Author's response to reviews

Title: Invasive Haemophilus influenzae infections in Germany: impact of non-type b serotypes in the post-vaccine era

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

Thank you for considering our manuscript for publication in your journal and for the helpful comments of Dr. McVernon and Prof. Scheifele which we are happy to include in the amended version. In addition, we added (1) a sentence with ethical considerations of the study (last sentence methods section), (2) more context information within the background section of our abstract (first sentence of abstract) and (3) corrected the spelling error in the Competing Interests section, as proposed by you.

In the following we comment on the reviewers suggestions.

Reviewer: Jodie McVernon

Minor essential revisions:

1. When comparing the features of Hib infections in the post-vaccine era with other Hi disease, I believe it is important to make note of the vaccination status of the type b cases. The median age of onset of 11 months is relatively young, suggesting to me that these are cases occurring following incomplete vaccination. Historical studies comparing conjugate vaccine failures with polysaccharide vaccine failures or unvaccinated cases have found a higher incidence of underlying conditions, mainly immunologic abnormalities, in the first group.
We added the following paragraph
(results; serotype b; paragraph 2)
Vaccination status of 63 of all 64 Hib cases was known. 40 were not vaccinated and 23 were vaccinated at least once before disease onset. Of the 23 vaccinated cases, 6 were considered to be vaccine failures of the incomplete primary vaccination schedule, 10 were considered to be vaccine failures of the primary vaccination schedule (2 or 3 doses in the first year of life, depending on the vaccine used) and 7 were considered to be vaccine failures of the full immunisation schedule (primary vaccination plus booster dose or a single dose in the second year of life). Four of the 23 vaccinated cases were reported to have potential predisposing conditions (17%). None of the vaccinated Hib cases died.

2. The use of the word ‘anamnestic’ is perhaps inappropriate in this context – my best understanding of the authors’ true meaning is that they are referring to possible predisposing conditions? This would be a clearer wording in English, if indeed the true meaning

Thank you very much for correcting the English wording: we replaced ‘anamnestic’ with ‘possible predisposing conditions’ throughout the text.

Discretionary revisions

1. Figure 1 – it would be interesting to represent nc Hi separately from non b capsulated strains here, if possible without compromising readability. Perhaps a single column, shaded with 4 different colours/patterns, could be used for each reporting year to allow easier interpretation of trends?

We followed the reviewer’s suggestions. See figure 1.

2. Similarly, it would be of interest to know whether the Poisson analysis was used to assess numbers of non-b capsulated strains reported over the years separately from the non capsulated strains (appears all non b included together). If there were reasons for doing so, based on statistical power, it would be helpful to mention these.

We now made this more transparent
(methods, analyses)
To describe annual trends in the different Hi serotypes we used all cases detected in the two surveillance systems from January 1998 to December 2005. Trends in cases with Hib, non-type b and untyped Hi infections were analysed using a Poisson model. Differentiation in capsulated and uncapsulated non-type b cases was not performed due to the low number of capsulated cases.

Reviewer: David Scheifele

Specific comments for minor revisions:

1. The surveillance systems have been described in earlier publications but the response rates within the two systems should be stated, along with the proportion of reported cases detected by each system. If the surveillance varied in completeness, the consequences for
case totals over time need to be addressed (one wonders about the 1999 figures, for instance).

We now added a paragraph ‘characteristics of the surveillance system’ in the results section, describing response rates within the two systems, proportion of reported cases and proportion typed at the central reference center. See also points 2 and 5.

Characteristics of the surveillance systems
In the years 1998 to 2005, response rates ranged between 95% in 1998 / 1999 and 98% in all other years for Clinical ESPED and between 94% in 2005 and 100% in 2000 for Laboratory ESPED. Per year, Clinical ESPED detected between 47% (2005) and 66% (2003) of all reported children with invasive Hi disease, Laboratory ESPED detected between 79% (2000) and 98% (2001) of all cases. The National H. influenzae Consulting Laboratory analysed between 64% (2000) and 79% (2005) of all Hi cases per year.

2. Figure 1 shows that a greater proportion of isolates were typed in the latter years of the survey but the text does not indicate what proportion of the typing was done at the central reference center versus the (less consistent) local laboratories.

We now added a paragraph ‘characteristics of the surveillance system’ in the results section, describing response rates within the two systems, proportion of reported cases and proportion typed at the central reference center. See also points 1 and 5.

3. A few words puzzled this reviewer, particularly “anamnestic information” (page 6) which I took to mean medical history.

This issue has also been stated by Jodie McVernon. Throughout the whole text we changed ‘anamnestic’ to ‘possible predisposing conditions’.

4. Biotype data are mentioned in Methods and Discussion but not in Results, apart from Table 1.

We now corrected this inconsequence by describing biotype distribution in the text of the results section, too.

5. The discussion asserts that surveillance system response rates were high but these data are so central to interpreting the results that they should be included in the Results, as mentioned above

We now added a paragraph ‘characteristics of the surveillance system’ in the results section, describing response rates within the two systems, proportion of reported cases and proportion typed at the central reference center. See also points 1 and 2.

6. Figure 1: the case numbers in 1999 seem anomalous overall and for Hib. This would seem to merit a comment, particularly if system variation occurred.

The reviewer is right, case numbers of the year 1999 are lower than in the years 1998 and especially in 2000. Since response rates of this year were similar to the other reported years, we have no explanation for the lower case number in 1999. On the other hand, 1999
numbers are not lower than in years 2004 and 2005, and very similar with years 2002 and 2003, what can now be better seen in the revised version of figure 1; in addition, the high Hi case numbers in the year 2000 leads to the impression that 1999 Hi case numbers are anomalous low. However, we think that these case numbers in 1999 and 2000 are within the normal fluctuation.

We would be pleased if the amended paper would now be accepted for publication.

Yours sincerely

Dr. Helen Kalies, MPH

For all authors