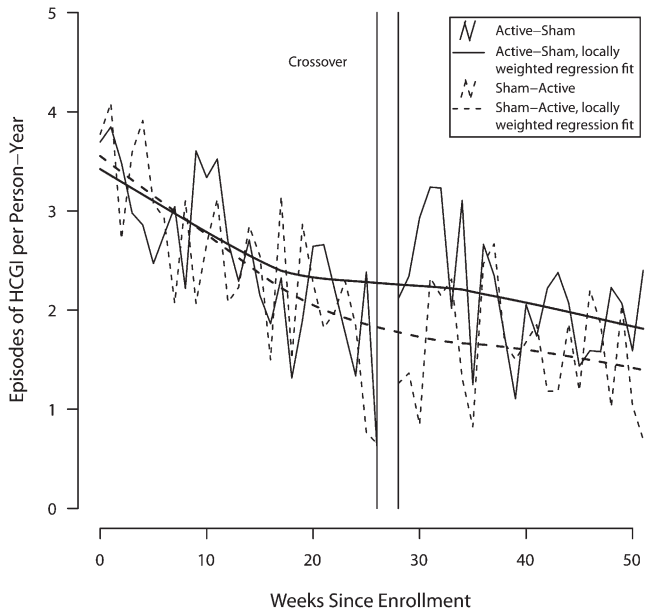

FIGURE 1—Decline of highly credible gastrointestinal illness (HCGI) over time, by study arm: Sonoma Water Evaluation Trial, Sonoma County, CA, 2001–2006.

Note. *P. R. Hunter has undertaken consultant work for Suez Environment and Danone beverages. He is also chair of the board of directors of the Institute for Public Health and Water Research.*

References

1. Colford JM, Hilton JF, Wright CC, et al. The Sonoma Water Evaluation Trial: a randomized drinking water intervention trial to reduce gastrointestinal illness in older adults. *Am J Public Health.* 2009;99(11):1988–1995.

2. Sibbald B, Roberts C. Understanding controlled trials. Crossover trials. *BMJ.* 1998;316(7146):1719.

3. Colford JM, Wade TJ, Sandhu SK, et al. A randomized, controlled trial of in-home drinking water intervention to reduce gastrointestinal illness. *Am J Epidemiol.* 2005;161:472–482.

4. Swift L, Hunter PR. What do negative associations between potential risk factors and illness in analytical epidemiological studies of infectious disease really mean? *Eur J Epidemiol.* 2004;19(3):219–223.

5. Frost FJ, Roberts M, Kunde TR, et al. How clean must our drinking water be: the importance of protective immunity. *J Infect Dis.* 2005;191:809–814.

COLFORD ET AL. RESPOND

In his letter, Hunter raises interesting issues: treatment-period interaction and carry-over effects in an AB–BA crossover trial.[1]

The treatment effect (active versus sham water filtration devices), stratified by sequence, suggests interaction: sequence active–sham (relative risk [RR]=1.23; 95% confidence interval [CI]=1.03, 1.48) and sequence sham–active (RR=0.61; 95% CI=0.50, 0.74). These estimates, however, are confounded by a strong period effect: highly credible gastrointestinal illness (HCGI) incidence declines in both study arms with time (Figure 1). An observed secular decline over time in incidence and prevalence (that is, a period effect) of self-reported outcome has been noted in studies of gastrointestinal illness.[2–6] The cause remains unknown; hypotheses are that the decline is caused by genuine health improvement over time simply from participation ("Hawthorne Effects") or by bias in self-reported outcomes. The decline due to bias could result from over-reporting early, under-reporting late (because of respondent fatigue), or both. Irrespective of the cause, the active filtration device appears harmful in sequence active–sham because incidence is higher in period 1 and lower in period 2. The device appears protective for sequence sham–active for this