Author's response to reviews

Title: What potential could there be for a S. aureus vaccine in a hospital setting on top of other preventative measures? A model-based analysis.

Authors:

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Version: 4 Date: 24 January 2014

Author's response to reviews: see over
Reviewer's report

Title: What potential could there be for a S. aureus vaccine in a hospital setting on top of other preventative measures? A model-based analysis.

Version: 3

Date: 2 December 2013

Reviewer: Leigh Anne Shafer

Reviewer's report:

The authors have responded well to previous suggestions. Specifically, their description of the model is much better now. Some additional comments remain:

Authors: We would like to thank the reviewer for the additional work on this 2nd round of review and suggestions.

Major

1. What is the basis on which you decided to model that 10% of daily admissions were among colonized patients? (Give a ref?)

Authors: This is the baseline assumption from D’Agata et. Al. [23], which was listed in Table 1, with corresponding split into CA-MRSA and HA-MRSA.

2. One of the nice aspects of your model is the ability to simultaneously model HA-MRSA and CA-MRSA, both with different infection duration, infectiousness, colonization duration, etc. However, Figure 1 suggests that the model does not allow dual colonization or dual infection with both CA and HA. This would be a limitation. Please update your model description if dual infection is possible, or discuss the limitation in the Discussion if it is not possible.

Authors: Indeed, following the original model in [23], in this simplified modeling framework, dual colonization is not explicitly considered. Information/data about co-colonization with CA-MRSA and HA-MRSA is currently largely missing, as most studies tend to look at colonization separately. Co-existence in this modeling framework is enabled via corresponding steady influxes of colonized/infected patients into the hospital. More discussions can be found in references [23, 24].

We have added paragraph in the Discussion section (5th paragraph, line 375-381).

Minor

1. In the Introduction, most of your evidence suggests a positive impact of Bundle prevention strategies against MRSA, you do also report one study that did not show the positive impact. Also, as you know, negative result studies are more difficult to publish than positive result studies, thus suggesting that there may be others that have not shown the positive impact of MRSA. I would therefore suggest that you modify your statement, starting, “Although bundle measures have proved efficient...” You could just change it slightly, such as, “Although the bulk of the evidence suggests that bundle measures are efficient...”
2. Describing your model as state-of-the-art is over-board. You need to tell us what is state-of-the-art about it. Including vaccination compartments is not state of the art. Your model seems quite ordinary. (It is a fine model, but seems quite ordinary.)

**Authors:** We actually intended this remark with respect to the original modeling framework from [23] and in the sense that it is a current up-to-date model, reflecting epidemiology and such. We have now removed the “state-of-the-art” term throughout the manuscript, to avoid misinterpretation.

3. In discussion, it should be mentioned that your estimates are likely maximum additional efficacy of the potential vaccine. In your models, you assumed 100% bed occupancy at all times, which is likely untrue, and would maximize the number of infections averted by the vaccine.

**Authors:** Actual bed occupancy in this context is not essential, what truly matters here is that we keep a constant fixed number of patients. This enables a fair head-to-head comparison across all different scenarios. Especially that added benefits due to vaccination are computed relative to various other preventative measures. The same would then stand true for any type of preventative measure, and here we are computing relative differences only, so nothing is biased towards vaccine.

4. Figure 3 is very nice. However, this statement in your results, describing the table, needs to be corrected: “In each of the plots shown, the baseline parameters were similar (i.e. same level of hygiene compliance, same screening compliance and decolonization efficacy).” In fact, hygiene compliance varies in each plot, so the statement needs to be corrected.

**Authors:** We have edited the paragraph in the Results section.

5. The two left panels of Figure 4 were a good way to present your data. I did not understand the two right panels. It seems to be saying that as hygiene compliance rises, the annual number of vaccine doses also rises – which doesn’t make sense.

**Authors:** An explanation was provided in the legend of figure 4: the slight variations in the number of doses here for the same level of vaccine coverage reflect the corresponding differences in the number of daily admissions, which is allowed to vary in each instance to ensure full hospital occupancy at all times.

These variations are quite small here compared to the actual orders of magnitude, and we magnified the scale on the y-axis for each right panel separately here on purpose, to make these slight differences visible (please note the y-axis scales in the left panels in figures 4 and 5).

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:** I declare that I have no competing interests.
Reviewer's report

Title: What potential could there be for a S. aureus vaccine in a hospital setting on top of other preventative measures? A model-based analysis.

Version: 3

Date: 30 November 2013

Reviewer: Laura Temime

Reviewer's report:

The authors have satisfactorily addressed a number of my concerns in this revised version of the paper, including all the minor revisions I requested. However, I believe that some major issues still need to be addressed (at least in the form of relevant new paragraphs in the Discussion, and possibly with appropriate sensitivity or uncertainty analyses) for the paper to be acceptable for publication.

Authors: We would like to thank the reviewer for this 2\textsuperscript{nd} round of careful review and suggestions.

Major compulsory revisions

1. I remain unconvinced that the choice of the model developed by D'Agata and Webb et al. was an obvious one in this context and believe that the authors should try and justify their choice in the Discussion (other than by mentioning that including both CA and HA-MRSA is adequate here). In particular, they should discuss the potential implications of this choice (vs. other models they could have chosen) on the results they obtain.

