Reviewer's report

Title: Incidence and etiology of hemolytic-uremic syndrome in children in Norway, 1999-2008 - a retrospective study of hospital records to assess the sensitivity of surveillance

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Reviewer: Zelal Ekinci

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Major Compulsory Revisions

My recommendations for the manuscript “Incidence and etiology of hemolytic-uremic syndrome in children in Norway, 1999-2008 – a retrospective study of hospital records to assess the sensitivity of surveillance”

Title:

Sensitivity (also called the true positive rate) measures the proportion of actual positives which are correctly identified as such (e.g. the percentage of sick people who are correctly identified as having the condition). In this manuscript it is not possible to find out “the sensitivity of surveillance”. Because of this the title should be revised.

Abstract - Background:
2nd sentence:
“As EHEC surveillance is complex due to diagnostic challenges in detecting non-O157 infections, surveillance of HUS can be used as an indicator of the burden of EHEC infection.” This sentence could not be used as an excepted scientific knowledge in the abstract. The aim in recent years is to prove the presence or absence of STEC in HUS patients (Mody RK, Luna-Gierke RE, Jones TF, Comstock N, Hurd S, Scheftel J, Lathrop S, Smith G, Palmer A, Strockbine N, Talkington D, Mahon BE, Hoekstra RM, Griffin PM. Infections in pediatric postdiarrheal hemolytic uremic syndrome: factors associated with identifying shiga toxin-producing Escherichia coli. Arch Pediatr Adolesc Med. 2012;166:902-9). Even in aHUS diagnosis, search of STEC is the first step (Zuber J et al; French Study Group for aHUS/C3G. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. Nat Rev Nephrol. 2012;8:643-57).

Abstract - Methods:
1st sentence:
“In order to assess the sensitivity of EHEC and HUS surveillance and describe
the incidence and etiology of HUS in children in Norway, we conducted a nationwide retrospective study collecting data from medical records from pediatric departments for the period 1999-2008 and compared them with data from MSIS.”

The authors do not have any “two methods” to apply to all the patients to find out the sensitivity of the method for diagnosing EHEC and/or HUS. It is not possible to calculate sensitivity in this cohort and I cannot see any information through the manuscript regarding this calculation.

Introduction:
Is it necessary to write such a long introduction?
2nd paragraph, 2nd sentence:
“Shiga toxins are produced and released by EHEC bacteria and are an important part of EHEC-HUS pathogenesis.”

Stx is not an important part of the EHEC-HUS pathogenesis. Stx is the main cause of STEC HUS (Trachtman H, Austin C, Lewinski M, Stahl RA. Renal and neurological involvement in typical Shiga toxin-associated HUS. Nat Rev Nephrol. 2012 ;8:658-69). Recently instead of D+ HUS or EHEC HUS, STEC HUS is preferred. It is meaningful for description of etiology, pathophysiology and classification of HUS. I recommend the usage of “STEC HUS” throughout the manuscript.

5th paragraph (last paragraph of introduction):
The sensitivity issue (as told in the title and abstract-methods sections) should be re-evaluated.

Methods:
Design and data collection:
1st paragraph 1st sentence:
Why did the authors select the time interval as 1st Jan 1999-31st Dec 2008? 2006 is a special year, after that year the notification rules for HUS was changed. So it would be wise to choose a longer interval after 2006, to compare the results. Authors must explain the causes for the chosen time interval. If there is no special impediment, time interval should be arranged to increase the value of the manuscript.

Case definition:
2nd paragraph:
“A diarrhea-associated HUS (D+HUS) case was defined as a HUS case with either:
- a clinical presentation of prodromal diarrhea, without verifiable causative etiology
or
- EHEC-HUS, defined as a HUS case with laboratory-verified EHEC-infection”

An infectious event, mainly upper respiratory tract infection or

Results:

Sensitivity of the HUS surveillance:

1st paragraph:

“In the period 1999 to 2008 27 HUS cases among children <16 years of age were notified to MSIS. One case from 2007 was identified and excluded from this study as it was initially admitted to a hospital abroad. In the same period, 102 cases of EHEC infection were notified in the same age group (Fig 1). Accordingly, 23% of EHEC- cases notified to MSIS in the period were cases with HUS.”

There are some confictions which I could not solve in this paragraph.

1- Cases notified to MSIS: 27 HUS cases- 1 case excluded = 26 cases. In table 1 there are 25 cases? In table 2 there are 23 EHEC identified HUS cases. Then 2 cases after 2006 in MSIS must be EHEC-? EHEC status of 5 patients after 2006 should be clarified. Where is the 26th case? Before 2007 all reported cases should be EHEC+ and the number is 20. However when I count figure 1, I found 21 EHEC+ HUS patients before 2007, and 26 EHEC+ HUS patients in total. Total
D+? HUS: 25, 26, 27? and The number before 2007? 20, 21?

2- Figure 1: EHEC and HUS cases? Are these EHEC+HUS cases? Or D+HUS?
Counts are confusing: 23 # 26?

