Reviewer's report

Title: Searching For the Elusive Typhoid Diagnostic

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Reviewer: Robert Breiman

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The manuscript is well-written, entertaining and provides insight into S. Typhi that is useful and a pleasure to read.

While the focus is clearly on diagnostics, it would be nice to have a little focus upfront on burden of disease and more on potential for vaccines in preventing burden. Then, some discussion on the importance of diagnostic tests not only for clinical management but for use in field studies of new vaccines.

My other comments are relatively minor.

Line 84/5, While I do think that the writing style is entertaining some of the expressions used may get in the way of reader comprehension. “Typhi has predominantly forsaken the luminal lifestyle of most enteric bacteria”. Maybe it is the word “lifestyle” that is most distracting here. Do the authors mean “habitat” or some version of that?

Line 95, there is a word missing—probably “polysaccharide”

Line 117/8: Run on sentence. Not sure what it means, regardless. Please clarify. “Another signature present in the Typhi genome is the lack of obvious evidence for immune selection, many systemic pathogens exhibit antigenic variation.

Line 121: If authors want to use the term “stealth lifestyle”, will need to expand substantially on what they mean.

Line 123 The sentence is not grammatically correct, but also needs explanation of what they mean by “immune privilege”

Line 139 What is meant by “bespoke” vessels

Line 157 Could the authors expand for the uninformed on “metabolomic modeling”?

Line 246 Regarding future for typhi diagnostics, the most cutting edge/interesting part of the paper is the “Host factor other than antibody” section. Use of Mass spec, proteomics, NMR, and physiologic signatures would be nice to have discussed in greater detail, as they potentially relate to typhi diagnostics.