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AMTABU RESEARCH PROJECT

Antimicrobial consumption in Belgian hospitals for selected diagnoses 1999-2010

and association with policies aimed at promoting rational use

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Executive summary

Background and objectives

Inappropriate use of antimicrobials (AM), and its consequences in terms of infections due to antimicrobial resistant organisms are a major public health problem. Belgium has been a pioneer in this field, through the creation of the Belgian Antibiotic Policy Coordination Committee (BAPCOC) in 1999. Although the largest part of AM consumption in absolute terms takes place in the community, hospitals concentrate the risks: in a prevalence survey (2011-2012), 35% of hospitalized patients in Europe were taking at least one AM. AM stewardship, conducted by AM management teams (AMT), is widely recognized as a key strategy to improve AM prescribing, and reduce AM resistance in hospitals. The largest part of BAPCOC budget now goes to staffing and technical support for AMT in all Belgian acute hospitals. This initiative was first piloted in 37 voluntary hospitals (2002); then extended to another 24 hospitals (2006), then to the remaining 55 hospitals in 2007.

The objectives of this study, funded by the WIV-ISP , were (1) to describe trends in AM consumption for selected diagnoses/ procedures in Belgian hospitals since 1999, and (2) to analyze their association with the funding of AMT, and with a new financing mechanism for hospital drugs (not only AM) implemented in 2006, intended to provide an incentive for a more rational use of drugs.

Methods

We obtained from the competent body[a] administrative data routinely collected on all hospital stays in all acute care hospitals in Belgium over a 12 year period (1999-2010). These use the all-patient-refined diagnosis related group (APR-DRG) classification system and include patient-level data on all AM prescribed during the stay (identification of the molecule, dose and route of administration). The timing of administration is lacking. We selected the APR-DRG with the highest number of patients receiving AM (302: major lower limb orthopaedic surgery without trauma - mainly hip or knee replacement - or revision), and the APR-DRG accounting for the highest AM consumption at national level (139: simple pneumonia, or community-acquired pneumonia). We defined 3 quality indicators taking into account the limitations of the data. (1) Compliance with guidelines for AM surgical prophylaxis was defined as: cefazolin, dose in the expected range (2-8 gr), and no other AM given during the stay. We selected stays where it could fairly be assumed that there was no other reason than surgical prophylaxis for prescribing an AM. For pneumonia, we used as quality indicator (2) the ratio of oral defined daily doses (DDD) / parenteral DDD (as early parenteral to oral switch is recommended to reduce length of stay, adverse events related to intravenous line, and costs), as well as (3) the total number of DDD other than Beta-lactam penicillins, per 100 hospital-days (stays for pneumonia only). Beta-lactam penicillins were excluded because recommended daily doses have increased over the year.

Using statistical modelling we explored whether the trends observed in these quality indicators displayed "change points" - that is, a change in secular trends before, and after, particular years (e.g. year of funding received for AMT). Analyses were adjusted for case-mix and caseload differences between hospitals. We tested whether results were different if one year before, or one year after, were introduced

[a]National Sick Fund and Ministry of Health (Technische cell / cellule technique, INAMI/RIZIV + SPF/FOD)

in the model (a one-year time lag). This was done because change might not occur suddenly (eg technical support was provided to the hospitals before, and after, they received funding for AMT) .

Results

Compliance with guidelines for antibiotic prophylaxis in case of major lower limb orthopaedic surgery increased from 53% of eligible stays in 1999, to 71% in 2010; the number of hospitals where at least 80% of eligible stays complied with guidelines, went from one in ten (11%), to one in three (33%). AM use for pneumonia showed a trend towards more patients who received large spectrum penicillin (mainly amoxicillin and enzyme inhibitor), and at higher doses (as recommended by evolving guidelines); during the same period use of cephalosporins and macrolides decreased, while use of carbapenems and fluoroquinolones increased. The indicator "mean consumption of AM other than beta-lactam penicillin" decreased from 96 DDD to 64 DDD/ 100 hospital-days, and ratio of oral / parenteral DDD increased from 0.72 to 0.97.

The statistical modelling exercise showed that baseline values for all 3 indicators, as well as change overtime, varied widely across hospitals. In 2001, a statistically, and clinically significant decrease was observed for the pneumonia indicator: "N DDD other than J01C". No clinically significant changes were detected in 2006 for the pneumonia indicators. Similarly, no clinically significant changes for any of the 3 QI studied, could be detected the year hospitals started receiving funding for their AMT.

Discussion and conclusions

AM use for patients admitted to Belgian hospitals for pneumonia, and major lower limb orthopaedic surgery without trauma, has improved steadily between 1999 and 2010 in Belgium; these improvements have benefited a very large number of patients. The reason for the change observed in 2001 is unclear. A large public awareness campaign was initiated during the winter season 2000/2001 but it targeted inappropriate use of antibiotics for viral respiratory tract infections in the community. The year 2006 (change in financing for hospital drugs) was not in our study associated with improvement for our 2 pneumonia indicators, although it has been demonstrated elsewhere that this change in financing lead to reduction in drugs costs, and some decrease in AM consumption at national level. Our study could not detect at the national level an improvement on any of the 3 QIs studied relevant to the year hospitals received funding for their AMT. There are several possible explanations for this finding. One is that there was no mechanism in place to ensure that the funding received by the hospitals for the AMT would be used for that particular purpose; another is that AMT choose other priorities for interventions than what we analyzed here, because in practice, they had not been given clear targets.

This study has only looked at a limited number of quality indicators for a limited number of indications, and falls short of providing a global picture of trends in quality of AM use in Belgian hospitals, and of the impact of funding AMT. This is intrinsically complex and requires the development and monitoring of a more complete set of quality indicators. This should be done in order to make the best of the unique political, and financial commitment that Belgium demonstrates in this field. High heterogeneity between hospitals suggest that data could be used to identify outliers and target interventions. AMT in hospitals might benefit from more guidance in terms of identifying priorities for action and setting targets for improvement of quality of care.

Abbreviations

AM	Antimicrobial
AMR	Antimicrobial resistance
AMT	Antimicrobial management team
APR-DRG	All patient-refined diagnosis-related group
ATC	Anatomical Therapeutic Chemical (classification system)
CAP	Community-acquired pneumonia
DDD	Defined Daily D ose
DoS	Degree of severity
P25-P50-P75	Percentile 25 – percentile 50 – percentile 75
QI	Quality indicator
ICD	International Classification of Diseases
LoS	Length of stay
LCTF	Long Term Care Facility
MO	Microorganism
INAMI- RIZIV	Institut National d'Assurance Maladie Invalidité Rijkinstituut voor Ziekte and Invaliditeit Verzekering
SPF Santé Publique	Service Public Fédéral Santé Publique, Sécurité de la chaine alimentaire, et Environnement.
FOD Volksgezondheid	Federale Overheidsdienst Volksgezondheid, Veiligheid van de Voedselketen en Leefmilieu
O / P	Oral / parenteral
WIV- ISP	Wetenschapelijk Instituut Volksgezondheid / Institut Scientifique de la Santé Publique
y.o.	Years old

ATC classification (selected molecules)

J01C	Beta-lactams antibacterials, penicillin
J01CR	Combinations of penicillins, including Beta-lactamase inhibitors
J01D	Other beta-lactam antibacterials
J01DB	C1G
J01DB04	Cefazolin
J01DC	C2G
J01DC02	Cefuroxime
J01DD	C3G
J01DE	C4G
J01DH	Carbapenems
J01DF	Monobactams
J01F	Macrolides, Lincosamides, Streptrogramins
J01FA	Macrolides
J01M	Quinolones
J01MA	Fluoroquinolones
J01MA14	Moxifloxacine

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1 INTRODUCTION

1.1 Background and objectives

Inappropriate use of antimicrobials (AM), and its consequences in terms of antimicrobial resistance (AMR) are a major public health problem. Antimicrobial resistance has even been described as "a threat as grave as climate change" by the chief medical officer for England.[1] Belgium has been a pioneer in tackling the problem, through the creation of the Belgian Antibiotic Policy Coordination Committee (BAPCOC) in 1999.[2]

Although the largest part of antibiotic consumption in absolute terms takes place in the community, hospitals concentrate the risks: during the 2011-2012 point prevalence survey of healthcare-associated infections and AM use in European acute care hospitals, 35% of surveyed patients were taking at least one antimicrobial.[3] AM stewardship, conducted by AM management teams (AMT), is widely recognized as a key strategy to improve AM prescribing, and reduce antimicrobial resistance in hospitals.[4, 5] The largest part of BAPCOC budget now goes to staffing and technical support for AMT in all Belgian hospitals.[2]

The objectives of this study, funded by WIV-ISP, are (1) to describe trends in antimicrobial (AM) consumption for selected diagnoses/ procedures in Belgian hospitals, and (2) to analyze their association with policies aimed at improving the rational use of antimicrobials in hospitals.

The objectives of this study were **not**(but could eventually lead) to provide individual feed-backs on quality of AM use at hospital level.

1.2 Policies to be evaluated

1.2.1 New financing mechanism for hospital drugs

A new financing mechanism for all drugs used in hospitals (with some exceptions) took effect on **July 1st, 2006**. In practice, most drugs (including AM) are paid to the hospitals on the basis of a reference amount for each hospital stay for a given All-Patient-Refined Diagnosis Related Group (APR-DRG)[6] and degree of severity (DoS) (whereas before, all expenses were billed for reimbursement, with a few exceptions).[7] This was intended to provide an incentive for a more rational use of drugs in hospitals, and proved to be associated at national level with overall diminishing drugs cost, as well as some decrease in overall AM consumption.[7] Such a mechanism was nevertheless already in place since 1997 for AM used for surgical antibiotic prophylaxis

1.2.2 Financing of antibiotic management teams (AMT) in hospitals.

The Belgian government provides financial support and a legislative framework for the establishment of AMT in acute care hospitals. This initiative was first piloted in 37 voluntary hospitals (10/2002); then extended to another 24 hospitals (7/2006), then to the remaining hospitals (55) in 2007.[8] As of July 2007, all acute care hospitals in the country received financial support for hiring a trained manager for their AMT; the minimum composition, mandate, and tasks of hospitals AMT have a legal basis since 2008.[8] The main responsibilities of the AMT are the development of an antibiotic formulary and clinical practice guidelines on antibiotic therapy and prophylaxis, active initiatives to limit the inappropriate use of antibiotics, training of health care workers, audits and feed-backs, etc.

The level of AMT activities was assessed through a national, self-reporting survey in 2007. The study concluded to the successful implementation of AM stewardship program across the national hospital care system.[8] However the impact of this policy on AM use has not yet been evaluated.

1.3 Diagnoses and procedures selected for this study, and rationale

In Belgium routinely collected data on hospital stays are classified using the APR-DRG system .[6] We choose the 2 APR-DRG with the highest number of hospital stays with AM (see annex 7.1), as it seems logical to evaluate interventions aimed at improving AM use in hospitals by focusing on those where higher return can be expected from the intervention. Another reason is that sufficient numbers of stays were needed at hospital level.

1) APR-DRG 302: "major joint & limb reattachment procedure of lower extremities, without trauma" This APR-DRG includes mainly orthopaedic surgery of lower limbs, such as hip or knee replacement (or revision). This APR-DRG ranks first in terms of number of hospital stays with AM (37,525 stays in 2009); it is also (relatively) easy to assess AM consumption against well established guidelines for surgical antibiotic prophylaxis.
2) APR-DRG 139: "Simple pneumonia": this APR-DRG ranks second in terms of hospital stays with AM, and first in terms of AM consumption (combination of high number of stays - 34.000 stays in 2009, and high consumption of AM per stay).

2 METHODS

2.1 Source and description of data

We obtained from the competent body[b] data collected in routine in Belgium on all hospital stays between 1999 and 2010. The APR-DRGs and degree of severity of the stay (DoS, 1-4) are assigned by a "grouper" program based on International Classification of Diseases (ICD) diagnoses, procedures, age, sex, discharge status, and the presence of complications or comorbidities.[6] Data available for the purpose of this study were:

- Patient data: age in years, sex, place of origin before admission, such as home or long-term care facility (LTCF).
- Stay data: APR-DRG and DoS, primary and secondary diagnoses and procedures for the stay(ICD-9 CM coding); length of stay (LoS) in days, month of admission and discharge, status at discharge, (dead or alive), specialty of the ward(s) where the patient was admitted – ex intensive care unit (ICU), hospital identification code.
- AM use during the stay: total dose given per route of administration (oral or parenteral) for every molecule. These data are derived from billing data : the timing of AM administration (day the AM was given) and the ward the AM was given (in case the patient stayed in different wards) are not available.

[b] National Sick Fund and Ministry of Health (Technische cell / cellule technique, INAMI/RIZIV + SPF/FOD)

2.2 General approach

For this study, we have analyzed the data on AM consumption using the Anatomical Therapeutic Chemical classification system (ATC); doses have been converted in Defined Daily Doses. The main purpose of ATC/DDD system is as a tool for presenting drug utilization statistics with the aim of improving drug use.[9] For converting doses in mgr or units in DDD for each molecule (ATC), version WHO 2010 has been applied to all 12 years in the database.[10]

The identification of the hospital, and the date the AMT was implemented in each hospital, were crucial for this study. We had to address some specific issues related to administrative reorganizations that took place over the 12 years under study in Belgian hospitals, making it sometimes difficult to build coherent and complete 1999-2010 data series for each hospital. The way this was handled is detailed in the annex 7.2.

2.2.1 First part: descriptive and exploratory

First part of the study describes trends in AM consumption for the selected APR-DRGs between 1999 and 2010 at national level, and compares hospitals where AMT where implemented in 2002, and hospitals where AMT were implemented later. It describes variation between hospitals for the given indicators. It explores possible quality indicators suitable for use in the second, analytical part of the study (association with policies).

Because data are collected primarily for administrative and financing purposes, they lack the level of clinical details which might be necessary to assess appropriateness of treatment at patient level (in particular in this case, lack of data on timing of administration of AM). We assessed possible quality indicators identified from the literature and expert opinion taking into account the strengths and limitations of the available data; final selection was made in consultation with the expert working group.

2.2.1 Second part: analytical

The second part of the study (analytical) analyses the trends in the selected quality indicators; its specific objectives are to measure the association **at national level** of the **policies** described above, with these indicators, taking into account secular trends and other possible confounding variables. (The full statistical report is provided in annex 7.8.)

3 PART 1: DESCRIPTION OF TRENDS AND EXPLORATORY ANALYSES

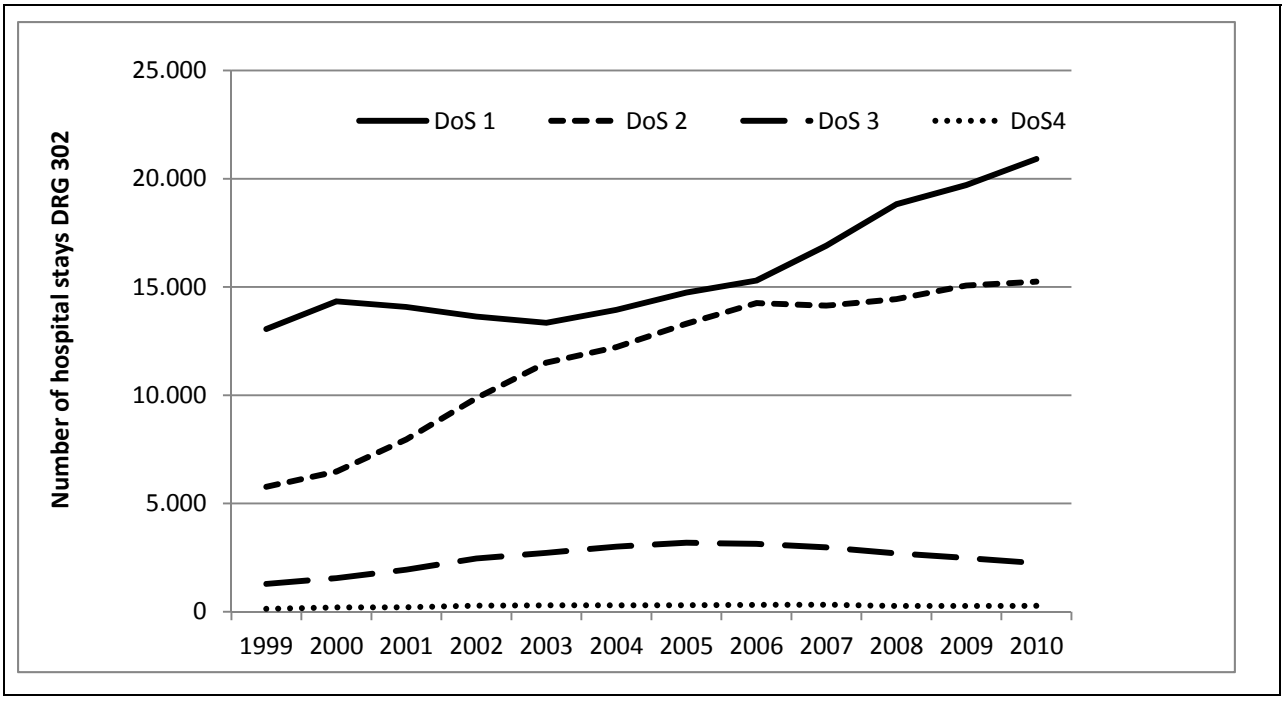
3.1 MAJOR LOWER LIMB ORTHOPAEDIC SURGERY WITHOUT TRAUMA

3.1.1 Number of hospital stays 1999-2010

APR-DRG302: "major joint & limb reattachment procedure of lower extremities, without trauma."

