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Impact of the Belgian policy of funding and implementing antimicrobial stewardship in hospitals: a longitudinal study using routinely collected patient-level data

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Impact of the Belgian policy of funding and implementing antimicrobial stewardship in hospitals: a longitudinal study using routinely collected patient-level data.

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ABSTRACT

Objectives

In order to improve antimicrobial use, a policy of providing technical and financial support to antimicrobial management teams (AMT) was rolled out in all Belgian hospitals between 2002 and 2008. We aimed to analyze the association of this policy with antimicrobial use for the two indications accounting for the largest number of patients receiving antimicrobials: prophylaxis for major lower limb orthopedic surgery and pneumonia.

Design, setting, participants

We used patient-level data routinely collected in all Belgian acute care hospitals between 1999 and 2010. We modeled trends for selected quality indicators using the year of AMT implementation in each hospital as the main "change point", with fine-tuned case-mix adjustment. Of all admissions for lower limb orthopedic surgery, and pneumonia between 1999 and 2010, 90% (325,094) and 95% (327,635) respectively, were found eligible for analyses.

Outcomes

The surgery quality indicator (QI) was defined as: cefazolin, dose in the expected range, and no use of other AM. For pneumonia, quality indicators were: ratio of oral/parenteral defined daily doses (DDD) (O/P QI), and mean number of DDD minus penicillin , per 100 days of hospitalization (DDD QI).

Results

Between 1999 and 2010, the surgery QI improved from 59% to 71%; the O/P QI from 0.72 to 0.97, and the DDD QI from 96 to 64. Heterogeneity between hospitals was high. Overall no association was found with the year of implementation of the AMT.

Conclusions

Improvements have been observed but could not be related at national level to the policy under study. 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. However these results cannot be extrapolated to other QIs for AM use in hospitals.

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STRENGTHS AND LIMITATIONS OF THIS STUDY

- First study to evaluate a national policy of implementing and financing antimicrobial management teams in hospitals with a longitudinal study design
- Exhaustive database, on all admissions in Belgian hospitals over 11 years for the indications accounting for the largest number of patients receiving antimicrobials in hospitals (antimicrobial prophylaxis for lower limb orthopedic surgery, pneumonia)
- Fine-tuned case-mix adjustment when comparing hospitals before/after, and with/without the policy, taking into account possible time lag between implementation and results
- Quality indicators selected for this study measure some important aspects of quality, but fall short of providing a global picture of overall quality of antimicrobial use in hospitals. This is intrinsically complex, and other indicators might provide different results.
- This study has shown no impact of the policy at national level, but has not investigated determinant of success or failure at hospital level.

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INTRODUCTION

Inappropriate use of antimicrobials (AM), and its consequences in terms of infections due to AM resistant microorganisms represents a major public health problem.[1] Although the largest part of AM consumption takes place in the community[2], the risks are concentrated in hospitals: 35% of hospitalized patients in Europe[3] and 52% in the US[4] are taking an AM. Over a third of prescriptions might not be compliant with evidence-based guidelines.[5] AM stewardship, conducted by AM management teams (AMT), is a key strategy to improve AM prescribing, to ensure effective treatment of patients and to reduce AM resistance in hospitals.[6] The need for a legal basis, regulatory mechanisms, funding for AM stewardship programs, and research, are widely endorsed.[7,8]

Belgium has been a pioneer in this field. The Belgian Antibiotic Policy Coordination Committee (BAPCOC) was created in 1999 in order to improve AM use in Belgium and has been very active since at different levels.[9] Since July 2007, all acute care hospitals in the country have been receiving financial and technical support for hiring a trained manager for their AMT; the initiative was first piloted in 37 voluntary hospitals (2002) then extended to another 24 hospitals (2006), and finally to the remaining hospitals (55) in 2007. A national, self-reporting survey of AMT activities in hospitals in 2007 led to the conclusion that implementation of AM stewardship programs had been successful.[10] The minimum composition, mandate, and tasks of hospitals AMT have a legal basis since 2008. The largest part of the BAPCOC budget now goes to staffing and technical support for AMT in all Belgian acute hospitals.[9] To our knowledge, Belgium has been the first country to provide hospitals with structural, ear-marked funding for AMT, making the experience a test case for such a policy.

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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METHODS

Source of data and quality indicators

We obtained patient-level data routinely collected between 1999 and 2010 in all Belgian acute care hospitals for pathology-based financing purposes. These include the all-patient-refined diagnosis related group (APR-DRG, version 15) and associated severity of illness (SoI, 1-4)[11] as well as details on each AM used during the stay (molecule, dose, and route of administration); however the timing of AM administration is lacking. We used the WHO anatomical therapeutic chemical (ATC)/defined daily doses (DDD) method[12], applying version WHO 2010 to all 12 years in the database.

Comparing hospitals (with or without the policy, as well as before and after implementation of the policy) was done per APR-DRG to facilitate case-mix adjustment. 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. Compliance with guidelines for antibioprophylaxis in APR DRG 302 ("surgery QI") was defined using three criteria at patient level as: (1) choice of AM (cefazolin), dose in the expected range (2-8 gr), and (3) no other AM given during the stay.[13] We excluded from the analyses hospital stays with secondary infectious diagnoses and SoI 3 and 4, so that it could fairly be assumed that there was no other reason for prescribing an AM than antibioprophylaxis. For pneumonia, the data did not allow assessing appropriateness of treatment at patient level. In addition treatment guidelines can differ between hospitals. Aggregating data at hospital level, we selected two QI: (1) the ratio of oral DDD / parenteral DDD ("O/P QI"), as early parenteral to oral switch is recommended to reduce length of stay (LoS), adverse events related to intravenous line, and costs[13,14,15] and (2) total DDD (J01) minus penicillin (J01C), per 100 days in hospital for pneumonia ("DDD QI"), under the assumption "less is better". Penicillin use was excluded because recommended daily doses have increased over the year.

Statistical approach and adjustment for confounding

We used a change point model.[16] Such a model tests whether the slope of a trend is different before and after the change point. We included as change points the year each hospital received funding for its AMT (2002, 2006, 2007), as well as the years 2001 (the year of a very large awareness campaign for AM) and - for pneumonia only - 2006 (when a new financing mechanism for hospital drugs was introduced; however this mechanism did not apply to AM prophylaxis). We then tested the need to include additional change points. The surgery QI was a dichotomous variable at patient (stay) level, and variables adjusted

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for were LoS, age (continuous), gender, SoI (1-2), and ICU stay (at some point, hospitalized in intensive care unit). For pneumonia, outcomes were continuous variables at hospital level and required aggregation of patient (stay) level data. Hospital variables for pneumonia stays were: median LoS, distribution of the stays (%) according to SoI (1-4), gender, ICU stay, patient origin at admission (home, long term care facility, other or unknown), discharge status (death/alive), and age categories (< 1y, 1-5yr, 6-10y, 11-16y, >16y). Caseload (number of hospital stays included in the analyses for each QI, per hospital, and per year) was also included in the model, as a variable at hospital level.

For pneumonia results were weighted for caseload. A time lag (+/- one year) was introduced to account for the fact that the effect of AMT funding might have started before the hospitals received the money (e.g. because preparation included AM stewardship training) and might need some time to be fully implemented (e.g. because of possible delays in recruiting an AM specialist).

Statistical model and software

A somewhat abrupt but continuous change in the evolution of the outcome over time can be modeled by including a change point in the generalized linear mixed model (GLMM).[17] A GLMM is an extension of a generalized linear model in which the correlation between measurements from the same hospital is taken into account using so-called random effects. Whereas the outcome is considered to belong to the exponential family (including the normal and the Bernoulli distribution), the systematic component of a GLMM is given by:

$$g(\mu_{ij}) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_2 (t_{ij} - CP)_+ + \sum_{q=3}^{Q} \beta_q X_{qij}$$

where μ_{ij} is the average outcome for hospital *i (i = 1, 2,..., N)* at time points t_{ij} *(j =1, 2,..., n_i), g(.)* is a link function (e.g. an identity link or a logit link), N is the total number of hospitals, n_i is the number of observations from the *i-th* hospital, $t_{ij} = 1$ corresponds to the start of the study, β_0 is the fixed intercept, b_{0i} is the hospital-specific deviation from intercept β_0, β_1 is the fixed slope, b_{1i} is the hospital-specific deviation from slope β_1, $x_+ = \max(x,0)$ such that β_2 is the global difference in the linear trend before and after the change-point, CP is a global change-point, β_q *(q = 3, 4,..., Q)* are the fixed effects for the explanatory variables X_{qij} and Q is the number of explanatory variables. All models were fitted using SAS version 9.3.

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RESULTS

Surgery QI

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). Median LoS in this population decreased from 15 days in 1999 to 8 days in 2010. Trends in the number of hospital stays, and compliance to the three criteria as defined earlier, are shown in Table 1. Compliance increased from 53% of included stays in 1999 to 71% in 2010.

