Author's response to reviews

Title: Assessing the role of undetected colonization and isolation precautions in reducing Methicillin-Resistant Staphylococcus aureus transmission in intensive care units.

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Version: 3 Date: 2 October 2009

Author's response to reviews: see over
October 2, 2009

Dr Melissa Norton
Editor-in-Chief

*BMC Infectious Diseases*
BioMed Central Ltd (publisher)
Floor 6, 236 Gray's Inn Road
London WC1X 8HL

Dear Dr Norton,

We have recently received the comments of the two reviewers with regards to our research article initial submission to *BMC Infectious Diseases* entitled “Assessing the role of undetected colonization and isolation precautions in reducing Methicillin-Resistant Staphylococcus aureus transmission in intensive care units.”

We would like to thank the referees for their valuable comments and suggestions. Enclosed please find a revised version of our original submission. We also attach point-by-point responses to the concerns/comments/questions raised by the reviewers. Finally, a revised version of Table 1 is also attached.

Many thanks for your consideration of this work.

Sincerely,

Theodore Kypraios, PhD
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Reviewer’s report

Title: Assessing the role of undetected colonization and isolation precautions in reducing Methicillin-Resistant Staphylococcus aureus transmission in intensive care units.

Version: 2 Date: 16 July 2009
Reviewer: Martin Bootsma

Reviewer’s report:

I feel this is a well-performed analysis of clinical data obtained in a non-study setting, which tries to answer a relevant medical question. Unfortunately, despite reasonably long study periods, the data do not allow a clear conclusion about the effect of isolation measures.

Minor Essential Revisions

Abstract:

-Remove comma in last line of introduction.
  Done

-Methods: If the admission cultures consisted of nasal swabs, add the word “Nasal” as first word.
  Done (nares screening has been made more consistent throughout)

-Methods: Add that the ICUs consisted of single beds. This is important for the interpretation of the term isolation.
  Done. Added the words “single-bed” before the word “ICUs”

-Conclusions: I think the conclusion is a bit too strong. No ICU showed significant evidence of a benefit of isolation and neither did the pooled estimate, so I would avoid terms like clinically significant reductions.
  Done

Materials and methods:

-Given the huge difference between countries in MRSA prevalence, I would prefer if the country and city of the tertiary academic medical center were provided in the first sentence.
  Done – location now provided

- It was not completely clear to me which sites were cultured on admission.
  This has been clarified in the text. Only bilateral nares cultures were performed
- Mention more clearly that clinical cultures are also used for the analysis and mention which cultures are used (only blood cultures and wound cultures, or also urine cultures, this influence the interpretation of the low sensitivity of detecting MRSA by non-nasal cultures. Also mention somewhere the frequency (or the total number) of clinical cultures.

We have clarified this point in the text.

- What was the size of the ICUs? This can be inferred from table 1, but I think explicit mentioning is useful to provide the readers with a feeling of the data.

This is mentioned in the Data collection section of the “Materials and Methods”.

- The study period mentioned is incorrect. September 2003-January 2004 is only 5 months, not 17.

We corrected this typo to January 2005

- Was the cleaning protocol for the room identical after discharge of an MRSA-positive or MRSA-negative patient?

Yes, no difference. This was not added to the text.

- From the discussion it can be inferred that conventional microbiological tests were used to detect MRSA colonization. I think this should be mentioned in the methods.

This has been explicitly added.

Data analysis
Stochastic model

- In the definition of #(t), the cross transmission terms do not depend on the total number of patients in the unit (i.e., #(t) is not #0+$1C(t)/N+$2I(t)/N.)

First, comment somewhere to what extent the number of patient within an ICU changes over time. Second, inclusion of the total number of patient in the unit in the formula for the force of infection rescales the estimates of #1 and #2. Although the sizes of the ICUs seem to be more or less identical (same number of total patient days, as suggested by Table 1), a remark on this is useful (for instance to interpret the sentence in the Results that the estimates of #1 were fairly consistent).

This has been clarified in the text.

- What are the assumptions about the sensitivity and specificity on clinical cultures? If a clinical culture is positive, the patient is considered to be MRSA positive, but what are the assumptions if a clinical culture in negative?

Negative clinical cultures were not included in this study and did not affect the model. This is clarified in the text.
- Is the likelihood of the observed data computationally intractable if the specificity of a test is assumed to be 100% and subsequent test results of a single patients are assumed to be independent?

Even if the above is true (100% specificity etc) the times at which individual become colonised are unknown and therefore the likelihood of the observed data is intractable. The text already states that colonization times are added, so we have not changed the text.

Results:
The estimates of #1 seem to differ a factor 3 between wards, which is quite a lot.

The text already mentions between-ward variation so we have not added anything more.

Mention the results of the swab sensitivity also in the text. Especially, that nasal cultures have a sensitivity of 60% of detecting MRSA colonization (at any site) is a relevant result, which is worth mentioning.

