PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The Belgian policy of funding antimicrobial stewardship in hospitals, and trends of selected quality indicators for antimicrobial use, 1999-2010: a longitudinal study.
AUTHORS	Lambert, Marie-Laurence; Bruyndoncks, Robin; Goossens, Herman; Hens, Niel; Aerts, Marc; Catry, Boudewijn; Neely, Fiona; Vogelaers, Dirk; Hammami, Naima

VERSION 1 - REVIEW

REVIEWER	Nick Daneman
	Sunnybrook Health Sciences Centre, University of Toronto, Canada
REVIEW RETURNED	24-Nov-2014

| GENERAL COMMENTS | Thank you for the opportunity to review this fascinating study. The investigators have performed a population-based retrospective cohort study involving all admissions for pneumonia and lower-limb non-traumatic orthopaedic surgery in Belgium between 1999-2010. Their objective was to examine the impact of a Belgian national antimicrobial stewardship funding policy on selected antibiotic quality indicators. They detected no significant association of policy implementation timing with improvement in these quality indicators. However, they did find a substantial temporal improvement in each quality indicator. This is a vitally important study given the worldwide recognition that antimicrobial overuse is contributing to worsening antimicrobial resistance, and because apparently Belgium is the first country to institute a national funding strategy for antimicrobial stewardship in acute care hospitals.

Major:
-why study the orthopaedic indicators at the patient level, but aggregate the pneumonia indicators to the hospital level .... why not study both at the patient level?
-"Median LoS in this population decreased from 15 days in 1999 to 8 days in 2010"...might this be evidence of selection bias?
-The authors state:"We decided against clinical outcome measures such as mortality, readmission, and length of stay because these are too indirectly related to appropriate AM prescribing". I agree that these should not be primary outcome measures, but I would like to see them reported as balancing measures to ensure that antibiotic reductions were not associated with a worsening of these important patient outcomes.
- I agree with the authors that the lack of association of AMT funding with a change in QI slope, may indicate that "implementation and funding of AMT was rather a consequence than a primary driver". However, some other possibilities are worth considering. For example, hospitals may have invested their own resources into antimicrobial quality of care, with the knowledge that they would be |

soon receiving national resources to sustain their impact.
-Another potential explanation is that the chosen QIs might be ones that don't require institution of substantial economic resources. Would it be possible to test some other antibiotic QIs that would require more resources (e.g., reduction in broad spectrum DDDs, reduction in antibiotic use in ICU patients, ...), such that the slope of improvement could be more flat prior to provision of Belgian financial support to hospitals

Minor:
-severity of illness scores (SoI 1-4) are referenced, but it might help to have them defined in the manuscript
-were major lower limb orthopaedic surgery and pneumonia chosen a priori? Are their plans to examine some other clinical groups

REVIEWER	Camilla Wiuff
	Health Protection Scotland, Scotland, United Kingdom
REVIEW RETURNED	08-Dec-2014

GENERAL COMMENTS	It is a highly relevant study that examines the relationship between investment in national antimicrobial stewardship and outcome with regards to quality in antimicrobial use. The main problem with assessing any impact of the Belgium stewardship program, seems to be a lack of coordination of the policies at a national level, as hospitals could between a range of priorities and start dates for specific policies also seemed to vary and clarity around whether the funding actually was spent on what it was intended for is lacking. Under these circumstances, it is not surprising that no strong correlation was found for any of the QIs.The fact that funding for AMTs was given to hospitals at different times also makes it very hard to characterise confounding factors including other policies, interventions and campaigns that could have affected the antimicrobial use pattern. I suggest the authors discuss the complexity of confounders in the wider context of the hospital setting.
	Specific points:
	Abstract:
	in the conclusion of the abstract - it is speculated that 'implementation and funding of AMTs was rather a consequence than a driver'. I don't see any evidence of that association in the results, which in fact show improvement in selected areas following the change points although not very strong. I therefore suggest that part of the sentence is deleted.
	Methods:
	Were all patient-level data obtained from the same database (described as for financing purposes), or was it a combination of data sets used (i.e. on pharmacy expenditure and diagnoses and severity)?
	If linked data were used, were ethical permissions obtained?
	What type of personal information identifiers were used to extract the data?
	How were the data validated (and cases included/excluded)?