This includes hip and knee replacement (or revisions). The total number of stays for this APR-DRG has almost doubled between 1999 and 2010 (2010/1999: + 191%) .

Figure 1.Number of hospital stays for major lower limb surgery* per degree of severity (DoS). Belgium, 1999-2010



**APR-DRG 302*

In 2010, 38.684 hospital stays were classified into APR-DRG 302; 15.405 (40%) for total hip replacement (ICD9CM 81.51); 18.479 (48%) for total knee replacement (ICD9CM 81.54). Remaining stays were for revisions, or for other articulations.

3.1.2 Quality indicators for use of antimicrobials in APR-DRG 302

There is a large consensus across guidelines on antibiotic prophylaxis for orthopaedic surgery (aimed at preventing post-operative infections). If no (secondary) infectious diagnosis has been recorded during the hospital stay, prophylaxis should be the only reason for using AM during these hospital stays.

- **Treatment guidelines**

Source	Recommendation
Sanford 2012-2013, Belgian/ Luxemburg edition[11] (p192)	Primary choice (adults): Cefazolin intravenous (IV), 1-2 gr (initial dose) at induction. Additional doses if necessary (prolonged surgery, > 3h, or major blood loss). No doses required after surgery apart from exceptional cases.
Katholieke Universiteit Leuven (KUL) (guideline 2011)	2g cefazolin IV at induction (+2g if >3h) + 2x2g (8/16h)
Université Catholique de Louvain (UCL) MtGodinne	2g cefazolin IV at induction (+1g if >3h) + 2x1g (8/16h) or 2x2g (if bodyweight>80kg)

Guidelines vary little according to patient's characteristics. Some criteria (proper molecule, dose within the expected range, , and no other antimicrobial) can be evaluated with our data. NB: **compliance with guidelines is never expected to be 100%**- there are always clinically justified exceptions (an example in this case would be allergy to penicillins) - that our data do not permit to evaluate.

- **Quality indicators (**Consensus working group)

Compliance with guidelines at hospital/ national level	Criterion A: cefazolin is given Criterion AB: cefazolin , dose in expected range (2 – 8g) Criterion ABC: No other AB but cefazolin (2-8g)	Numerator: stays (APR-DRG 302) compliant with criterion A/ or AB / or ABC Denominator: total stays (APR-DRG 302) at hospital/ national level
Compliance with guidelines: hospitals meeting target	Target = 80% of all stays comply with guidelines	Numerator : N hospitals with 80% of stays (APR-DRG 302) complying with ABC criteria Denominator: all hospitals included

3.1.3 Selection of stays and exclusions

We excluded from the original database stays with DoS 3 and 4, and stays with a secondary infectious diagnoses (ex: urinary tract infection). The underlying assumption is that for stays with DoS1 and 2, without any recorded infectious diagnosis, there is no other indication for antimicrobials, than surgical antibiotic prophylaxis. We also excluded children, and very long length of stays (> 60 d) , as well as stays with hospital codes unknown, or from chronic hospitals (Table 1): 90% of all stays in APR-DRG 302 remained available for analyses.

Of note, post-operative infections (ICD-9 998.59) were reported in 0.13% of all stays (all DoS) over this 12 years period.

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

Total hospital stays – APR-DRG 302 1999-2010	361957	100%
Reasons for exclusion		
Degree of severity 3-4	32888	9,1%
Unknown hospital code	258	0,1%
Chronic hospital code	495	0,1%
Age < =15	98	0,0%
Secondary infectious diagnose	1592	0,4%
Length of stay > 60 d	1532	0,4%
Total excluded	36863	10%
Remaining for analyses	*325094*	*89,8%*

Death occurred in 122 (0.04%) of these 325094 hospital stays.

3.1.4 Trends 1999-2010: hospitals, stays, patients

Table 2.Caseload per hospital, major lower limb surgery*, Belgium 1999-2010.

Year	*N hospitals*	*Number of stays (P: percentile)*		
		P25	*P 50*	*P75*
1999	110	73	124	215
2000	110	81	154	237
2001	110	92	151	247
2002	110	92	162	254
2003	110	95	183	282
2004	110	91	198	288
2005	110	104	213	322
2006	110	113	227	330
2007	108	125	228	347
2008	107	139	247	371
2009	106	144	254	379
2010	104	148	266	396

** APR-DRG 302, Degree of severity 1 & 2.*

Table 3.Number of hospital stays, age of patients, length of stay for major lower limb surgery*, Belgium 1999-2010.

Year	N stays	Age (years)			Length of stay (days)		
		P25	P50	P75	P25	P50	P75
1999	18.562	63	70	75	12	15	18
2000	20.559	63	70	75	11	14	17
2001	21.790	63	70	75	10	13	16
2002	23.254	62	70	75	9	12	16
2003	24.606	62	70	76	9	11	15
2004	25.917	61	70	76	8	10	14
2005	27.756	61	70	76	8	10	13
2006	29.267	61	70	76	8	9	12
2007	30.727	61	69	76	7	9	12
2008	32.708	61	69	76	7	9	11
2009	34.256	60	69	76	7	8	11
2010	35.692	60	69	76	6	8	10

**APR-DRG 302, DoS 1 and 2 only*

Length of stay has decreased sharply between 1999 and 2010; no clear change in age.

3.1.5 Trends 1999-2010: compliance with guidelines and year of implementation of antibiotic management teams

3.1.5.1 Analyses per hospital stay

Table 4. Hospital stays for major lower limb surgery* complying with guidelines for surgical antibiotic prophylaxis, Belgium, 1999-2010

Year	*Total number of stays (100%)*	*Cefazolin (A)*		*Cefazolin, 2-8 g (AB)*		*Cefazolin, 2-8gr, no other AM (ABC)*	
		N	%	N	%	N	%
1999	18.562	15.855	85%	13.881	75%	9.802	53%
2000	20.559	18.169	88%	16.123	78%	11.691	57%
2001	21.790	19.179	88%	17.005	78%	12.597	58%
2002	23.254	20.315	87%	18.179	78%	13.274	57%
2003	24.606	21.654	88%	19.400	79%	14.823	60%
2004	25.917	23.771	92%	21.510	83%	16.942	65%
2005	27.756	25.858	93%	23.549	85%	18.551	67%
2006	29.267	27.372	94%	25.150	86%	19.761	68%
2007	30.727	28.900	94%	26.642	87%	21.336	69%
2008	32.708	30.811	94%	28.407	87%	22.796	70%
2009	34.256	32.320	94%	29.831	87%	23.930	70%
2010	35.692	33.800	95%	31.248	88%	25.264	71%

** APR-DRG 302, DoS 1 and 2 only.*

Table 5. Hospital stays for major lower limb surgery* complying with guidelines for surgical antibiotic prophylaxis, according to the year the antimicrobial management team (AMT) was implemented in the hospitals. Belgium, 1999-2010

	Hospitals with AMT implemented in 2002			*Hospitals with AMT implemented in 2006*			*Hospitals with AMT implemented in 2007*			*Hospitals with no AMT or cannot be assigned***			*Total*		
Year	N	ABC***	% ABC	N	ABC	% ABC	N	ABC	% ABC	N	ABC	% ABC	N	ABC	% ABC
1999	7356	4350	59%	4558	2220	49%	6226	3034	49%	422	198	47%	18562	9802	53%
2000	8076	4886	61%	4900	2494	51%	7083	4044	57%	500	267	53%	20559	11691	57%
2001	8579	5136	60%	5248	2766	53%	7445	4398	59%	518	297	57%	21790	12597	58%
2002	9819	5880	60%	5239	2642	50%	7635	4425	58%	561	327	58%	23254	13274	57%
2003	10226	6353	62%	5705	3078	54%	8025	4975	62%	650	417	64%	24606	14823	60%
2004	10784	7339	68%	6002	3749	62%	8463	5420	64%	668	434	65%	25917	16942	65%
2005	11568	8083	70%	6328	4074	64%	9187	5976	65%	673	418	62%	27756	18551	67%
2006	12216	8585	70%	6670	4414	66%	9689	6340	65%	692	422	61%	29267	19761	68%
2007	12940	9142	71%	6896	4749	69%	10216	6962	68%	675	483	72%	30727	21336	69%
2008	13780	9788	71%	7438	4947	67%	10771	7544	70%	719	517	72%	32708	22796	70%
2009	14462	10002	69%	7939	5635	71%	11115	7718	69%	740	575	78%	34256	23930	70%
2010	14755	10485	71%	8535	6231	73%	11696	8038	69%	706	510	72%	35692	25264	71%

** APR-DRG 302, DoS 1 & 2. ** See annex 7.3 for details on these hospitals*

****ABC: patient received Cefazolin, 2-8gr, and no other AM during his/her hospital stay.*

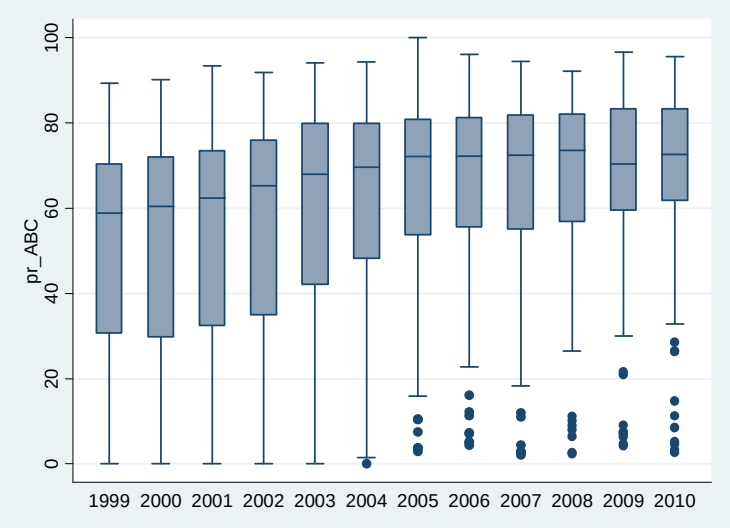
3.1.5.2 Analyses per hospital

Table 6. Hospitals with at least 80% of stays for major lower limb surgery* complying with surgical antibiotic prophylaxis guidelines Belgium, 1999-2010

Year	N hospitals	Hospitals meeting target (80% of stays complying with guidelines)* N	% total
1999	110	12	11%
2000	110	12	11%
2001	110	15	14%
2002	110	17	15%
2003	110	27	25%
2004	110	27	25%
2005	110	30	27%
2006	110	31	28%
2007	108	32	30%
2008	107	33	31%
2009	106	32	30%
2010	104	34	33%

** APR-DRG 302 DoS 1 and 2 only.** Cefazolin, 2-8gr, no other AM given during the hospital stay.*

Figure 2. Hospital stays for major lower limb surgery* : distribution of proportion of stays complying with surgical antibiotic prophylaxis guidelines across Belgian hospitals, 1999-2010



pr_ABC: proportion of stays complying with cefazolin, 2-8gr, no other antimicrobial given during the hospital stay

** APR-DRG 302, DoS 1 &2*

3.1.6 Summary points

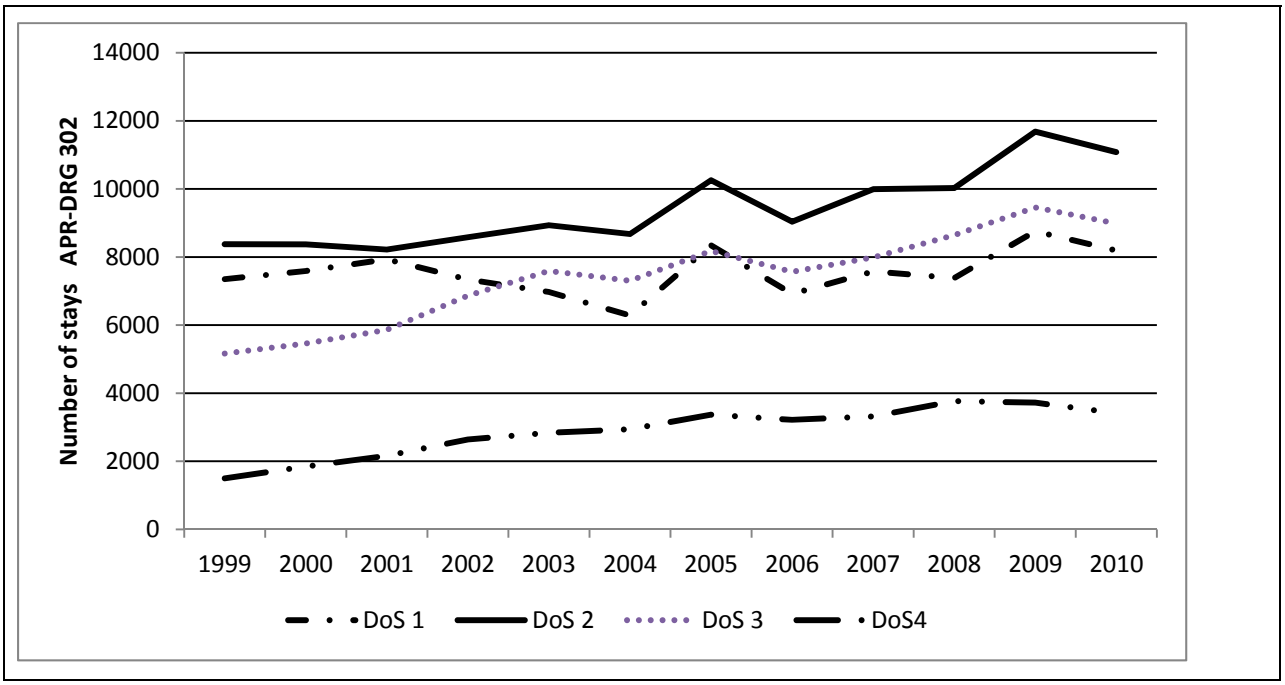
- Compliance with guidelines has increased from 53% of all stays in 1999 to 71% in 2010.
- The proportion of hospitals with at least 80% of compliant stays has increased from 13% (1999) to 33% (2010).
- Large variation between hospitals. (NB: guidelines are basically the same for all patients: differences in case mix are unlikely to contribute much to the variation observed.)

3.2 PNEUMONIA

3.2.1 Number of hospital stays 1999-2010

The total number of stays for APR-DRG 139 ("simple pneumonia") has increased by 141% between 1999 and 2010.

Figure 3.Number of hospital stays for simple pneumonia*, per degree of severity (DoS). Belgium, 1999-2010



** APR-DRG 139*

The vast majority of these stays relate to community-acquired pneumonia (CAP). Indeed in the case of APR-DRG 139, the ICD-diagnosis recorded on admission was always a pneumonia[c] (see annex 7.5: data for 2010); and the majority of patients are admitted from home, or long-term care facility (see Table 7, 2010 data). We cannot however exclude that these data include some health-care associated pneumonia acquired in another institution, or complicating the initial reason for admission.

Table 7. Place before admission in hospital for simple pneumonia*, Belgium, 2010.

Place before admission in hospital	N	%
Home	27.034	85%
Long term care facility	3.187	10%
Other hospital	699	2%
Other (ex: boarding school, prison…)	751	2%
Total hospital stays	31.671	100%

**APR-DRG 139*

[c] The assignment of an APR-DRG is based on the primary diagnosis (ICD9), which is the diagnosis that better explains the hospitalization; it is most of the time - but not necessarily - the diagnosis that is the reason for admission.

3.2.2 Quality indicators for use of antimicrobials in APR-DRG 139 (Pneumonia)

- Treatment guidelines

Reference document: Sanford 2012-2013, Belgian/ Luxemburg edition, p 96[11] : treatment of community-acquired pneumonia (CAP). Recommendations are for empirical treatment of immunocompetent patients, and should be adapted to local epidemiology and conditions. Changes in guidelines over the years covered by this study have been mainly in the recommended dosage for amoxicillin+clavulanic acid (amoxiclav); moxifloxacin appeared on the market at the end of 2003.

