PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Budget impact analysis of routinely using whole-genomic sequencing of six multidrug-resistant bacterial pathogens in Queensland, Australia
AUTHORS	Gordon, Louisa; Elliott, Thomas; Forde, Brian; Mitchell, Brett; Russo, Philip; Paterson, David; Harris, Patrick N. A.

VERSION 1 – REVIEW

REVIEWER	Anna s. Levin Universidade de Sao Paulo, Brazil
REVIEW RETURNED	21-Jul-2020

GENERAL COMMENTS	I read this manuscript with interest. I have the following comments. 1- The manuscript is very interesting and food for thought and reflexion. 2- I confess that I do not have the knowledge necessary to evaluate the mathematical model in depth and the soundness of its application. I suggest that the manuscript be reviewed by an expert in this field. 3- On page 8 there is a section on expected deaths. Would all deaths have really been prevented had infections by MRO been avoided? Sometimes, as in VRE and Acinetobacter infections, MRO seem to be a marker of severity of the patient's clinical condition or a marker of bad prognosis. If so, the primary cause of death would not be the infection itself. This point requires discussion. 4- The use of this tool (WGS) would require standardised algorithms leading to early alarms and detection of problems, and interventions for all hospitals. The most obvious and uncertain issue is if infection control teams will immediately and effectively respond on receiving these data. I feel that this point deserves some consideration in the Discussion. 5- Minor points: - in eEquation 1,infection fraction is not clearly explained. - On page 6 (Estimeted patients infected with MROs) I could not understand what the percentages were, as they dthey did not add up to 100%

REVIEWER	Dag Harmsen Univ. Münster, Germany
REVIEW RETURNED	05-Oct-2020

GENERAL COMMENTS	This manuscript tries to answer the important question whether a state-wide prospective whole genome sequencing (WGS) strategy of multidrug-resistant (MDR) bacterial pathogens might be health economically justifiable. Studies like this are certainly needed. As the authors note the validity of such a study critically depends on the accuracy of the estimates used. According to the reviewer's opinion all variables are reasonably estimated except one that is the single most important factor for success or failure as also noted by the authors, i.e., the number of avoidable infections/colonizations when using WGS. The authors extract this information from the unpublished sequencing records of three hospitals. No details are given what isolates were sequenced, e.g., random selection of infected and colonized patient isolates or if only one isolate per patient was considered? If as indicated later in the discussion (page 11 line 37) only isolates of suspected outbreaks were sequenced, then the number of isolates being in clusters and thus potential avoidable infections/colonizations is substantially overestimated. The two terms 'Cluster frequency' and 'decreased cluster size' of Table 1 certainly need better explanation. If correctly understood 'the expected success of intervening to break the chain of transmission' is set by the authors implicitly to 100 percent. This should be explicitly stated and justified. Aren't in the three sequencing hospitals no contact precautions/isolations for patients harboring MDR bacteria in place?! If there are already some sort of measurements for such patients in place, why does the authors still expect a 100% success of intervening?! Minor comments: p. 3, l. 29: for clarity it should stated here that '97,539 patients in Queensland are …' p. 8, l. 42: the number of expected deaths for the various organisms are not stated in Table 1 as indicated by the authors p. 10, l. 40: Guess that it should state correctly here '100,000 patients will be infected or colonized with potentially …'

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments to Author

I read this manuscript with interest. I have the following comments.

1. The manuscript is very interesting and food for thought and reflexion.

Response: Thank you, no changes made.

2. I confess that I do not have the knowledge necessary to evaluate the mathematical model in depth and the soundness of its application. I suggest that the manuscript be reviewed by an expert in this field.

Response: The analysis is quite basic mathematically with no high-level technical modelling. We would like to reassure the reviewer by stating that standardised budget impact principles were used in the conduct of the study ie. the International Society for Pharmacoeconomics and Outcomes

Research good-practice guidelines for budget impact analyses. We have stated this already on Page 5, Methods, Overview, last paragraph.

3. On page 8 there is a section on expected deaths. Would all deaths have really been prevented had infections by MRO been avoided? Sometimes, as in VRE and Acinetobacter infections, MRO seem to be a marker of severity of the patient's clinical condition or a marker of bad prognosis. If so, the primary cause of death would not be the infection itself. This point requires discussion

Response: We agree that this point should be discussed. We have also added a sensitivity analysis on the death rates which is now mentioned on Page 7 *'Sensitivity analyses were performed on the 95% confidence limits of these mortality rates.'* and in the results on Page 9 *'When higher and lower values were used for expected rates of deaths from the six MROs (simultaneously), the deaths potentially avoided ranged from 411 to 893 in Year 1 to 316 to 694 in Year 5.'*
In the Discussion, the following text has been added on Page 11, discussion in the strengths and limitations paragraph. This now reads (underlined text was added):

'This study should be viewed with some caution as it depends on the accuracy of the estimates used. For example, it is feasible that the estimates of deaths avoided with WGS are over-estimated due to not being the main cause of death if the patient's underlying clinical condition is severe and advanced. Other than the best available evidence for the estimates used in the analysis, the appropriate way to address this is through sensitivity analyses. To deal with the possible uncertainty in the estimates, 95% confidence limits were tested in sensitivity analyses. These found the cost savings were stable……'

4. The use of this tool (WGS) would require standardised algorithms leading to early alarms and detection of problems, and interventions for all hospitals. The most obvious and uncertain issue is if infection control teams will immediately and effectively respond on receiving these data. I feel that this point deserves some consideration in the Discussion.

