Author's response to reviews

Title: Recurrent severe invasive pneumococcal disease including meningitis in an adult with previously unknown hyposplenia

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Author's response to reviews: see over
Dear Editor,

Regarding manuscript "Recurrent severe invasive pneumococcal disease including meningitis in an adult with previously unknown hyposplenia": MS 2021281024144551

Thank you for giving us the opportunity to improve our manuscript. As requested we have revised the manuscript according to the comments of the two expert reviewers. We have responded to all comments and suggestions point-by-point, and we hope you will consider the revised manuscript for publication in BMC Infectious Diseases.

Attached please find the point-by-point response below. The revised manuscript is attached in two versions one with and one without visible alterations.

All authors have contributed to the work presented and have seen and approved the final version of the manuscript.

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Yours sincerely,

Vibe Ballegaard
Reply to Review.

We thank you for the valuable comments provided by the reviewers and for giving us the opportunity to revise and improve our paper for BMC Infectious Diseases. We have revised the paper according to the reviewers’ suggestions as described in detail in the point by point reply below. Responses from the authors are formatted in italic.

Reviewer #1: Comments

1. I agree with the observation that if an adult suffers from a repeat invasive disease from encapsulated organism, a more thorough evaluation of the immunological status of the patient is in order. These kinds of studies are not commonly available in most health care facilities especially in the third world countries and would therefore need referrals to more advanced centers.

   Response: We agree with the reviewer that immunological evaluation and screening for spleen dysfunction are not commonly available in most health care facilities and would need referrals. We have modified the conclusion chapter (p 9-10), and included a sentence reading “Individuals with predisposing medical conditions and a history of invasive infections with encapsulated bacteria’s or recurrent episodes of invasive infections should be referred to a specialist unit with expert knowledge in infectious diseases and with the ability to perform screening for spleen dysfunction assessed by erythrocyte scintigraphy, pitted erythrocyte counting, or Howell-Jolly body detection” on p 9, l 261-265.

2. Protective levels of response from active vaccinations need to be better defined for adults, especially in similar patients as was reported in the case. In efficacy trials for the development of PCV 13 for adults, geometric mean titers of opsonophagocytosis activity, defined as titer that will result in death of 50% population of inoculum of a specific serotype of pneumococcus, was used to compare the response to the PPV 23 against the response to PCV 13. This might be a better way of evaluating the functional immune response to a vaccine as an intervention to a hyposplenic patient and/or those suffering from multiple levels of immune suppression.
Response: We agree with the reviewer regarding the need for a better definition of protective level for adults, especially in risk groups. Measurement of functional antibodies (opsonophagocytic activity, OPA) in combination with specific pneumococcal IgG antibodies would certainly be a better way of measuring the vaccine response. However, we do not currently have possibilities to measure functional antibodies. The model with comparison of OPA titers (complement-mediated killing of 50% of the assay bacteria) would apply for vaccine comparisons, but not necessarily for individual patient evaluation. If measuring functional antibodies, the question of defining a protective level would still remain.

3. Once identified, patients with hyposplenism will probably benefit not only from vaccination against Strep. Pneumoniae but also against H. Influenzae and N. Meningitidis. Polysaccharide vaccines have showed inconsistent benefits for such individuals and are probably better covered with the new conjugated vaccines, if only we have an access to an accurate way of measuring their functional response to such interventions.

Response: We agree that hyposplenic / asplenic patient are at increased risk for infections caused by capsular bacteria and will probably benefit from the vaccines mentioned by the Reviewer

Reviewer #2: Major compulsory revisions

1. Better to change the title to “Recurrent severe invasive pneumococcal disease in an adult with previously unknown hyposplenia” as IPD already implied the possibility of meningitis.

Response: We agree that the proposed title would be sufficient and have changed it in accordance with the reviewer’s request.

2. No need to list all the diseases associated with hyposplenia and figure 1 (which is a table) should be removed.

Response: We agree that a list of associated diseases is not necessary in this context and we have removed figure 1 from the manuscript.
3. Please discuss the possibility of B-cells hyporesponsiveness induced by the PPV-23 initially given to the patient.

**Response:** The possibility of B-cell hyporesponsiveness induced by the PPV-23 is an important question, and we agree with the reviewer that it is important to discuss this subject. We have modified the discussion chapter (p. 8-9) reading “The presented case emphasizes that even after vaccination and when serotype-specific IgG responses seems to be protective, hyposplenic patients can be vulnerable to IPD. Currently, measurement of IgG-pneumococcal antibodies does not seem very useful for determining the degree of protection against IPD in hyposplenic patients, and no studies have established the necessary protective levels. Moreover, decreased quality of the antibodies and inefficient cellular immune responses could probably have a greater impact on the risk of IPD than the actual amount of antibody in this patient group. Measurement of specific memory B cells and functional antibodies (opsonophagocytic activity, OPA) could further elucidate a possible hyporesponsiveness, but these studies are not available in our laboratory, nor are commonly used methods for assessing vaccination response in most clinical settings.

In this case the patient received a dose of PPV23 at the first episode of IPD. Thus, the possibility of PPV23-induced immunological hypo-responsiveness upon re-vaccination has to be considered. A recent study demonstrated impaired antigen-specific B-cell responses in asplenic patients with β-Thalassemia previously vaccinated with PPV23. Antigen-specific memory B-cells and IgG-pneumococcal antibodies were measured, and a time- and dose-dependent negative effect of previous PPV23 vaccination was detected21.” on p 8-9, l 277-244.

**Minor essential revisions:**

1. Line 55 - prophlaxis

**Response:** the error has been corrected.