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:

Cosmina S Hogea (cosmina.s.hogea@gsk.com)
Thierry Van Effelterre (THIERRY.VAN-EFFELTERRE@GSK.COM)
Adrian Cassidy (ADRIAN.X.CASSIDY@GSK.COM)

Version: 3 Date: 19 November 2013

Author’s response to reviews: see over
The authors would like to thank all the reviewers and the editor for all their work. We have revised the manuscript, with edits highlighted in yellow in the text. Our point by point responses to the reviewers' comments are below.

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: 29 September 2013

Reviewer: Laura Temime

Reviewer's report:

In this paper, the authors investigate the impact of a hypothetical S. aureus vaccine on MRSA infections in a hospital setting, using a modeling approach. Because of the current interest in developing such a vaccine, being able to assess its potential impact is an important issue, especially taking into account the other infection control strategies that are already being used. To my knowledge, this is the first study to do so. In addition, mathematical modeling is an obviously pertinent approach in this context, as no data is available yet.

Authors: We would like to thank the reviewer for this very careful review and suggestions, we have tried to address as many as possible.

Minor essential revisions

1. p.8, line 162. I think "eta" actually works as a composite parameter, describing both hygiene compliance and hygiene efficacy. This should be clarified.

Authors: We have now added a whole new table (Table 2) with clear mathematical definitions and expressions, including the 'eta' parameter and interpretation.

2. It is fine to refer the reader to the paper by Webb for "technical details" and mathematical equations (provided the choice to keep the exact same model is valid, see comment 8). However, I would still have liked to find some more explanation of the model structure and parameters without having to refer to the Webb paper (for instance in the legend of Figure 2 or in the Methods).

Authors: Please see answer to comment 1, above. The legend of the figure with model description was also expanded, and the Methods section has been edited.

3. p. 13, line 279. The paper should specify how many doses are assumed to be necessary per person, and possibly discuss this assumption which may impact model predictions.

Authors: We have now specified that we assumed 1 dose of vaccine per patient in the results.

4. Table 1. The description of parameters betaCC, betaCH, betaIC and betaIH is unclear and should be reformulated.

Authors: We have edited these definitions in the Methods section and in Table 1.
Major compulsory revisions

5. Even though the basic control strategies are fully described in the original papers by D’Agata and Webb, I think that this should also be the case in the current paper. In particular, the reader shouldn’t need to refer to the original papers to be able to understand exactly how these strategies translate in terms of model parameters (and equations).

For instance, it wasn’t clear to me why a screening and decolonization strategy with assumed 100% screening compliance and decolonization efficacy did not lead to total disappearance of MRSA infections, because I had not understood that screening was assumed to occur among already hospitalized patients rather than at admission.

Authors: We have edited the Methods section and added material (e.g., Table 2) that should help unequivocally clarify the correspondence between the verbal description of each control strategy and the mathematical representation in the model, including the cases verbally labeled as “100% compliance” in the context.

As this paper was originally written primarily with a more clinical/medical audience in mind, we have tried using more verbal descriptions that would better resonate with such audiences, but we agreed it can be misleading occasionally; hence we included explicit mathematical expression and referred specifically to corresponding parameters.

6. On a related note, why wasn’t a "screening at admission" strategy investigated? It seems to me that this a relatively frequent control strategy which has been explored using modeling approaches before, and could prove to be more efficient than the other investigated strategies, hence changing the main results.

Authors: CDC does not currently recommend routine pre-admission screening in the US for MRSA. Also, for simplicity here, we chose to stay as close to the original D’Agata model assumptions/structure as possible. This is a first step only, and it does not preclude one from using such frameworks in the future to investigate other control strategies.

7. I couldn’t find a precise description of the chosen model outcomes in the paper. While the authors mention that they are looking at "the number of MRSA infections" and at the reduction in these infections, they do not specify over which time period they do so. I gather that these are steady-state outcomes? This should be clarified.

Authors: We have made edits to clarify that we are showing results at steady-state throughout the paper, as transients here are short-lived (a couple of months) and not of main interest for longer term hospital infection control policies.