By definition: CAP3= hospitalized CAP; CAP4: hospitalized CAP with a stay in intensive care units (ICU) These are categories for clinical use; not to be confused with APR-DRG Degree of severity of the hospital stay (as computed by an algorithm taking into account co-morbidities and other factors) .

	Recommendations
CAP 3	Initial conditions allow oral treatment: moxifloxacin, amoxyclav. Parenteral therapy initially needed: amoxiclav or cefuroxime, sequential switch to oral treatment as soon as possible
CAP 4	(Amoxyclav or cefuroxime) +clarithromycine or ciprofloxacine or levofloxacine Previously hospitalized patients, or recently (< 15d) exposed to beta-lactams ceftriaxone+clarythro or cipro or levo

Note that these recommendations are controversial. Eg moxifloxacine is now (2014) listed as a "do-not-use" drug by the prestigious revue Prescrire.[12]

However data available for this study do not include timing of the AM, nor reliable data on the microorganism (MO) involved: they do not allow to evaluate empirical treatment on admission, or de-escalation, or sequential therapy based on microbiology results.

- **Quality indicators**

As it is not possible to evaluate appropriateness of treatment at the level of the hospital stay**,** quality indicators (QI) need therefore to be defined in terms of (positive) trends at hospital and national level (some similar approach is taken for monitoring the quality of outpatient AM use in Europe[13, 14]; however these are ecological studies and consumption data at country level are analyzed using as denominator the entire country population, whereas we used patient-based data).

Criteria	Comment	QI suitable for this study
Stays with or without selected AM		
Recommended molecule(s) was (were) used	Too many molecules could be considered as adequate in the absence of clinical data.	No
Trends in total DDD used, ratio oral/parenteral (O/P)		
Total DDD (excluding JO1C) /100 hosp-day	Numerator: sum of all DDD (excluding DDD Beta-lactam penicillins -(J01C) used in hospital stays for APR-DRG 139 (at national or hospital level) *100 Denominator: sum of all length of stays for stays in APR-DRG 139 *NB: Exclude J01C because recommended doses have increased over the year*.	Yes (Less=better)
Ratio O/P : Total DDD , JO1C (Peni)	Numerator: sum of all oral DDD used in hospital stays for APR-DRG 139 (at national/ hospital level) Denominator: sum of all parenteral DDD used in hospital stays for APR-DRG 139 (at national / hospital level)	Yes :higher =better (early oral switch recommended)[11]
Outcomes indicators		
Case-fatality rate	*Against*: only data on death in hospital available (30-d mortality would be better, not sensitive to discharge policy) ; majority of patients do not die, so not very sensitive; even if AM treatment not according to guidelines (ex: overshooting), patient might still be cured.	No
Readmissions	Same limitations as case-fatality rate; also data on readmissions can be identified only if readmissions in same hospital.	No
Length of stay	Decreasing LoS in hospital is a general trend for most diagnoses in Belgium (and elsewhere) , also influenced by discharge policy	No

NB: A recently published Cochrane review (including studies up to 2006)[15] concluded that interventions aimed at improving AM prescribing for pneumonia in hospital might reduce mortality; however overall quality of the evidence was low (that is, further research very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.)

3.2.3 Selection of stays

Inclusion: all hospital stays with APR-DRG 139 (simple pneumonia). Exclusions: hospital stays without antimicrobials, chronic hospitals, unknown hospital code, hospital stays > 60 days (outliers).

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

Total hospital stays for APR-DRG 139 1999-2010	346091	100%
Reason for exclusion		
Unknown hospital code	355	0,1%
Chronic hospital	396	0,1%
LoS>60	2656	0,8%
No antimicrobials	15049	4,3%
Total excluded	18456	5,3%
Remaining for analysis	327635	94,7%

** APR-DRG 139*

3.2.4 Trends 1999-2010: hospitals, stays and patients

Table 9. Hospital stays for simple pneumonia* in Belgium, 1999-2010: number of hospitals, and distribution of caseload

Year	N Hospitals	Number of stays for pneumonia per hospital		
		P25	P50	P75
1999	112	113	159	247
2000	112	117	179	254
2001	112	131	180	282
2002	112	137	210	275
2003	112	141	207	307
2004	112	138	193	289
2005	112	161	241	326
2006	112	135	203	307
2007	110	148	228	337
2008	110	160	231	342
2009	109	197	260	368
2010	107	183	241	340

**APR-DRG 139*

Table 10.Number of hospital stays for simple pneumonia*, and case-fatality, per degree of severity (DoS), Belgium, 1999-2010

DoS	*1*			*2*			*3*			*4*			*Total*		
Year	N	Deaths		N	Deaths		N	Deaths		N	Deaths		N	Deaths	
1999	7347	115	2%	8374	461	6%	5165	749	15%	1499	593	40%	22385	1918	9%
2000	7590	131	2%	8370	475	6%	5462	814	15%	1846	691	37%	23268	2111	9%
2001	7932	99	1%	8217	437	5%	5858	807	14%	2158	779	36%	24165	2122	9%
2002	7339	60	1%	8582	385	4%	6865	879	13%	2638	974	37%	25424	2298	9%
2003	6971	62	1%	8934	322	4%	7589	919	12%	2837	1055	37%	26331	2358	9%
2004	6282	46	1%	8676	287	3%	7302	853	12%	2941	980	33%	25201	2166	9%
2005	8345	31	0%	10254	272	3%	8176	836	10%	3370	1108	33%	30145	2247	7%
2006	6918	27	0%	9036	256	3%	7566	770	10%	3219	1024	32%	26739	2077	8%
2007	7577	33	0%	9989	310	3%	7989	789	10%	3317	1064	32%	28872	2196	8%
2008	7383	40	1%	10026	292	3%	8644	889	10%	3770	1258	33%	29823	2479	8%
2009	8755	68	1%	11684	408	3%	9453	970	10%	3719	1250	34%	33611	2696	8%
2010	8191	36	0%	11082	381	3%	8983	913	10%	3415	1125	33%	31671	2455	8%
2010/1999															
	111%			*132%*			*174%*			*228%*			*141%*		

**APR-DRG 139*

The number of stays has increased by141% over this 12-year period, with a disproportionate increase in stays with higher degree of severity. Despite this apparent increase in severity, the proportion of stays in intensive care units has decreased (see annex, Table 22) as have case fatality rates and length of stay.

Table 11.Age (years), of patients hospitalized for simple pneumonia* per degree of severity, Belgium, 1999-2010

DoS	*1*	*2*	*3*	*4*	*all combined*		
year	Median	Median	Median	Median	p25	median	p75
1999	9	72	76	78	16	66	80
2000	8	72	77	78	11	67	80
2001	6	70	77	77	7	63	79
2002	5	69	77	79	8	65	80
2003	5	67	77	78	8	66	80
2004	4	66	77	79	8	65	80
2005	5	64	77	78	7	62	80
2006	5	63	77	79	7	63	80
2007	5	68	78	78	10	65	81
2008	5	68	77	79	17	67	81
2009	5	66	77	79	10	64	81
2010	5	68	77	79	11	65	81

**APR-DRG 139*

Table 12.Length of stay (days) in hospital for simple pneumonia*, per degree of severity, Belgium, 1999-2010

DoS	*1*	*2*	*3*	*4*	*all combined*		
year	Median	Median	Median	Median	p25	median	p75
1999	6	10	13	15	5	9	14
2000	5	10	13	15	5	9	14
2001	5	9	12	15	5	8	13
2002	5	8	12	16	5	8	13
2003	5	8	11	15	5	8	13
2004	5	8	11	15	5	8	13
2005	4	7	11	15	4	7	12
2006	4	7	11	15	4	7	12
2007	4	7	11	15	4	7	12
2008	4	7	11	14	4	7	12
2009	4	7	11	14	4	7	12
2010	4	7	10	14	4	7	12

***APR-DRG 139*

3.2.5 Trends 1999 - 2010 Antimicrobial consumption and year of implementation of antimicrobial management team.

3.2.5.1 Analyses per hospital stay

Table 13. Proportion of hospital stays for simple pneumonia*, in which a given class of AM was given, Belgium, 1999-2010

year	Tot stays 100%	J01C B-lacta peni	J01CR Peni-combi	J01D Other B-lacta	J01DH Carbap	J01D_DE C3G or C4G	J01FA Macrolides	J01MA Fluoro quinolones
1999	22385	64%	59%	47%	2%	21%	19%	10%
2000	23268	65%	61%	46%	2%	22%	21%	10%
2001	24165	65%	61%	44%	2%	22%	22%	11%
2002	25424	67%	64%	41%	2%	23%	20%	13%
2003	26331	69%	65%	38%	2%	22%	17%	14%
2004	25201	72%	66%	35%	2%	20%	14%	15%
2005	30145	72%	64%	32%	2%	19%	18%	16%
2006	26739	74%	65%	29%	2%	17%	16%	17%
2007	28872	76%	67%	26%	2%	16%	14%	19%
2008	29823	76%	67%	25%	3%	16%	13%	19%
2009	33611	77%	66%	23%	3%	15%	14%	19%
2010	31671	77%	66%	22%	3%	15%	14%	21%

APR-DRG 139, all degrees of severity combined

Table 14.Mean DDD , and ratio oral / parenteral , hospital stays for simple pneumonia * Belgium 1999-2010.

	Mean DDD** / 100 hosp-days			Ratio: DDD oral / DDD parenteral		
yr	J01C (penicillins)	Other	Total	J01C (penicillins)	Other	Total
1999	66	96	161	0,57	0,84	0,72
2000	67	97	164	0,58	0,87	0,74
2001	70	100	170	0,62	0,91	0,77
2002	75	97	172	0,66	0,81	0,74
2003	83	89	172	0,69	0,83	0,76
2004	91	82	172	0,79	0,82	0,80
2005	97	81	178	0,83	0,93	0,87
2006	99	74	173	0,87	0,96	0,91
2007	99	68	167	0,89	1,04	0,95
2008	101	65	166	0,90	1,02	0,95
2009	102	63	165	0,90	1,11	0,98
2010	106	64	170	0,88	1,12	0,97

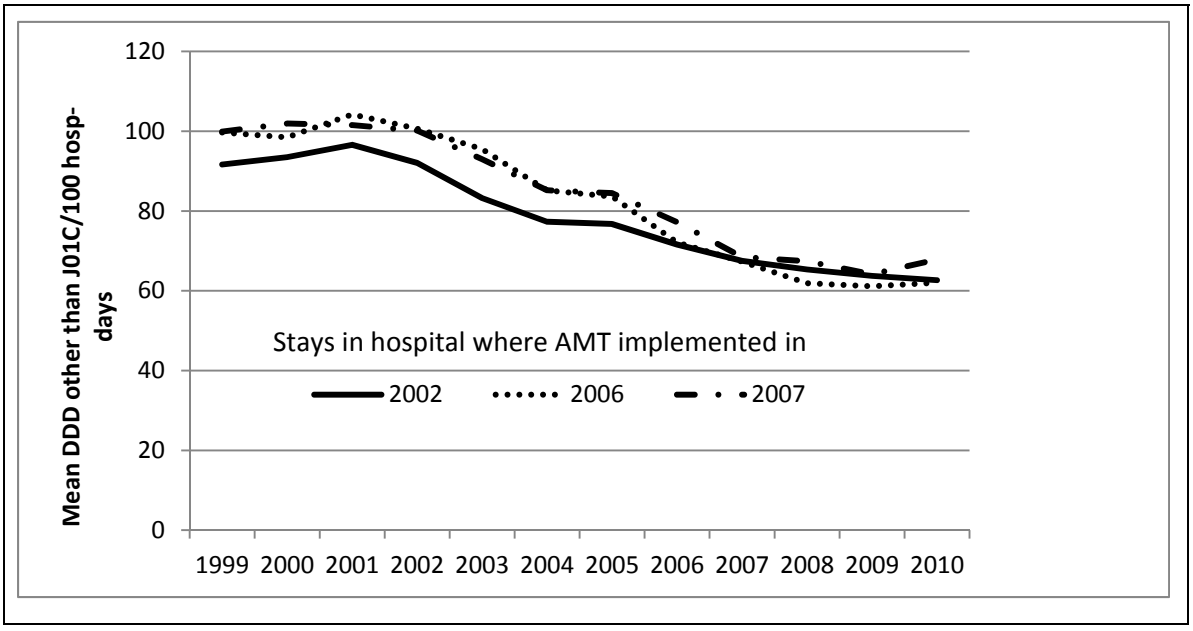
**APR-DRG 139 , all degrees of severity combined **Numerator: sum of all DDD given in patients hospitalized for pneumonia x 100. Denominator: sum of all lengths of stays for patients hospitalized for pneumonia (including also those stays where the molecules of interest where not given)*

Table 15.Indicators for simple pneumonia*, according to year of implementation of antibiotic management team (AMT) in the hospitals. Belgium, 1999-2010

	Mean DDD other than J01C ** / 100 hosp-days			Ratio: DDD oral / DDD parenteral		
	Hospitals where AMT officially implemented in…					
yr	2002	2006	2007	2002	2006	2007
1999	92	100	100	0,70	0,72	0,74
2000	93	98	102	0,72	0,74	0,76
2001	97	104	102	0,78	0,78	0,77
2002	92	101	100	0,75	0,71	0,76
2003	83	96	93	0,77	0,76	0,75
2004	77	85	85	0,80	0,82	0,80
2005	77	84	84	0,93	0,84	0,83
2006	72	72	77	0,94	0,87	0,90
2007	67	67	68	0,96	0,88	0,99
2008	65	62	67	0,97	0,93	0,92
2009	64	61	64	0,98	1,01	0,95
2010	63	62	68	1,04	0,95	0,90

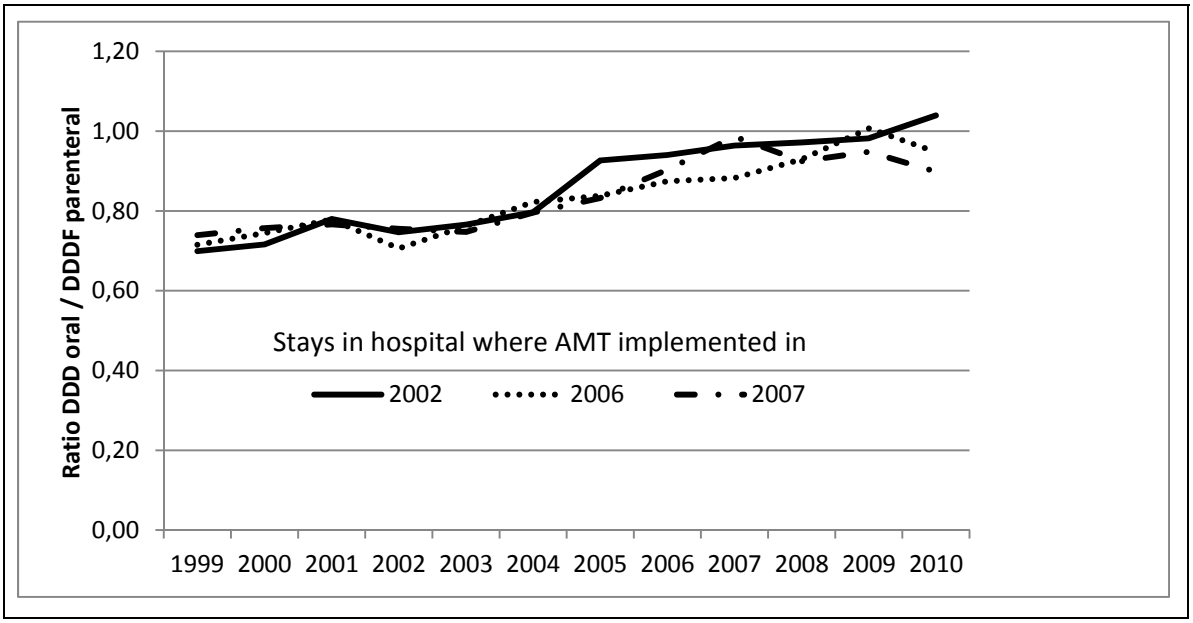
**APR-DRG 139 , all degrees of severity combined **Numerator: sum of all DDD given in patients hospitalized for pneumonia x 100. Denominator: sum of all lengths of stays for patients hospitalized for pneumonia (including also those stays where the molecules of interest where not given)*

Figure 4. Mean number of DDD other than beta-lactam penicillins (J01C) per 100 patient-days given during hospital stays for simple pneumonia*, according to year of implementation of antibiotic management team (AMT) in the hospitals. Belgium, 1999-2010