Table 1. Hospital stays for lower limb orthopedic surgery* and compliance with guidelines for surgical prophylaxis, Belgium, 1999-2010

Year	N hospitals	N stays 100%	Stays with cefazolin, 2-8 gr, no other antimicrobials N	%
1999	110	18,562	9,802	53%
2000	110	20,559	11,691	57%
2001	110	21,790	12,597	58%
2002	110	23,254	13,274	57%
2003	110	24,606	14,823	60%
2004	110	25,917	16,942	65%
2005	110	27,756	18,551	67%
2006	110	29,267	19,761	68%
2007	108	30,727	21,336	69%
2008	107	32,708	22,796	70%
2009	106	34,256	23,930	70%
2010	104	35,692	25,264	71%

** APR-DRG 302, severity of illness 1 and 2*

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Based on likelihood ratio (LR) tests comparing models with, and without specific change points, the change point "year of AMT" was retained in the model ($p < 0.0001$); the change point "year 2001" was identified as statistically significant ($p < 0.0001$). All changes were negative, and weak (meaning that compliance increased, but at a slower pace than before). The final model had a pseudo-R^2 value of 0.1927. Although R^2 values for models on binary outcomes are typically much lower than for models on continuous outcomes, this indicates that there still is a lot of unexplained residual variability. Observed and predicted values for the full model, and for hospitals according to the year of funding AMT are shown in **Figure 1**.

Figure 1. Averaged observed (dotted) and predicted evolution of compliance with guidelines for surgical antibiotic prophylaxis for lower limb surgery*, Belgium, 1999-2010.

(insert Figure 1)

Pneumonia QI

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). All had "pneumonia" as an admission diagnosis, so we assume that the vast majority of patients were admitted for community-acquired pneumonia. (In theory it is possible that some patients were transferred from another hospital with an hospital-acquired pneumonia). 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).

Trends in the number of hospital stays, and the QI are shown in table 2. Between 1999 and 2010, the mean DDD of AM other than J01C decreased from 96 to 64 /100 days of hospitalization for pneumonia; the O/P ratio (all AM) increased from 0.72 to 0.97.

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Table 2. Hospital stays for simple pneumonia* and quality indicators for antimicrobial treatment, Belgium, 1999-2010

Year	N Hospitals	N stays	Mean DDD / 100 patient-days			DDD oral / DDD parenteral		
			J01C	Other	Total	J01C	Other	Total
1999	112	22385	66	96	161	0,57	0,84	0,72
2000	112	23268	67	97	164	0,58	0,87	0,74
2001	112	24165	70	100	170	0,62	0,91	0,77
2002	112	25424	75	97	172	0,66	0,81	0,74
2003	112	26331	83	89	172	0,69	0,83	0,76
2004	112	25201	91	82	172	0,79	0,82	0,80
2005	112	30145	97	81	178	0,83	0,93	0,87
2006	112	26739	99	74	173	0,87	0,96	0,91
2007	110	28872	99	68	167	0,89	1,04	0,95
2008	110	29823	101	65	166	0,90	1,02	0,95
2009	109	33611	102	63	165	0,90	1,11	0,98
2010	107	31671	106	64	170	0,88	1,12	0,97

*APR-DRG 139

DDD: defined daily dose; patient-days: only patients hospitalized for pneumonia. J01C: ATC code, Beta-lactam penicillin.

Based on LR tests comparing models with, and without specific change points, the change point "year of AMT" was not retained in the models for the DDD QI (p = 0.4659) nor for the O/P QI (p: 0.0997). This means that there was no statistically significant change in slope for these outcomes, i.e the year a hospital received funding for their AMT.

For the DDD QI the years 2001 and 2006 were identified as statistically significant change points (p < 0.0001 and 0.0009, respectively). In 2001, the QI decreased, the effect was strong. In 2006, the QI decreased at a slower pace than before. The adjusted R^2 for the final model was 0.8072. For the O/P ratio QI, the year 2001 was not retained in the model (p = 0.9884) while the year 2006 was identified as a statistically significant change point (p = 0.0310): the QI increased, but at a slower pace than before. The adjusted R^2 for the final model was 0.7559. For these two pneumonia outcomes, the high adjusted R^2 indicate that the models perform well in explaining the variability in the data. The effect of the "2006" change point on both QI was weak and of doubtful clinical significance.

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Figure 2. Averaged observed (dotted) and predicted evolution of quality indicators for antimicrobial treatment of community-acquired pneumonia*in hospitals, Belgium, 1999-2010

(Figure 2)

General features of statistical modeling

All 3 QI showed high heterogeneity: baseline values, as well as changes overtime, varied widely across hospitals. Another feature was the complexity of the predicting models, which involved many parameters, and interactions, rendering interpretation sometimes difficult, so that the effect of "change points" is better assessed visually on the figures presented. Of importance, the introduction of time lags in the models (that is, taking into account the year before or the year after the "change points") did not improve the models. A complete description of the results, interaction terms and estimates, is available in the full study report.[18]

DISCUSSION

Key findings

In 1999, 53% of patients admitted in hospital for major lower limb orthopedic surgery received the recommended AM for surgical antibioprophylaxis, with a dosage in the expected range, and no other AM. This figure was 71% in 2010. For patients treated for pneumonia over the same period, mean consumption of AM other than penicillin decreased from 96 DDD to 64 DDD / 100 hospital-days, and the ratio of oral / parenteral DDD increased from 0.72 to 0.97. There was high heterogeneity between hospitals. No positive effect could be detected at national level for these 3 QI in relation to the timing of implementation of the policy. In 2001, the decrease in the pneumonia DDD indicator was a statistically and likely clinically significant deviation from expected trends.

Strengths and limitations

To our knowledge, this is the first study specifically evaluating a national policy of implementing and funding antimicrobial stewardship program at hospital level. (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]) Its major strengths are an exhaustive patient-based

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database including all Belgian hospitals over 12 years, analyses of AM use per indication and fine-tuned case-mix adjustment that guarantee the validity of inter and intra hospital comparisons, which are crucial to this study. The 2 APR-DRG studied account for the largest number of patients receiving AM in hospitals. The trend in improvement for the surgery QI is robust, even if true compliance is less than what we measured, as our QI does not include timing of AM administration. We used state-of-the art statistical methods for modeling the trends of our QI, and acknowledged that change can take time by introducing time lags in the model (taking into account one year before, one year after the "change point"), nonetheless these did not improve the model. However we only looked at 3 QI, but one of them is questionable. The decreasing trends in the consumption of DDD other than penicillin mainly reflects a decrease in cephalosporins and macrolides which offsets an increase in carbapenems and fluoroquinolones. The decrease is also partly explained by a shift towards broad-spectrum penicillin (J01CR, or combinations, such as amoxicillin – clavulanic acid).[18] It is therefore unclear whether the decrease in this QI indeed represents a true improvement in quality.

Interpretation

At least 2 out of 3 of our QI describe a true improvement in AM use for patients admitted to hospital for pneumonia and lower limb surgery between 1999 and 2010 in Belgium; these improvements have benefited a very large number of patients. Exactly why this happened is unclear. Although 2001 (a "change point" for the DDD QI) was the year of a very large awareness campaign for AM, this campaign targeted upper respiratory tract infections in the community.

There are several possible explanations for the lack of association between improvement in the QIs and the year of implementation of AMT in hospitals. 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. 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. (In 2013 however AMT in Belgium conducted audits for antibioprophylaxis in surgery in which serious gaps were identified.[21]) It is also possible that the earmarked AMT funding was not always used directly for AMT implementation. A major shortcoming resides in the absence of data on the actual use of funding within hospitals, which may not be easily extracted from the annual AMT activity reports.

Generalizability

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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. For instance worrying trends are observed for hospital use of some AM; between 1999 and 2010, the use of colistine quadrupled and the use of carbapenem more than doubled (6 to 24 DDD, and 118 to 265, per 10,000 patient-days, respectively).[18]

Political commitment for tackling the problem of AM resistance in general, and improving AM use in hospitals in particular, has clearly been increasing in the last decade in Europe, North America, and elsewhere. [7, 22-26] Recommendations for strengthening the legal basis and core funding of antibiotic stewardship programs acknowledge the urgent need for building an evidence-base for such policies through good quality research[7, 8] and we believe that this study contributes to this objective.

CONCLUSIONS

Our study has shown improvement on selected quality indicators for AM use in the treatment of pneumonia, and in antibioprophylaxis for lower limb orthopedic surgery in Belgian hospitals between 1999 and 2010. These improvements could not be related to a policy of funding AMT. Changes observed therefore 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.

Our findings do not question the need for AMT, nor the need for continuation of AMT funding. Several recommendations could be made in order to make the best of the Belgian unique political, and financial commitment in that field. Transparency in use of ear-marked funding for AMT at hospital level could be improved. Trends of other AM quality indicators deserve more research. AMTs in hospitals should benefit from more guidance in terms of identifying priorities for action.

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AUTHORS CONTRIBUTION

MLL, NaHa, HG,DV designed the study; MLL, NaHa, RB wrote the first draft; RB, NiHe, MA conducted the statistical analyses; FN, BC, HG, DV revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript

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CONFLICTS OF INTEREST

Conflicts of interest in relation to this study: none.

DATA SHARING

Legal restrictions apply to these data, which cannot be shared.

