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: 2 Date: 4 October 2013

Reviewer: Radboud Duintjer Tebbens

Reviewer's report:

Assessment of overall quality questions:
1. Is the question posed by the authors well defined?
The objective needs more clarification.

2. Are the methods appropriate and well described?
The existing parts are appropriate and well described, but more details are needed.

3. Are the data sound?
Not applicable; the authors use a model to explore the impact of mostly very variable and uncertain model inputs, which is useful and the main contribution of this work.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
The presentation of model and results does not meet sufficiently high standards for publication. I included suggestions for improvement.

5. Are the discussion and conclusions well balanced and adequately supported by the data?
Yes.

6. Are limitations of the work clearly stated?
No, the manuscript requires more discussion of the limitations.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Yes

8. Do the title and abstract accurately convey what has been found?
Yes.

9. Is the writing acceptable?
Yes
Major Compulsory Revisions

1. The objective remains somewhat vague. Is it a sensitivity to demonstrate how the model behaves in response to key assumptions or one to find out which of the unknown inputs (about vaccine effect, but also about the other preventative measures) most affect the results? If the former, then the paper should include more discussion of the dynamic results (see comment #3 below). If the latter, then the authors might consider more formal ways to summarize rank the importance of model inputs (see e.g., Duintjer Tebbens et al, Medical Decision Making 2008, 28:182-200) in addition to or instead of by providing a subset of the high-dimensional space of model inputs' relationships to model outputs.

2. The methods fail to explain several important aspects, which makes it difficult to assess the appropriateness of the model. Most importantly, the authors do not explain the time frame of the model outputs presented in the results section. Do they present equilibrium annual prevalence of MRSA infection (or is it in fact incidence of new infections?) or the prevalence over some defined time period? This is of particular importance in light of the duration of protection derived from the vaccine, which the authors bring up in the discussion and suggest to equal several months, but which the model does not appear to take into account. Depending on the time frame for the model output and the frequency of repeated hospital visits by at-risk-patients, this may merely present a minor limitation (if the time frame is on the order of months) or a serious omission that raises questions about the validity of the results (if the time frame is year, or if the results refer to equilibrium levels of infection).

3. One of the advantages of using a dynamic model, besides providing more realistic estimates than static model, is to better understand the dynamics behavior of the system. This analysis remains entirely silent about how things change over time by focusing on prevalence levels over some undefined time frame, and therefore misses an opportunity for potentially interesting and valuable insights. At a minimum, it would be good to show the impact of vaccination as a function of time and perhaps variation of one or more key model parameters, which will also help MRSA experts to better assess the credibility of the model results.

4. The paper remains silent about validation of the previously published model. It does not appear that D’Agate et al. (2009) (Ref. 23) includes any comparison against MRSA prevalence data over time. The authors should acknowledge this as an important limitation of the results presented in this manuscript.

5. Generally, the limitations require more thorough discussion. Limitations includes:

   a. Lack of model validation (comment #4)
   b. Possible effect of including duration of protection from the vaccine (see comment #2)
   c. Assumptions of constant, exogenous fractions of HA- and CA-MRSA infected and colonized patients entering the hospital (lambda’s), which in reality dynamically interact with the intervention (e.g., widespread adoption of
vaccination would alter these fractions)

d. While I understand the benefits of using a deterministic model for this type of analysis, the authors should discuss the potential implications of the choice of a deterministic model vs. a stochastic, individual-based model (which for the population size considered in the model represents a feasible option as well).

e. Any other limitations that the reader should know about

6. The authors elected to only provide benefits of vaccination in addition to other measures. Even if purely theoretical, it may be relatively simple and quite informative to directly compare only vaccination to only preventative measures. Moreover, without any explanation of the choice to omit this, the authors run the risk of speculation that the results look more favorable for vaccination in addition to other preventative measures than for vaccination-only.

Minor Essential Revisions

7. Last paragraph of Mathematical Modeling Overview, “In this scenario, we hypothesize that patients are vaccinated with a S. aureus vaccine before 128 hospital admission, i.e. in a timeframe to allow an adequate immune response (e.g. planned 129 hospitalization, vaccination of high-risk individuals).”: The use of the word scenario is misleading because it suggests that this represents but one of a number of different scenarios, whereas in fact what the authors mean is the entire analysis. I suggest starting the sentence with “In this analysis” or “In this study”. This appears to be the most optimistic possible assumption. At a minimum, the manuscript should inform the reader about the expected timeframe of adequate immune response and the proportion of actual patients for whom admission is planned in advance of this timeframe. If this proportion may be low, then the authors should explicitly add a model inputs for its effect on the fraction of new patients that flows to the vaccinated compartment for assessment of its importance in the sensitivity analyses or preferably for the base case.