Authors: We believe that we have clearly asserted in the abstract and end of introduction that “the main objectives were mainly to propose a versatile simulation framework for assessing potential added benefits of a hypothetical S. aureus vaccine in conjunction with other preventative measures and to illustrate possibilities in a given hospital setting”. To this end, we chose a model that we considered appropriate for the scope, and we do not make the claim that is the only model possible or the best. We have provided full rationale and justification for our choice throughout the manuscript; while we agree that other models could be envisioned as well, we see no strong reason/argument against building on top of an existing published model developed by a reputable group of researchers in the field, which is developed and well-suited for the US setting, and well-cited in the literature.

Further studies are necessary to both collect and collate data from different hospital settings reflecting inherent heterogeneities (e.g., different geographical location, different type of hospital, patient population/community served, etc.) in order to ascertain actual ranges and variability for the different input parameters (e.g., inflow of colonized/infected patients into the hospital, transmission/progression rates) to guide better defined additional sensitivity analyses. We believe that in the absence of robust multiple setting studies any model/parameter choice could be equally challenged when applied/extrapolated in another context.

We have added paragraphs in the Discussion section to address this topic.
2. I think that telling the reader that "baseline estimates for the model parameters were provided in full" in the original model is misleading. Indeed, as mentioned in my earlier review, while it is indeed true that many baseline parameter estimates were obtained from epidemiological data in the original study by D'Agata et al., this was not the case for the transmission parameters, for which no source was provided except for in-vitro studies. Moreover, I disagree with the authors when they write that there are no robust estimates available for MRSA transmissibility. There are a number of studies in which MRSA transmission parameters in hospital settings were estimated using well-adapted statistical methods and detailed longitudinal data; see for instance (Worby et al., Am. J. Epidemiol., 2013, 177 (11): 1306-1313) for a very recent effort. Hence, the fact that the transmission parameters used in this study were not based on reliable estimates should be at least mentioned in the Discussion. Ideally, as, from my experience, model predictions will be strongly dependent on the assumed values of these transmission parameters, sensitivity and uncertainty analyses should be performed.

Authors: By “provided in full” here we simply meant that values for all these parameters could be found in the original publication, nothing more. We have specifically stated that we accepted these values at “face-value”, and it was not in the scope of the present manuscript to challenge them, particularly that we were not in possession of hospital data that we could employ for actual model calibration for comparison, etc.

We thank the reviewer for pointing out the recent publication, where “prospectively collected MRSA surveillance data from 10 general wards at Guy’s and St. Thomas’ hospitals, London, United Kingdom, in 2006–2007 were used, comprising 14,035 patient episodes. Data were analyzed with a Markov chain Monte Carlo algorithm to model transmission dynamics.” We agree that this publication provides another piece in the puzzle, but we consider it rather complementary and independent of the work we chose to build on in the present manuscript. First, the settings for these models are different: the original one in D’Agata that we employed is for a US hospital setting, and particularly for S. aureus there may be differences in the US vs UK (for instance the strong shift towards CA-MRSA in the hospital setting observed in the last decade in the US). Second, in both papers, conclusions/estimates were drawn based on different models, which we regard as complementary and not mutually exclusive (see also our answer above to comment 1. regarding the need for further studies to collect/collate heterogeneous data). At the moment, as far as we can ascertain, in the absence of additional studies/data it can be hard to reliably extrapolate between settings, countries, etc., and that is what we meant when we previously stated that no robust gold/universal standards exist yet.

Our focus here was to conduct sensitivity analyses with respect to different preventative measures, which already translated into varying 6 corresponding model parameters. Carrying out and interpreting additional analyses where any of the baseline model input parameters (equally important in this model as the transmission parameters) are further varied can become intractable and rather difficult to present in a manuscript such as this one.

We fully agree that model predictions will depend on the choice of baseline input parameters, and we have edited the Discussion as requested. We have also now highlighted throughout the manuscript the US setting.
3. Although a paragraph was added to the Discussion in order to underline that the results are hospital and setting-dependent, I still feel that the assumptions regarding the investigated vaccination coverage should be interpreted and debated in the Discussion. For instance, in which setting and under which conditions would a 100% coverage be realistic? How would this coverage be reduced in other settings? How may this be influenced by the duration before full immunity is reached following vaccination? Such a discussion would to my mind strongly enhance the paper's value, as it would help the reader better understand its implications.

Authors: We have edited the Discussion section and added additional paragraphs as suggested.

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
Reviewer's report

**Title:** What potential could there be for a S. aureus vaccine in a hospital setting on top of other preventative measures? A model-based analysis.

**Version:** 3

**Date:** 4 December 2013

**Reviewer:** Radboud Duintjer Tebbens

Reviewer's report:

**Authors:** We would like to thank the reviewer for all his work on this manuscript, and all the valuable comments and suggestions.

**Discretionary Revisions**

I am generally satisfied with the way the authors addressed my comments. Their addition of a clear statement of objectives, the more complete description of the methods and results, and more comprehensive discussion of the limitations significantly improved the manuscript. With respect to my original comment 3, I think it would be helpful if the authors include an explicit reference to the appropriate results in the D’Agata paper (probably Figure 2) to support their statement that the transient dynamics are short-lived and therefore of little interest. With respect to my comment 8c, my view is that it takes more effort from the reader to interpret the meaning of the collection of figures when the y-axis scales change, although I understand that the authors should ultimately decide how to present their results as long as the text helps the reader appreciate the key messages from the figures.

**Authors:** Reference to figure included as suggested for original comment 3 (results section, 1st paragraph). Regarding comment 8c, we chose to magnify the scale on the y-axis for each right panel separately here on purpose, to make otherwise slight differences visible.

**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