******APR-DRG 139,all degrees of severity combined*

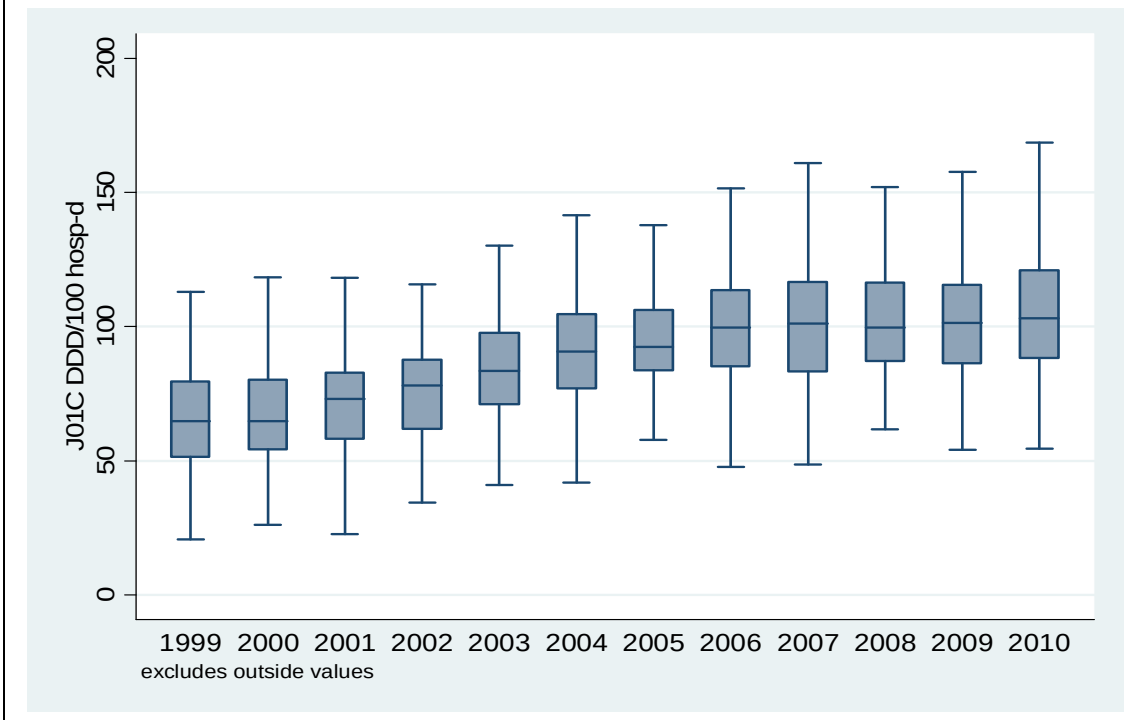
Figure 5. Ratio of oral DDD / parenteral DDD, hospital stays for simple pneumonia*, according to year of implementation of antibiotic management team (AMT) in the hospitals. Belgium, 1999-2010

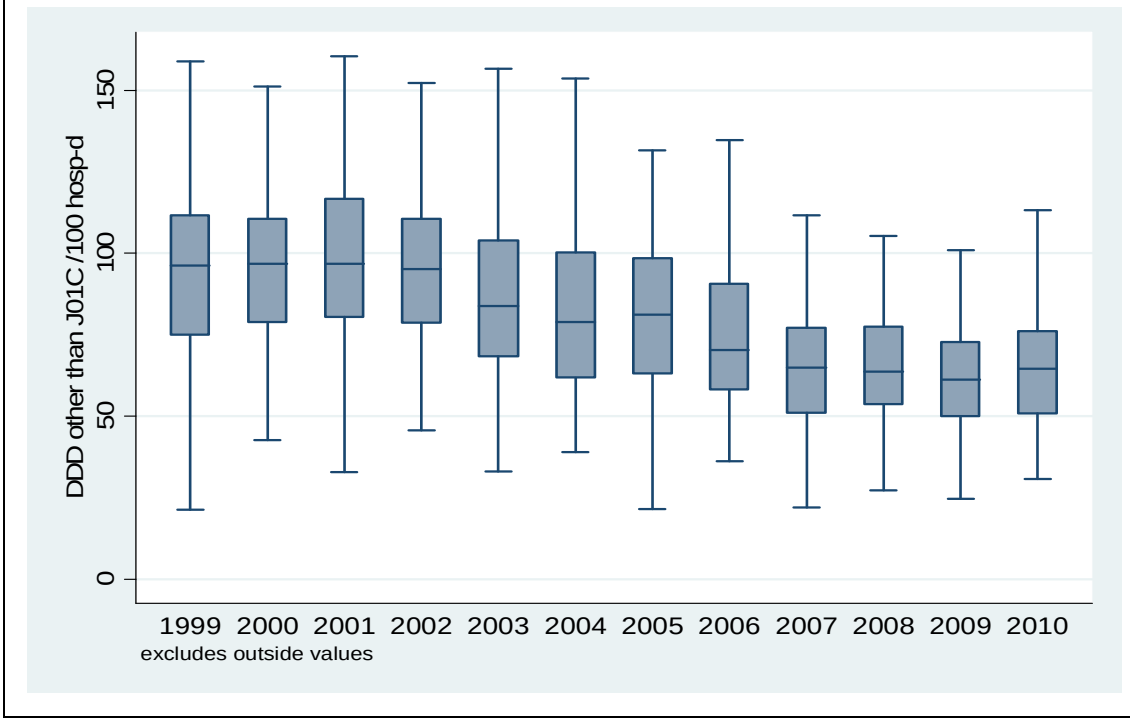


*****APR-DRG 139, all degrees of severity combined*

3.2.5.2 Analyses per hospital

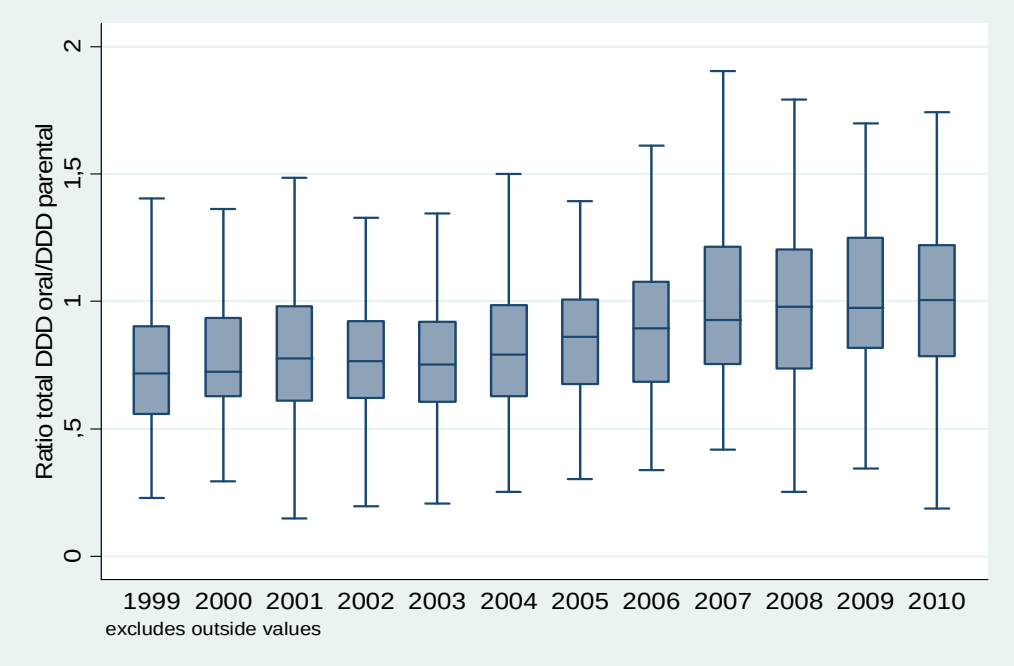
Figure 6. Distribution of hospitals according to mean DDD / 100 hospital-days in hospital stays for simple pneumonia* , Belgium, 1999-2010: penicillins (J01C) and other antimicrobials.





**APR-DRG 139, all DoS combined.*

Figure 7. Distribution of hospitals according to ratio oral/ parenteral of DDD given for simple pneumonia, Belgium, 1999-2010.



***APR-DRG139, all DoS combined**

3.2.6 Summary points

Trends 1999-2010:

- A 141% increase in the number of hospital stays for "simple pneumonia" (2009/1999); with a disproportionate increase in the highest degree of severity (+246%). Some data indirectly suggest that this might be at least partly explained by other factors than a true increase in severity (eg the proportion of stays in intensive care units has decreased, as have case-fatality rates, and length of stay)
- Higher use of penicillin (mainly combinations): higher number of stays where AM pertaining to this class was given, higher doses given per stay. Less use of other Beta-lactams, higher use of quinolones (mainly fluoroquinolones).
- A decrease in the mean number of DDD par 100 hospital-days for molecules other than beta-lactam penicillins ; an increase in the ratio oral/ parenteral DDD, for penicillins, and total DDD
- Marked variation between hospitals

4 PART 2. IMPACT OF POLICIES ON OBSERVED TRENDS FOR SELECTED QUALITY INDICATORS

4.1 Statistical methods

(Full statistical report is provided in annex 7.8)

4.1.1 General approach and adjustment for confounding

We used a change point model.[16] When analyzing trends, such a model tests whether the slope is different before and after the change point. Change points variables were: (1) 2001 (this is the year a very large antimicrobial awareness campaign was launched in Belgium;[17] it was included following expert (S. Coenen) advice); (2) the year the hospital got funding for its AMT (2002, 2006, 2007), and (3) for pneumonia outcomes only, 2006 (the year a new financing mechanism for hospital drugs was introduced). For hip and knee surgery, outcome (compliance with guidelines) was a dichotomous variable at patient (stay) level, and variables adjusted for were length of stay and age (continuous), gender, degree of severity of the stay (1-2), ICU stay (at some point, hospitalized in intensive care unit). The number of hospital stays for hip and knee surgery in the database, per hospital, and per year, was also included in the model as a variable at hospital level . For pneumonia, outcomes were continuous variables at hospital level and required aggregation of patient (stay) level data. Hospital variables for pneumonia stays were: total number of pneumonia stays, median length of stay, distribution (%) of the degree of severity of the stay (1-4), gender, ICU stay, patient origin at admission (home, long term care facility, other or unknown), discharge status (death/alive), age categories (< 1y, 1-5yr, 6-10y, 11-16y, >16y). Age was categorized to take into account different treatments in the paediatric population, but also as a proxy for weight (closely related to AM dosage).

For pneumonia analyses were weighted for the number of hospital stays in the APR-DRG for each hospital (this could not be done for the binomial outcome in surgery). A time lag (+/- one year) was introduced to account for the fact that the effect of policies might start before implementation (eg there was some AMT training before hospitals received specific funding) and might need some time to be fully implemented (eg hospitals might have delayed in recruiting an AM specialist). Correlation between observations from the same hospital over the years was accounted for.

Mathematical model and software

A somewhat abrupt but continuous change in the evolution of the outcome over time can be modelled by including a change point to the generalized linear mixed model. Such a model is given by:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_2 (t_{ij} - CP)_+ + \beta_q X_{qij} + \varepsilon_{ij},$$

where Y_{ij} is the outcome for subject i ($i = 1, 2,\ldots, N$) at time points t_{ij} ($j = 1, 2,\ldots, n_i$), N is the total number of observations, n_j is the number of observations from the ith subject, time = 1 corresponds to the start of the study, β_0 is the fixed intercept, b_{0i} is the subject-specific intercept, β_1 is the fixed slope, b_{1i} is the subject-specific slope, $x_+ = \max(x,0)$, β_2 is the global difference in the linear trend before and after the change-point, CP is a global change-point, β_q ($q = 3, 4,\ldots, Q$) are the fixed effects for the explanatory variables X_{qij}, Q is the number of explanatory variables and ε_{ij} is the unexplained error term for subject i at time point t_{ij}.

All models were fitted using SAS version 9.3.

4.2 **Results**

Some general features were common to all 3 outcomes, such as high heterogeneity: baseline values, as well as change overtime, varied widely across hospitals. Another feature was the complexity of the predicting models, which involved many parameters, and interactions, rendering interpretation sometimes difficult. The effect of "change points" is better assessed visually on the figures presented.

Finally, the introduction of time lags in the models (that is, taking into account the year before and the year after the "change points") did not improve the models. We present for each outcome figures comparing observed values with values predicted by the final models, and discuss the main results, in relation with the objectives of the study. A detailed statistical report with full description of the models, is provided in annex 7.8 .

4.2.1 Pneumonia outcomes

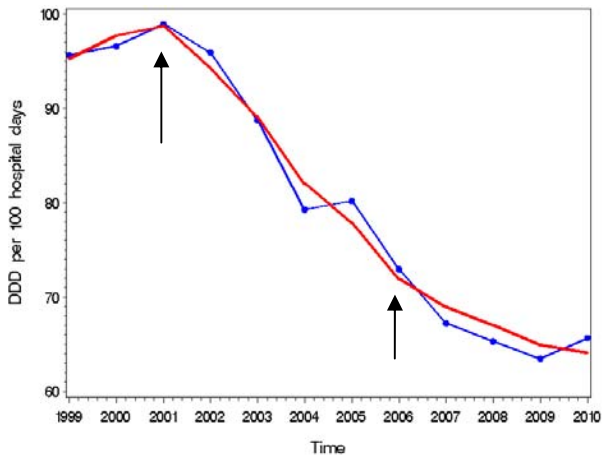
Number of DDD other than J01C, per 100 hospital-days

Based on likelihood ratio (LR) tests comparing models with, and without specific policies, the AMT "change point" was not retained in the final model (p-value 0.4659). This means that there was no statistically significant change in the trend (slope) of this outcome the year hospitals received funding for their AMT (taking into account the precise year for each hospital). The other "change points" were included in the model. After adjustment for patient's characteristics, there was a statistically significant change in slope after 2001 (negative: the outcome decreased) and after 2006 (positive: although the outcome continued to decrease, it decreased at a lesser pace than the years before). Both these effects showed interactions with patient's characteristics. The adjusted R^2 for the final model was 0.8072, indicating that the final model performs well, explaining 81% of the variability for this outcome. Average observed , and predicted evolution of this outcome are presented in Figure 8.

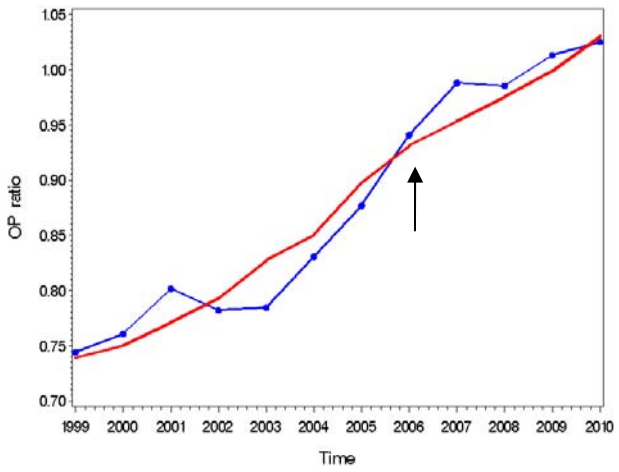
Ratio of DDD oral/DDD parenteral

Based on LR tests comparing models with, and without specific change points, the change point "2001" (p-value LR test: 0.9884) and AMT (p-value LR test: 0.0997) were not retained in the final model. The slope of the increase in the O/P ratio changed slightly in 2006 (pace of change decreased). The adjusted R^2 for the final model was 0.7559, indicating that the final model explains the variability of the data quite well. Average observed , and predicted evolution of this outcome are presented in Figure 8

Figure 8. Averaged observed (blue, dotted) and predicted (red) evolution of quality indicators for antimicrobial treatment of simple pneumonia*in hospitals, Belgium, 1999-2010



Number of DDD other than JO1C, per 100 patient-days



Ratio of oral DDD/ parenteral DDD

*APR-DRG 139, all degree of severity.

Arrows indicate a statistically significant change in slope in the predicted (red) trend.