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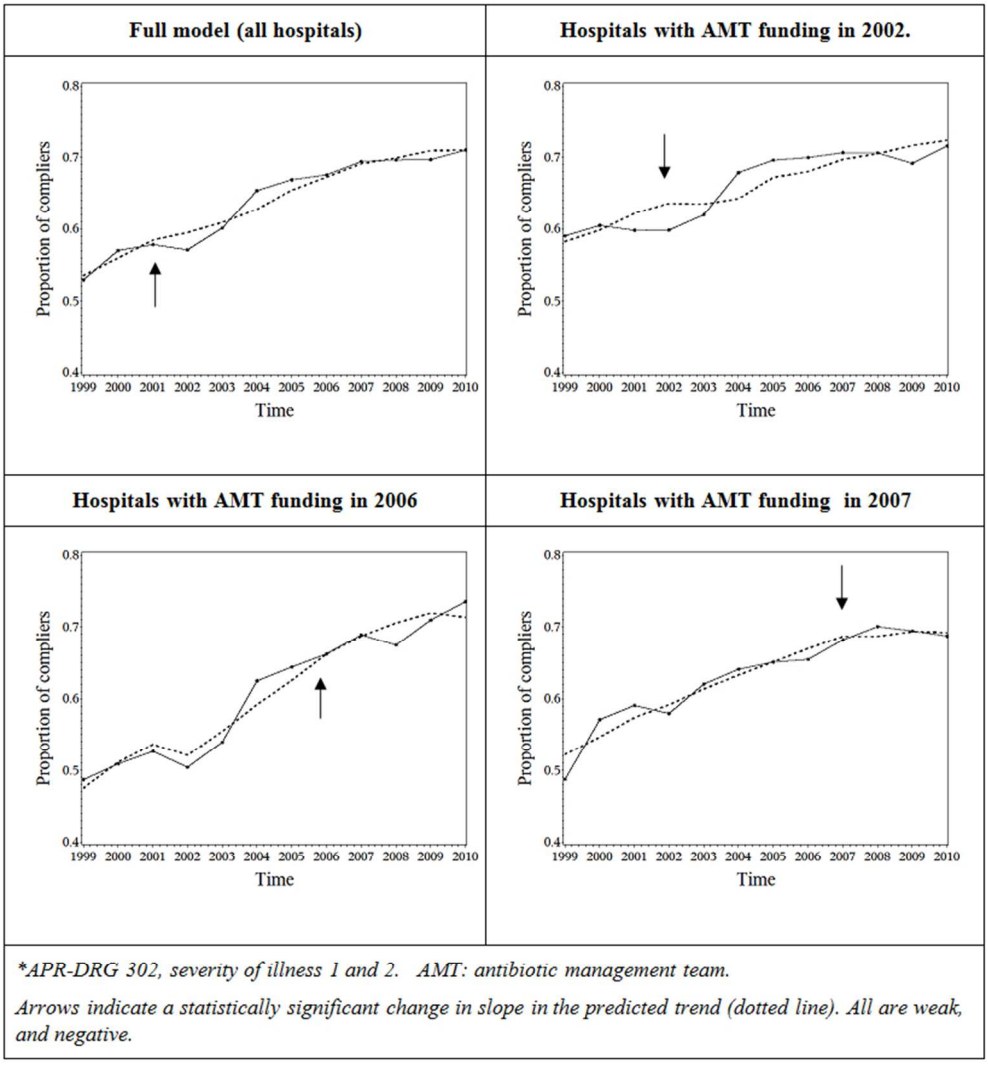

**APR-DRG 302, severity of illness 1 and 2. AMT: antibiotic management team.*

Arrows indicate a statistically significant change in slope in the predicted trend (dotted line). All are weak, and negative.

Figure 1. Averaged observed and predicted (dotted line) evolution of compliance with guidelines for surgical antibiotic prophylaxis for lower limb surgery*, Belgium, 1999-2010.

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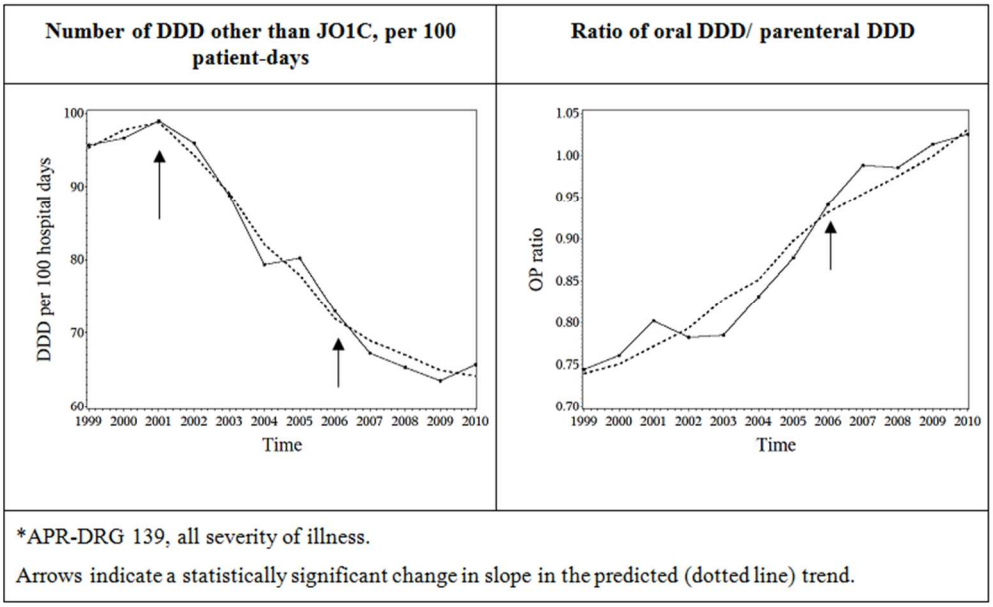

Figure 2. Averaged observed and predicted (dotted line) evolution of quality indicators for antimicrobial treatment of community-acquired pneumonia*in hospitals, Belgium, 1999-2010

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	P10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P11
Generalisability	21	Discuss the generalisability (external validity) of the study results	P11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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The Belgian policy of funding antimicrobial stewardship in hospitals, and trends of selected quality indicators for antimicrobial use, 1999-2010: a longitudinal study.

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~~Impact of~~T ~~t~~he Belgian policy of funding ~~and implementing~~ antimicrobial stewardship in hospitals, and trends of selected quality indicators for antimicrobial use, 1999-2010: a longitudinal study ~~using routinely collected patient level data.~~

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Running title: improvements observed could not be related to the policy under study

Keywords: antimicrobial use, hospitals, antimicrobial stewardship, health policy, evaluation

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ABSTRACT

Objectives

In order to improve antimicrobial use, a policy of providing technical and financial support to antimicrobial management teams (AMT) was rolled out in all Belgian hospitals between 2002 and 2008. We aimed to analyze the association of this policy with antimicrobial use for the two indications accounting for the largest number of patients receiving antimicrobials: prophylaxis for major lower limb orthopedic surgery and pneumonia.

Design, setting, participants

We used patient-level data routinely collected in all Belgian acute care hospitals between 1999 and 2010. We modeled trends for selected quality indicators using the year of AMT implementation in each hospital as the main "change point", with fine-tuned case-mix adjustment. Of all admissions for lower limb orthopedic surgery, and pneumonia between 1999 and 2010, 90% (325,094) and 95% (327,635) respectively, were found eligible for analyses.

Outcomes

The surgery quality indicator (QI) was defined as: cefazolin, dose in the expected range, and no use of other AM. For pneumonia, quality indicators were: ratio of oral/parenteral defined daily doses (DDD) (O/P QI), and mean number of DDD minus penicillin , per 100 days of hospitalization (DDD QI).

Results

Between 1999 and 2010, the surgery QI improved from 59% to 71%; the O/P QI from 0.72 to 0.97, and the DDD QI from 96 to 64. Heterogeneity between hospitals was high. Overall no association was found with the year of implementation of the AMT.

Conclusions

Improvements have been observed but could not be related at national level to the policy under study. ~~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.~~ However these results cannot be extrapolated to other QIs for AM use in hospitals.

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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STRENGTHS AND LIMITATIONS OF THIS STUDY

- First study to evaluate a national policy of implementing and financing antimicrobial management teams in hospitals with a longitudinal study design
- Exhaustive database, on all admissions in Belgian hospitals over 11 years for the indications accounting for the largest number of patients receiving antimicrobials in hospitals (antimicrobial prophylaxis for lower limb orthopedic surgery, pneumonia)
- Fine-tuned case-mix adjustment when comparing hospitals before/after, and with/without the policy, taking into account possible time lag between implementation and results
- Quality indicators selected for this study measure some important aspects of quality, but fall short of providing a global picture of overall quality of antimicrobial use in hospitals. This is intrinsically complex, and other indicators might provide different results.
- This study has shown no impact of the policy at national level, but has not investigated determinant of success or failure at hospital level.