8. Please consider the following to improve the presentation of the model and results:

a. The authors briefly mention Figure 1 in the methods without explanation. All the needed explanation and detail to understand the model structure is in Figure 2 and the related text in the methods section. Therefore, Figure 1 does not add much and the authors should consider omitting it. If they do include it, would be easier to follow Figure 1 if the equations in the boxes include all variables (like COV and DA) and not their values. So instead of 10% and 0.67%, gives variable names to these and describe them in the lower white box (with the values provided there if desired).

b. Figure 2 would be much easier to read if it includes a list of symbols so that the reader does not have to look each of them up in the text.

c. Figures 4-6: The choice of different y-axis scales distorts the visual impression of the sensitivity to different model inputs (e.g., how close together and steep the lines are, and where they lie in the overall range of possible value). Although I understand that some lines will become difficult to distinguish, I suggest that using consistent y-axis scales (e.g., y-axes in left panels of Figs 5-6 always from
0 to 400, right panels always from 0 to 22,000) gives a much more direct picture
of the impact of different model inputs (i.e., if the lines become indistinguishable,
then the sensitivity to a model input is not consequential).

9. The statement in the discussion that “Employing a previously published model
also served to minimize the number of assumptions and reduce bias” is
questionable. Why would using an existing model reduce the number of
assumptions (it may reduce the number of assumptions to explain and vary), and
why does it reduce bias?

10. Decision makers assessing investments in S. aureus vaccine development or
implementation benefit from a better understanding of its impact on prevalence,
but they also need to consider the costs. The authors should include more
context about this and point to any data that exist on the cost of vaccination and
other preventative measures.

11. Second paragraph of Mathematical Modeling Overview, “Furthermore, for
simplicity, we have assumed identical vaccine-related parameters for both
HA-MRSA and CA-MRSA, although in the theoretical model structure they can
have different values”: are there reasons to believe that important differences
exist in vaccine-related parameters for HA- vs. CA-MRSA? If so, in what way and
how would that affect the results qualitatively, or if possible, quantitatively?

Discretionary Revisions

12. The statement in the Model Parameters section “We emphasize that this is a
mechanistic and deterministic framework, which enables better tractability when
varying different parameters, and assessing/comparing corresponding outcomes”
belongs to the Mathematical modelling overview.

13. Table 2 appears more appropriate to include as part of the methods section.

Minor issues not for publication

14. Line 70: “programs” should be singular

15. Line 86: I suggest replacing “3-years intervention period” with “a 3 year
intervention period”

16. Line 97: please add “to” after “complimentary

17. Line 112: improper and unnecessary use of the word “respectively”

18. Line 131-2: “A schematic representation is illustrated in Figure 1” is
redundant, I suggest replacing “illustrated” with “given”

19. Line 140: please delete the word “subscript” as the “V” does not always
appear as a subscript

20. Line 143: please is “in-flow and out-flow” instead of “flow-in and flow-out” to
be consistent with the rest of the text and the more commonly used term in the
dynamic modeling field.

21. Lines 144-7, “… with fractions of patients admitted with CA-MRSA
colonization, CA-MRSA infection, HA-MRSA colonization, and HA-MRSA
infection expressed as #CC(V), #IC(V), #CH(V), and #IH(V), respectively
(unvaccinated/vaccinated)” I suggest changing this to “… with fractions of
(vaccinated) patients admitted with CA-MRSA colonization, CA-MRSA infection, HA-MRSA colonization, and HA-MRSA infection expressed as #CC(V), #IC(V), #CH(V), and #IH(V), respectively”

22. Line 155: please define HCW as this is the first occurrence of the acronym instead of in line 186.

23. Line 157-8, “CC(V), IC(V), CH(V), and IH(V) denote the number of patients with CA-MRSA colonization, CA-MRSA infection, HA-MRSA colonization, or HA-MRSA infection, respectively.” Please delete sentence as these were already defined above.

24. Line 240: please add the city in MA (Natick) for MathWorks

**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