8. More importantly, I am not convinced that the choice of the model developed by D’Agata and Webb et al. is pertinent here. This model was developed specifically for exploring CA-MRSA transmission dynamics within hospitals, in competition with HA-MRSA. Not only is exploring the CA-MRSA/HA-MRSA dynamics not part of the objectives of the current study, this aspect is actually completely ignored here by assuming identical vaccine effects on these two strains (which is a fully justified assumption, considering that the vaccine is still hypothetical). Hence, I think that using a simpler model with MRSA described as a whole would have been more appropriate. This could have been done by using either another (possibly older) MRSA transmission model, or a simplified
version of the D’Agata model in which the CA-MRSA and HA-MRSA compartments would be fused together.

The authors justify their use of this specific model by writing that it “minimizes the number of assumptions” and “reduces bias”. However, in this case, 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. In the D’Agata et al. study, this was made necessary by the absence of available data on relative CA-MRSA vs. HA-MRSA transmissibility. In the current study, this seems to me to be a relatively large assumption, which may have a large impact on model predictions, and which could have been avoided had the authors used a simpler MRSA-only model (for which robust estimates of the transmission parameters are available).

For instance, simply using a simplified version of the D’Agata model (as suggested earlier) would also allow to use those among the parameters that are well documented, while avoiding the introduction of unnecessary uncertainty in this study.

Authors: To our knowledge, gold standards in transmission estimates for MRSA are currently unavailable. On the other hand, the explicit inclusion of HA-MRSA and CA-MRSA is adequate here as CA-MRSA is a growing problem in US hospitals, with CA-MRSA strains genetically distinct from HA-MRSA strains and thought to have evolved separately. We do not know if any vaccine will succeed in being equally efficacious against both, in which case this becomes even more important. One of our goals here was to propose a versatile framework that adequately reflects the underlying epidemiological status quo.

It is true that in the current analyses, for simplicity, we have not considered any differences from a vaccine perspective, but this is just a first step and certainly not exhaustive. And since such a model that well reflects the state of the art in the field already exists, why not use it to create a broader framework that could be later employed for more analyses?

The reviewer is right about additional levels of uncertainty, etc. – and this is not meant to be some sort of definitive conclusion. It is merely intended to illustrate the potential and propose a feasible simulation framework that one could further adapt to different settings, scenarios, etc. Ideally, as we already discussed, any such framework should be re-calibrated to available epidemiological data in different settings, etc. Here we illustrate with one potential situation, relying on the transmission parameters chosen at baseline in the D’Agata model, which are all provided in full and used as such here. We do not perform any sort of estimation here.

9. In this study, vaccination is assumed to occur before hospital admission, “in a timeframe to allow an adequate immune response”. While this seems a reasonable enough hypothesis, I think it has implications which are not fully taken into account in this study. As mentioned by the authors, such a vaccination procedure would only be possible in individuals identified as high-risk, or in cases of planned hospitalizations. Hence, investigating a vaccination coverage as high as 100% (or even 75%) is probably unrealistic. It seems to me that it should be possible to compute a rough estimate for a realistic upper bound for this vaccination coverage, based on available data on hospitalization causes (i.e., what portion of hospitalized patients do high-risk patients and patients with planned hospitalizations actually represent?). If it is indeed lower than 75%, this realistic upper bound should then be used in model simulations instead. Another important parameter is the necessary duration
between vaccination and immunity. Depending on this duration (and in particular whether it is superior to the average delay between a hospitalization is planned and hospitalization actually occurs), vaccine coverage may be lower than expected.

**Authors:** This would be highly hospital-dependent. In specialty hospitals, like cardiac or orthopedic, planned surgeries are probably preponderant. For instance, Hospital for Special Surgery in NY with 13,457 admissions in the most recent year reported, performed 13,305 inpatient surgeries, with 0 Emergency Room visits reported.

Our purpose here was to simply illustrate the full spectrum for completeness, and we made the point in the discussion that such measures will probably have to take into account the nature of the hospital, specific setting, etc.

**Discretionary revisions**

10. p.9, lines 182-184. I am not sure that this introductory paragraph is necessary.

**Authors:** This paragraph has been removed.

11. The discussion could include a paragraph on possible applications of this work for cost-effectiveness analyses, which would no doubt prove necessary before systematic pre-hospitalization vaccination is recommended.