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INTRODUCTION

Inappropriate use of antimicrobials (AM), and its consequences in terms of infections due to AM resistant microorganisms represents a major public health problem.[1] Although the largest part of AM consumption takes place in the community[2], the risks are concentrated in hospitals: 35% of hospitalized patients in Europe[3] and 52% in the US[4] are taking an AM. Over a third of prescriptions might not be compliant with evidence-based guidelines.[5] AM stewardship, conducted by AM management teams (AMT), is a key strategy to improve AM prescribing, to ensure effective treatment of patients and to reduce AM resistance in hospitals.[6] The need for a legal basis, regulatory mechanisms, funding for AM stewardship programs, and research, are widely endorsed.[7,8]

Belgium has been a pioneer in this field. The Belgian Antibiotic Policy Coordination Committee (BAPCOC) was created in 1999 in order to improve AM use in Belgium and has been very active since at different levels.[9] Since July 2007, all acute care hospitals in the country have been receiving financial and technical support for hiring a trained manager for their AMT; the initiative was first piloted in 37 voluntary hospitals (2002) then extended to another 24 hospitals (2006), and finally to the remaining hospitals (55) in 2007. A national, self-reporting survey of AMT activities in hospitals in 2007 led to the conclusion that implementation of AM stewardship programs had been successful.[10] The minimum composition, mandate, and tasks of hospitals AMT have a legal basis since 2008. The largest part of the BAPCOC budget now goes to staffing and technical support for AMT in all Belgian acute hospitals.[9] To our knowledge, Belgium has been the first country to provide hospitals with structural, ear-marked funding for AMT, making the experience a test case for such a policy.

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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METHODS

Source of data and quality indicators

We obtained patient-level data routinely collected between 1999 and 2010 in all Belgian acute care hospitals for pathology-based financing purposes. These include the all-patient-refined diagnosis related group (APR-DRG, version 15) and associated severity of illness (SoI, 1-4)[11] as well as details on each AM used during the stay (molecule, dose, and route of administration); however the timing of AM administration is lacking. 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).[11]

We used the WHO anatomical therapeutic chemical (ATC)/defined daily doses (DDD) method[12], applying version WHO 2010 to all 12 years in the database.

Comparing hospitals (with or without the policy, as well as before and after implementation of the policy) was done per APR-DRG to facilitate case-mix adjustment. 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. Compliance with guidelines for antibioprophylaxis in APR DRG 302 ("surgery QI") was defined using three criteria at patient level as: (1) choice of AM (cefazolin), dose in the expected range (2-8 gr), and (3) no other AM given during the stay.[13] We excluded from the analyses hospital stays with secondary infectious diagnoses and SoI 3 and 4, so that it could fairly be assumed that there was no other reason for prescribing an AM than antibioprophylaxis. For pneumonia, the data did not allow assessing appropriateness of treatment at patient level. In addition treatment guidelines can differ between hospitals. Aggregating data at hospital level, we selected two QI: (1) the ratio of oral DDD / parenteral DDD ("O/P QI"), as early parenteral to oral switch is recommended to reduce length of stay (LoS), adverse events related to intravenous line, and costs[13,14,15] and (2) total DDD (J01) minus penicillin (J01C), per 100 days in hospital for pneumonia ("DDD QI"), under the assumption "less is better". Penicillin use was excluded because recommended daily doses have increased over the year.

Statistical approach and adjustment for confounding

We used a change point model.[16] Such a model tests whether the slope of a trend is different before and after the change point. We included as change points the year each hospital received funding for its AMT

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(2002, 2006, 2007), as well as the years 2001 (the year of a very large awareness campaign for AM) and - for pneumonia only - 2006 (when a new financing mechanism for hospital drugs was introduced; however this mechanism did not apply to AM prophylaxis). We then tested the need to include additional change points. The surgery QI was a dichotomous variable at patient (stay) level, and variables adjusted for were LoS, age (continuous), gender, SoI (1-2), and ICU stay (at some point, hospitalized in intensive care unit). For pneumonia, outcomes were continuous variables at hospital level and required aggregation of patient (stay) level data. Hospital variables for pneumonia stays were: median LoS, distribution of the stays (%) according to SoI (1-4), gender, ICU stay, patient origin at admission (home, long term care facility, other or unknown), discharge status (death/alive), and age categories (< 1y, 1-5yr, 6-10y, 11-16y, >16y). Caseload (number of hospital stays included in the analyses for each QI, per hospital, and per year) was also included in the model, as a variable at hospital level.

For pneumonia results were weighted for caseload. A time lag (+/- one year) was introduced to account for the fact that the effect of AMT funding might have started before the hospitals received the money (e.g. because preparation included AM stewardship training) and might need some time to be fully implemented (e.g. because of possible delays in recruiting an AM specialist).

Statistical model and software

A somewhat abrupt but continuous change in the evolution of the outcome over time can be modeled by including a change point in the generalized linear mixed model (GLMM).[17] A GLMM is an extension of a generalized linear model in which the correlation between measurements from the same hospital is taken into account using so-called random effects. Whereas the outcome is considered to belong to the exponential family (including the normal and the Bernoulli distribution), the systematic component of a GLMM is given by:

$$g(\mu_{ij}) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_2 (t_{ij} - CP)_+ + \sum_{q=3}^{Q} \beta_q X_{qij}$$

where μ_{ij} is the average outcome for hospital *i (i = 1, 2,..., N)* at time points t_{ij} *(j =1, 2,..., n_i), g(.)* is a link function (e.g. an identity link or a logit link), N is the total number of hospitals, n_i is the number of observations from the *i-th* hospital, $t_{ij} = 1$ corresponds to the start of the study, β_0 is the fixed intercept, b_{0i} is the hospital-specific deviation from intercept β_0, β_1 is the fixed slope, b_{1i} is the hospital-specific deviation from slope β_1, $x_+ = \max(x,0)$ such that β_2 is the global difference in the linear trend before and after the change-point, CP is a global change-point, β_q *(q = 3, 4,..., Q)* are the fixed effects for the

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explanatory variables X_{qij} and Q is the number of explanatory variables. All models were fitted using SAS version 9.3.

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RESULTS

Surgery QI

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). Median LoS in this population decreased from 15 days in 1999 to 8 days in 2010. Trends in the number of hospital stays, and compliance to the three criteria as defined earlier, are shown in Table 1. Compliance increased from 53% of included stays in 1999 to 71% in 2010.

Table 1. Hospital stays for lower limb orthopedic surgery* and compliance with guidelines for surgical prophylaxis, Belgium, 1999-2010

Year	N hospitals	N stays 100%	Stays with cefazolin, 2-8 gr, no other antimicrobials N	%
1999	110	18,562	9,802	53%
2000	110	20,559	11,691	57%
2001	110	21,790	12,597	58%
2002	110	23,254	13,274	57%
2003	110	24,606	14,823	60%
2004	110	25,917	16,942	65%
2005	110	27,756	18,551	67%
2006	110	29,267	19,761	68%
2007	108	30,727	21,336	69%
2008	107	32,708	22,796	70%
2009	106	34,256	23,930	70%
2010	104	35,692	25,264	71%

** APR-DRG 302, severity of illness 1 and 2*

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Based on likelihood ratio (LR) tests comparing models with, and without specific change points, the change point "year of AMT" was retained in the model ($p < 0.0001$); the change point "year 2001" was identified as statistically significant ($p < 0.0001$). All changes were negative, and weak (meaning that compliance increased, but at a slower pace than before). The final model had a pseudo-R^2 value of 0.1927. Although R^2 values for models on binary outcomes are typically much lower than for models on continuous outcomes, this indicates that there still is a lot of unexplained residual variability. Observed and predicted values for the full model, and for hospitals according to the year of funding AMT are shown in ~~Figure 1~~Figure 1.

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~~Figure 1~~Figure 1. Averaged observed (dotted) and predicted evolution of compliance with guidelines for surgical antibiotic prophylaxis for lower limb surgery*, Belgium, 1999-2010.

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(insert Figure 1)

Pneumonia QI

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). All had "pneumonia" as an admission diagnosis, so we assume that the vast majority of patients were admitted for community-acquired pneumonia. (In theory it is possible that some patients were transferred from another hospital with an hospital-acquired pneumonia). 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).

Trends in the number of hospital stays, and the QI are shown in table 2. Between 1999 and 2010, the mean DDD of AM other than J01C decreased from 96 to 64 /100 days of hospitalization for pneumonia; the O/P ratio (all AM) increased from 0.72 to 0.97.

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Table 2. Hospital stays for simple pneumonia* and quality indicators for antimicrobial treatment, Belgium, 1999-2010

Year	N Hospitals	N stays	Mean DDD / 100 patient-days			DDD oral / DDD parenteral		
			J01C	Other	Total	J01C	Other	Total
1999	112	22385	66	96	161	0,57	0,84	0,72
2000	112	23268	67	97	164	0,58	0,87	0,74
2001	112	24165	70	100	170	0,62	0,91	0,77
2002	112	25424	75	97	172	0,66	0,81	0,74
2003	112	26331	83	89	172	0,69	0,83	0,76
2004	112	25201	91	82	172	0,79	0,82	0,80
2005	112	30145	97	81	178	0,83	0,93	0,87
2006	112	26739	99	74	173	0,87	0,96	0,91
2007	110	28872	99	68	167	0,89	1,04	0,95
2008	110	29823	101	65	166	0,90	1,02	0,95
2009	109	33611	102	63	165	0,90	1,11	0,98
2010	107	31671	106	64	170	0,88	1,12	0,97

*APR-DRG 139

DDD: defined daily dose; patient-days: only patients hospitalized for pneumonia. J01C: ATC code, Beta-lactam penicillin.

Based on LR tests comparing models with, and without specific change points, the change point "year of AMT" was not retained in the models for the DDD QI (p = 0.4659) nor for the O/P QI (p: 0.0997). This means that there was no statistically significant change in slope for these outcomes, i.e the year a hospital received funding for their AMT.