We have added something to the text to cover these points.

Discretionary Revisions

Explain the abbreviation ICU.

Done

Last word of the abstract: replace the intervention with isolation.

Done – replaced “intervention” with “barrier precautions”

Second paragraph of the introduction: to minimize the number of unknown MRSA-positive patient days; and to minimize MRSA transmission from known carriers.

We prefer to keep our original language

Data analysis: Stochastic model. Is Poisson process the right term (as only one infection event can occur per patient)?

Since we explain this terminology explicitly in the text, we prefer to leave it as it is.

Percentage of new admissions already colonized: Remove “having had”?

Done

Discussion: Remove “we calculate that only about”

Done
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: Assessing the role of undetected colonization and isolation precautions in reducing Methicillin-Resistant Staphylococcus aureus transmission in intensive care units.
Version: 2 Date: 22 July 2009
Reviewer: Maria Clara Clara Padoveze
Reviewer’s report:
July 20th, 2009
Dr Melissa Norton
Editor-in-Chief

Dear Dr. Norton:
Follow my review report of the paper entitled “Assessing the role of undetected colonization and isolation precautions in reducing Methicillin-Resistant Staphylococcus aureus transmission in intensive care units”, by Kypraïos et al.
Best regards,
Maria Clara Padoveze
Escola de Enfermagem da Universidade de São Paulo
Department of Nursing in Public Health.

1. Is the question posed by the authors well defined?
Yes.

2. Are the methods appropriated and well described?
The methods are appropriated for the objectives proposed.

Minor Essential Revisions
The description of methodology would be clarified if the authors give more information about:

a) If there is homogeneity regarding the number of staff caring for the patients in every ICU (nursing-patients and physician-patients number relationship). In the real world it is a very important component to understand the efficacy of any measures for microorganism transmission control.

This was not measured and is unknown. It is thus not added to the text.

b) The test sensitivity was done based on collected data from swabs following first positive culture. The methods description state that the screening is done on weekly bases in ICU; while the median length of stay is around two days. How many swabs were supposed to be collected per patient after the first positive cultures? What is the interval between samples? The table 1 shows the number of swab per patient but it is not clear what is the number of swabs collected after the positive one.

An additional column has been added to Table 1 to give the numbers of swab tests taken after the first MRSA+ culture.
c) What is the protocol for collecting samples from other sites than nares? Please clarify which types of cultures were included in the group of “any body site” (blood, catheter tip, wound, urine, or skin cultures?)

This has been clarified in the text.

d) Please clarify the assumption in the model for the HCW compliance to contact precautions. The 70% of HCW compliance cited in the discussion (references 9,10) was used in the model? The compliance of HCW is assumed to be the same for any professional category (ex.: nurses, physicians, others…)?

The model takes no account of HCW compliance, and this has been clarified in the text.

e) It is not so clear the components on which are based the estimation of B0, B1 and B2. This is the main subject to better understand the results of the present study.

A line has been added to clarify which data are used to estimate the key model parameters.

f) What was the role of the length of stay in the model? It was assumed to increase the risk for transmission as any increment of the days of stay?

This is implicit in the model and now clarified in the text.

g) Phidden and Pwait should be first explained in the methods section and not only in the results section.

The text has been changed accordingly.

h) The method for comparison of isolation effectiveness (B1/B2) should be described first in the methods section and not only in the results section.

Text has been added to the methods section.

Please clarify the statement: “all other analysis was performed using programs we wrote in C”

Text added to clarify.

3. Are the data sound?
Yes.

Discretionary Revisions
a) I suggest grouping some data from tables aiming to be more suitable for readers (ex.: table 4 and 5).

_We appreciate the comment, but prefer to retain our tables as provided._

b) I suggest clarify the epidemiological plausibility for estimation of 30% chance that isolation actually increases transmission.

_This has been provided in the discussion._

**Minor Essential Revisions**

a) Regarding the statement “In the two general surgery ICUs, however, there was no evidence to support the effectiveness of such measures, and in these cases several models estimated that there was at most a 50% probability that B1 exceeded B2”, however table 3 shows probability much less than 50% for GS1 and above 50% for GS2. Why both ICUs were considered in the same level of probability?

_The original comment has been removed._

b) Regarding the statement “…we recognize that these estimates have considerable uncertainty despite including over 11 ward-years of data…” There is no mention for this period of data collection in the methods section.

_There was a typo which is now corrected and reflects the proper time window._

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes

5. Are the limitations of the work clearly stated?

**Discretionary Revisions**

a) Some limitations of the study were discussed, but not in deep. There is no doubt about the role of baseline comorbidities as well the rates of devices use regarding the infection control in ICUs. I recommend that the authors present suggestions to overcome these limitations in the future studies.

_These epidemiologic factors are being addressed in other work and is beyond the scope of this study._

6. Are the discussion and conclusion well balanced and adequately supported by the data?
   Yes.
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.

**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.