	Discussion: It is not clear what is being said about the Scottish antimicrobial stewardship programme. Year 2008 has been used as baseline year in many of the Scottish Quality Indicator reports (including hospital use) if relevant with regards to the policy in question.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Nick Daneman
Institution and Country Sunnybrook Health Sciences Centre, University of Toronto, Canada
Please state any competing interests or state 'None declared': None Declared

Please leave your comments for the authors below

Thank you for the opportunity to review this fascinating study. The investigators have performed a population-based retrospective cohort study involving all admissions for pneumonia and lower-limb non-traumatic orthopaedic surgery in Belgium between 1999-2010. Their objective was to examine the impact of a Belgian national antimicrobial stewardship funding policy on selected antibiotic quality indicators. They detected no significant association of policy implementation timing with improvement in these quality indicators. However, they did find a substantial temporal improvement in each quality indicator. This is a vitally important study given the worldwide recognition that antimicrobial overuse is contributing to worsening antimicrobial resistance, and because apparently Belgium is the first country to institute a national funding strategy for antimicrobial stewardship in acute care hospitals.

Major:
Q/ -why study the orthopaedic indicators at the patient level, but aggregate the pneumonia indicators to the hospital level .... why not study both at the patient level?
****
A/The "surgery" indicator is a dichotomous indicator that is easily defined at patient level (compliance with guidelines: yes/no).
By contrast the pneumonia indicators (ratio oral/parenteral; and mean number of DDD) are continuous and cannot be dichotomized and interpreted qualitatively at patient level – there is no "right" or "wrong" value of these indicators at patient level. This is why we aggregated them at hospital level.

-"Median LoS in this population decreased from 15 days in 1999 to 8 days in 2010"...might this be evidence of selection bias?
Our database is exhaustive, so there cannot be any selection bias. This decrease in length of stays reflects a general decrease in length of stays in hospitals, in Belgium as in in most OECD countries (see:
OECD: Health Data Statistics and Indicators for 30 Countries. Paris, France.
http://stats.oecd.org/index.aspx selected health data, Average length of stay for acute care). Reasons include changes in medical technology and customary medical practice, and financial pressures including changes in hospital reimbursement.
****

Q/-The authors state:"We decided against clinical outcome measures such as mortality, readmission, and length of stay because these are too indirectly related to appropriate AM prescribing". I agree that these should not be primary outcome measures, but I would like to see them reported as balancing measures to ensure that antibiotic reductions were not associated with a worsening of these important patient outcomes.

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A/ Some figures are already given in the article:
•Surgery (under "results" / surgery QI– second sentence:) : Median LoS in this population decreased from 15 days in 1999 to 8 days in 2010."

•Pneumonia - (under "results" / pneumonia QI, first $ lines 193-196) :
From 1999 to 2010, median LoS in this population decreased from 9 to 7 days, percentile 25 for age decreased from 16 to 11 years old. Case-fatality decreased in all 4 categories of SoI, from 1,6 to 0,4% in less severe illness (SoI 1), and from 40% to 33% in more severe illness (SoI 4).

More details (apart from readmissions) can be found in the original research report (reference 18 in the article, with link to full-time text), in particular data on case-fatality per year and degree of severity (showing regular decrease). There is no indication of a negative trend that could be attributed to changes in antimicrobial use.

https://www.wiv-isp.be/nsih/download/Home/AMTABU_FINAL_REPORT.pdf

Table 3.Number of hospital stays, age of patients, length of stay for major lower limb surgery*, Belgium
1999-2010. (p18)
Table 10.Number of hospital stays for simple pneumonia*, and case-fatality, per degree of severity (DoS), Belgium, 1999-2010 (p27)
Table 12.Length of stay (days) in hospital for simple pneumonia*, per degree of severity, Belgium, 1999-2010 (p29)

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Q/- I agree with the authors that the lack of association of AMT funding with a change in QI slope, may indicate that "implementation and funding of AMT was rather a consequence than a primary driver". However, some other possibilities are worth considering. For example, hospitals may have invested their own resources into antimicrobial quality of care, with the knowledge that they would be soon receiving national resources to sustain their impact.-

****
A/ We agree with that and believe this is addressed in the following sentence :

((See l 270-273, under Discussion// interpretation)
"The selected items for QI, i.e. prophylaxis for major limb orthopedic surgery and antimicrobial therapy in community acquired pneumonia are items/topics likely to have been addressed in the hospital antimicrobial policy at different time points, fully or largely independent from the implementation of AMT".