**Authors:** The few scenarios presented in the results are just intended to illustrate the potential of this simulation framework that one could further adapt to different settings and scenarios, including cost-effectiveness analyses. This is now clarified in the discussion.

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: 2 Date: 30 September 2013

Reviewer: Leigh Anne Shafer

Reviewer's report:

In this study, the authors employ mathematical modelling to assess the potential impact of a hypothetical s. aureus vaccine, when used as part of a prevention bundle in hospitals. The topic is good and timely, in order to assess the importance of continued work on developing such a vaccine. The modeling scenarios run answered the question well. However, there are a number of concerns, most of them about the structure of the model and assumptions.

Authors: We would like to thank the reviewer for this review; we have tried to address as many comments as possible.

Major Revisions

1. Did you use D’Agata’s model, and update it with the potential to include a vaccine intervention? That is, did D’Agata give you his model (the programming code) and you used it? If so, why isn’t D’Agata a co-author? If you used the description of a model that D’Agata provided in a previously published manuscript, but wrote your own model program, we need more detail. What programming language did you use? How did you incorporate human mixing patterns in the hospital? Although you provide quite a bit of model detail in the methods of the manuscript, we need more. We probably need a detailed appendix of the model that you developed (or modified), so that we can evaluate it. I disagree with your statement that providing the mathematical details of the model is beyond the scope of this paper since the pre-modified model was described previously (p. 12, line 237). You have made enough changes that it warrants a full description of your model.

Authors: We did not request nor receive any programs from the D’Agata group. All the information we used is published in full and available for anybody interested. We specified that we used Matlab for all our numerical simulations.

We have edited the Methods section and added material (e.g., current Table 2, which explicitly lays out the mathematical descriptions of interest) that should help better clarify. We have provided a detailed full model schematic (model compartments and corresponding inflows and outflows) which is the typical representation/description of such models, and which can be used to easily reconstruct the underlying ordinary differential equations which are standard for this type of compartmental model for infectious disease transmission, based on the law of mass action. We believe that the level of information now provided in this context is consistent with the usual standards in similar papers in the field, particularly that 2 recent other papers have made the object of the actual base model in detail and we feel that re-rendering everything here in full would not be appropriate. It is not unusual in the field of modeling to build on existing published models, and usually appropriate referencing suffices. This is not a
transmission model with age structure or any other finer granularity in terms of population considered, so mixing is assumed homogeneous by default.

We would also like to clarify that this was intended primarily as a publication focused on applications for the more medical community, and not mainly a methodology paper.

2. The originally published modelling work provided baseline parameters relevant to a general MRSA infection. You have specific HA-MRSA and CA-MRSA. How did you determine the parameter values for your updated model? Although I agree that explicitly including HA-MRSA and CA-MRSA allows “potential different transmission aspects to be adequately accounted for”, as you state on p. 7 line 118, you need to give much more detail on this model (e.g., an appendix fully describing the updated model), so that we can evaluate how you determined parameter values related to the different transmission aspects.

Authors: We have accepted the CA-MRSA and HA-MRSA baseline values from the original model in the absence of more/other relevant data, as a starting point. We have now added explanations in the Methods section, tried to better present information in Table 1 and added Table 2 with additional information that should hopefully help better clarify.

3. You wrote in the manuscript text that # is the number of hospital admissions per day. Yet, it appears in Figure 2 (hard to tell for sure because it is too blurry when magnified), that you have people leaving the hospital from the two infection states, at a rate of #*(the relevant lambda for the respective hospital leave rate). This cannot be right. If this reflects what the model is doing, then the model needs updating and re-fitting. If it is just a typo, the revision is simple.

Authors: If the reviewer is concerned about some overall mass-balance preservation, here that is ensured by varying the number of daily admissions over time so that the overall patient population in the hospital remains constant at full capacity over time. People symptomatically infected leave at the corresponding related death rates; the “star” notations here in the Vaccinated component are included merely to show the full spectrum of possibilities one could consider further for vaccine effects, like for instance potentially lower infection-related death rates. We explained this in the legend of the figure depicting the model structure. In the simulations here, however, we do not consider such enhanced vaccination effects and work with similar rates in both the Unvaccinated and Vaccinated compartments. We have expanded the corresponding legend to better explain and clarify.

4. The FOI is wrong unless you only assume 1 effective contact per time unit (day?). According to p. 8, lines 153-154, your FOI appears to be, essentially, the fraction of hospitalizations that are colonized or infected patients, times their respective (colonized or infected) transmission rate. What happened to the contact rate – number of people each colonized or infected person contacts per time unit? If your betas somehow incorporate the contact rate into the estimated transmission rates, then you need to explain this in detail.

Authors: Expression of the FOI here is legitimate and typical for a model of this sort, and it depends on the proportion of infectious (colonized/infected) patients out of the total patient population. Betas here indeed represent effective transmission rates, with units of 1/time, which implicitly represent the contact rate multiplied by transmission risk.
5. The baseline parameter values that you give in your Abstract do not match those from Table 1. For example, in the Abstract, you assume 50% hygiene compliance, but in Table 1, you state that the baseline is 60%. In the Abstract, you assume 50% decolonization, but in Table 1, you state that the baseline is 0%.

Authors: We have made edits that will hopefully help clear the confusion. The now edited Table 1 in conjunction with the newly added Table 2 should make clear how different parameters are used, along with the corresponding mathematical representation. We agree that calling a scenario with 50% screening and 50% decolonization in this context may be confusing, hence we now replaced with “average scenario” instead.

6. Explain why there are no already infected admissions to hospital among those vaccinated (figure 1). You don’t assume that vaccination cures those already infected, do you?

Authors: Indeed, we do not. In this flexible modeling framework, one can input their own assumptions about vaccination coverage levels for different patient compartments, these are input parameter that can be varied based on setting, logistic, patient population, etc. For the analysis presented here, for simplicity and in order to reduce the number of input parameters that could be varied, we just assumed that coverage represents a percentage of all the daily admissions, and distributed it accordingly among the vaccinated compartments (Susceptible, Colonized, Infected) keeping the same proportions as in the unvaccinated counterparts. There was a typo/misrepresentation in figure 1 for the infected compartment, should follow the same pattern as the Susceptible and Colonized compartments. Figure 1 has now been removed as suggested by another reviewer, and the explicit mathematical description of vaccination is now included in the new Table 2 for clarity. We also edited the legend of current Figure 1 (former figure 2) with the model schematic to try and better explain.

7. The figure resolution was too low, so it was almost impossible to see Figure 2, which was key to understanding the model, given your sparse description of it. When I magnified the Figure 2 page size by 250% (so that the words would almost be large enough to be legible), then the figure became too blurry. Anything less than 250% magnification and the words and symbols were too small to read. Also, as a minor detail, you do not have one vaccinated compartment and one unvaccinated compartment, as your Figure 2 headers imply. Rather you have multiple compartments in each group.

Authors: We are very sorry to read about the reviewer’s troubles with the pdf. Unfortunately we experienced lots of issues with the way the journal’s pdf converter managed the figures. The figures on their own are of fairly good quality, and they passed the journal automatic QC check when uploaded separately, but when converted to the default pdf by the journal, indeed, they did not result in a decent quality. We have tried everything we could when we submitted, and converted many times, without success. We have now tried again to increase the resolution. If this problem persists, we should probably notify the journal about it.

8. In your background prevention bundles, how quickly do you assume that screening or decolonization occurs? Please describe the rates used in order to achieve the different scenarios of Figure 3. E.g., what rate was used in order to achieve 100% screening and 100% decolonization? This is necessary
in order to assess why 100% screening, 100% decolonization, and 100% hygiene results in ~75% reduction in MRSA.

Authors: We have now added a full table (Table 2) with a full technical description of the model parameters governing the different control strategies and the related mathematical expressions, and we have also edited text accordingly. That should now provide the missing link between the actual verbal description (which is intended to more readily resonate with a clinical audience) and the corresponding mathematical representation in the model, with clear definition of corresponding rates and such.

9. Like Figure 2, Figure 4 was very difficult to read. Resolution is too low and figure is too small.

Authors: Please see our answer to Comment 7. above.

10. For your analysis of number of vaccine doses (Figure 5), are you assuming that people are vaccinated before each hospital admission, so that people could be vaccinated many times (once for each hospital admission)? So you are assuming a very fast waning rate of the vaccine? Please explain.