3- If the total is 26 (actually I included the 2 - which I suppose clinically
diagnosed, EHEC- after 2007) than 26/102 is not 23%, it is 25,4%. If the authors
did not use the 2 EHEC- HUS( is my finding correct?) than 23/102 is 22,5%.

4- In this part, as far as I understand authors are reporting D+ HUS. Then the title
must be “Sensitivity of the D+HUS surveillance”. I don’t discuss sensitivity subject
again. Definition of sensitivity is presented in the title chapter.

2nd paragraph:
“Twenty of the HUS cases in MSIS were notified from the start of the study
period up to and including 2006, and five after 2006. The corresponding numbers
from the medical records search were 33 and five for the period 1999-2006 and
2007-2008, respectively (Table 1).”

1- 13 patients were found from the medical records: Were these 13 patients all
diagnosed as D+HUS in the medical records or were there any patient found
from the AKI group? How many criteria were found for each patient, how many
were diagnosed with a pediatric nephrology consultation? A table would be
helpful for the convincing of reader.

2- First sentence of this paragraph should be changed as “20 of the D+HUS
cases...” They are not D- or aHUS? Throughout the manuscript there is
confusion because of terminology. “Possible STEC HUS” should be used
generally instead of D+; EHEC+ should be used specially where required.

3- Figure 1 show 21, table 1 and this part shows 20? cases.
It is very confusing and like a puzzle. I will propose a table like this. Then authors
also will see the missing or excess cases

1999-2006 2007-2008 Total
MSIS cases (text number 26, table 25) 20-21(EHEC+HUS) 5(There must be 2
possible STEC HUS) 25-26?
EHEC+HUS cases 20-21?
(figure1: 21) 3?,5?
(Text 3?,figure1: 5?) 23-24?
(figure 1: 26, table 2: 23?, table 3: 23?)
Medical records D+HUS cases 33(there must be 13 possible STEC HUS)
5(There must be 2 possible STEC HUS) 38
Medical records D-HUS cases 9-x X=0? 9

Incidence and etiology of all types of HUS in children 1999-2008
In the 1st paragraph 1st sentence total case number is 47, in table 2 total case
number is 48??
Three cases, all D+HUS, were identified as HUS through the diagnostic code for acute kidney injury (AKI); N17.

What did the authors find to change the diagnosis for each patient?

The remaining 15 cases presented with diarrhea, but without verified EHEC infection or etiology.

The follow up information of these patients should be clarified from the medical records. As I presented in case definition part diarrhea can precede aHUS in 1/3 of aHUS patients. Medical history of presence of diarrhea may cause a mistake.

D-HUS / atypical HUS


- Infection-induced
  Shiga toxin-associated: E. coli (STEC), Shigella dysenteriae Type 1
  and other bacteria
  Invasive infection with Streptococcus pneumoniae (p-HUS)

- Complement dysregulation

- Genetic
- Acquired
- ADAMTS13 protease deficiency

- Genetic
- Acquired (including ticlopidine)
- Defective cobalamin (B12) metabolism
- Quinine
- Disease associations

(Adapted from Besbas et al.)

This classification is in accordance with etiology and avoids misdiagnosis of diarrhea preceded aHUS. I would recommend figure 2 to be like this:

HUS cases: 47

Infection induced

STEC (EHEC+, D+ should be included in this group with pointing the suspects (how many bloody, how many watery? Afew of them could be aHUS triggered by diarrhea. Follow up information of these patients with follow up time could decrease suspect)

Strep
Campylobacter
Genetic
CD46 and C3
CD46
CD46 and FH ab
Unknown (Are these cases presented with recurrences? Review of their medical records also is important?)

Discussion
1st paragraph 1st sentence: 2 years and 5 patients? Are these data really enough to conclude like this?
2nd paragraph 2nd sentence: what about aHUS triggered by diarrhea??
2nd paragraph 4th sentence: “This may reflect that the HUS cases were caused by other etiological agents causing D+HUS that we were not able to recognize, but it is more likely due to problems with diagnosing EHEC in stool samples from HUS patients.”

Bacteriologically all EHECs are not STEC, but all STECs are EHEC and the cause of the disease (HUS) is STEC. Than the suspected point should be the HUS patients with D+ but unknown STEC status is really STEC HUS (according to authors EHEC HUS)? At this point such a retrospective data could be strengthen just with review of medical records of these suspected cases for the presence of recurrence, for misdiagnosis of aHUS.

2nd paragraph 8th sentence
“In our study, we found that 64% of verified EHEC cases were non-O157 when the outbreak-related EHEC-HUS cases are excluded.”

I could not find this information in the text of results also in the tables. In table 3 there is 7 non-O157; 7/14 is 50%?

2nd paragraph 9th sentence:
“However, O157 was the most frequently isolated serogroup causing sporadic HUS in Norway”

Isn’t this sentence contradicts with 2nd paragraph 8th sentence?

3rd paragraph 1st sentence:
23%? Is it correct? (Detailed discussion is in results part)

References
References should be written according to the rules. Month and journal number should be erased. The authors copied the references just from pubmed summary (text).

Level of interest: An article of importance in its field

Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests