PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Impact of prior probabilities of MRSA as an infectious agent on the accuracy of the emerging molecular diagnostic tests: A model simulation
AUTHORS	Zilberberg, Marya; Shorr, Andrew

VERSION 1 - REVIEW

REVIEWER	Luc Bissonnette, Ph. D. Adjunct professor Département de microbiologie-infectiologie et d'immunologie, Faculté de médecine Université Laval, Québec City, Canada I declare having no conflict of interest with regards to the authors of the manuscript.
REVIEW RETURNED	17-Oct-2012

GENERAL COMMENTS	The manuscript of Zilberberg and Schorr describes a mathematical model suggesting that an increase in the positive predictive value (PPV) of a (molecular) diagnostic test would significantly decrease the probability of false-positive results and thus diminish antimicrobial over-treatment in the management of infections, in the present case infections caused by Staphylococcus aureus. In addition, they also suggest that increasing the pre-test probability shall also contribute to improve the diagnostic process and the appropriateness of the antimicrobial regimen. I believe that this work deserves publication in BMJ Open after minor revisions. Indeed, the empiric (traditional) management of infectious diseases is generally driven by factors such as the experience of the physician and his/her knowledge of the "local" microbial knowledge (epidemiology) which dictate in part the request for a particular diagnostic test. In these conditions, the main advantage offered by rapid molecular diagnostic tests over classical microbiology is speed. For a particular diagnostic test, increasing its specificity might represent a major investment to technology developers; in fact, specificity can be increased by improving the ubiquity of the test (ability to detect all strains of a species for example). Another means of increasing the probability of identifying a culprit pathogen in a clinical sample, albeit at similar costs, might be to implement multiparametric tests in clinical microbiology laboratories (see Bissonnette and Bergeron, Clin. Microbiol. Newslett. **34**: 159-168, 2012). The

	authors may want to address this in a revised manuscript. Here is a list of suggestions, modifications, and observations: Introduction Most readers may not be competent or proficient in statistics; a brief definition of Bayesian statistics should be included P6 L37 "for each disease of interest" instead of "for each of the diseases of interest" P7 L17 "for each population in question" instead of "for each of the populations in question" P8 L3 "Thus, for the MRSA cSSSI volumes, we relied on a study by Klein which…" P8 L17 "the Agency for Healthcare Research and Quality recent" P11 L8 "stakeholders" instead of "stake holders" P12 L27-29 "Our study has a number of limitations, the most important being that, since it is merely a mathematical model, it relies by necessity on the accuracy…" P14-15 References 1-15 are not properly formatted: number of authors, journal title should be italicised, journal volume should be in boldtype, issue number not necessary, page numbers Figures The resolution of Figs 1 and 2 appear insufficient

REVIEWER	Marcos I. Restrepo, MD, MSc, FCCP Associate Professor Division of Pulmonary and Critical Care Medicine Department of Medicine University of Texas Health Science Center at San Antonio Investigator at VERDICT at South Texas Veterans Health Care System Audie L. Murphy Division Support: Dr. Restrepo time is partially protected by (Award Number K23HL096054 from the National Heart, Lung, And Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, And Blood Institute or the National Institutes of Health.”
REVIEW RETURNED	31-Oct-2012

GENERAL COMMENTS	The authors developed a mathematical model to better understand the impact of rapid molecular diagnosis in different infectious populations in order to limit overdiagnosis and overtreatment. Major comments I applaud the efforts and novel design by the authors to address the important interaction between new rapid molecular diagnosis and the impact of antimicrobial use according to the pre-test probability of complicated skin and skin structure infections, pneumonia or sepsis. Although I agree with the authors about the importance of preventing overdiagnosis and antimicrobial overtreatment, I would recommend to balance the findings and conclusions according to the following factors: - Current practice is driven by empiric therapies and culture results (that may take 48-72 for antimicrobial susceptibility results) that leads to overtreatment. Therefore, I belief that at least rapid molecular diagnosis will have no change to current practice. - De-escalation therapies may be promoted by the negative