Authors: We have edited the text to clarify, both in the Methods section and in the expanded legend of the model schematic. This model is focused on what happens within the hospital and there is no explicit modeling of dynamic exchange with the community outside the hospital, account for vaccine waning, etc. We indicated that as a limitation in the Discussion section. We do not keep track of the individual history of patient vaccination here – it is all implicitly in the vaccination coverage, which will reflect how many patients were actually eligible for vaccination for the current hospitalization. One could, of course, go to the next level and assume varying levels of coverage over time, etc. – but again, this is outside the scope of this analysis which we regard as a starting point only.

Minor Revisions

11. Abstract: Using an existing model with published baseline estimates of model parameters would neither reduce assumptions, nor reduce bias. Assumptions (e.g., assumptions about mixing or about infectiousness of s. aureus) were made in the previously published model, right? And what bias are you talking about? Do you mean that you reduced uncertainty (not bias)? If that is what you mean, using an existing model did not reduce that either. You might have been able to reduce uncertainty by fitting your model to different populations settings, with the same assumptions about things like infectiousness that would not change between populations.

Authors: In the absence of robust estimates/gold standards for the various parameters needed in a baseline transmission model, as well as in the absence of data that could reliably be used for actual model calibration, one would inherently need to supply corresponding assumptions (extrapolate from literature, different sources, etc.) if one started to build such a model from scratch. The model already published is at least fully documented and coherent, it can be legitimately be referred to, and reflects the current status quo of MRSA transmission in the hospital (e.g., CA-MRSA vs. HA-MRSA). Hence, it seems reasonable to employ it readily as is and put additional simulations on top of it as a starting point. What we meant by “reducing bias” in this instance was that we start from an independent model developed by another group
as the baseline pre-vaccination, and we just add vaccination on top of it, rather than starting from
developing our own model for both baseline and vaccination and ignoring what is already available.

We understand that it was confusing and have now removed sentence, and also made edits throughout the
text wherever appropriate to indicate that we have accepted the D’Agata original model at face value as
plausible in their given hospital setting.

Here we did not fit anything, as we unfortunately do not possess any raw epidemiological data in hospital
settings that would enable performing an actual parameter calibration via model-data fitting.

12. Typo on p. 4, line 77. The word “program” should be singular. On p. 5, line 80. “… during 6-month
intervention…” should read, “… during a 6-month intervention…” Throughout the manuscript, some
prepositions and articles (“a”, “the”) are missing.

Authors: Typos were corrected throughout the text.

13. Did you consider waning?

Authors: This is a model focused on within-hospital transmission and infection spread, and we do assume
that patients do remain protected for the duration of their hospital stay if they have been vaccinated within
a reasonable time-frame prior to vaccination. So there is no waning here in the hospital. We have edited
the text, both in the Methods section and in the extended legend of the model schematic to try and better
clarify.

14. We have people leaving the unvaccinated susceptible and entering the vaccinated susceptible
compartment at a rate of #SV, according to the manuscript text. Yet, this flow of people between
unvaccinated and vaccinated states is not seen in Figure 2. Perhaps you simply forgot to add it to
Figure 2 because you were only modelling pre-hospital vaccination rates and assumed that
vaccination in hospital was 0? So #SV would be 0. However, if this flow is part of the model, it
should be depicted even if all of the scenarios for this study had a flow rate of 0.

Authors: This is a model where all patients are assumed vaccinated prior to hospital admission, so there is
no actual exchange between the unvaccinated compartments and their vaccinated counterparts here, as
customary for such other models at population level, for instance. We have made edits both in the
Methods section and in the extended legend of the model schematic to try and better clarify.

15. Are the rates in the model per day? Daily rates?

Authors: Yes, all rates are per day, with corresponding values indicated in Table 1.

16. On p. 12, line 250, you state that, “…a model-projected reduction of at least 48% can be achieved…”
Please explain what you mean by “at least”. From Figure 3, it appears that all of your modelling
results are based on just one best-fitting baseline scenario, and varying intervention rates. If your
model results are based on a range of good-fitting scenarios, and 48% was the lowest predicted
impact of the intervention rates you describe, then you need to explain this in the methods and show
this in your Figure 3. This applies to all of the “at least” statements in the manuscript. E.g., “… a
reduction of at least 64% is projected…”.
Authors: For clarity sake, we have now removed the “at least” and referred specifically which scenario the corresponding reduction is for.

