Reviewer's report

Title: Is Drinking Water A Risk Factor For Endemic Cryptosporidiosis? A Case-Control Study In The Immunocompetent General Population Of The San Francisco Bay Area

Authors:

Dr Asheena Khalakdina (asheena@socrates.berkeley.edu)
Dr Duc J. Vugia (DVugia@dhs.ca.gov)
Joelle Nadle (nadle@mindspring.com)
Gretchen A. Rothrock (gar_ceip@mindspring.com)
John M. Colford Jr (colford@socrates.Berkeley.edu)

Version: 1 Date: 9 Dec 2002

Reviewer: Dr Joseph F Perz

Level of interest: A paper of considerable general medical or scientific interest

Advice on publication: Accept after discretionary revisions

Overall Comment
This was a carefully conceptualized study and as the authors note, it appears to be the first case-control study to examine risk factors for sporadic cryptosporidiosis cases among immunocompetent persons in the US. In general, the manuscript is clearly written. The findings themselves are interesting, however, the paper is at least as important for the methodologic issues and challenges it raises for consideration. For this reason, the level of detail that is provided regarding the study's methods seems reasonable, and revision might be aimed at further clarification and expanded discussion of methodologic issues.

Specific Comments:
1. Abstract: Results before Methods?
2. In general, suggest limiting presentation of odds ratios to 2-3 significant digits.
3. In the title, abstract and background sections, the authors are careful to differentiate cryptosporidiosis, the clinical disease (characterized by prolonged watery diarrhea), from Cryptosporidium infection. This is important because many infections are asymptomatic or are associated with mild symptoms. The Discussion section might address this distinction, with respect to Cryptosporidium's epidemiology and/or disease burden considerations (see also comment #11).
4. The information regarding the increase in cryptosporidiosis cases outside SF during CEIP's first year is a bit distracting. It may be more useful to clarify at that point that cryptosporidiosis surveillance covers certain Northern CA counties and give the readers a sense of the annual numbers of cases.
5. Cases: comment on how enrolled cases compare to immune competent cases that were not enrolled (demographics, and also broad risk factor information that may be available from standard CEIP case report forms).
6. Controls: participation rates among controls should be presented. Suggest including this in Methods (Selection of cases and controls section) or at the beginning of Results.
7. Par. 1 of Background correctly states that cryptosporidiosis is under-diagnosed and under-reported. It is true that Cryptosporidium is often not part of a standard ova and parasite exam. What is known about this in the study area? This leads to questions regarding differential ascertainment that might bias a study such as this. For example, half of the cases were associated with foreign travel: does this reflect
heightened awareness or clinical suspicion of Cryptosporidium infection among SF-area physicians? It would be interesting to know if most cases were diagnosed in relation to particular settings (e.g. travel medicine clinic(s) or university hospital(s) that do include Crypto as part of standard O&P. A related question: From the ongoing surveillance, is anything known regarding the prevalence of travel among cryptosporidiosis cases.

8. A primary aim of this investigation was to evaluate the role of local drinking water sources and consumption habits, therefore some additional details on water-related variables would be useful. At a minimum, clarify whether the boiled/bottled-filtered/tap water categories refer to the subjects' usual practice or to the two weeks prior to diagnosis (including travel periods?).

9. Categorization of food source exposures is somewhat unclear because unpasteurized foods seem to be a subset of "risky" foods in the first paragraph of Exposures but appear to be a separate category in the second paragraph.

10. Calculation of univariate odds ratios using conditional logistic regression is first mentioned in Results (Par. 2) but also needs to appear in Methods/Analyses. Analyses section should also give a clearer sense of the number of individual variables evaluated.

11. The last paragraph in Conclusions, which raises the question of the role of immunity, seems out of place and ought to be moved to the Discussion. This aspect of Cryptosporidium's epidemiology impacts study design and interpretation and deserves expanded treatment, (for example, see McAnulty et al; Epidemiol Infect 2000 Aug;125(1):79-86 as well as McDonald et al; JID 2001; 183;1373-9 and Frost et al; Ann Epidemiol 13;4:222-7 which include discussion of seroconversion as an alternate endpoint).

12. Given that this journal does not provide editing services, I am passing on a few typos:
- Abstract: Italicize Cryptosporidium (check other occurrences)
- Par. 1: "a reportable" should appear as two words.
- Results/multivariate analyses: missing word in first sentence ("were constructed").
- Results/last paragraph: "point estimates" instead of "relative risks"?

**Competing interests:**

None declared.