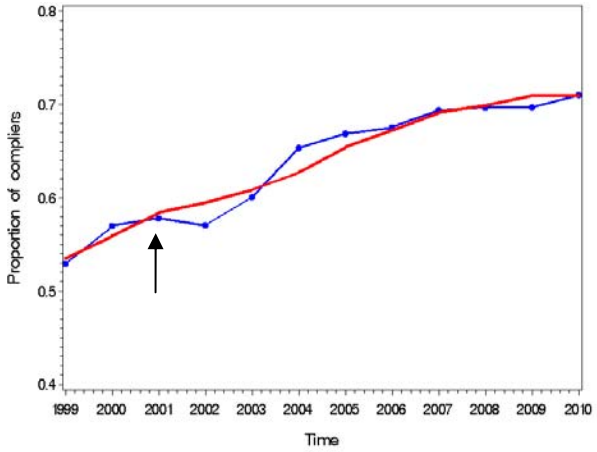
4.2.2 Compliance with guidelines for surgical antibiotic prophylaxis

Based on LR tests comparing models with, and without specific change points, both change points ("2001", and year of AMT) were retained in the model ($p < 0.0001$). The association for 2001 was negative: compliance increased, but at a lower pace than before. A statistically significant change point (negative) was observed the year the hospitals got funding for AMT. The model included several interaction terms.

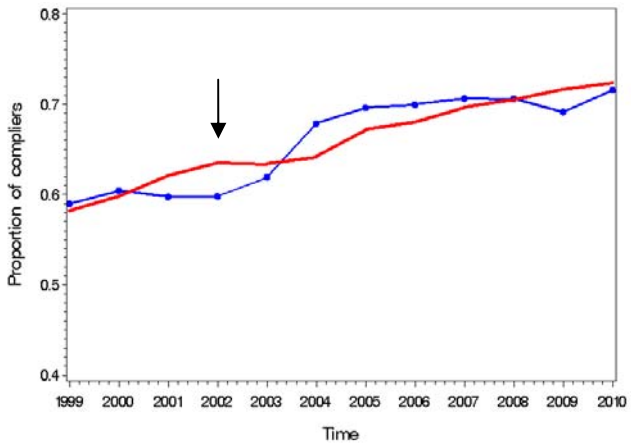
The final model had a pseudo-R^2 value of 0.1927.Although R^2 values for models on binary outcomes are typically much lower than for models on continuous outcomes, this indicates that there still is a lot of residual variability unexplained by the model. (Figure 9)

Figure 9. Averaged observed (blue, dotted) and predicted (red) evolution of compliance with guidelines for surgical antibiotic prophylaxis for lower limb surgery*, Belgium, 1999-2010.

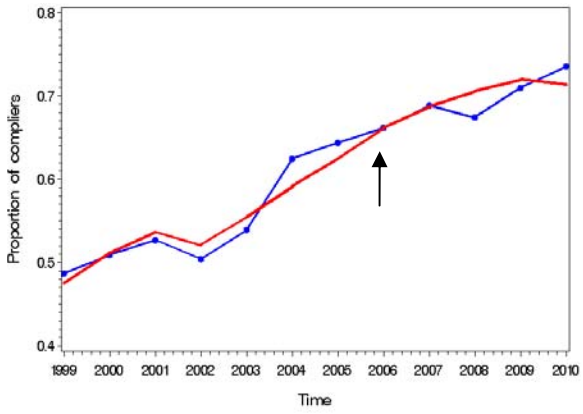
Full model



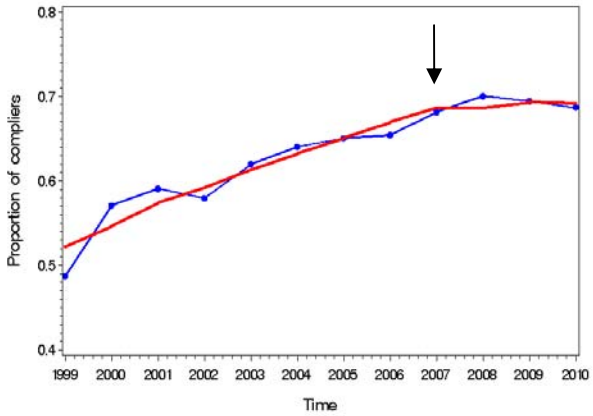
Hospitals with AMT implementation in 2002.



Hospitals with AMT implementation in 2006



Hospitals with AMT implementation in 2007



**APR-DRG 302, DoS 1 and 2. AMT: antibiotic management team.*

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

4.2.3 Summary of modelling finding, and interpretation

Table 16. Summary of mathematical modelling findings

Change points	*Statistical significance*	*Clinical significance*	*Conclusion: Association with improvement?*
2001			
Pneumonia: DDD outcome	Yes – (decrease, desirable)	Yes – strong effect	Yes
Pneumonia: O/P outcome	No	NA	No
Surgery outcome	Yes – (decrease, not desirable)	Doubtful - very weak effect	No
2006			
Pneumonia: DDD outcome	Yes – (increase, not desirable)	Doubtful - very weak effect	No
Pneumonia: O/P outcome	Yes (decrease, not desirable)	Doubtful - very weak effect	No
Year AMT funding			
Pneumonia outcomes	No	NA	No
Surgery outcomes	Yes (decrease, not desirable)	Doubtful – very weak effect	No

5 GENERAL DISCUSSION

5.1 Key findings

All 3 selected QIs for antimicrobial use in Belgian hospitals show a continuous improvement over the 12 years under study. Compliance with guidelines for antibiotic prophylaxis in case of hip and knee surgery (defined as the recommended molecule, with dosage in the expected range, and no other antimicrobial given during the hospital stay) increased from 53% in 1999, to 71% in 2010; the number of hospitals where at least 80% of eligible patients complied with guidelines, went from one in ten, to one in three. For patients treated for pneumonia, over the same period, mean consumption of antimicrobials other than penicillin decreased from 96 DDD to 64 DDD/ 100 hospital-days, and ratio of oral / parenteral DDD increased from 0.72 to 0.97.

By use of statistical modeling, we explored whether these favorable trends displayed "change points" - that is, a change in slope before, and after, particular years that could be related to specific policies or interventions intended to improve antimicrobial use. This modeling exercise showed that baseline values for all 3 indicators, as well as change overtime, varied widely across hospitals, that models were complicated, involving many interaction terms, and that conclusions drawn at national level might not apply to any given hospital. In 2001, a change was observed in the desirable direction for the pneumonia indicator: "N DDD other than J01C". No changes in the desirable direction occurred in 2006 for the pneumonia indicators (this change point was not relevant for the surgery indicators). Similarly, no improvement on any of the 3 QI studied, could be detected the year hospitals started receiving funding for their AMT.

5.2 Strengths and limitations

The major strength of this study is its exhaustive, and detailed patient-based database including all admissions for hip and knee surgery, and pneumonia, for all Belgian hospitals over 12 years. These admissions rank respectively first and second in terms of the number of patients receiving antimicrobials in hospitals. The trends shown in the quality indicators we have chosen are real and do not require statistical inference. We also used state-of-the art statistical methods for the modeling of these trends, 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"), although these did not improve the model.

This study also has limitations. First, routine data are not perfect. There are some indications for instance that (particularly for pneumonia) practices for coding the degree of severity of the stay might have changed over the years (upcoding). However there is no reason to believe this happened in a non-random way in relation with the outcomes and change points studied. Another limitation has to do with the indicators themselves. As we lack an important dimension of compliance to guidelines – timing – true compliance to guidelines can only be less than what we have measured. The trend in improvement shown by our data is nevertheless robust: more patients receive the right AM, with a dosage in the expected range, and without unnecessary other AM. Another indicator which might be difficult to interpret is the number of DDD other than J01C, per 100 patient-days, for patients treated for pneumonia. The underlying assumption is that overall "less is better", but 1) this reflects mainly a decrease in cephalosporins (J01D) and macrolides (J01FA) while carbapenems(J01DH) and fluoroquinolones (J01MA) increased ; on the other hand more patients received large spectrum penicillin (J01CR) at larger doses. Interpreting the global trends in type and quantity of AM used for treating pneumonia is difficult. The indicator oral

DDD/parenteral DDD is more straightforward as there seems to be a global consensus on early parenteral to oral switch, in order to reduce length of stay , risks related to IV drug use, and cost.

5.3 Interpretation

Some indicators 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 has happened is not clear. BAPCOC was created in 1999 in order to improve AM use in Belgium and has been very active since at different levels, organizing multimedia campaign, training courses, publishing clinical guidelines, implementing AMT in hospitals etc[2]. Our study does not permit to relate the effect of one of its particular activities with changes in the quality indicators we used. Although 2001 was the year of a very large awareness campaign for antimicrobial use, this campaign targeted upper respiratory tract infections in the community - the effect observed this year on hospital indicators might simply reflect some "kick-off effect" after little more than one year of BAPCOC existence. Change in financing of hospital drugs in 2006 included all hospitals drugs (with some exceptions) and was associated at national level with overall diminishing drugs cost, as well as some decrease in overall AM consumption (per DDD).[7] However in our study it was not associated with improvement of quality for AM treatment for pneumonia. At national level no improvement was observed on the 3 QIs studied from the year hospitals received funding for their AMT, still funding AMT might have helped in some hospitals – or on other QIs. There are possible explanations to this finding. One could be that in hospitals already committed to improving AM use, funding made no difference in quality; in hospitals where improving AM use was not a priority, funding made no difference either because there was no mechanism in place to ensure that the extra money would be used for that particular purpose, as was reported by some actors in the field (MLL, personal communication). It is possible also that AMT choose other priorities for interventions than the indicators we analyzed here. However we could argue that a criterion for identifying priorities should be the number of patients who could benefit from the intervention. In practice, AMTs in Belgium were not given clear targets, although more recently (2013) they were asked to conduct audits on antimicrobial prophylaxis in case of orthopaedic surgery, in which gaps were identified.

5.4 Generalizability

This study has demonstrated improvement in the quality of AM use in Belgian hospitals but only looked at a limited number of quality indicators for a limited number of indications, and falls short of providing a global picture of trends in quality of AM use in Belgian hospitals. For instance, carbapenem use per 100 patient-days has more than doubled in Belgian hospitals between 1999 and 2010; colistin use has increased a four-fold, these are non-desirable trends. (see annexes - Table 23) Generalizability of our study findings is limited by the intrinsic complexity of measuring quality of AM use of hospitals; if funding AMT in hospitals does not seem to have had an effect, at national level, on the 3 quality indicators studied, we cannot exclude that it might have had an effect on other measures of quality.

6 CONCLUSIONS AND RECOMMENDATIONS

Compliance with guidelines for antibioprophylaxis in hip and knee surgery has steadily improved in Belgium between 1999-2010; as have some indicators measuring quality of AM use for patients admitted for pneumonia. This period correlates with intense activity of the BAPCOC, but improvements at national level could not be related to specific interventions, or policies, such as funding of AMT, although this certainly had an effect in some hospitals. High heterogeneity between hospitals suggest that data could be used to identify outliers and target interventions.

Measuring quality of AM use in hospitals requires the development of a more complete set of quality indicators that are likely to provide a more nuanced picture of the situation, and hopefully could identify priorities for action, at national and hospital level. Trends in one class of AM, cannot be interpreted in isolation, without searching for possible shifts of replacement by another class. Evaluating interventions such as funding of AMT in hospitals, should also be complemented by looking at other quality indicators, in order to make the best of the unique political, and financial commitment that Belgium demonstrates in this field. AMTs in hospitals might benefit from more guidance in terms of identifying priorities for action.

7 ANNEXES

7.1 Top 10 APR-DRG in 2009 in Belgium, by use of antimicrobials

APRDRG (version 15)	Hospital stays	Hospital stays with AM		
		N	% total	Total DDD
Top 10, by number of hospital stays with antimicrobials				
302 major joint & limb reattach proc of lower extremexc for trauma	37525	36858	98%	160.657
139 simple pneumonia	35334	33966	96%	549.437
560 vaginal delivery	95525	30349	32%	80.171
310 back & neck procedures except dorsal & lumbar fusion	23584	21292	90%	42.709
315 shoulder, elbow & forearm procedure	31190	21058	68%	40.968
140 chronic obstructive pulmonary disease	24579	17472	71%	329.240
540 cesarean delivery	23393	16972	73%	45.094
313 knee & lower leg procedures except foot	22465	16866	75%	62.972
463 kidney & urinary tract infections	16441	15536	94%	164.977
513 uterine & adnexa procedures for ca in situ &nonmalignancy	21236	14309	67%	35.126
Top 10, by number of DDD				
139 simple pneumonia	35334	33966	96%	549.437
140 chronic obstructive pulmonary disease	24579	17472	71%	329.240
221 major small & large bowel procedures	14558	14274	98%	214.709
004 tracheostomy except for face, mouth & neck diagnoses	2368	2329	98%	210.455
137 respiratory infections & inflammations	7003	6696	96%	179.217
720 septicemia	7405	7152	97%	166.246
463 kidney & urinary tract infections	16441	15536	94%	164.977
302 major joint & limb reattach proc of lower extremexc for trauma	37525	36858	98%	160.657
144 respiratory system signs, symptoms & other diagnoses	26021	11505	44%	144.406
383 cellulitis	9770	9223	94%	140.476

So: Cellule technique de l'INAMI - Technische cell, RIZIV

7.2 Comparison of quality indicators for use of antimicrobials in hospital stays for orthopaedic surgery, and pneumonia

	APR-DRG 302 MAJOR LOWER LIMB SURGERY	APR-DRG 139 PNEUMONIA
Main characteristics	Not infectious. Guidelines for AM use simple and same for all patients. Differences in case-mix should explain little of the variation observed between hospitals.	Infectious diagnosis. Appropriate treatment differ between patients (age, MO, AM resistance patterns…). Different case-mix can potentially explain some variation between hospitals
Quality indicator for AM use at patient/stay level		
Appropriateness of AM use	Compliance to guidelines can be approximated. Criteria (Proper molecule, dose within expected range, no other AM used) measure elements of quality, even if data on timing not available. Each stay can be classified as "compliant" or not.	Cannot be measured with available data given unavailable clinical information. Stays cannot be classified as "compliant" or "not"
Quality indicators for AM use at hospital level		
	% of stays compliant with guidelines derived from assessment of compliance at stay level. (NB: "Gold standard" can be defined in absolute terms even if target NOT 100%)	Aggregated data measuring overall use of AM for the APR-DRG in the hospital: DDD / 100 hosp-days (with exception of J01C) and ratio DDD O/P. No "Gold standard" ; only comparisons are meaningful (between hospitals, within hospital over the years)
Patient or stay data relevant to patient-based case-mix adjustment in analyzing trends		
DoS of stay	Unlikely to play a role because only DoS 1 or 2 included; infectious diagnoses excluded	Important - AM treatment depend on severity of the stay; all DoS included in data analysed
Place before admission to hospital	Unlikely to play a role	Patients admitted from LTCF or other hospitals might have different MO/ resistance patterns than patients coming from the community.
Status at discharge	99,96 % patients are discharged alive in stays included (DoS 1 or 2)	Could complement DoS as marker for severity of disease (+/- 8% discharged dead).
Stay in ICU	Many patients admitted in ICU for short post-op stay; unlikely to play a role	Could complement DoS as marker for severity of disease.
LoS	Extended stay unrelated to infectious disease does not justify more AM use	Could complement DoS as marker for severity of disease, however LoS also very much dependent on other factors such as quality of care .
Age	The (very few) children in this APR-DRG have been excluded. Treatment does not depend on age	Many children in this APR-DRG; for children molecules used and doses depend on age (also proxy for weight) .
Sex	No reason why treatment would depend on sex, unless sex would act as some "distant" proxy for weight? (Males on average weight more than females; AM doses depend on weight.	
Quality indicators for AM use at national level		
	Proportion of stays compliant with guidelines derived from assessment of compliance at stay level.	Aggregated data measuring overall use of AM for the APR-DRG at national level DDD / 100 hosp-days (with exception of J01C) (less=better) and ratio DDD O/P. (higher = better)

7.3 Specific issues regarding the identification of hospitals in the database, and the date the AMT was implemented.

The identification of the hospital, and the date the AMT was implemented in each hospital, are crucial for this study. We had to address some specific issues related to administrative reorganizations that took place over the 12 years under study in Belgian hospitals. Indeed it happened in some cases two or more hospitals were regrouped under one single name (code) previously used for only one of them. We had to (manually) check the status of each hospital for each year, and in some cases grouped some hospitals under the same identification code to ensure complete (1999-2010) series. For instance, if 3 hospitals were administratively grouped under the same code in 2005, we recoded these 3 hospitals to the same code since 1999. This explains why the number of hospitals does not always exactly match the numbers found from other sources. In a few cases, administrative regrouping of hospitals occurred between hospitals where the implementation of the AMT had taken place in different years. We did not group these hospitals, some of them therefore do not report data for the complete 1999-2010 period. Finally, some hospitals have been closed; for these the series 1999-2010 are incomplete.

Table 17. Explanations why some hospital codes have incomplete 1999/2010 data series, and/or no year for AMT was assigned.