Response: We agree this is an uncertain issue for infection control teams and it takes significant organisational change and time to implement new protocols. We have integrated some additional text into the Discussion as follows:

'Implementation of WGS into routine infection control practice would require standardised algorithms leading to early alarms and detection of problems, and intervention for all hospitals. Although many hospitals do have systems and decision rules currently in place, a key issue is whether infection control teams would immediately and effectively respond on receiving these advanced data. This is uncertain as is any significant organisational change and would require infection control teams to undergo training and time to transition to new protocols. Our analysis assumes full adherence to a new scenario as presented here, as if it were established, and the result of effective change and uptake by hospitals. Nevertheless, predictions about resource use and costs that might result from routine WGS are useful for decision-makers to understand whether it is warranted on an economic basis to proceed further with new resource allocations.'

5. Minor points
   a) In Equation 1, infection fraction is not clearly explained.

Response: We have amended to the relevant text on Page 6 as follows:

'….and the denominator is the infection fraction (I/(I+C)). The infection fraction is the number of infections as a fraction of the total number of colonisations and infections. This is required on the denominator to increase the N and account for colonisations AND infections as the true burden of HAI numbers. The infection fraction was calculated from five years of MRO surveillance data…'

   b) On page 6 (Estimated patients infected with MROs) I could not understand what the percentages were, as they did not add up to 100%

Response: Apologies for the confusion. We included only the six MROs targeted here with WGS, the remaining numbers make up the 363 HAIs and 100%. We have amended the sentence as follows (underlined new text):

'Using Russo et al. (2019) data on 363 HAIs[10], the frequency of organisms detected were: 50 (14%) S. aureus, 32 (9%) E. coli, 21 (6%) E. faecium, 16 (4%) K. pneumoniae, 7 (2%) E. cloacae and 4 (1%) A. baumannii (with 216 (62%) other organisms making up the remainder).'

Reviewer 2 Comments to Author

This manuscript tries to answer the important question whether a state-wide prospective whole genome sequencing (WGS) strategy of multidrug-resistant (MDR) bacterial pathogens might be health economically justifiable. Studies like this are certainly needed. As the authors note the validity of such a study critically depends on the accuracy of the estimates used. According to the reviewer's opinion all variables are reasonably estimated except one that is the single most important factor for success or failure as also noted by the authors, i.e., the number of avoidable infections/colonizations when using WGS. The authors extract this information from the unpublished sequencing records of three hospitals.

1. No details are given what isolates were sequenced, e.g., random selection of infected and colonized patient isolates or if only one isolate per patient was considered? If as indicated later in the discussion (page 11 line 37) only isolates of suspected outbreaks were sequenced, then the number of isolates being in clusters and thus potential avoidable infections/colonizations is substantially overestimated.

Response: We have now raised this earlier in the Methods on Page 6 where sequencing data is introduced. We argue that indiscriminate testing is not the goal of routine use of WGS but rather the judicious use for suspected outbreaks. The following text has been added:

'Data from isolates that were sequenced came from a research demonstration project of prospective WGS for isolates of suspected outbreaks, to detect clusters before they became established as larger outbreaks. The routine use of WGS for widespread adoption would also be in this context and not for indiscriminate testing.'

2. The two terms 'Cluster frequency' and 'decreased cluster size' of Table 1 certainly need better explanation.

Response: These have now been defined in the footnotes and notes column in Table 1 which clarify their meanings.

3. If correctly understood 'the expected success of intervening to break the chain of transmission' is set by the authors implicitly to 100 percent. This should be explicitly stated and justified. Aren't in the three sequencing hospitals no contact precautions/isolations for patients harboring MDR bacteria in place?! If there are already some sort of measurements for such patients in place, why does the authors still expect a 100% success of intervening?!

Response: We have added a sentence in the Methods as follows:

'An implicit assumption in this analysis is that the chain of transmission is broken when the WGS data is acted on immediately.'

We further discuss the 'effectiveness' and 'implementation' issues at Reviewer 1 #4 with a new paragraph in the Discussion. Patients currently are subject to usual infection control practices, but we are assessing the use of WGS and previously unsuspected and unidentified patients with MROs.

Minor comments:

p. 3, l. 29: for clarity it should stated here that ‘97,539 patients in Queensland are …’

Response: This has been amended.

p. 8, l. 42: the number of expected deaths for the various organisms are not stated in Table 1 as indicated by the authors

Response: We have removed reference to the Table in the text. The table includes costs only and deaths were separately calculated.

p. 10, l. 40: Guess that it should state correctly here ‘100,000 patients will be infected or colonized with potentially …’

Response: The words ‘or colonized’ were added to the sentence.