The hospitals who participated to the pilot project in 2002 were selected on the basis of their commitment to improving antimicrobial use and had probably already started implementing some actions. It might indeed be a plausible explanation for the fact that there was no change in trends for the QI associated with AMT funding.
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Q/ Another potential explanation is that the chosen QIs might be ones that don't require institution of substantial economic resources. Would it be possible to test some other antibiotic QIs that would require more resources (e.g., reduction in broad spectrum DDDs, reduction in antibiotic use in ICU patients, ...), such that the slope of improvement could be more flat prior to provision of Belgian

financial support to hospitals

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A/ We indeed acknowledge as a limitation of this study that it only addresses a limited number of indicators, and that looking at other indicators might provide different results – whether positive – or negative. We hope to be able to look at other indicators, but funding for this new study is uncertain. On the other hand, we chose these particular indications in our study because they account for the largest number of patients receiving antimicrobials in hospitals, so these should be priorities for intervention (and evaluation) anyway.
(See text: under "conclusions/generalizibilty" ll 282-285)

"We looked at a limited number of QI for a limited number of indications, and fall short of providing a global picture of trends in quality of AM use in Belgian hospitals, and of the effect of implementing and funding AMT in hospitals. This study should ideally be complemented by other indicators, which might provide different results"
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Minor:
Q/-severity of illness scores (SoI 1-4) are referenced, but it might help to have them defined in the manuscript
****
We have added in the manuscript – method section –(ll 108-111) insert in blue - some more details on the severity of illness score:

The severity of illness for the hospital stay is assigned following a complex computerized algorithm that takes into account the patient's primary and secondary diagnoses, procedures, and age (the underlying clinical principle is that patients with high severity of illness are characterized by multiple serious diseases or illness)
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Q/-were major lower limb orthopaedic surgery and pneumonia chosen a priori?

****

A/ The rationale for choosing prophylaxis for orthopaedic surgery and pneumonia was that these are the two indications accounting for the largest number of patients receiving antimicrobials in hospitals (see introduction, last paragraph, ll98-100).
The objectives of our study were to analyze the association of this policy with trends of selected quality indicators (QI) for AM use in hospitals. We focused on the indications accounting for the largest number of patients receiving AM.

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Q/Are their plans to examine some other clinical groups
A/We hope to be able to examine some other clinical groups, but this will depend on the availability of funding for this research.

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Reviewer Name Camilla Wiuff
Institution and Country Health Protection Scotland, Scotland, United Kingdom
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
General:
Q/It is a highly relevant study that examines the relationship between investment in national antimicrobial stewardship and outcome with regards to quality in antimicrobial use. The main problem with assessing any impact of the Belgium stewardship program, seems to be a lack of coordination of the policies at a national level, as hospitals could between a range of priorities and start dates for specific policies also seemed to vary and clarity around whether the funding actually was spent on what it was intended for is lacking. Under these circumstances, it is not surprising that no strong correlation was found for any of the QIs.
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A/The fact that the policy was implemented at different times in different hospitals does not reflect a lack of coordination of the policy, but rather a phased implementation (3 phases). The first (pilot) phase – was on a voluntary basis. Indeed the other problems mentioned (no priority themes, transparency in budget use) can help explain why no correlation was found for any of the indicators; these are part of the interpretation of our results.
****
Q/The fact that funding for AMTs was given to hospitals at different times also makes it very hard to characterise confounding factors including other policies, interventions and campaigns that could have affected the antimicrobial use pattern. I suggest the authors discuss the complexity of confounders in the wider context of the hospital setting.