	predictive value as suggested by the authors in the results (Figure 1). - Clinical response and duration of antimicrobials should be mentioned in the discussion as a possible factor that may be influenced by a rapid diagnosis. - Cost of the tests and devices needed to implement this technology should be mentioned. - Differentiation between colonization and infection may be addressed also by the use of rapid molecular methods. I found figure 1 very interesting, but in contrast to the view of the authors, the consistent good negative predictive value (>95%), may have important implications in clinical practice. For example, if the test is negative for MRSA it may precludes clinicians to use Vancomycin or Linezolid or even double coverage for Pseudomonas, which may limit significantly the use of antimicrobials.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Luc Bissonnette, Ph. D.
Adjunct professor
Département de microbiologie-infectiologie et d'immunologie, Faculté de médecine
Université Laval, Québec City, Canada

I declare having no conflict of interest with regards to the authors of the manuscript.

The manuscript of Zilberberg and Schorr describes a mathematical model suggesting that an increase in the positive predictive value (PPV) of a (molecular) diagnostic test would significantly decrease the probability of false-positive results and thus diminish antimicrobial over-treatment in the management of infections, in the present case infections caused by Staphylococcus aureus. In addition, they also suggest that increasing the pre-test probability shall also contribute to improve the diagnostic process and the appropriateness of the antimicrobial regimen. I believe that this work deserves publication in BMJ Open after minor revisions.
Indeed, the empiric (traditional) management of infectious diseases is generally driven by factors such as the experience of the physician and his/her knowledge of the "local" microbial knowledge (epidemiology) which dictate in part the request for a particular diagnostic test. In these conditions, the main advantage offered by rapid molecular diagnostic tests over classical microbiology is speed. For a particular diagnostic test, increasing its specificity might represent a major investment to technology developers; in fact, specificity can be increased by improving the ubiquity of the test (ability to detect all strains of a species for example). Another means of increasing the probability of identifying a culprit pathogen in a clinical sample, albeit at similar costs, might be to implement multiparametric tests in clinical microbiology laboratories (see Bissonnette and Bergeron, Clin. Microbiol. Newslett. 34: 159-168, 2012). The authors may want to address this in a revised manuscript.
AU: While we are grateful to Prof. Bissonnette for bringing up multiparametric tests, we feel that the discussion of such tests is outside the scope of what we were trying to accomplish. A multiparametric approach requires that a separate model be built to address those issues adequately.

Here is a list of suggestions, modifications, and observations:
Introduction Most readers may not be competent or proficient in statistics; a brief definition of Bayesian statistics should be included
AU: On page 6 we have added the following sentence:
“This approach fits in with the Bayesian decision making, whereby the prior probability of an event informs the interpretation of the diagnostic data.”

AU: The suggestions below were taken on a case-by-case basis, as many were stylistic. Where we did not adopt the reviewer's suggestions, we chose to maintain the current structure and work closely with the BMJ Open production staff on the changes, should the manuscript be accepted. We once again thank Dr. Bissonnette for his careful review of our work.
P6 L37 "for each disease of interest" instead of "for each of the diseases of interest"
P7 L17 "for each population in question" instead of "for each of the populations in question"
P8 L3 "Thus, for the MRSA cSSSI volumes, we relied on a study by Klein which…"
P8 L17 "the Agency for Healthcare Research and Quality recent"
P11 L8 "stakeholders" instead of "stake holders"
P12 L27-29 "Our study has a number of limitations, the most important being that, since it is merely a mathematical model, it relies by necessity on the accuracy…"
P14-15 References 1-15 are not properly formatted: number of authors, journal title should be italicised, journal volume should be in boldtype, issue number not necessary, page numbers
Figures The resolution of Figs 1 and 2 appear insufficient

Reviewer: Marcos I. Restrepo, MD, MSc, FCCP

Associate Professor
Division of Pulmonary and Critical Care Medicine
Department of Medicine
University of Texas Health Science Center at San Antonio
Investigator at VERDICT at South Texas Veterans Health Care System Audie L. Murphy Division
7400 Merton Minter Blvd. (11C6)
San Antonio, TX 78229

Support: Dr. Restrepo time is partially protected by (Award Number K23HL096054 from the National Heart, Lung, And Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, And Blood Institute or the National Institutes of Health."