For the DDD QI the years 2001 and 2006 were identified as statistically significant change points (p < 0.0001 and 0.0009, respectively). In 2001, the QI decreased, the effect was strong. In 2006, the QI decreased at a slower pace than before. The adjusted R^2 for the final model was 0.8072. For the O/P ratio QI, the year 2001 was not retained in the model (p = 0.9884) while the year 2006 was identified as a statistically significant change point (p = 0.0310): the QI increased, but at a slower pace than before. The adjusted R^2 for the final model was 0.7559. For these two pneumonia outcomes, the high adjusted R^2 indicate that the models perform well in explaining the variability in the data. The effect of the "2006" change point on both QI was weak and of doubtful clinical significance.

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Figure 2. Averaged observed (dotted) and predicted evolution of quality indicators for antimicrobial treatment of community-acquired pneumonia*in hospitals, Belgium, 1999-2010

(Figure 2)

General features of statistical modeling

All 3 QI showed high heterogeneity: baseline values, as well as changes overtime, varied widely across hospitals. Another feature was the complexity of the predicting models, which involved many parameters, and interactions, rendering interpretation sometimes difficult, so that the effect of "change points" is better assessed visually on the figures presented. Of importance, the introduction of time lags in the models (that is, taking into account the year before or the year after the "change points") did not improve the models. A complete description of the results, interaction terms and estimates, is available in the full study report.[18]

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DISCUSSION

Key findings

In 1999, 53% of patients admitted in hospital for major lower limb orthopedic surgery received the recommended AM for surgical antibioprophylaxis, with a dosage in the expected range, and no other AM. This figure was 71% in 2010. For patients treated for pneumonia over the same period, mean consumption of AM other than penicillin decreased from 96 DDD to 64 DDD / 100 hospital-days, and the ratio of oral / parenteral DDD increased from 0.72 to 0.97. There was high heterogeneity between hospitals. No positive effect could be detected at national level for these 3 QI in relation to the timing of implementation of the policy. In 2001, the decrease in the pneumonia DDD indicator was a statistically and likely clinically significant deviation from expected trends.

Strengths and limitations

To our knowledge, this is the first study specifically evaluating a national policy of implementing and funding antimicrobial stewardship program at hospital level. (Another country – Scotland – funds AMT in hospitals since 2008[19], as part of a comprehensive policy to improve antimicrobial prescribing. The

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policy as a whole appears to be successful - but to what extent did the funding of AMT contribute to this success remains unknown.[20]

~~(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])~~ Its major strengths are an exhaustive patient-based database including all Belgian hospitals over 12 years, analyses of AM use per indication and fine-tuned case-mix adjustment that guarantee the validity of inter and intra hospital comparisons, which are crucial to this study. The 2 APR-DRG studied account for the largest number of patients receiving AM in hospitals. The trend in improvement for the surgery QI is robust, even if true compliance is less than what we measured, as our QI does not include timing of AM administration. We used state-of-the art statistical methods for modeling the trends of our QI, and acknowledged that change can take time by introducing time lags in the model (taking into account one year before, one year after the "change point"), nonetheless these did not improve the model. However we only looked at 3 QI, but one of them is questionable. The decreasing trends in the consumption of DDD other than penicillin mainly reflects a decrease in cephalosporins and macrolides which offsets an increase in carbapenems and fluoroquinolones. The decrease is also partly explained by a shift towards broad-spectrum penicillin (J01CR, or combinations, such as amoxicillin – clavulanic acid).[18] It is therefore unclear whether the decrease in this QI indeed represents a true improvement in quality.

Interpretation

At least 2 out of 3 of our QI describe a true improvement in AM use for patients admitted to hospital for pneumonia and lower limb surgery between 1999 and 2010 in Belgium; these improvements have benefited a very large number of patients. Exactly why this happened is unclear. Although 2001 (a "change point" for the DDD QI) was the year of a very large awareness campaign for AM, this campaign targeted upper respiratory tract infections in the community.

There are several possible explanations for the lack of association between improvement in the QIs and the year of implementation of AMT in hospitals. 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. 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. (In 2013 however AMT in Belgium conducted audits for antibioprophylaxis in surgery in which serious gaps were identified.[21]) It is also

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possible that the earmarked AMT funding was not always used directly for AMT implementation. A major shortcoming resides in the absence of data on the actual use of funding within hospitals, which may not be easily extracted from the annual AMT activity reports.

Generalizability

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. For instance worrying trends are observed for hospital use of some AM; between 1999 and 2010, the use of colistine quadrupled and the use of carbapenem more than doubled (6 to 24 DDD, and 118 to 265, per 10,000 patient-days, respectively).[18]

Political commitment for tackling the problem of AM resistance in general, and improving AM use in hospitals in particular, has clearly been increasing in the last decade in Europe, North America, and elsewhere.[7, 22-26] Recommendations for strengthening the legal basis and core funding of antibiotic stewardship programs acknowledge the urgent need for building an evidence-base for such policies through good quality research[7, 8] and we believe that this study contributes to this objective.

CONCLUSIONS

Our study has shown improvement on selected quality indicators for AM use in the treatment of pneumonia, and in antibioprophylaxis for lower limb orthopedic surgery in Belgian hospitals between 1999 and 2010. These improvements could not be related to a policy of funding AMT. Changes observed therefore 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.

Our findings do not question the need for AMT, nor the need for continuation of AMT funding. Several recommendations could be made in order to make the best of the Belgian unique political, and financial commitment in that field. Transparency in use of ear-marked funding for AMT at hospital level could be improved. Trends of other AM quality indicators deserve more research. AMTs in hospitals should benefit from more guidance in terms of identifying priorities for action.

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AUTHORS CONTRIBUTION

MLL, NaHa, HG,DV designed the study; MLL, NaHa, RB wrote the first draft; RB, NiHe, MA conducted the statistical analyses; FN, BC, HG, DV revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript

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CONFLICTS OF INTEREST

Conflicts of interest in relation to this study: none.

DATA SHARING

Legal restrictions apply to these data, which cannot be shared.

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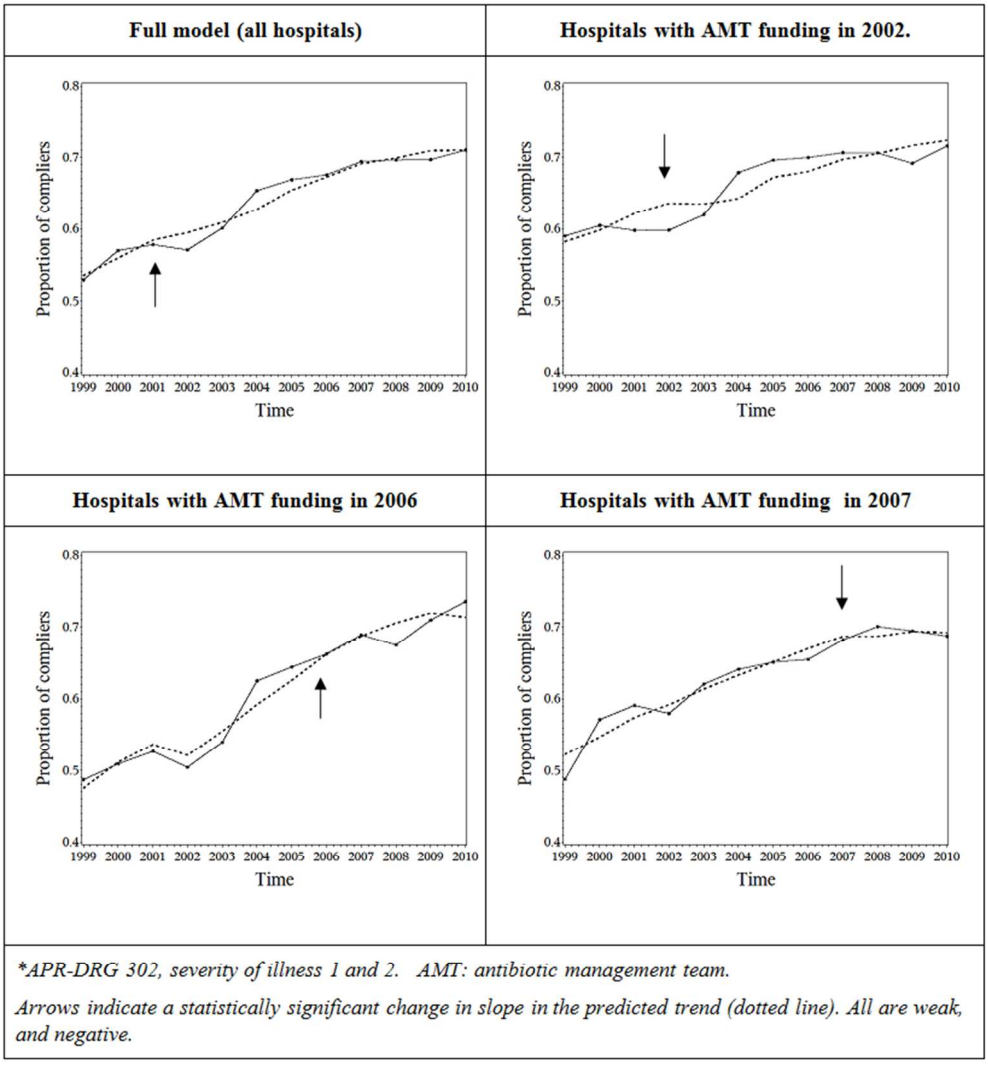

*APR-DRG 302, severity of illness 1 and 2. AMT: antibiotic management team.