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A/ The fact that funding was given to hospitals at different times would make it very hard indeed to assess confounding if our study had been using an ecological design. It is a great advantage for a study using patient-based data, because our change point model - adjusting for differences in case-mix – allows us to compare not only each hospital with itself - before and after implementation of the policy – but also hospitals with, and without the policy.
Our study focused on the effect of a particular policy at national level – it was not the purpose to explain the (positive) trends observed : it would indeed be difficult to account for all possible confounding. We also stress that the policy did not show any effect on national trends, but – given the high heterogeneity observed - might have worked in some hospitals.
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Specific points:

Q/Abstract:
in the conclusion of the abstract - it is speculated that 'implementation and funding of AMTs was rather a consequence than a driver'. I don't see any evidence of that association in the results, which in fact show improvement in selected areas following the change points although not very strong. I therefore suggest that part of the sentence is deleted.
****

A/ This is speculation indeed. We have deleted that sentence from the abstract. It is true that there was improvement in the selected area following the change points but the trend did not deviate from the trends of improvement observed before the change point.

deleted:
Changes observed may reflect the more multifactorial and continuous change process of quality improvement, of which the implementation and funding of AMT was rather a consequence than a primary driver
replaced by:

Our findings do not question the need for AMT, nor the need for continuation of AMT funding. Several recommendations can be made in order to make the best of Belgium's unique political, and financial commitment in that field.

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Q/ Methods:
Were all patient-level data obtained from the same database (described as for financing purposes), or was it a combination of data sets used (i.e. on pharmacy expenditure and diagnoses and severity)? If linked data were used, were ethical permissions obtained? That type of personal information identifiers were used to extract the data? How were the data validated (and cases included/excluded)?

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A/All patient-level data came from the same database, generated as part of the routine work of the Ministry of Health and National Sick Fund. Data were anonymised and only variables (and level of details) relevant to the study objectives were available to us. Eg, we had no data on date of admission and discharge (only year of discharge, and length of stay).

Validation: these are routinely collected data, and validation is done at several steps. There is a specialized team responsible for these data in each hospital (ex: assigning ICD-9 codes) , and regular additional controls are performed in hospitals by health authorities. Assignment of APR-DRG and severity of illness level is done by a specialized software (called router). Other quality checks are performed when data collated at national level. The whole process of compiling and validating the national database takes more than two years.

Cases included / excluded: the database we received is exhaustive (all hospital stays for the APRDRG of interest). For the purpose of the study we excluded some records, as mentioned in the article:

Under "Results – surgery QI" (ll166-168) : "A total of 325,094 hospitals stays between 1999 and 2010 were available for analyses (90% of total number of stays coded APR DRG 302, after exclusion of SoI 3 and 4, stays with infectious diagnoses, and errors in hospital coding)".

Under "Results – Pneumonia QI" (ll189-190) : "A total of 327,635 hospitals stays between 1999 and 2010 were available for analyses (95% of the total number of stays coded APR DRG 139, after exclusions for coding errors)."

More details on these exclusions can be found in the study report (ref 18 in the article) https://www.wiv-isp.be/nsih/download/Home/AMTABU_FINAL_REPORT.pdf

(p 17)
Table 1.Number of stays in APR-DRG 302 in Belgium, 1999-2010, and exclusions for further analyses.

(p26)
Table 8.Exclusions from total database, admissions for simple pneumonia*, Belgium 1999-2010

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Q/Discussion:
It is not clear what is being said about the Scottish antimicrobial stewardship programme. Year 2008

has been used as baseline year in many of the Scottish Quality Indicator reports (including hospital use) if relevant with regards to the policy in question.
****

A/ We have deleted the following sentence referring to Scotland

(Although Scotland also funds AMTs at hospital level since 2008,19 this specific aspect was not isolated from other components of the Scottish antimicrobial policy in an impact evaluation.20)

And replaced it by the following one , hoping this is more clear:

Another country – Scotland – funds AMT in hospitals since 2008, as part of a comprehensive policy to improve antimicrobial prescribing. The policy as a whole appears to be successful; but to what extent did the funding of AMT contribute to this success remains unknown.