Name hospital	Hosp code	Date AMT	Codes merged	Decision	Consequences	
				Recode?	Incomplete 1999-2010 serie :	Date AMT assigned
Wilrijk	**99**	2006			No	Yes
St Vincente, Antwerp	**100**	2002	99+100= 99 on 1-7-2009	NO	Yes (missing;2010)	Yes
Hasselt	**159**	2007	159+243= 243, 01-01-2010		Yes (missing;2010)	Yes
Hasselt	**243**	2002		NO	No	Yes
St Niklaas	**256**	Never	256+595=595		Yes (missing from 2007)	No
St Niklaas	**595**	2002	1-1-2007	NO	No	Cannot be assigned for whole period
HôpitalFrançais	**547**	Never	Closed in 2007	No	Yes (missing from 2008)	No

7.4 Major lower limb surgery : other analyses

Table 18. Hospital stays for major lower limb surgery* in Belgium, 1999-2010: stays during which a given class of AM was given

year	Tot stays 100%	J01C	J01CR	J01D	J01F	J01G	J01MA	Other class
1999	18562	7%	5%	98%	3%	6%	10%	17%
2000	20559	7%	6%	98%	4%	6%	9%	16%
2001	21790	7%	5%	98%	4%	6%	9%	16%
2002	23254	7%	5%	98%	4%	6%	8%	16%
2003	24606	6%	5%	98%	4%	6%	7%	15%
2004	25917	6%	5%	98%	4%	5%	7%	14%
2005	27756	5%	4%	98%	3%	4%	6%	13%
2006	29267	5%	4%	98%	4%	4%	5%	14%
2007	30727	5%	4%	97%	4%	3%	5%	13%
2008	32708	5%	4%	97%	4%	4%	5%	14%
2009	34256	5%	4%	97%	5%	4%	5%	14%
2010	35692	5%	4%	97%	5%	4%	4%	14%

**APR-DRG 302, DoS 1 & 2.*
J01C: Beta-lactams penicillins. J01CR: Combinations (ex: amoxy-clav) J01D: Other Beta-lactams penicillins (include cephalosporins ;J01F: Macrolides, Lincosamides, Streptogramins; J01MA: Fluoroquinlones

Table 19. Hospital stays for major lower limb surgery* in Belgium, 1999-2010: Number of AM given per stay.

Year	Total stays 100%	Number of AM given during the hospital stay					
		None		1		> 1	
1999	18.562	356	2%	12.522	67%	5.684	31%
2000	20.559	393	2%	14171	69%	5.995	29%
2001	21.790	412	2%	15303	70%	6.075	28%
2002	23.254	438	2%	16299	70%	6.517	28%
2003	24.606	542	2%	18047	73%	6.017	24%
2004	25.917	524	2%	19553	75%	5.840	23%
2005	27.756	408	1%	21239	77%	6.109	22%
2006	29.267	395	1%	22501	77%	6.371	22%
2007	30.727	364	1%	24137	79%	6.226	20%
2008	32.708	545	2%	25700	79%	6.463	20%
2009	34.256	606	2%	26884	78%	6.766	20%
2010	35.692	665	2%	28177	79%	6.850	19%

**APR-DRG 302, DoS 1 & 2.*

Table 20. Number of hospital stays for major lower limb surgery* used in evaluation of compliance with antibiotic prophylaxis guidelines

Year	*Total number of stays (all DoS)*	*Stays with Dos1 or 2*	*Stays available for analyses after other exclusions (% of total)*	
1999	20.258	18.835	18.737	92%
2000	22.574	20.817	20.731	92%
2001	24.197	22.041	21.957	91%
2002	26.254	23.506	23.410	89%
2003	27.872	24.856	24.733	89%
2004	29.480	26.172	26.052	88%
2005	31.542	28.049	27.910	88%
2006	33.003	29.550	29.431	89%
2007	34.340	31.043	30.914	90%
2008	36.228	33.257	33.107	91%
2009	37.525	34.778	34.661	92%

**APR-DRG 302*

ICD-9 code 998.59 (Post-operative infection) was reported for 0.14% of all stays (total over 12 years) with no clear trend over the years.

7.5 Simple pneumonia: other analyses

Table 21.Diagnostic on admission for hospital stays for simple pneumonia*, Belgium, 2010

Diagnostic on admission	ICD-9 code	N	%
pneumonia, organism nos	486	19.468	61,5%
bronchopneumonia org nos	485	6.300	19,9%
bacterial pneumonia nos	482.9	2.055	6,5%
pneumococcal pneumonia	481	1.680	5,3%
pneumycplsmpneumoniae	483.0	1.056	3,3%
pneumonia d/t chlamydia	487.0	344	1,1%
viral pneumonia nos	483.1	268	0,8%
pneumonoth spec orgnsm	480.9	131	0,4%
influenza with pneumonia	483.8	108	0,3%
adenoviral pneumonia	480.0	62	0,2%
viral pneumonia nec	480.8	54	0,2%
pneumoniaoth strep	482.39	51	0,2%
streptococcalpneumnnos	482.30	35	0,1%
parinfluenza viral pneum	480.2	24	0,1%
pneumoniastrptococcus a	482.31	18	0,1%
pneumoniastrptococcus b	482.32	8	0,0%
Other- missing		9	0,0%
Total		**31.671**	**100%**

Nos: not otherwise specified

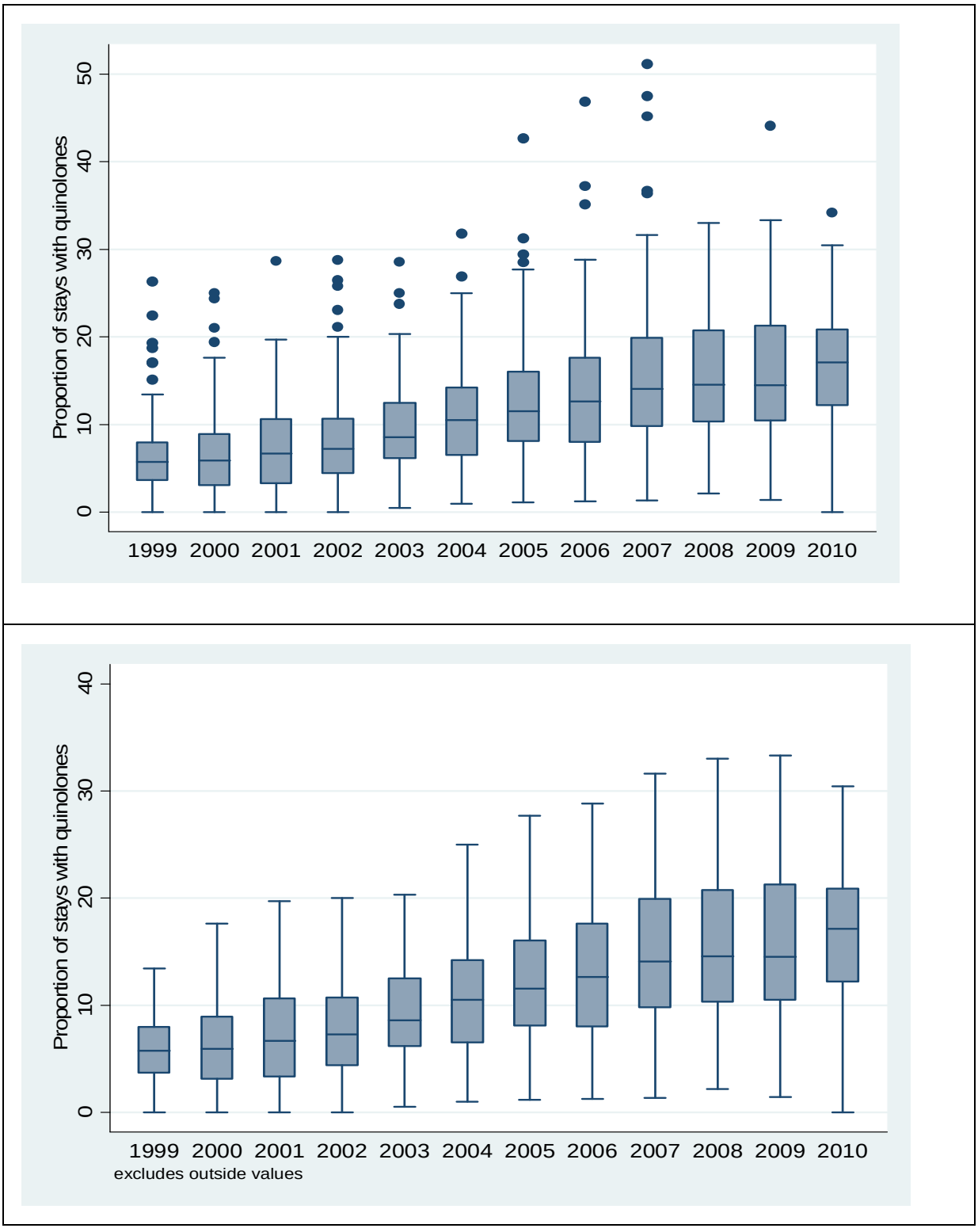
**APR-DRG 139*

Table 22.Hospital stays for simple pneumonia*, with a stay in intensive care units, Belgium, 1999-2010

	Stays in IC U		*Total stays (100%)*
	N	%	N
1999	2.031	9%	22.385
2000	2.273	10%	23.268
2001	2.699	11%	24.165
2002	2.641	10%	25.424
2003	2.646	10%	26.331
2004	2.351	9%	25.201
2005	2.455	8%	30.145
2006	2.158	8%	26.739
2007	2.315	8%	28.872
2008	2.360	8%	29.823
2009	2.214	7%	33.611
2010	2.025	6%	31.671

** APR-DRG 139, all DoS*

Figure 10.Distribution of hospitals according to the proportion of stays for simple pneumonia* in which a quinolone was given. Belgium 1999-2010.



** APR-DRG 139, all DoS combined*

7.6 General issues to consider when choosing the appropriate statistical model

(Following the meeting with statisticians in Diepenbeek on August 19,2013, we attempt here to clarify some of the issues discussed.)

The objective is to evaluate the impact of policies on trends observed **at national level**between 1999 and 2010.

1. This needs to account for factors **at hospital level**:
    - trends before and after implementation of these policies (particularly implementation of AMT) **in each hospital.** Indeed it is possible that those hospitals with better quality indicators after implementation of AMT, or those volunteering for the implementation of the pilot phase, were already more motivated, and better before the implementation of the AMT.
    - Case load: obviously larger hospitals (treating more patients with the APR-DRGs of interest) will have a bigger impact on trends observed at national level (cluster effect)
    - particular case-mix (and trends) for each hospital. For instance in absolute terms use of AM for pneumonia at hospital level will depend (obviously) not only on caseload, but also, eg, on the proportion of more severe cases, or children. As data are available at patient level, this allows **patient-based case-mix adjustment** (thus avoiding the ecological fallacy[18]) NB: characteristics of the hospital itself, such as number of beds, or category – eg tertiary hospitals - are unlikely to provide additional useful information above that provided by their particularly case mix for the APR-DRGs analyzed here).
2. The analyses need to account for secular trends in decreasing LoS for **all** hospital stays. This results from different factors, and is more pronounced for some APR-DRG than for others.
3. The policies to be evaluated differ. The " change in financing" occurred at a particular date (1st July 2006) similar in all hospitals, with a clear cut "before/after" one-day date. The policy "implementation of AMT" occurred at different times in different hospitals. This is a complex policy involving different components (contract signed with the Ministry of health, funding received by hospital, trained manager hired …); with no such a clear-cut one-day date to use as a "before/after" in analyzing change. For instance, some hospitals might have delayed hiring the trained manager . It seems advisable to use a larger time period to define a "before/after" period of change.
4. Although seasonality is expected for the number of hospital stays and maybe for the severity of the stays (definitely for pneumonia, more admissions, more severe in winter months) , there seems to be no obvious reason why indicators relating to treatment would display seasonality if adjustments are made for DoS, LoS, age…. In addition, indicators for pneumonia relate to aggregated data at hospital level; looking at seasonal variation at hospital level will leave few stays in each month.

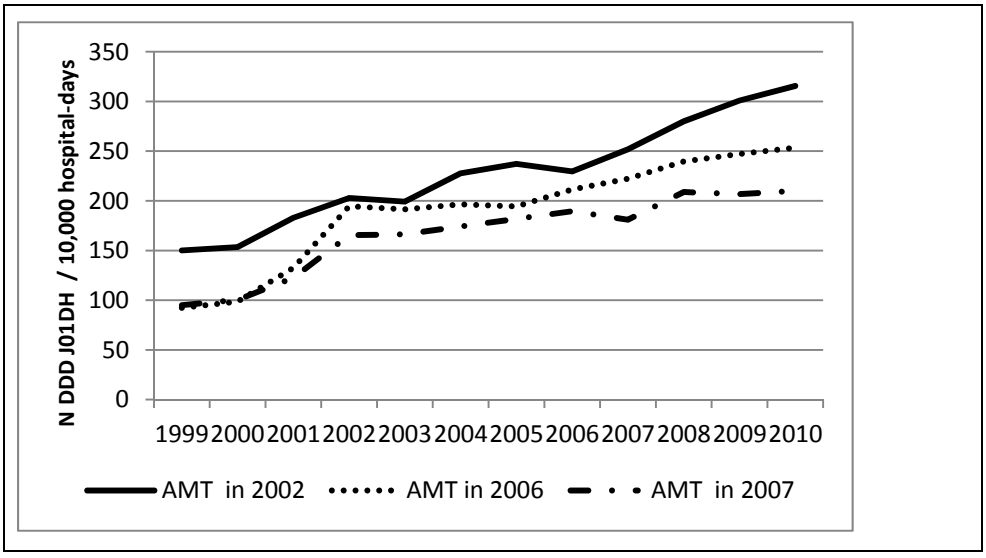
7.7 Consumption of selected AM molecules, selection of hospital stays*, 1999-2010

Table 23.N DDD / 10.000 patient-days, selection of stays*, acute hospitals, Belgium, 1999-2010

	Linezolid	Tigecycline	Voriconazole	Colistine	Carbapenems
yr	J01XX08	J01AA12	J02AC03	J01XB01	J01DH
1999	0,00	0,00	0,00	5,91	118,14
2000	0,00	0,00	0,00	8,00	122,89
2001	0,00	0,00	0,00	5,37	150,13
2002	0,45	0,00	0,00	1,92	187,07
2003	5,95	0,00	8,24	3,34	184,97
2004	11,93	0,00	18,96	4,60	201,78
2005	14,15	0,00	18,03	7,88	209,47
2006	15,50	0,00	18,27	7,39	213,00
2007	11,88	0,08	22,28	15,18	221,64
2008	12,16	3,95	23,84	19,14	245,99
2009	13,06	8,52	23,86	22,27	256,28
2010	12,41	12,60	27,05	24,44	265,25

*Selection of 75 APR-DRG. These stays accounted for 60% of all hospital stays with AM in Belgium in 2010

Figure 11. Consumption of carbapenems (J01DH) in acute hospitals (selection of stays*) grouped according to the year the antibiotic management team was implemented. Belgium 1999-2010



*Selection of 75 APR-DRG. These stays accounted for 60% of all hospital stays with AM in Belgium in 2010

7.8 FULL STATISTICAL REPORT

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7.8.1 Introduction

Longitudinal data are generally modelled with a linear mixed model, which describes an outcome in terms of fixed effects, reflecting the average trend, and random effects, reflecting the subject-specific deviation from this average trend.[1-2] A general mixed model can be written as:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_2 X_{2ij} + ... + \beta_Q X_{Qij} + \varepsilon_{ij}, \quad (1)$$

where Y_{ij} is the outcome for *ith* subject (i = 1, 2, …, N) at time points t_{ij} (j = 1, 2, …, n_i), n_i is the number of observations from the *ith* subject, time = 1 corresponds to the start of the study, β_0 is the fixed intercept, b_{0i} is the subject-specific intercept, β_1 is the fixed slope, b_{1i} is the subject-specific slope, X_{qij} is the *ith* observation at the *jth* time point for the *qth* independent variable (q = *2, 3,…, Q)*, β_q are the associated fixed effects and ε_{ij} is the unexplained error term for subject *i* at time point *j*.

A somewhat abrupt change in the evolution of the outcome over time can be modelled with a change-point.[3-4] This is done by adding a change-point component to the general mixed model (equation (1)). The change-point component is given by

$$\beta_{cp1}(t_{ij} - CP_1)_+ + ... + \beta_{cpK}(t_{ij} - CP_K)_+, \quad (2)$$

where $x_+ = \max(x,0)$, β_{cpk} is the *kth* global difference in the linear trend before and after the change-point (k = *1, 2,…, K)* and CP_k is the *kth* global change-point.