Arrows indicate a statistically significant change in slope in the predicted trend (dotted line). All are weak, and negative.

Figure 1. Averaged observed and predicted (dotted line) evolution of compliance with guidelines for surgical antibiotic prophylaxis for lower limb surgery*, Belgium, 1999-2010.

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	P10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P11
Generalisability	21	Discuss the generalisability (external validity) of the study results	P11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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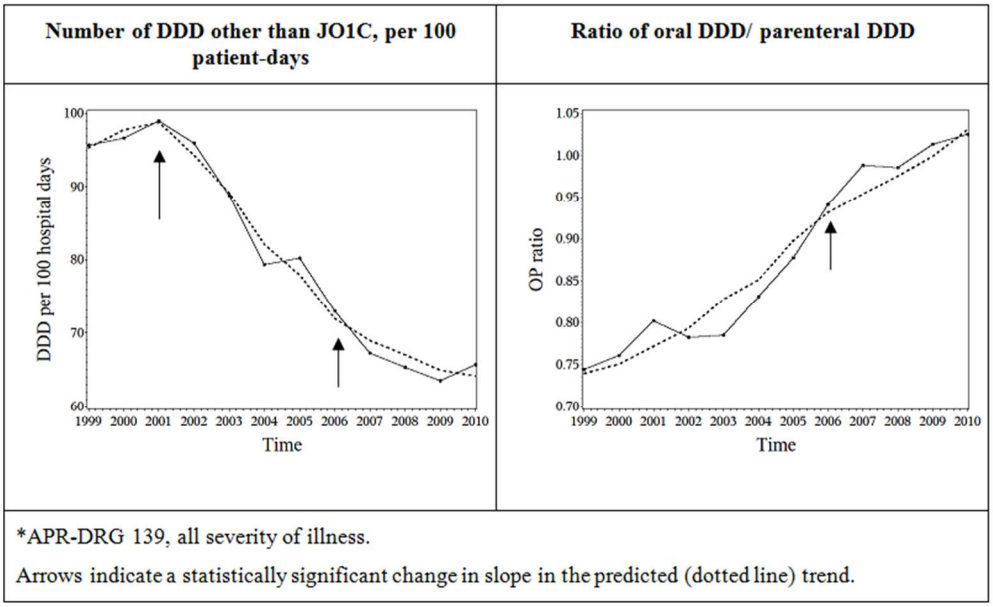

Figure 2. Averaged observed and predicted (dotted line) evolution of quality indicators for antimicrobial treatment of community-acquired pneumonia*in hospitals, Belgium, 1999-2010

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The Belgian policy of funding antimicrobial stewardship in hospitals, and trends of selected quality indicators for antimicrobial use, 1999-2010: a longitudinal study.

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Primary Subject Heading:	Health policy
Secondary Subject Heading:	Health services research, Pharmacology and therapeutics, Epidemiology
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, EPIDEMIOLOGY, Respiratory infections < THORACIC MEDICINE, Hip < ORTHOPAEDIC & TRAUMA SURGERY, Knee < ORTHOPAEDIC & TRAUMA SURGERY

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The Belgian policy of funding antimicrobial stewardship in hospitals and trends of selected quality indicators for antimicrobial use, 1999-2010: a longitudinal study.

Running title: improvements observed could not be related to the policy under study

Keywords: antimicrobial use, hospitals, antimicrobial stewardship, health policy, evaluation

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ABSTRACT

Objectives

In order to improve antimicrobial use, a policy of providing technical and financial support to antimicrobial management teams (AMT) was rolled out in all Belgian hospitals between 2002 and 2008. We aimed to analyze the association of this policy with antimicrobial use for the two indications accounting for the largest number of patients receiving antimicrobials: prophylaxis for major lower limb orthopedic surgery and pneumonia.

Design, setting, participants

We used patient-level data routinely collected in all Belgian acute care hospitals between 1999 and 2010. We modeled trends for selected quality indicators using the year of AMT implementation in each hospital as the main "change point", with fine-tuned case-mix adjustment. Of all admissions for lower limb orthopedic surgery, and pneumonia between 1999 and 2010, 90% (325,094) and 95% (327,635) respectively, were found eligible for analyses.

Outcomes

The surgery quality indicator (QI) was defined as: cefazolin, dose in the expected range, and no use of other AM. For pneumonia, quality indicators were: ratio of oral/parenteral defined daily doses (DDD) (O/P QI), and mean number of DDD minus penicillin , per 100 days of hospitalization (DDD QI).

Results

Between 1999 and 2010, the surgery QI improved from 59% to 71%; the O/P QI from 0.72 to 0.97, and the DDD QI from 96 to 64. Heterogeneity between hospitals was high. Overall no association was found with the year of implementation of the AMT.

Conclusions

Improvements have been observed but could not be related at national level to the policy under study. However these results cannot be extrapolated to other QIs for AM use in hospitals. 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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STRENGTHS AND LIMITATIONS OF THIS STUDY

- First study to evaluate a national policy of implementing and financing antimicrobial management teams in hospitals with a longitudinal study design
- Exhaustive database, on all admissions in Belgian hospitals over 11 years for the indications accounting for the largest number of patients receiving antimicrobials in hospitals (antimicrobial prophylaxis for lower limb orthopedic surgery, pneumonia)
- Fine-tuned case-mix adjustment when comparing hospitals before/after, and with/without the policy, taking into account possible time lag between implementation and results
- Quality indicators selected for this study measure some important aspects of quality, but fall short of providing a global picture of overall quality of antimicrobial use in hospitals. This is intrinsically complex, and other indicators might provide different results.
- This study has shown no impact of the policy at national level, but has not investigated determinant of success or failure at hospital level.

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INTRODUCTION

Inappropriate use of antimicrobials (AM), and its consequences in terms of infections due to AM resistant microorganisms represents a major public health problem.[1] Although the largest part of AM consumption takes place in the community[2], the risks are concentrated in hospitals: 35% of hospitalized patients in Europe[3] and 52% in the US[4] are taking an AM. Over a third of prescriptions might not be compliant with evidence-based guidelines.[5] AM stewardship, conducted by AM management teams (AMT), is a key strategy to improve AM prescribing, to ensure effective treatment of patients and to reduce AM resistance in hospitals.[6] The need for a legal basis, regulatory mechanisms, funding for AM stewardship programs, and research, are widely endorsed.[7,8]

Belgium has been a pioneer in this field. The Belgian Antibiotic Policy Coordination Committee (BAPCOC) was created in 1999 in order to improve AM use in Belgium and has been very active since at different levels.[9] Since July 2007, all acute care hospitals in the country have been receiving financial and technical support for hiring a trained manager for their AMT; the initiative was first piloted in 37 voluntary hospitals (2002) then extended to another 24 hospitals (2006), and finally to the remaining hospitals (55) in 2007. Apart from funding, the intervention included technical guidance and advanced specialist training for the formal establishment and follow-up of AMTs. However 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%).[10] The minimum composition, mandate, and tasks of hospitals AMT have a legal basis since 2008. The largest part of the BAPCOC budget now goes to staffing and technical support for AMT in all Belgian acute hospitals.[9] To our knowledge, Belgium has been the first country to provide hospitals with structural, ear-marked funding for AMT, making the experience a test case for such a policy.

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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METHODS

Source of data and quality indicators

We obtained patient-level data routinely collected between 1999 and 2010 in all Belgian acute care hospitals for pathology-based financing purposes. These include the all-patient-refined diagnosis related group (APR-DRG, version 15) and associated severity of illness (SoI, 1-4)[11] as well as details on each AM used during the stay (molecule, dose, and route of administration); however the timing of AM administration is lacking. 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).[11]

We used the WHO anatomical therapeutic chemical (ATC)/defined daily doses (DDD) method,[12] applying version WHO 2010 to all 12 years in the database. Comparing hospitals (with or without the policy, as well as before and after implementation of the policy) was done per APR-DRG to facilitate case-mix adjustment. 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. Compliance with guidelines for antibioprophylaxis in APR DRG 302 ("surgery QI") was defined using three criteria at patient level as: (1) choice of AM (cefazolin), dose in the expected range (2-8 gr), and (3) no other AM given during the stay.[13] We excluded from the analyses hospital stays with secondary infectious diagnoses and SoI 3 and 4, so that it could fairly be assumed that there was no other reason for prescribing an AM than antibioprophylaxis. For pneumonia, the data did not allow assessing appropriateness of treatment at patient level. In addition treatment guidelines can differ between hospitals. Aggregating data at hospital level, we selected two QI: (1) the ratio of oral DDD / parenteral DDD ("O/P QI"), as early parenteral to oral switch is recommended to reduce length of stay (LoS), adverse events related to intravenous line, and costs[13,14,15] and (2) total DDD (J01) minus penicillin (J01C), per 100 days in hospital for pneumonia ("DDD QI"), under the assumption "less is better". Penicillin use was excluded because recommended daily doses have increased over the year.