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: 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

Authors: We would like to thank the reviewer for this very detailed review and comments, we have tried to address as many as possible.
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.

Authors: The main objective here was to propose a simulation framework which reflects the state of the art (e.g., transmission aspects, HA-MRSA vs. CA-MRSA) for assessing potential impact/added benefits of a hypothetical *S. aureus* vaccine in a hospital setting in conjunction with other preventative measures, and to simply illustrate possibilities in a given hospital setting with characteristics fully described in the original D’Agata paper. While we agree that there are different ways to organize and present outcomes, this work was primarily aimed at broader clinical audiences, so we chose to present results in a way that we found relevant and more intuitive. This work does not claim to be exhaustive, and we regard it merely as a starter. We have tried to edit the text accordingly to emphasize these points.

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).

Authors: We have edited the Methods section and added material (e.g., new Table 2) that should help better clarify.

The transient dynamics here are short-lived, a couple of months at most (see also Figure 2 in the D’Agata paper), thus an endemic equilibrium state (steady-state) is reached quickly and transients are of no great interest in this particular context. Results are thus reported at steady-state. Regarding vaccine duration of protection, here we assume that patients would be vaccinated prior to hospital admission and remain protected for the duration of the current hospital stay.

This model does not keep track of patient’s individual history or account for frequency of hospitalization, etc., or model explicitly what happens to the patient after hospital discharge. It is strictly a hospital model, with no explicit exchange modeled with community, continuity in terms of repeat-visits, etc. It is an average simplified framework, focused on reducing transmission and infection within the hospital.
We have edited the text to explicitly state these aspects. Prevalence here is meant as customary, as point prevalence at steady state.

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.

Authors: Please see answer to comment 2. above, transients are of no great interest in this context, we really are interested in potential for sustained reduction in transmission and infection at the hospital level in the longer term. We have hundreds of simulations here, and we need to focus on summarizing and presenting results that we consider most relevant in a concise manner that can be useful and accessible to the more clinical community.

The fact that we present results at steady-state does not in any way undermine or misrepresent the dynamic modeling framework, which constitutes the most realistic way to capture transmission-related aspects; the steady-state here constitutes an end-result for such a dynamic model.

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.

Authors: The actual validation of the previously published model was not in the scope of this manuscript, as the authors of the original model have already argued their case in 2 related publications which we do not challenge here but rather employ at face value. We understand and agree that one can challenge any model, but in the absence of a gold standard or available hospital-specific epidemiological data (which we do not possess at the moment), this is all that we could do as a pertinent starting point. Performing such analyses could serve as incentives in the future for collection of more data, etc, and should such data become available, then such models should certainly be re-evaluated and re-calibrated. This was mentioned in our Discussion section under Limitations.

5. Generally, the limitations require more thorough discussion. Limitations includes:
   a. Lack of model validation (comment #4)

Authors: Please see answer to comment 4 above.

   b. Possible effect of including duration of protection from the vaccine (see comment #2)

Authors: Please see answer to comment 2 above.

   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)
Authors: Please see answer to comment 2 above. This model focuses on what happens inside a hospital setting and it does not model explicitly dynamic exchange or impact of vaccination on the community outside the hospital. This was listed as a limitation in the Discussion section.

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).

Authors: We agree with the reviewer, but the fact that other possible modeling approaches could be considered does not constitute a limitation of the one presented here. Neither have we claimed anywhere that this is the only or best way, etc.

We agree that individual-based models would have a big appeal particularly in settings with a small number of patients, etc.

We have edited the text in the Discussion section accordingly.

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.

Authors: This analysis (vaccination only) was performed. However, we do not think it is realistic in an actual clinical context to have vaccination in a complete absence of any other preventative measures, so we did not include it here in order to keep things more concise and focused (if too many different results, plots, etc. are shown, the dispersion risks run high, particularly as this is primarily intended for a broader clinical audience).