Combining equations (1) and (2) yields a more general model:

$$Y_{ij} = (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \beta_{cp1}(t_{ij} - CP_1)_+ + ... + \beta_{cpK}(t_{ij} - CP_K)_+ + \beta_2 X_{2ij} + ... + \beta_Q X_{Qij} + \varepsilon_{ij}, \quad (3)$$

where all components are defined as before.

In this analysis we aim to determine the significance of three hypothesized change-points (K=3). This can be done by testing the hypothesis $\beta_{cpk} = 0$, which indicates that there was no difference in the slope before and after the change-point.

7.8.2 AMTABU data

Data on all hospital stays in Belgium were collected yearly between 1999 and 2010 by the National Sick Fund and Ministry of Health. For each hospital stay information was collected on the patient, the hospital, the antimicrobial consumption and the stay itself. Two "all-patient related diagnosis groups" (APR-DRGs) were selected, being simple pneumonia and hip and knee surgery.

For hip and knee surgery the investigated outcome was compliance to guidelines at stay-level. Recorded variables at stay-level include severity of the stay (sev1-2), gender of the patient, intensive care unit stay

(ICU0-1), length of the stay (los)(in days), age of the patient (in years), hospital code and the number of hip and knee surgeries that were conducted in that hospital during the year of the patients stay (size). Figure 12 shows that there is a lot of variability between hospitals, which suggests the need for subject-specific intercepts and slopes.

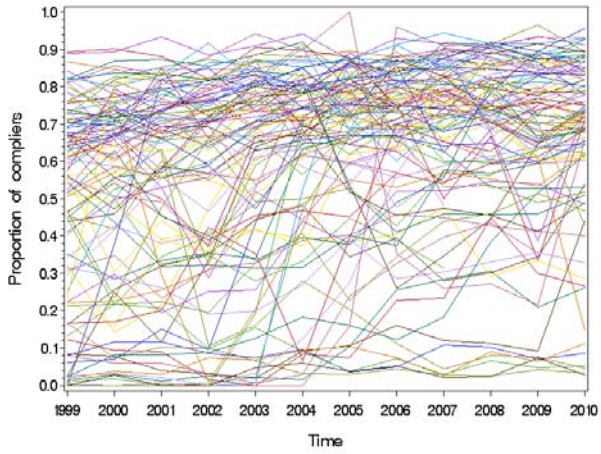

Figure 12.Hospital-specific profiles for the proportion of compliers over time.

For pneumonia the information on stays was aggregated per hospital per year. Two outcomes at hospital-level were investigated further, being the number of total DDD (excluding J01C) per 100 hospital days and the oral/parenteral ratio. Recorded variables at hospital-level include hospital code, the number of pneumonia stays, the median length of stay (los), the distribution (in %) of the severity of the stay (sev1-4), of the gender, of the intensive care unit stay
(ICU0-1), of the patient origin (pt_ori1: home, pt_ori2: long term care, pt_ori3: other hospital and pt_ori4: other/unknown), of the discharge status (dis_st0: alive and dis_st1: dead) and of the age categories (ag1: < 1, ag2: 1-5, ag3: 6-10, ag4: 11-16 and ag5: > 16).
Figure 13 shows that for both pneumonia outcomes there is a lot of variability between hospitals, which suggests that there is a need for subject-specific intercepts and slopes.

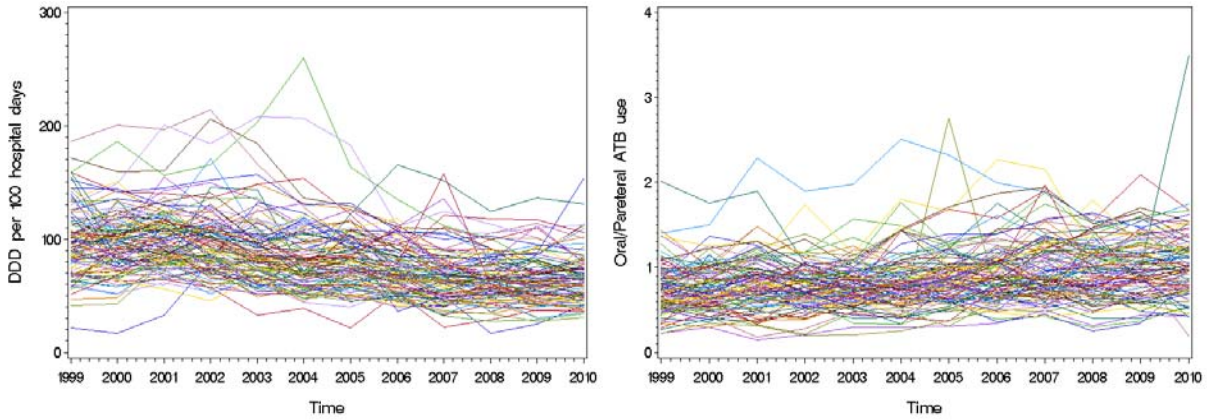

Figure 13.hospital-specific profiles for the DDD per 100 hospital days (left) and the oral/parenteral ratio (right) over time.

Outliers for both pneumonia outcomes were detected using a box plot where an outlier is defined as an observation outside the lower and upper far fences. The lower far fence is located at 3 times the interquartile range (IQR) below the 25th percentile and the upper far fence is located at 3 times the IQR above the 75th percentile, with IQR defined as the distance between the 25th and the 75th percentile. Far outliers, listed in Table 24, were removed from the analyses.

Table 24.Outlying observations for DDD per 100 hospital days and oral/parenteral ratio.

DDD per 100 hospital days	Hospital code	716				
	Year	2004				
Oral/parenteral ratio	Hospital code	713	713	713	96	37
	Year	2001	2004	2005	2005	2010

For some hospitals the data series was incomplete. These hospitals as well as reason for incompleteness and decision on how to handle these hospitals are reported in Table 25.

Table 25.Hospital code for hospitals with incomplete data series, reason for incompleteness and decision on how to handle these hospitals.

Hospital code	Reason for incomplete series	Decision
100	Merge of 100 with 99 on 1-7-2009	Keep 99 (AMT =2006) and 100 (AMT =2002) up to 2009. Drop combined hospital after 2009 as AMT is different.
159	Merge of 159 with 243 on 1-1-2010	Keep 159 (AMT =2007) and 243 (AMT =2002) up to 2009. Drop combined hospital after 2009 as AMT is different.
256	Merge of 256 with 595 on 1-1-2007	Keep 595 (AMT =2002) up to 2006. Drop 256 as AMT =never. Drop combined hospital after 2006 as AMT is different.
547	Hospital closed in 2007	Drop 547 as AMT=never
231	Merge of 231 with 9 on 1-7-2007	Keep 231 (AMT=2006) and 9 (AMT=2002) until 2007. Drop combined hospital after 2007 as AMT is different.
719 (only for Surgery)	Failure to report	Keep incomplete series for 719 (up to 2007)

7.8.3 Methods

All statistical analyses were conducted with SAS version 9.3

7.8.3.1 Change-point variables

Three change-points were hypothesized based on either the implementation of policies or expert advice. The first change-point is 2001 which is the year the first large antimicrobial awareness campaign was launched in Belgium. This change-point was included following expert advice and can be modelled by including the following term in the general mixed model:

$$\mu_i^{AW} = \beta_{AW}(t_{ij} - 2001)_+$$

The second change-point is the year the hospital got funding for its antimicrobial management teams (AMT) (2002, 2006 or 2007). This change-point can be modelled by including the following term:

$$\mu_i^{AMTIN} = \left(\beta_{AMTIN02}(t_{ij} - 2002)_+\right)X_{AMT02} + \left(\beta_{AMTIN06}(t_{ij} - 2006)_+\right)X_{AMT06} + \left(\beta_{AMTIN07}(t_{ij} - 2007)_+\right)X_{AMT07},$$

withX_{AMT02}= 1 if AMT was implemented in 2002 and 0 otherwise, X_{AMT06}= 1 if AMT was implemented in 2006 and 0 otherwiseand X_{AMT07}= 1 if AMT was implemented in 2007 and 0 otherwise. These explanatory variables serve as indicators assigning the correct change-point to each observation.

The third change-point is 2006, which is the year a new funding mechanism for hospital drugs was introduced. This change-point was included only for pneumonia-related outcomes and can be modelled by including the following term:

$$\mu_i^{FIN} = \beta_{FIN}(t_{ij} - 2006)_+$$

7.8.3.2 Need for a time lag

In order to account for the fact that the effect of polices might start before implementation or might need some time after implementation, a time lag (+/- one year) was included. The time lag was modelled by a hospital-specific shift in time, which could range from –1 year before to +1 year after the fixed change-point.

In order to test the need for a hospital-specific time lag, we fitted a model containing a fixed and random intercept, a fixed and random slope, all change-points and a random time lag for each change-point. Variances were set equal to one and covariances to zero in order to reach convergence.
This model failed to converge for the data on hip and knee surgery. Hence, we fitted a model containing the fixed and random intercept, fixed and random slope and one change-point with its time lag at a time. The likelihoods for the models with and without time lags were compared in order to assess the need for the lags.

For all models (on DDD per 100 hospital days, oral/parenteral ratio and compliance) the time lags (+/- one year) were redundant.

This procedure was repeated for a bigger time lag (+/- two years). For the models on DDD per 100 hospital days and oral/parenteral ratio the big time lags were redundant. For the data on hip and knee surgery, convergence could not be reached in two models (including a big time lag for AMTIN06 and for AMTIN07) while in the two other models (including a big time lag for ATMIN02 and AW) the big time lag was redundant.

7.8.3.3 Major lower limb surgery

As compliance is a binary outcome, a logit link and a binary distribution were used to model the data. This was done in SAS using PROC NLMIXED. Because this procedure implements only maximum likelihood (ML), all analyses were conducted under ML rather than restricted maximum likelihood (REML).

The starting model contained the fixed effects severity, gender, ICU, los and age, the change-point variables for AMT (AMTIN) and 2001 (AW), the interactions between the change-point variables and the fixed effects, time, the interactions between time and the fixed effects, AMT and the interaction between AMT and time. As there was a lot of between-hospital variability (Figure 12), random intercepts and slopes were included in the model.

Likelihood ratio tests were used to compare models with and without each change-point. Redundant change-points (change-point variable and its interactions) were removed from the model in a backwards fashion. In order to test if random effects could be removed from the model, likelihood ratio tests based on an equally weighted mixture of χ^2 distributions were used.5The mean structure was reduced in a backwards-hierarchical fashion.

Size variables (size, interaction between size and time and interaction between size and all included change-point variables) were added to the model. A likelihood ratio test comparing the model with an without the size variables was used to test if size was an important variable.

As a measure for goodness of fit the pseudo-R^2 (McFadden's) for the final model was calculated as follows:

$$R^2 = 1 - \frac{LR\left(\hat{\theta}\right)}{LR(0)}$$

with $LR\left(\hat{\theta}\right)$ the likelihood for the model including all parameters and $LR(0)$ the likelihood for the model containing only the general intercept. The contribution of the fixed effects was determined by calculating the pseudo-R^2 for the model containing only fixed effects and dividing it by the pseudo-R^2 for the final model. The contribution of the random effects was calculated by subtracting the fixed effects' contribution from 100%.

7.8.3.4 Pneumonia

The starting model contained the fixed effects for median los and the distribution of severity, of gender, of ICU stay, of patient origin, of discharge status and of age categories, the change-point variables for AMT (AMTIN), 2006 (FIN) and 2001 (AW), the interactions between the change-point variables and the fixed effects, time, the interactions between time and the fixed effects, AMT and the interaction between AMT and time. As there was a lot of variability between hospitals (Figure 13), random intercepts and slopes were included in the model. Because hospitals were observed yearly and we assumed that observations closer in time would be more alike than observations further apart, we used an autoregressive (AR(1)) residual structure.
As the observations were aggregated by hospital and year, all information on the size of the hospital was lost. For this reason we weighted the observations according to the number of pneumonia stays per hospital per year.

Likelihood ratio tests were used under ML to compare models with and without each change-point. Redundant change-points (change-point variable with its interactions) were removed in a backwards fashion. A likelihood ratio test based on a χ_1^2 distribution was used under REML to test if the AR(1) structure could be simplified. In order to test if random effects could be removed from the model,

likelihood ratio tests based on an equally weighted mixture of χ^2 distributions were used under REML. The mean structure was reduced in a backwards hierarchical fashion under ML.

Size variables (size, interaction between size and time and interaction between size and all included change-point variables) were added to the model. A likelihood ratio test comparing the model with and without these variables was used under ML to test if size was an important variable (after weighting observations according to size).

The final model was refitted under REML in order to obtain parameter estimates.
As a measure for goodness of fit the adjusted R^2 was calculated as follows:

$$\left(1-\frac{\sum\left\{size_i\left(y_i-f_i\right)^2\right\}}{\sum\left\{size_i\left(y_i-\bar{y}\right)^2\right\}}\right)\left(\frac{n-1}{n-m}\right),$$

with y_i the observed outcome, f_i the predicted outcome, $\bar{y}$ the weighted average of the observed outcomes, n the number of observations and m the number of parameters. The contribution of the fixed effects was determined by calculating the adjusted R^2 for the model containing only fixed effects and dividing it by the adjusted R^2 for the final model. The contribution of the random effects was calculated by subtracting the fixed effects' contribution from 100%.

7.8.4 Results

7.8.4.1 Major lower limb surgery: proportion of compliers

Likelihood ratio tests showed that both change-points were required (p-values < 0.0001) so change-point variables AMTIN and AW and their interactions were kept in the model. Likelihood ratio tests based on an equally weighted mixture of χ_1^2 and χ_2^2 showed that both random effects were required (p-values < 0.0001). Removal of redundant fixed effects resulted in the final model. Addition of the size variables to that model appeared to be necessary
(p-value < 0.0001).

Significance of the parameters in the final model is shown in Table 26. Some insignificant main effects were kept in the model because they are part of a significant interaction term. Although AMT is not significant and no significant interaction term is included, it is kept in the model because AMT serves as an indicator to assign the correct change-point to each observation. Hence the indicator should not be dropped as long as the AMTIN change-point is required in the model. Estimates for all included parameters are shown in

Table 27.

On Figure 14 it can be seen that the model fits the data quite well as the predicted line approximates the observed data. The observed and predicted evolution of the proportion of compliers over time per AMT group is visualized in Figure 15.

Table 26.Significance for parameters in the final model for the proportion of compliers.

Parameter	p-value	Parameter	p-value	Parameter	p-value
age	0.1324	time*age	0.0010	AW*ICU	< 0.0001
los	< 0.0001	time*sev	0.0016	AMTIN	< 0.0001
AMT	0.6488	time*gender	0.0020	AMTIN *sev	< 0.0001
sev	< 0.0001	AW	0.0092	AMTIN *ICU	0.0001
gender	0.0028	AW*age	0.0005	size	< 0.0001
ICU	< 0.0001	AW*los	0.0009	time*size	< 0.0001
time	0.9848	AW*sev	0.0633	AW*size	< 0.0001
		AW*gender	0.0012	AMTIN*size	< 0.0001

Table 27. Parameter estimates and standard error for parameters in the final model for the proportion of compliers.