VERSION 2 – REVIEW

REVIEWER	Nick Daneman Sunnybrook Health Sciences Centre, University of Toronto, Institute for Clinical Evaluative Sciences
REVIEW RETURNED	18-Dec-2014

GENERAL COMMENTS	I appreciate the authors' thoughtful responses to my questions and comments.

REVIEWER	Camilla Wiuff Health Protection Scotland, Scotland, Inuted Kingdom
REVIEW RETURNED	09-Jan-2015

GENERAL COMMENTS	The authors have clarified a number of specific and general points around methodology and limitations extensively in their repsonse letter to the editor. However, it would strengthen the paper if those points could be included in the discussion of the paper (for example in the section Strengths and Limitations). This should include a more in-depth discussion of the choice of type of quality indicators, the diversity of stewardship themes/intervention areas among the hospitals, the phased-in implementation of stewardship and confounding.

VERSION 2 – AUTHOR RESPONSE

We adress separately the suggestions of the reviewer:
1) the choice of type of quality indicators 2) the diversity of stewardship themes/intervention areas among the hospitals, 3) the phased-in implementation of stewardship and confounding.
Additions to the text are marked in blue in the Word documents

Q/ choice of type of quality indicators
A/This has been added to the text (discussion section – heading strength and limitations – l255):
The major limitation of this study is that we only looked at 3 QI, for only 2 indications. These QI do not measure patient's outcomes such as surgical site infection, or mortality (but these are only indirectly related to appropriate AM prescription eg, overshooting could also cure a patient).

We would like to underline that explanations on choice of QI, and limitations, are already discussed in the article:
1) Choice of QI is explained in the method section (l120)
" The 2 APR-DRG with the highest number of patients receiving AM were APR DRG 302 (major lower limb orthopedic surgery without trauma - mainly hip or knee replacement - or revision) and APR DRG 139 (simple pneumonia). We decided against clinical outcome measures such as mortality, readmission, and length of stay because these are too indirectly related to appropriate AM prescribing."

2) Limitations related to choice of QI are also addressed in the discussion section, under "generalizability" heading (l 288)
"The generalizability of our study finding is limited by the intrinsic complexity of evaluating quality of AM use in hospitals. We looked at a limited number of QI for a limited number of indications, and fall short of providing a global picture of trends in quality of AM use in Belgian hospitals, and of the effect of implementing and funding AMT in hospitals. This study should ideally be complemented by other indicators, which might provide different results"

Q/ the diversity of stewardship themes/intervention areas among the hospitals
A/ As stressed in the article, our study focused on the effect of a particular policy at national level, See eg abstract, l 55: "Improvements have been observed but could not be related at national level to the policy under study." Or under strengths and limitations (5th bullet, l 74) "This study has shown no impact of the policy at national level, but has not investigated determinant of success or failure at hospital level. "

This study did not look at the determinants of success or failure at hospital level, because we had no individual details on what was exactly done in each hospital. In practice, hospitals were not given precise targets and were left to devise their own themes and intervention.

We agree with the reviewer that more details on the intervention can improve the article.
We have added in the introduction section (l92):

Apart from funding, the intervention included technical guidance and advanced specialist training for the formal establishment and follow-up of AMTs. Hospitals were not given targets, and were left to devise their own interventions and themes. A self-reporting survey was conducted in 2007. Antibiotic stewardship tools used by AMTs included (non-exhaustive list): an antibiotic formulary (96% of hospitals), practice guidelines for antibiotic therapy and surgical prophylaxis (92%, and 96%, respectively), a list of restricted antimicrobial agents (76%), sequential intravenous/oral therapy with equivalent bioavailaibility (79%) . (ref)

Please note we refer that the fact that AMT were not given targets as a possible explanation for our finding, (under section "discussion, heading "interpretation", l280)
"AMT were not given targets, and therefore might have chosen other priorities for interventions than the indications analyzed here, despite these being the indications with the highest volume of patients receiving AM."

C/ the phased-in implementation of stewardship and confounding
A/ We have added in the discussion section, under "strengths and limitations" l254

The fact that the intervention was implemented at different times allowed to compare QIs both within and between hospitals (hospitals before and after implementation of the policy, as well as hospitals with, and without the policy); our fine-tuned case-mix adjustment removed confounding due to differences in patient population.