It suffices to look at the plots already included in old Figure 4 (new Figure 3) to clearly see that at lower levels of hygiene compliance, for instance, there is more room for additional added benefits due to vaccination, which gradually decrease with increased levels of hygiene.

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 input 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.

**Authors:** Text edited accordingly. We made it clear that this refers to a purely hypothetical *S. aureus* vaccine, and illustrated potential additional benefits due to vaccination under various assumptions. Actual duration to build an adequate immunity cannot be specified in the absence of an actual vaccine, and it is not directly relevant for the analysis here. Regarding proportion of patients with planned admissions, again, this is likely to vary depending on specific hospital setting.

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.

**Authors:** We have made edits to try and accommodate points a-b; Figure 1 was removed and more explanations were added in the Methods section, newly added Table 2, as well as the legend of the new figure 1 illustrating the model structure.

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).

**Authors:** We have tried different resolutions, scales, etc. already, and decided to visualize things this way to that the reader can have full visibility of the results rather than just overlapping curves in some instances. We believe the scale difference is easily visible, and the reader should be able to judge and make the distinction without a lot of effort.

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?

**Authors:** In the absence of robust estimates/gold standards for the various parameters needed in a baseline transmission model, as well as in the absence of data that could reliably be used for actual model calibration, one would inherently need to supply corresponding assumptions (extrapolate from literature,
different sources, etc.) if one started to build such a model from scratch. The model already published is at least fully documented and coherent, it can be legitimately be referred to, and reflects the current status quo of MRSA transmission in the hospital (e.g., CA-MRSA vs. HA-MRSA). Hence, it seems reasonable to employ it readily as is and put additional simulations on top of it as a starting point. What we meant by “reducing bias” in this instance was that we start from an independent model developed by another group as the baseline pre-vaccination, and we just add vaccination on top of it, rather than starting from developing our own model for both baseline and vaccination and ignoring what is already available.

For clarity, however, we have now removed the sentence and tried to better explain the base model choice and corresponding parameters.

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.

Authors: We agree, and that is why we provided as an illustration the corresponding number of vaccine doses necessary to achieve each level of additional infection reduction to put things into perspective, but this was not intended as an economic evaluation in the first place, so it is at the moment out of the current paper scope. Data on potential costs for vaccination will not be available before a vaccine is closer to licensure, etc.

Once again, this is intended as just a starter in that direction, to get people (both vaccine developers and clinicians) thinking in a more quantitative way and to provide a framework to model any future scenarios that might be relevant in other given contexts.

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?

Authors: As we mentioned already, this is meant as a first step here, and more could be further done, various additional analyses, etc. For now, we are attempting to propose a state-of-the-art simulation framework and simply illustrate the potential. HA-MRSA and CA-MRSA are very different strains genotypically, and nobody knows yet if a vaccine may be equally efficient against both, and this will probably not be known again until a vaccine reaches more advanced clinical trials. It is important, however, for models to reflect the state of the art in the field, and strive to be more realistic. We do know that in the US, CA-MRSA is partially replacing HA-MRSA and invading the hospitals, so this is an important feature and distinction to be included. In the proposed modeling framework, it is possible to run scenarios with different vaccine efficacies for HA and CA-MRSA if that would seem the case in future trials.
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.

   Authors: This paragraph was removed from the text.

13. Table 2 appears more appropriate to include as part of the methods section. Minor issues not for publication

   Authors: The method section and Table 2 was revised.

14. Line 70: “programs” should be singular

   Authors: statement changed to plural: “…and institutional culture change programs.”

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

   Authors: This wording was kept to be consistent throughout the text (eg 6-month period).

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

   Authors: Reworded as suggested.

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

   Authors: This word was removed from the text.

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

   Authors: Figure 1 and this sentence was removed from the text.

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

   Authors: changed to “V” notation.

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.

   Authors: changed as suggested.

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”
Authors: changed as suggested.

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

Authors: HCW now defined at first occurrence. In most cases, HCW hygiene/compliance was replaced by ‘hospital hygiene/compliance’ throughout the text.

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.

Authors: Sentence was kept, but (V) component specified with ‘unvaccinated and vaccinated’.

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

Authors: changed into “MATLAB R2010b The MathWorks, Inc., Natick, Massachusetts, United States.”

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