Statistical approach and adjustment for confounding

We used a change point model.[16] Such a model tests whether the slope of a trend is different before and after the change point. We included as change points the year each hospital received funding for its AMT (2002, 2006, 2007), as well as the years 2001 (the year of a very large awareness campaign for AM) and

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- for pneumonia only - 2006 (when a new financing mechanism for hospital drugs was introduced; however this mechanism did not apply to AM prophylaxis). We then tested the need to include additional change points. The surgery QI was a dichotomous variable at patient (stay) level, and variables adjusted for were LoS, age (continuous), gender, SoI (1-2), and ICU stay (at some point, hospitalized in intensive care unit). For pneumonia, outcomes were continuous variables at hospital level and required aggregation of patient (stay) level data. Hospital variables for pneumonia stays were: median LoS, distribution of the stays (%) according to SoI (1-4), gender, ICU stay, patient origin at admission (home, long term care facility, other or unknown), discharge status (death/alive), and age categories (< 1y, 1-5yr, 6-10y, 11-16y, >16y). Caseload (number of hospital stays included in the analyses for each QI, per hospital, and per year) was also included in the model, as a variable at hospital level.

For pneumonia results were weighted for caseload. A time lag (+/- one year) was introduced to account for the fact that the effect of AMT funding might have started before the hospitals received the money (e.g. because preparation included AM stewardship training) and might need some time to be fully implemented (e.g. because of possible delays in recruiting an AM specialist).

Statistical model and software

A somewhat abrupt but continuous change in the evolution of the outcome over time can be modeled by including a change point in the generalized linear mixed model (GLMM).[17] A GLMM is an extension of a generalized linear model in which the correlation between measurements from the same hospital is taken into account using so-called random effects. Whereas the outcome is considered to belong to the exponential family (including the normal and the Bernoulli distribution), the systematic component of a GLMM is given by:

$$g(\mu_{ij}) = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_2 (t_{ij} - CP)_+ + \sum_{q=3}^{Q} \beta_q X_{qij}$$

where μ_{ij} is the average outcome for hospital *i (i = 1, 2,..., N)* at time points t_{ij} *(j =1, 2,..., n_i), g(.)* is a link function (e.g. an identity link or a logit link), *N* is the total number of hospitals, n_i is the number of observations from the *i-th* hospital, t_{ij} = 1 corresponds to the start of the study, β_0 is the fixed intercept, b_{0i} is the hospital-specific deviation from intercept β_0, β_1 is the fixed slope, b_{1i} is the hospital-specific deviation from slope β_1, $x_+ = \max(x,0)$ such that β_2 is the global difference in the linear trend before and after the change-point, CP is a global change-point, β_q *(q = 3, 4,..., Q)* are the fixed effects for the explanatory variables X_{qij} and *Q* is the number of explanatory variables. All models were fitted using SAS version 9.3.

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RESULTS

Surgery QI

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). Median LoS in this population decreased from 15 days in 1999 to 8 days in 2010. Trends in the number of hospital stays, and compliance to the three criteria as defined earlier, are shown in Table 1. Compliance increased from 53% of included stays in 1999 to 71% in 2010.

Table 1. Hospital stays for lower limb orthopedic surgery* and compliance with guidelines for surgical prophylaxis, Belgium, 1999-2010

Year	N hospitals	N stays 100%	Stays with cefazolin, 2-8 gr, no other antimicrobials N	%
1999	110	18,562	9,802	53%
2000	110	20,559	11,691	57%
2001	110	21,790	12,597	58%
2002	110	23,254	13,274	57%
2003	110	24,606	14,823	60%
2004	110	25,917	16,942	65%
2005	110	27,756	18,551	67%
2006	110	29,267	19,761	68%
2007	108	30,727	21,336	69%
2008	107	32,708	22,796	70%
2009	106	34,256	23,930	70%
2010	104	35,692	25,264	71%

** APR-DRG 302, severity of illness 1 and 2*

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Based on likelihood ratio (LR) tests comparing models with, and without specific change points, the change point "year of AMT" was retained in the model ($p< 0.0001$); the change point "year 2001" was identified as statistically significant ($p< 0.0001$). All changes were negative, and weak (meaning that compliance increased, but at a slower pace than before). The final model had a pseudo-R^2 value of 0.1927. Although R^2 values for models on binary outcomes are typically much lower than for models on continuous outcomes, this indicates that there still is a lot of unexplained residual variability. Observed and predicted values for the full model, and for hospitals according to the year of funding AMT are shown in **Figure 1**.

Figure 1. Averaged observed (dotted) and predicted evolution of compliance with guidelines for surgical antibiotic prophylaxis for lower limb surgery*, Belgium, 1999-2010.

(insert Figure 1)

Pneumonia QI

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). All had "pneumonia" as an admission diagnosis, so we assume that the vast majority of patients were admitted for community-acquired pneumonia. (In theory it is possible that some patients were transferred from another hospital with an hospital-acquired pneumonia). 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).

Trends in the number of hospital stays, and the QI are shown in table 2. Between 1999 and 2010, the mean DDD of AM other than J01C decreased from 96 to 64 /100 days of hospitalization for pneumonia; the O/P ratio (all AM) increased from 0.72 to 0.97.

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Table 2. Hospital stays for simple pneumonia* and quality indicators for antimicrobial treatment, Belgium, 1999-2010

Year	N Hospitals	N stays	Mean DDD / 100 patient-days			DDD oral / DDD parenteral		
			J01C	Other	Total	J01C	Other	Total
1999	112	22385	66	96	161	0,57	0,84	0,72
2000	112	23268	67	97	164	0,58	0,87	0,74
2001	112	24165	70	100	170	0,62	0,91	0,77
2002	112	25424	75	97	172	0,66	0,81	0,74
2003	112	26331	83	89	172	0,69	0,83	0,76
2004	112	25201	91	82	172	0,79	0,82	0,80
2005	112	30145	97	81	178	0,83	0,93	0,87
2006	112	26739	99	74	173	0,87	0,96	0,91
2007	110	28872	99	68	167	0,89	1,04	0,95
2008	110	29823	101	65	166	0,90	1,02	0,95
2009	109	33611	102	63	165	0,90	1,11	0,98
2010	107	31671	106	64	170	0,88	1,12	0,97

*APR-DRG 139

DDD: defined daily dose; patient-days: only patients hospitalized for pneumonia. J01C: ATC code, Beta-lactam penicillin.

Based on LR tests comparing models with, and without specific change points, the change point "year of AMT" was not retained in the models for the DDD QI ($p = 0.4659$) nor for the O/P QI (p: 0.0997). This means that there was no statistically significant change in slope for these outcomes, i.e the year a hospital received funding for their AMT.

For the DDD QI the years 2001 and 2006 were identified as statistically significant change points ($p < 0.0001$ and 0.0009, respectively). In 2001, the QI decreased, the effect was strong. In 2006, the QI decreased at a slower pace than before. The adjusted R^2 for the final model was 0.8072. For the O/P ratio QI, the year 2001 was not retained in the model ($p = 0.9884$) while the year 2006 was identified as a statistically significant change point ($p = 0.0310$): the QI increased, but at a slower pace than before. The adjusted R^2 for the final model was 0.7559. For these two pneumonia outcomes, the high adjusted R^2 indicate that the models perform well in explaining the variability in the data. The effect of the "2006" change point on both QI was weak and of doubtful clinical significance, as shown in **Figure 2**.

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Figure 2. Averaged observed (dotted) and predicted evolution of quality indicators for antimicrobial treatment of community-acquired pneumonia*in hospitals, Belgium, 1999-2010

(Figure 2)

General features of statistical modeling

All 3 QI showed high heterogeneity: baseline values, as well as changes overtime, varied widely across hospitals. Another feature was the complexity of the predicting models, which involved many parameters, and interactions, rendering interpretation sometimes difficult, so that the effect of "change points" is better assessed visually on the figures presented. Of importance, the introduction of time lags in the models (that is, taking into account the year before or the year after the "change points") did not improve the models. A complete description of the results, interaction terms and estimates, is available in the full study report.[18]

DISCUSSION

Key findings

In 1999, 53% of patients admitted in hospital for major lower limb orthopedic surgery received the recommended AM for surgical antibioprophylaxis, with a dosage in the expected range, and no other AM. This figure was 71% in 2010. For patients treated for pneumonia over the same period, mean consumption of AM other than penicillin decreased from 96 DDD to 64 DDD / 100 hospital-days, and the ratio of oral / parenteral DDD increased from 0.72 to 0.97. There was high heterogeneity between hospitals. No positive effect could be detected at national level for these 3 QI in relation to the timing of implementation of the policy. In 2001, the decrease in the pneumonia DDD indicator was a statistically and likely clinically significant deviation from expected trends.

Strengths and limitations

To our knowledge, this is the first study specifically evaluating a national policy of implementing and funding antimicrobial stewardship program at hospital level. (Another country – Scotland – funds AMT in hospitals since 2008,[19] as part of a comprehensive policy to improve antimicrobial prescribing. The

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policy as a whole appears to be successful - but to what extent did the funding of AMT contribute to this success remains unknown. [20]

Its major strengths are an exhaustive patient-based database including all Belgian hospitals over 12 years. 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. The 2 APR-DRG studied account for the largest number of patients receiving AM in hospitals. The trend in improvement for the surgery QI is robust, even if true compliance is less than what we measured, as our QI does not include timing of AM administration. We used state-of-the art statistical methods for modeling the trends of our QI, and acknowledged that change can take time by introducing time lags in the model (taking into account one year before, one year after the "change point"), nonetheless these did not improve the model. 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). One QI is questionable. The decreasing trends in the consumption of DDD other than penicillin mainly reflects a decrease in cephalosporins and macrolides which offsets an increase in carbapenems and fluoroquinolones. The decrease is also partly explained by a shift towards broad-spectrum penicillin (J01CR, or combinations, such as amoxicillin – clavulanic acid).[18] It is therefore unclear whether the decrease in this QI indeed represents a true improvement in quality.

