Author's response to reviews

Title: The Epidemiology of Pediatric Aseptic Meningitis in Daejeon, Korea (1987 through 2003)

Authors:

Kyung-Yil Lee (leekyungyil@catholic.ac.kr)
David Burgner (dburgner@ichr.uwa.edu.au)
Hyung-Shin Lee (vitalina@hanmail.net)
Ja-Hyun Hong (nelson@mdhouse.com)
Mi-Hee Lee (lpedleemj@catholic.ac.kr)
Jin-Han Kang (kjhan@olmh.cuk.ac.kr)
Byung-Churl Lee (byungcl@catholic.ac.kr)

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Author's response to reviews: see over
Dear Dr. Newmark

We are pleased to enclose the revised manuscript (#MS: 5364325606076875) re-entitled “The Epidemiology of Pediatric Aseptic Meningitis in Daejeon, Korea (1987 through 2003). We appreciate your kind consideration and the careful reviews by three reviewers for our manuscript.

We corrected and revised our manuscript according to the directions of all reviewers. Our revised manuscript has been reviewed and redrafted by a native English MD (Dr. D Burgner, included co-author). We have replied to the reviewers how we have met their remarks in the following pages.

Sincerely Yours,
Kyung-Yil Lee, MD
Department of Pediatrics,
The Catholic University of Korea, Daejeon St. Mary's Hospital,
520-2 Daeheung-dong, Jung-gu, Daejeon 301-723, Republic of Korea
Tel: +82-42-220-9541, Fax: +82-42-221-2925,
E-mail: leekyungyil@catholic.ac.kr
Reply to Reviewers

1. Reviewer  (Marc Van Ranst)

Many thanks for your review of our manuscript.

General
Q. The weak point of the paper is that only a few enteroviruses in the cerebrospinal samples from the patients were genotyped. However, the paper is on ‘aseptic meningitis’ and not on enterovirus meningitis.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
The paper should be revised by a native English speaker. There are many spelling and grammatical errors that distract form the otherwise interesting study.

A. Our revised manuscript has been reviewed and redrafted by a native English MD (Dr. D Burgner).

Q. Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)
Recently, another paper on aseptic meningitis patients from South Korea (Seoul) was published in Intervirology (Joo CH, Ahn J, Seo I, Kim YK, Kim D, Hong H, Lee H. Characterization of nonpolio enteroviruses recovered form patients with aseptic meningitis in Korea. Intervirology. 2005 Mar-Jun; 48(2-3): 97-103). Although only a few isolates were genetically characterized, it would be nice to include this work in the reference list.

A. We corrected the figures and included 2 papers in the reference list and referred to them in this article.

Q. Discretionary Revisions (which the author can choose to ignore)
In 2002, the second-largest outbreak of aseptic meningitis coincided with the 2002 FIFA World Cup soccer which was hosted by Korea and Japan. The Daegwon Stadium hosted two first round matches, as well one second round game (12 June 2002: South Africa 2:3 Spain; 14 June 2002: Polan 3:1 U.S.A. and 18 June 2002; Second round match - Korea Republic 2:1 Italy). Hundreds of thousands spectators and their viruses from three continents were in the city. The authors could speculate that this might have been a potential etiological factor, although without enterovirus genotyping, this can never be proven. Maybe it would be interesting to look at the exact timing of the 2002 epidemic, i.e. to see if the peak of the meningitis epidemic came a couple of weeks after the World Cup games in Daejeon? It would be interesting to see if the echovirus 13 samples that the authors identified in 2002 were phylogenetically related to enteroviruses from one of the visiting countries.

A. Thank you for your interest in Daejeon in the 2002 FIFA World Cup. Your interesting speculation may be possible, although it is not proved. Indeed, epidemics with echovirus 13 meningitis were reported in Europe and the USA before the Korean epidemics and the phylogenetic type isolated in Korea was nearly identical to those isolated in Germany and Japan. These findings were described in this article.
Reviewer 2 (Remi Charrel)

Many thanks for your review of our manuscript.

This paper describes the epidemiology of aseptic meningitis in children in Daejon, a large city of South Korea, over a 16 year period from 1987 to 2003.

I applaud for such a large study covering a long period of time; this kind of studies is, in my opinion, of major interest to attempt to elucidate the factors driving enterovirus circulation emergence and reemergence over the world; however, virology documentation even partial is critical to be able to interpret clinical and epidemiological data. No virology data are presented in this paper, and the link between aseptic meningitis and enteroviruses is stated without solid evidence. It considerably weakens the paper, and I recommend to correct this point before publication can be considered.

To fit in a virology journal, the authors must provide virology data, or they should consider another type of scientific journal. With this type of data, this paper would more suited to an internal medicine, infectious disease, pediatric or epidemiology journal.

Title
Q. The title should mention that this study focused on children

A. We changed the title to “The Epidemiology of Pediatric Aseptic Meningitis in Daejeon, Korea (1987 through 2003)”.

Q. Abstract
Aseptic meningitis has always been a common disease in children, but before the era of antibiotics it was considered as benign by comparison with purulent meningitis which outcome was frequently fatal.

The association between enteroviruses and aseptic meningitis should be tempered since other causes are possible; indeed, before WWII in the US, the two major etiologic agents involved in aseptic meningitis were herpersviruses and lymphocytic choriomeningitis virus. It has been recently shown that in certain region of Italy, the major cause of summer aseptic meningitis was not enteroviruses but Toscana virus, an arthropod-borne virus.

Methods
The authors must decide what kind of data they want to present; either they provide documentation for these cases, and they can discuss the etiology of aseptic meningitis cases, or they don't suggest that most of these cases were due to enteroviruses since no evidence support this point.

They state that in Korea, aseptic meningitis are exclusively due to enteroviruses but they don't quote references to support this opinion; moreover, they report that some of the cases are due to mumps virus.

The 1997 and 2002 epidemics were studied at the virological level with the help of Korean NIH; 6/33 and 5/29 aseptic meningitis cases which were investigated were due to Echovirus 30 and 13, respectively. But there is no information provided about the etiology of the 27/33 and 24/29 cases; were they caused by enteroviruses belonging to other genotypes or to other viruses not related to enteroviruses. This point is of major importance in order to claim that most aseptic meningitis cases are due to enteroviruses.

A. We corrected and added the sentences on the Background and Material sections, and inserted Table 1 including information on enterovirus studies in Korea in order to claim that most aseptic meningitis cases are due to enteroviruses.

Discussion
Q. Line 5: viral meningitis should be replaced by aseptic meningitis since there is no virological documentation. The articles quoted in reference are clinical studies and I doubt they mention virus investigations.

A. We corrected ‘viral meningitis’ to ‘aseptic meningitis.’

Q. The point about the increasing occurrence of aseptic meningitis in children in South Korea is valid and these data support it strongly, but unsubstantiated conclusions on the nature of the agents involved in these cases should be more carefully addressed unless formal identification can be provided as evidence.

Page 6-8 discussion should be compacted to be more "to the point”.

Page 8 : data about the virological nature of aseptic meningitis from 1990 to 2002 should be presented in the introduction section to support the fact that most aseptic meningitis cases might be due to enteroviruses.

Percentage data should be provided of available; for instance, in 1990 KNII received xx CSFs for virus studies in aseptic meningitis, yy/xx were positive for enteroviruses and zz/yy were due to echovirus 30 or 13 or 6... This data should be compared with the identification given above for the 1997 and 2002
epidemics. A detailed presentation of these data should be summarized in a table to support the fact that most aseptic meningitis are due to enteroviruses. This point is of critical importance for this paper and to interpret the clinical data.

A. We revised the Discussion section in order for it to be more compacted. We transferred the sentences about etiologic viral studies to the Introduction section and inserted Table 1 including information on enteroviruses studies in Korea in order to claim that most aseptic meningitis cases are due to enteroviruses.

Q. Figures and tables
Figures 1-4 must be merged into a 4-panel figure

A. We changed the figure numbers.

3. Reviewer 3 (Bruno LINA)
General
The manuscript entitled “Epidemiological study of aseptic meningitis in Daejon, Korea (1987 through 2003)” submitted by KY Lee et al. to BMC infectious disease is reporting purely epidemiological information about 2001 cases of aseptic meningitis observed during epidemics. This descriptive work lacks of virological information and do not provide new information as compared to previously published work. Moreover, the authors assume that the frequency of these epidemics putatively related to the circulation of different EV serotype may be linked to the herd immunity. Nothing in the manuscript can support this since there is no information about the viruses detected in cases in the same period of time, except those already published.
Overall, this manuscript is providing very little information and should not be accepted for publication in BMC infectious disease.

A. Many thanks for your review of our manuscript.
Although enteroviral studies were not performed routinely during the study period, we performed enteroviral studies for a proportion of patients in the 1997 and 2002 epidemics (Table 1), and we introduced the enterovirus studies in Korea in order to claim that most aseptic meningitis cases are due to enteroviruses.
In this study, we found that aseptic meningitis epidemics in Korea have started in the 1990s and we postulated that the improvement in the public health environment following economic growth in Korea reduced the chance to exposure of enteroviruses. We also suggested that the age distribution pattern, especially < 1 year old of age, may reflect the herd immunity of the maternal generation. These two points have not yet been known in aseptic meningitis epidemiology.