Parameter	Estimate	SE	Parameter	Estimate	SE	Parameter	Estimate	SE
intercept	0.3246	0.2594	time*male	-0.0654	0.0207	AMTIN02*sev2	-0.0209	0.0061
age	-0.0037	0.0024	time*size	0.0005	0.0001	AMTIN06*sev2	0.0403	0.0161
los	-0.0437	0.0012	AW	0.0715	0.0270	AMTIN07*sev2	-0.0108	0.0212
amt06	0.2502	0.3342	AW *age	-0.0036	0.0010	AMTIN02* ICU1	0.0299	0.0127
amt07	-0.0246	0.2634	AW *los	0.0007	0.0002	AMTIN06* ICU1	0.0599	0.0386
sev2	-0.5575	0.0542	AW *sev2	-0.0462	0.0246	AMTIN07* ICU1	0.1884	0.03977
male	0.1642	0.0537	AW *male	0.0750	0.0225	AMTIN02*size	7.14E-06	0.00004
ICU1	-0.5161	0.0272	AW *ICU1	-0.0464	0.0096	AMTIN06*size	0.0004	0.00004
size	-0.0012	0.0002	AW *size	-0.0005	0.0001	AMTIN07*size	0.0001	0.00006
time	0.0005	0.0288	AMTIN02	0.0561	0.0217			
time*age	0.0031	0.0009	AMTIN06	-0.3500	0.0262			
time*sev2	0.0684	0.0211	AMTIN07	-0.1010	0.0259			

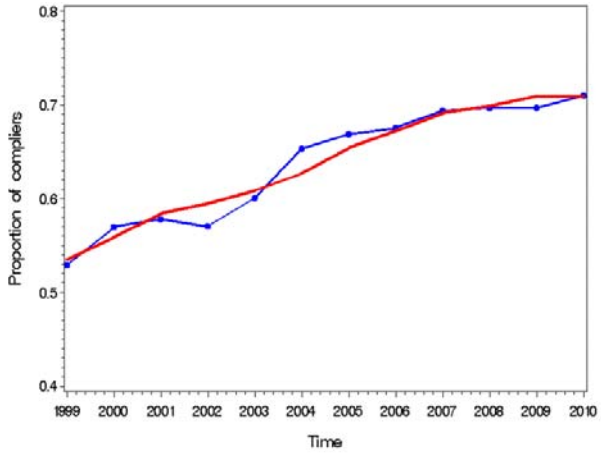

Figure 14. Average observed (blue) and predicted (red) evolution of the proportion of compliers over time

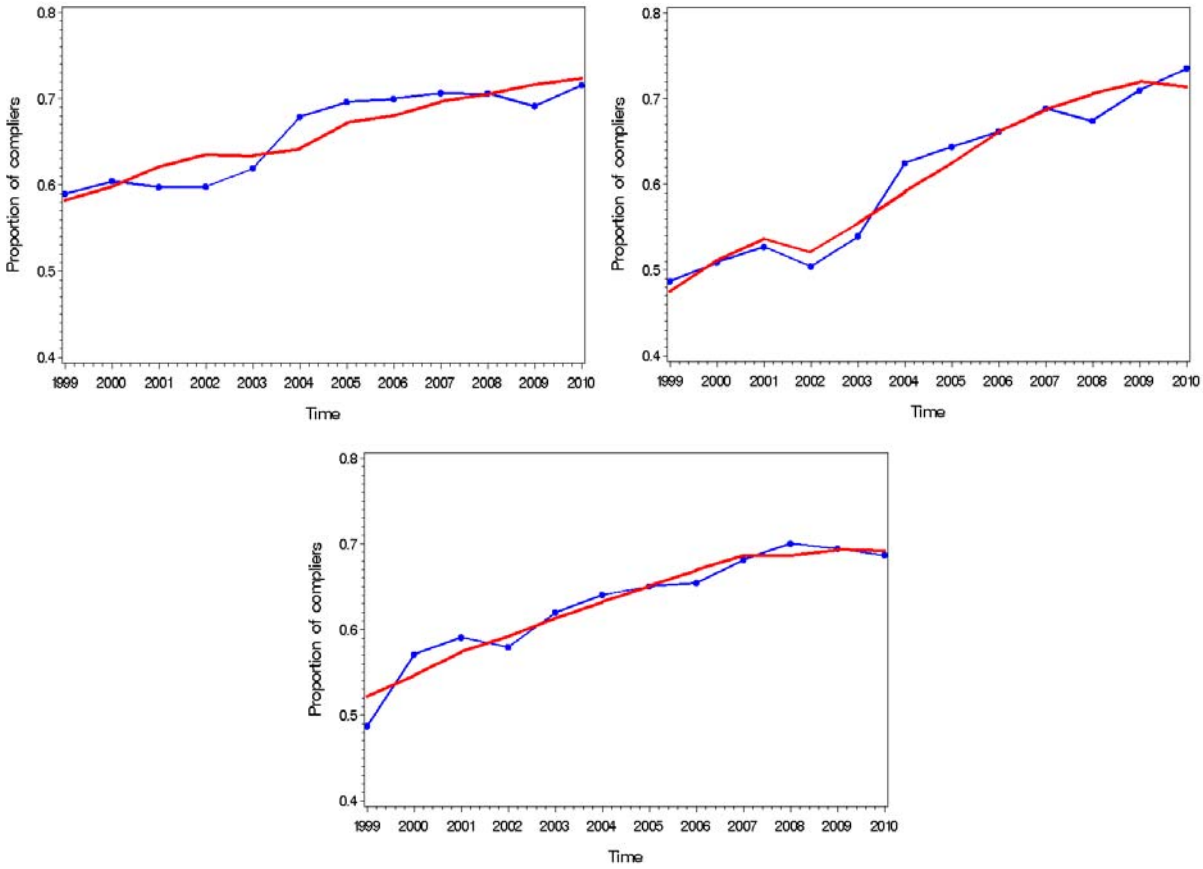

Figure 15.Average observed (blue) and predicted (red) evolution of compliers over time for the group of hospitals with AMT implementation in 2002 (top left), in 2006 (top right) and in 2007 (bottom).

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 residual variability that is unexplained by the model. Note that 17% of the explained variability comes from the fixed effects while 83% comes from the random effects. The importance of the inclusion of random effects is also stressed by the heterogeneity of the predicted outcomes for randomly selected hospitals (Figure 16).

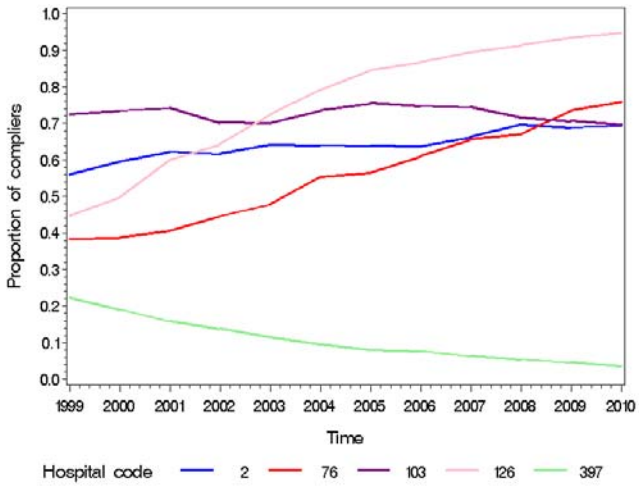

Figure 16.Predicted evolution of compliers over time for five randomly selected hospitals.

7.8.4.2 Pneumonia

7.8.4.2.1 DDD per 100 hospital days

Likelihood ratio tests showed that the change-point for AMT was redundant (p-value = 0.4659). After removal of the change-point variable ATMIN and its interactions, likelihood ratio tests indicated that the change-points for 2001 and 2006 were both required (p-values < 0.0001 and 0.0009, respectively). For this reason change-point variables AW and FIN and their interactions remained in the model. The AR(1)residual structure could not be simplified (p-value < 0.0001). Likelihood ratio tests based on an equally weighted mixture of χ_1^2 and χ_2^2 showed that both the random intercept and the random slopes needed to be retained in the model (p-values < 0.0001 and 0.0023, respectively). Removal of redundant fixed effects resulted in the final model. Addition of the size variable to this model appeared to be unnecessary (p-value = 0.9988).

Significance of the parameters in the final model is shown in Table 28. Some insignificant main effects were kept in the model because they are part of a significant interaction term. Estimates for all included parameters are given in

Table 29. On Figure 17 it can be seen that the model fits the data well as the predicted line approximates the observed data. This finding is verified by an adjusted R^2 value of 0.8072 which is very large. Note that 33% of the variability is explained by the fixed effects while 67% is explained by the random effects. The importance of the inclusion of random effects is also stressed by the heterogeneity of the predicted outcomes for randomly selected hospitals (Figure 18).

Table 28.Significance of parameters in the final model for DDD per 100 hospital days.

Parameter	p-value	Parameter	p-value
sev	0.0258	FIN	0.0022
pt_ori	0.3328	FIN*los	0.0026
dis_st	0.4272	FIN*pt_ori	0.0736
age	0.0202	FIN*dis_st	0.0263
los	0.4639	FIN*age	0.0026
time	0.6995	AW	0.0010
time*sev	0.0792	AW*pt_ori	0.0093
time*dis_st	0.0432	AW*age	0.0054
time*age	0.0326		

Table 29. Parameter estimates and standard error for parameters in the final model for DDD per 100 hospital days.

Effect	Estimate	SE	Effect	Estimate	SE	Effect	Estimate	SE
intercept	110.0800	12.4205	time*sev1	0.0078	0.0257	FIN*dis_st1	-0.4575	0.2057
sev1	0.0300	0.1895	time*sev3	0.0565	0.0298	FIN*ag1	-0.0240	0.0433
sev3	-0.3330	0.2207	time*sev4	-0.0600	0.0350	FIN*ag2	-0.1201	0.0586
sev4	0.6869	0.2608	time*dis_st1	0.1548	0.0765	FIN*ag3	-0.6792	0.2343
los	0.4159	0.5677	time*ag1	-0.0378	0.0627	FIN*ag4	0.0499	0.0359
pt_ori2	-0.0713	0.0625	time*ag2	0.0565	0.0652	AW	-7.7108	2.3298
pt_ori3	0.0643	0.0773	time*ag3	-0.2246	0.1021	AW*pt_ori2	-0.1367	0.0452
pt_ori4	-0.0694	0.0788	time*ag4	0.0870	0.0458	AW*pt_ori3	-0.0990	0.0593
dis_st1	-0.3209	0.4039	FIN	7.9860	2.6029	AW*pt_ori4	0.0481	0.0606
ag1	-0.1229	0.1784	FIN*los	-1.0438	0.3461	AW*ag1	0.0768	0.0732
ag2	-0.4775	0.1835	FIN*pt_ori2	0.2752	0.1306	AW*ag2	-0.0025	0.0773
ag3	0.2563	0.2222	FIN*pt_ori3	0.1858	0.1817	AW*ag3	0.4977	0.1639
ag4	-0.2140	0.1045	FIN*pt_ori4	-0.2535	0.1808	AW*ag4	-0.1099	0.0571
time	-0.9225	2.3837						

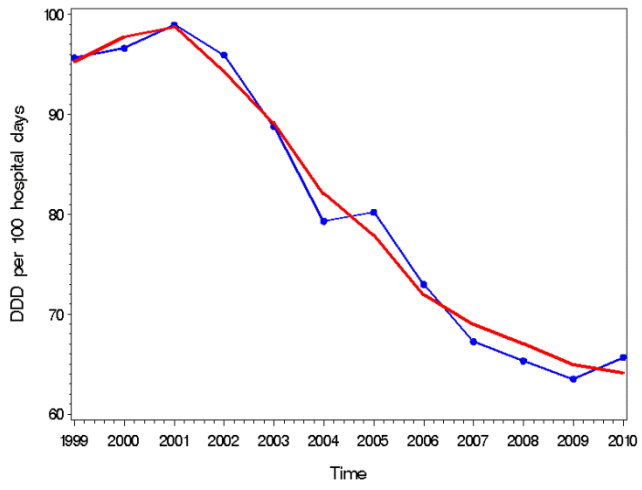

Figure 17. Average observed (blue) and predicted (red) evolution of DDD per 100 hospital days over time.

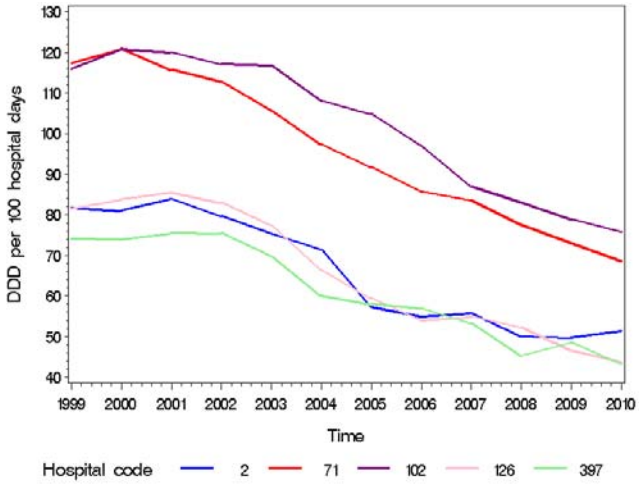

Figure 18.Predicted evolution of DDD per 100 hospital days over time for five randomly selected hospitals.

7.8.4.2.2 Oral/parenteral ratio

Likelihood ratio tests showed that the change-point for 2001 was redundant (p-value = 0.9884). After removal of the change-point variable AW and its interactions, likelihood ratio tests indicated that the change-point for AMT was also redundant (p-value = 0.0972). After removal of the change-point variable AMTIN and its interactions, likelihood ratio tests indicated that the change-point for 2006 was required (p-value = 0.0310). For this reason change-point variable FIN and its interactions remained in the model. The AR(1)residual structure could not be simplified (p-value < 0.0001). Likelihood ratio tests based on an equally weighted mixture of χ_1^2 and χ_2^2 showed that both random effects were required (p-values < 0.0001). Removal of redundant fixed effects resulted in the final model. Addition of the size variable to this model appeared to be unnecessary (p-value = 0.4235).

Significance of the parameters in the final model is shown in Table 30. Some insignificant main effects were kept in the model because they are part of a significant interaction term. Estimates for all included parameters are given in Table 31. On Figure 19 it can be seen that the model fits the data well as the predicted line approximates the observed data. This finding is verified by an adjusted R^2 value of 0.7559 which is very large. Note that 14% of the variability is explained by the fixed effects while 86% is explained by the random effects. The importance of the inclusion of random effects is also stressed by the heterogeneity of the predicted outcomes for randomly selected hospitals (Figure 20).

Table 30.Significance for parameters in the final model for oral versus parenteral antibiotic consumption.

Parameter	p-value	Parameter	p-value
sev	0.1038	time*sev	0.0031
gender	0.5360	time*los	0.0111
dis_st	<.0001	FIN	0.0047
age	0.0420	FIN*gender	0.0041
los	0.2625	FIN*los	0.0022
time	0.0006		

Table 31. Parameter estimates and standard error for parameters in the final model for oral versus parenteral antibiotic consumption.

Effect	Estimate	SE	Effect	Estimate	SE	Effect	Estimate	SE
intercept	0.5251	0.1523	dis_st1	-0.0114	0.0021	time*sev1	-0.0011	0.0003
sev1	0.0058	0.0024	ag1	-0.0011	0.0007	time*sev3	-0.0002	0.0004
sev3	0.0040	0.0027	ag2	-0.0016	0.0007	time*sev4	-0.0008	0.0004
sev4	0.0015	0.0031	ag3	-0.0014	0.0008	time*los	-0.0053	0.0021
female	0.0008	0.0014	ag4	-0.0006	0.0003	FIN	-0.1223	0.0432
los	0.0140	0.0125	time	0.0685	0.0193	FIN*female	0.0027	0.0009
						FIN*los	0.0151	0.0049

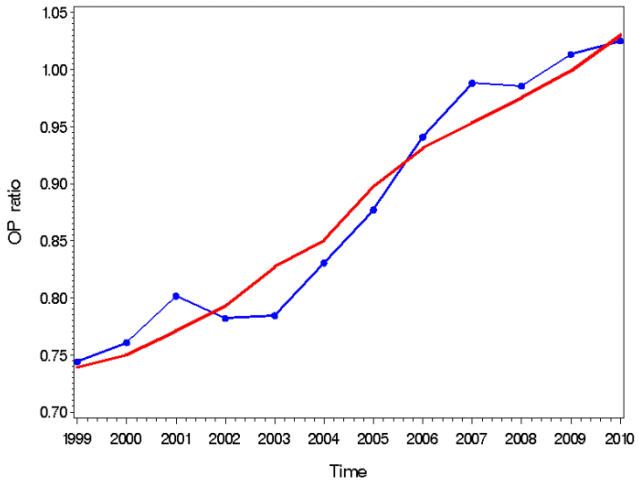

Figure 19. Average observed (blue) and predicted (red) evolution of the oral versus parenteral antibiotic consumption over time.

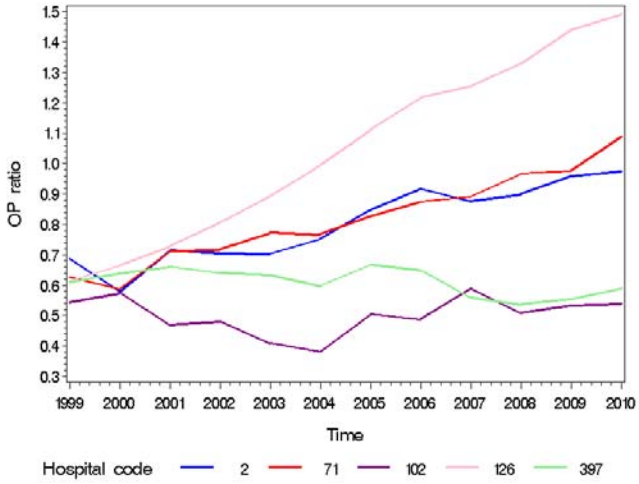

Figure 20.Predicted evolution of the oral versus parenteral antibiotic consumption over time for five randomly selected hospitals.

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