Interpretation

At least 2 out of 3 of our QI describe a true improvement in AM use for patients admitted to hospital for pneumonia and lower limb surgery between 1999 and 2010 in Belgium; these improvements have benefited a very large number of patients. Exactly why this happened is unclear. Although 2001 (a "change point" for the DDD QI) was the year of a very large awareness campaign for AM, this campaign targeted upper respiratory tract infections in the community.

There are several possible explanations for the lack of association between improvement in the QIs and the year of implementation of AMT in hospitals. 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. AMT were not given targets, and therefore might have chosen other priorities for interventions than the indications analyzed here, despite these being the

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indications with the highest volume of patients receiving AM. (In 2013 however AMT in Belgium conducted audits for antibioprophylaxis in surgery in which serious gaps were identified.[21]) It is also possible that the earmarked AMT funding was not always used directly for AMT implementation. A major shortcoming resides in the absence of data on the actual use of funding within hospitals, which may not be easily extracted from the annual AMT activity reports.

Generalizability

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. For instance worrying trends are observed for hospital use of some AM; between 1999 and 2010, the use of colistine quadrupled and the use of carbapenem more than doubled (6 to 24 DDD, and 118 to 265, per 10,000 patient-days, respectively).[18]

Political commitment for tackling the problem of AM resistance in general, and improving AM use in hospitals in particular, has clearly been increasing in the last decade in Europe, North America, and elsewhere. [7, 22-26] Recommendations for strengthening the legal basis and core funding of antibiotic stewardship programs acknowledge the urgent need for building an evidence-base for such policies through good quality research[7, 8] and we believe that this study contributes to this objective.

CONCLUSIONS

Our study has shown improvement on selected quality indicators for AM use in the treatment of pneumonia, and in antibioprophylaxis for lower limb orthopedic surgery in Belgian hospitals between 1999 and 2010. These improvements could not be related to a policy of funding AMT. Changes observed therefore 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.

Our findings do not question the need for AMT, nor the need for continuation of AMT funding. Several recommendations could be made in order to make the best of the Belgian unique political, and financial commitment in that field. Transparency in use of ear-marked funding for AMT at hospital level could be improved. Trends of other AM quality indicators deserve more research. AMTs in hospitals should benefit from more guidance in terms of identifying priorities for action.

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AUTHORS CONTRIBUTION

MLL, NaHa, HG,DV designed the study; MLL, NaHa, RB wrote the first draft; RB, NiHe, MA conducted the statistical analyses; FN, BC, HG, DV revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript

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CONFLICTS OF INTEREST

Conflicts of interest in relation to this study: none.

DATA SHARING

Legal restrictions apply to these data, which cannot be shared.

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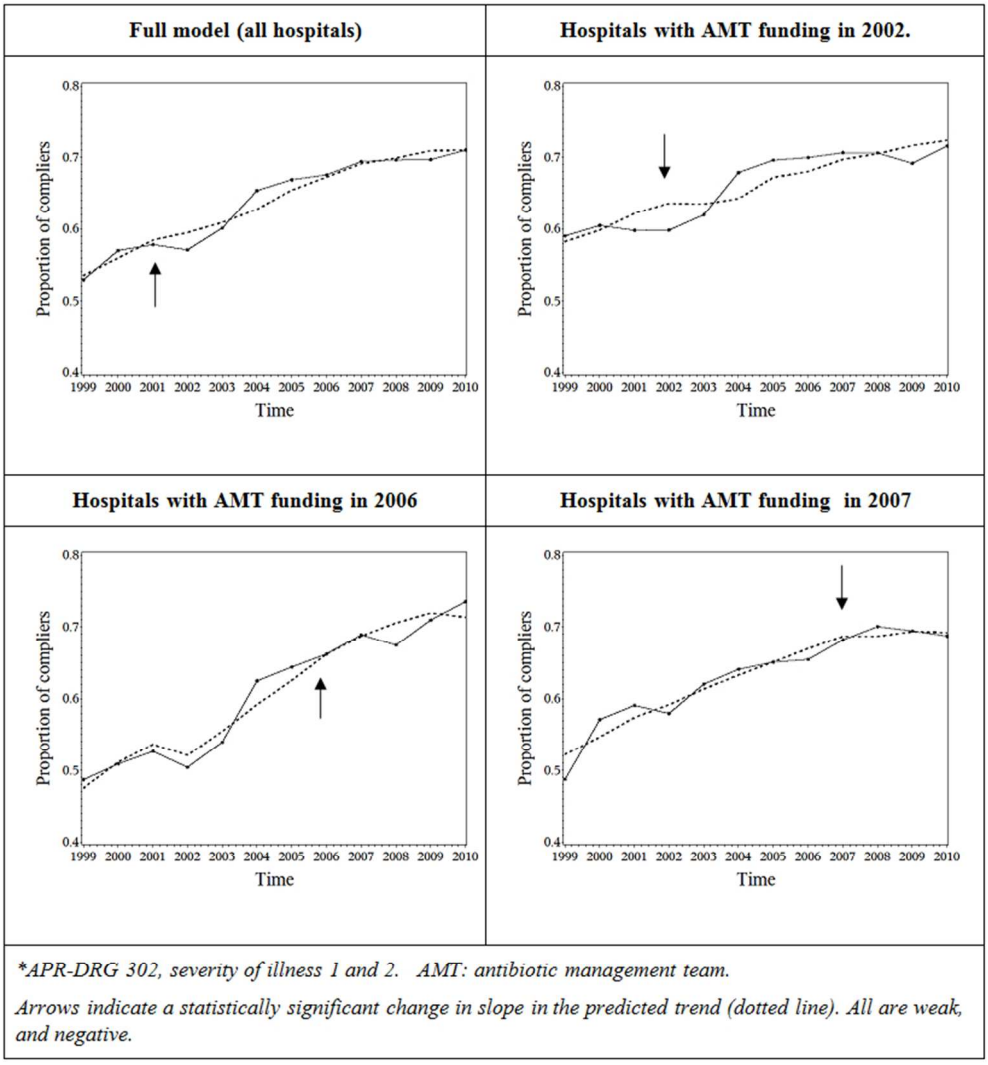

**APR-DRG 302, severity of illness 1 and 2. AMT: antibiotic management team.*

Arrows indicate a statistically significant change in slope in the predicted trend (dotted line). All are weak, and negative.

Figure 1. Averaged observed and predicted (dotted line) evolution of compliance with guidelines for surgical antibiotic prophylaxis for lower limb surgery*, Belgium, 1999-2010.

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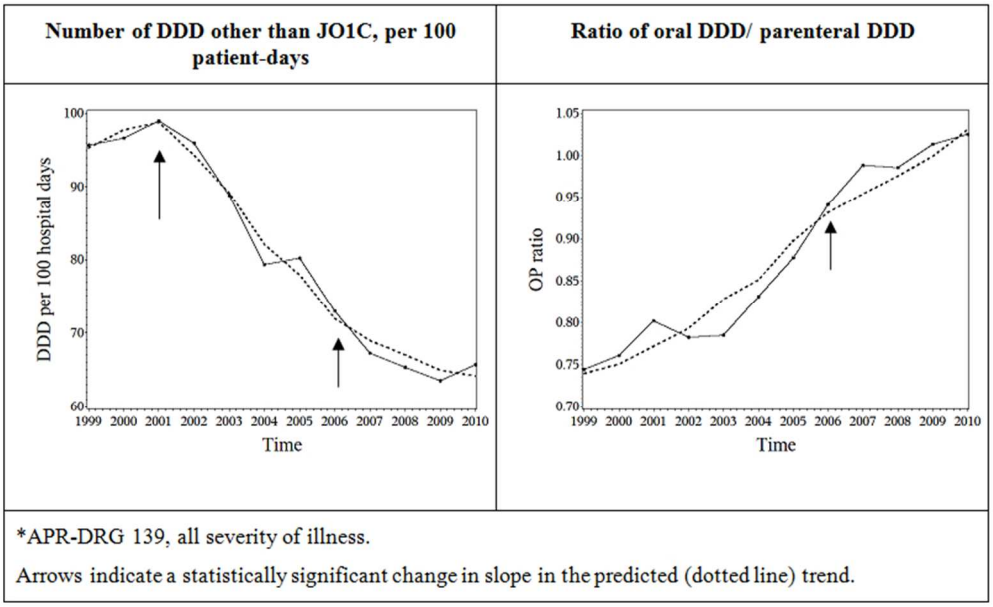

Figure 2. Averaged observed and predicted (dotted line) evolution of quality indicators for antimicrobial treatment of community-acquired pneumonia*in hospitals, Belgium, 1999-2010

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STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5*
Bias	9	Describe any efforts to address potential sources of bias	5-6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5-6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, explain how loss to follow-up was addressed	NA
		(*e*) Describe any sensitivity analyses	NA
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6-8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-8
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	P10
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P11
Generalisability	21	Discuss the generalisability (external validity) of the study results	P11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P13

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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