Reviewer's report

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Title: Virulence difference between the prototypic Schu S4 strain (A1a) and Francisella tularensis A1a, A1b, A2 and type B strains in a murine model of infection

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Francisella tularensis subspecies tularensis (type A) and holarctica (type B) are two clinically important subspecies. Recent studies from the authors of this manuscript and others have identified subpopulations within type A strain as A1a, A1b, and A2 by using molecular typing methods. F. tularensis Schu S4 is classified as an A1a strain.

In this manuscript, the authors compare the relative virulence of Schu S4 with A1a, A1b, A2, and type B strains in mice based on their previously published work (References 16 and 18). In their published studies, the authors compared the virulence differences among recent clinical isolates of A1a, A1b, A2 and type B F. tularensis strains in a murine model using temperature, fitted survival curve, organ bacterial burden, and gross pathology parameters. Here the authors further compared the virulence of Schu S4 with A1a, A1b, A2 and type B strains using the similar parameters. They showed that both the shape and scale parameters of the survival curve for mice infected with Schu S4 are significantly different from those for mice infected with two other A1a clinical isolates (Fig. 1), A1b, and A2 strains (Fig. 2); they also showed that the scale, but not the shape, parameter of the survival curve for Schu S4 infected mice was similar to that for type B infected mice (Fig. 2). Finally, they demonstrated that the bacterial burdens in the blood and spleen, but not in the liver and lung, of mice infected with Schu S4 were significantly lower than those from mice infected with an A1b clinical isolate (Fig. 3). The authors concluded that the Schu S4 strain is less virulent than other A1a, A1b, and A2 strains, and its virulence resembles type B strain.
Although some of the data presented in this manuscript have been published previously, as the authors clearly stated in the paper, the questions posed by the authors are well defined and the methods are appropriate and well described. Schu S4 is used as the major, if not sole, prototypic pathogenic strain for tularemia research, especially for tularemia vaccine and therapeutic studies. The findings from this study along with a study previously published by Twine et al (Reference 17) provide additional information on the relevant virulence of Schu S4 strain, which are useful to the field of tularemia vaccine and therapeutic researches. The conclusion of this paper could be further clarified and the strength of the paper enhanced by the following modifications:

Major comments:

1. The study is limited to small numbers of one mouse strain. A similar study comparing virulence difference between Schu S4 and other A1a isolates using a different mouse strain would enhance the strength of the conclusion.

2. Data comparing organ bacterial burdens between mice infected with Schu S4 and mice infected with other A1a clinical isolates are missing. Although the authors compared organ bacterial burdens between Schu S4 and A1b strain (Fig. 3), studies comparing organ bacterial burdens between Schu S4 infected mice and mice infected with other A1a isolates will further clarify the author’s conclusion on the virulence difference between Schu S4 and A1a.

Minor Comment:

1. Page 3, line 8. Please correct the typo in “and LD100”.

Level of interest: An article whose findings are important to those with closely related research interests

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.