Author's response to reviews

Title: Interventions for preventing diarrhea-associated hemolytic uremic syndrome: systematic review

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Version: 2 Date: 22 August 2013

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Replies to reviewers’ comments
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Reviewer 1
This is a comprehensive and well written report looking at interventions for preventing diarrhoea associated hemolytic uremic syndrome. The authors have used a broad search strategy but have found limited information assessing each of the many potential interventions.

| 1. The authors have largely followed the PRISMA guidelines for this type of review. Although they state the quality of the RCTs was assessed, the methods and results of this were not clear, particularly with respect to risk of bias. (Minor essential revision). | More detail has been added in the text. Methods: More detail has been included on assessment of quality in the methods. ‘The quality of RCTs was assessed by two reviewers, based on specific criteria for minimization of bias, assessing sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other biases [23, 24].’ (page 6) Results: Further detail on the quality of trials, particularly in relation to risk of bias, has been included in the results, for example: ‘There was low risk of bias in this study, with the interventions randomly assigned, with allocation concealment and staff blinded to treatment.’ (page 7) ‘Treatments were randomly assigned, there was allocation concealment, and study personnel, as well as laboratory personnel were blinded, indicating low risk of bias in this study.’ (page 8) ‘Treatments were randomly assigned with the allocation concealed, however blinding was not possible due to the differences in the treatments, so risk of bias is unclear.’ (page 11) ‘There is a potential risk of bias in this trial: although it was randomized using computer generation, allocation concealment was not specified, neither participants nor investigators were blinded and use of intention-to-treat analysis was not stated.’ (page 14) ‘There is also a risk of bias in this RCT since neither the method of randomization nor |
allocation concealment was specified, and intention-to-treat analysis was not stated, even though both participants and investigators were blinded.’ (page 15)

2. There is some repetition in areas, eg in the background section the incidence of HUS is presented in the first paragraph and again in the second last paragraph.

There also seems to be some repetition in the sections on food handling - perhaps this could be condensed a little more.

Duplication has been removed and the following paragraph now included (page 5):
In Australia and the USA the annual incidence of diarrhea-associated HUS in children under 5 years is ~1 per 100 000, with 3%-6% mortality [17, 18]. HUS in the elderly causes death in up to 90% [19, 20]. STEC 0157 infections cost the USA over US$400 million annually [21]. Approximately 8% of STEC infections progress to HUS [18]. Hence, prevention of HUS would significantly impact health outcomes and health expenditure.

The sections on food handling have been made more concise (pages 20-29)

3. In the PRISMA diagram (figure 1) the number of excluded human trials plus the number of assessed trials does not equal the number of screened trials.

This has been corrected (figure 1). There were 552 excluded trials.

4. On page 8 "there was insufficient evidence to support the effectiveness of bacteriophages and other food additives" - such as?

More detail has been added: ‘other feed additives such as oral polyclonal anti-\textit{E. coli} O157:H7 antibodies.’ (page 8).

5. page 8 - "A 10 year review also reported on probiotics" - and said what?

More detail from the 10 year review has been included: ‘A 10 year review also reported on probiotics, reporting that \textit{E. coli} could be significantly reduced by probiotics [5].’ (page 8).

6. page 23 - I would like to have seen more specific details about the public health response on the management and treatment of acute bloody diarrhoea in children.

A section on the public health response on the management and treatment of acute bloody diarrhoea in children has been added on pages 12-13 to address this point in more detail.

7. Table 1 - Farm practices. I found the intervention for the first RCT (ref 118) difficult to follow. Could you please clarify this paragraph?

The methods for this trial involved multiple interventions. More detail has been added to Table 1, page 35 to clarify the interventions for this RCT:
Multiple interventions were applied to 3 groups of farms of young animals. Group A: No new animals, no contact with other cattle and no shared water sources; bedding and animals kept dry; animals kept clean; animals
kept as a closed group; boot-dip and overcoat used. Group B: No new animals, no contact with other cattle and no shared water sources; water troughs emptied and cleaned weekly. Group C received all the interventions of A and B.

Control farms had no alteration in practices

8. There were a couple of very minor spelling/typing errors:

These points have all been attended to. See below.

p7 - 6 lines from the bottom there is a bracket missing around the p value

Bracket has been added (page 7).

p15 - line 2 soap

Soap has been changed to soap (page 15).

p 28 - the first line of the discussion doesn't read correctly

This sentence has been rewritten: ‘Our aim was to investigate means for the prevention of HUS in humans’ (page 29).

p29 - Second paragraph - should probably read "isolation of symptomatic children and adults

Adults have been added to this sentence: ‘isolation of symptomatic children and adults’ (page 30).

p35 - table 1 - vit D - typo in the intervention paragraph

This has been corrected (page 36).

Reviewer 2
Reviewer: Alexander W. Friedrich
Reviewer's report:
This is a well written manuscript on the public health importance of EHEC bacteria including publications from countries reflecting very well the clinical and public health importance of certain EHEC infections, but only unfortunately a part of the STEC/EHEC/HUSEC problem.

Method of systematic review:
It is not clear to me what search terms were really used: EHEC/E. coli infection and/or HUS only? Most publications included describe infections due to O157:H7. There is a description of the O111 outbreak in Australia and the O104 outbreak in Germany. This is now of utmost importance: There are many more HUS/outbreaks described that are caused by

The focus of this review is the prevention of HUS. We know that by far the majority of HUS is due to the E. coli serotype O157:H7, but acknowledge that Shigella dysenteriae and multiple serotypes of E.coli have been implicated, including O111. This is now stated in the text: ‘HUS may complicate diarrhea due to Shiga-toxin-producing organisms including Shigella dysenteriae and Shiga-toxin-producing E. coli
other serotypes than O157:H7. Next to the non-O157 related outbreaks, you need to include also the publication of severe infections and outbreaks caused by O157:HNM, which is described to have hypervirulent activity in comparison to other subclonal lineages. Therefore, you need to include the search terms STEC, VTEC and HUSEC and all different serogroups/-types in your systematic review otherwise you miss all data from countries with publications with the aforementioned terms.

(STEC). Worldwide STEC O157:H7 is the most common of the STEC causing HUS [1], although many other serotypes have been implicated.’ (page 4)

Regardless of the causative STEC serotype, the same principles apply to prevention of HUS. Our aim was to write a comprehensive review on prevention of HUS, including prevention of infection with STEC and other Shiga toxin-producing organisms. Thus, the focus of the search strategy was HUS rather than STEC/VTEC/HUSEC.

As STEC O157:H7 is the most common cause of HUS most of the literature in both animals and humans referred to O157.

We have addressed the following means of prevention: preventing carriage in animals, preventing transmission to humans from animals and other humans, treatment of STEC diarrhea and public health measures to both prevent bacterial diarrhea and prevent its spread in communities.

We considered that the key words in our search would identify the relevant papers on prevention of HUS. While a search for all other types of organisms having the potential to cause HUS would certainly yield more search results, this prohibitively enormous task would unlikely have yielded further relevant papers on HUS prevention.

The same counts for HUS. HUS is a – very important- disease, but STEC/EHEC cause also hemorrhagic colitis and (bloody diarrhea). Why did you exclude them? They have surely public health importance and are caused by EHEC/STEC that that can cause HUS. Focusing only on HUS does not reflect the real prevalence of the HUS causing agent.

As stated above and in the manuscript, our specific aim was to focus on the prevention of HUS, rather than the prevention of bacterial diarrhea and/or hemorrhagic colitis, though this is addressed in some detail. (Page 4)