The authors developed a mathematical model to better understand the impact of rapid molecular diagnosis in different infectious populations in order to limit overdiagnosis and overtreatment.

Major comments
I applaud the efforts and novel design by the authors to address the important interaction between new rapid molecular diagnosis and the impact of antimicrobial use according to the pre-test probability of complicated skin and skin structure infections, pneumonia or sepsis.
Although I agree with the authors about the importance of preventing overdiagnosis and antimicrobial overtreatment, I would recommend to balance the findings and conclusions according to the following factors:
- Current practice is driven by empiric therapies and culture results (that may take 48-72 for antimicrobial susceptibility results) that leads to overtreatment. Therefore, I belief that at least rapid molecular diagnosis will have no change to current practice.
AU: Dr. Restrepo makes an excellent educated guess. However, we are unable to quantify this in our model. Since the model already incorporates some assumptions, we would prefer not to introduce additional assumptions unless they are essential to the model.

AU: We would like to address 3 of the 5 of Dr. Restrepo's remaining comments together. Three comments below highlight the tests' negative predictive value and its potential for improving clinical practice vis-à-vis de-escalation and reduction in the use of overly broad antimicrobials. In general, our study focuses on the point at which treatment is initiated rather than attenuated or terminated. While it

is true that in any population with a low disease prevalence the negative predictive value is not subject to much influence by improving an already fairly accurate test, it remains difficult to predict how these rapid technologies will alter clinical practice in this regard. Namely, the gold standard against which these tests are measured is still microbiology culture. Therefore, while the tests may allow de-escalation to happen earlier in the treatment course, there is no reason to think that they will have any impact on the behavioral components of this strategy that is so frequently ignored. As for clinical response and duration of treatment, it is not clear to us what Dr. Restrepo is postulating. Similar to the de-escalation situation, there does not seem to be a reason to think that a clinician will be any more or less likely to pay attention to the clinical course based on conventional culture data vs. the RMD technologies. We would also ask for clarification on the colonization vs. infection point.

We do agree that rapid identification of the pathogen and its susceptibility may limit population exposure to broad-spectrum antibiotics, and have included a statement to highlight this on page 11: "In fact, given the already high NPV, the new molecular diagnostics have the potential to limit the use of empiric broad-spectrum coverage substantially."

Finally, we avoid the discussion of the costs of implementation, as the intent of the current study is to highlight the potential clinical pitfalls irrespective of the implementation costs. To do the latter justice, a formal cost-benefit model will be required.

- De-escalation therapies may be promoted by the negative predictive value as suggested by the authors in the results (Figure 1).
- Clinical response and duration of antimicrobials should be mentioned in the discussion as a possible factor that may be influenced by a rapid diagnosis.
- Cost of the tests and devices needed to implement this technology should be mentioned.
- Differentiation between colonization and infection may be addressed also by the use of rapid molecular methods.

I found figure 1 very interesting, but in contrast to the view of the authors, the consistent good negative predictive value (>95%), may have important implications in clinical practice. For example, if the test is negative for MRSA it may precludes clinicians to use Vancomycin or Linezolid or even double coverage for Pseudomonas, which may limit significantly the use of antimicrobials.

VERSION 2 – REVIEW

REVIEWER	Marcos I. Restrepo, MD, MSc, FCCP Associate Professor Division of Pulmonary and Critical Care Medicine Department of Medicine University of Texas Health Science Center at San Antonio Investigator at VERDICT at South Texas Veterans Health Care System Audie L. Murphy Division Support: Dr. Restrepo time is partially protected by (Award Number K23HL096054 from the National Heart, Lung, And Blood Institute. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Heart, Lung, And Blood Institute or the National Institutes of Health."
REVIEW RETURNED	20-Nov-2012

GENERAL COMMENTS	The authors appropriately addressed the reviewer comments.