Reviewer's report

Title: Public Health Impact of Strain Specific Immunity to Borrelia burgdorferi

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Reviewer: Klemen Strle

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The goal of this manuscript was to assess empirically the public health impact of strain-specific immunity to Borrelia burgdorferi in Lyme disease. The authors used analytical modeling to estimate the number of Lyme disease cases that may be prevented as a result of immunity against specific Borrelia burgdorferi OspC type if the person were to be re-exposed to the same OspC type. Assuming 3% reinfection rate and 300,000 new cases annually in the US, they concluded that between 319 and 2378 cases of Lyme disease may be averted each year due to strain-specific immunity. Although the data are derived using computational approaches, which makes it more difficult to assess their relevance in the actual disease, the findings provide a novel and unique insight into the possible impact of strain-specific immunity on B. burgdorferi infection, particularly in the northeastern US. Such modeling approaches may be applicable to estimate the effect of immunity in other regions of North America and possibly Europe where infection with B. burgdorferi is prevalent.

Discretionary Revisions: This is a well-written manuscript requiring only minor revision. The areas that would benefit from additional clarification and/or discussion are listed below.

1) This study relies on several postulates, including: that patients develop immunity following infection with any OspC type, that the immunity is targeted against the OspC of the infecting strain, and that such immunity will prevent reinfection with the same OspC type. These assumptions are in large part based on the authors’ published study of 17 patients with reinfection and on a subsequent study using computational approaches to determine the probability of being re-exposed to infection with a strain of the same OspC type. Due to the relatively small group of patients (N=17), all of whom were from northeastern US, it is not yet clear how these findings will hold up in larger numbers of patients and in other regions where the distribution of strains and the clinical picture of disease may be different. The Discussion section could be expanded to include these limitations. In addition, evidence of strain-specific immunity against B. burgdorferi is primarily empirical and it will be important to directly validate this concept using laboratory approaches to determine which Borrelia components
(OspC or other proteins and lipoproteins) immunity is directed against, the cellular responses that mediate the immunity, and whether immunity is generated and protective to the same degree against any OspC type. The manuscript would benefit from a brief overview of the laboratory evidence of strain-specific immunity (e.g. Probert WS et.al. 1997. J Infect Dis. 175:400-405...) and how such evidence supports the current findings derived from analytical models.

2) The potential health impact of strain-specific immunity is highly dependent on the geographical distribution of the Borrelia OspC types. Therefore, one would predict that the findings reported here are applicable primarily to the northeastern US. As stated in the manuscript, in the Lower Hudson Valley of New York approximately 80% of patients with EM are infected with one of 4 OspC types and thus the possibility of being reinfected with the same OspC type would be reduced about 25%, leading to significant impact on health. In contrast, in regions such as midwestern US where OspC types recovered from EM skin lesions are more diverse and there is not a dominant overrepresentation of one or few OspC genotypes, the impact of strain-specific immunity on human health may be minimal. Expanding the discussion to include these ideas would broaden the understanding and the implications of this work.

3) The last paragraph of the Results section could use some clarification. What is the significance of reporting the recovery of spirochetes from blood versus skin? Are the frequencies of OspC types recovered from blood and EM skin lesion similar? The authors indicate that due to strain-specific immunity, the probability of positive Borrelia culture from blood in patients with recurrence of EM would be reduced by 25.3%. Would one expect a similar decrease in probability of a positive culture from EM skin lesions? Additional discussion of the significance of Borrelia recovery from skin versus blood would be helpful.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests