Antibiotic prescribing for LRTIs and resistance of *Streptococcus pneumoniae* in Flemish primary care

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ABSTRACT

Inleiding: *S. pneumoniae* is een belangrijke bron van morbiditeit en mortaliteit en antibiotica-resistentie is een groeiend probleem. De meeste richtlijnen bevelen amoxicilline aan als eerste keuze voor lageluchtweginfecties (LLWI) bij volwassenen zonder risicofactoren. Ons doel was om de evolutie van het antibiotica voorschrijfgedrag van Vlaamse huisartsen voor LLWI bij volwassenen tussen 2001 en 2015 te bestuderen alsook het dragerschap en resistentie van *S. pneumoniae* in een gezonde populatie in de eerste lijn.

Methode: Alle LLWI bij volwassenen tussen 2001 en 2015 werden uit Intego geselecteerd en geëvalueerd voor antibioticavoorschrift en co-variabelen. Patiënten werden verdeeld in risicogroepen. Voor de bepaling van dragerschap en resistentie werden nasale wissers van gezonde personen ≥4j afgenomen bij gezonde personen gedurende de winter 2010-2011 in Intego-praktijken. De wissers werden onderzocht op dragerschap van *S. pneumoniae* en getest op resistentie tegen verschillende antibiotica. Daarnaast werd sociodemografische informatie van de deelnemende personen verzameld.

Resultaten: Bijna 90,000 LLWI werden geregistreerd in Intego. Het voorschrijven van antibiotica daalde van 84.13% in 2001-2005 naar 78.13% in 2011-2015. Amoxicilline werd voorgeschreven in 22.7% van de gevallen, terwijl amoxicilline-clavulaanzuur goed was voor 24.9% van alle voorschriften. Hoogrisico-patiënten kregen vaker amoxicilline-clavulaanzuur en fluorochinolones, terwijl laagrisico-patiënten eerder amoxicilline en macroliden kregen voorgeschreven. Voor het dragerschap werden 3025 wissers verzameld, waarvan 1.45% drager was van *S. pneumoniae.* Een jongere leeftijd (≤ 18j) en samenleven met kleine kinderen was significant geassocieerd met dragerschap, terwijl regelmatig naar de huisarts gaan een beschermende factor bleek te zijn. De meeste resistentie werd gevonden voor cefaclor (77.27%) en 29.55% van de wissers vertoonde multidrug-resistentie. Resistentie voor amoxicilline werd gevonden in bijna 16% van de gevallen. Geen van de variabelen was significant geassocieerd met resistentie.

Besluit: Er wordt nog te veel antibiotica voorgeschreven voor LLWI in de Vlaamse huisartsenpraktijken. Ondanks verschillende campagnes verandert er weinig. Meer veelzijdige en gevarieerde interventies zijn nodig om het antibioticagebruik verder te verminderen. De keuze van antibioticum is afhankelijk van de risico-evaluatie, maar bij alle risicogroepen worden de richtlijnen te weinig gevolgd. De keuze voor amoxicilline als voorkeur bij LLWI zonder risicofactoren in België is nog steeds aanvaardbaar, maar dit kan een probleem worden in de toekomst door de toenemende resistentie van *S. pneumoniae*. Het monitoren van resistentie in de eerste lijn is aan te raden om de richtlijnen aan te passen in functie van de resistentiepatronen.

ABSTRACT

Introduction: *S. pneumoniae* is a major source of morbidity and mortality and antibiotic resistance is a growing health concern. Most guidelines still recommend amoxicillin as first choice for LRTIs without risk factors. We aimed to evaluate the antibiotic prescription behaviour for LRTIs in adults in Flemish primary care between 2001 and 2015 based on the Intego-data collection system and additionally evaluate carriage and resistance of commensal *S. pneumoniae* in a healthy population.

Methods: In Intego, all LRTIs diagnosed in adults between 2001 and 2015 were selected and evaluated for antibiotic prescription and co-variables. Patients were divided in risk groups. Assessment of carriage and resistance was evaluated by collecting nasal swabs from healthy persons aged ≥4y during winter 2010-2011 in Intego-practices. The swabs were assessed for carriage of *S. pneumoniae* and tested for resistance against several antibiotics. Additionally, sociodemographic variables of the subjects were collected.

Results: Almost 90,000 events of LRTIs were registered in Intego. Antibiotic prescription behaviour declined from 84.13% in 2001-2005 to 78.13% in 2011-2015. Amoxicillin was prescribed in 22.7% of all cases, while amoxicillin-clavulanate accounted for 24.9% of all antibiotic prescriptions. High-risk patients were prescribed more amoxicillin-clavulanate and fluoroquinolones, while low-risks patients received more amoxicillin and macrolides. For carriage, 3025 swabs were collected, of which 1.45% (n=44) was carrier of *S. pneumoniae*. Having a younger age (≤ 18y) and living with little children were significantly associated with carriage, while frequently visiting a GP pointed out to be a protective factor. Most resistance was found for cefaclor (77.27%), while 29.55% showed multi-drug resistance. Resistance for amoxicillin was found in almost 16% of carriers. None of the variables were significantly associated with resistance.

Conclusion: In Flemish primary care, too many antibiotics are still prescribed for LRTIs. Despite several campaigns, little is changing. More and multifaceted interventions are needed to further reduce antibiotic consumption. Choice of antibiotic is dependent of risk assessment, but guideline compliance is scarce for all risk groups. The choice to recommend amoxicillin for LRTIs without risk factors in Belgium is still reliable, but can become a problem in future due to growing resistance of *S. pneumoniae*. Monitoring of resistance in primary care is recommended to adapt guidelines in function of resistance patterns.

INTRODUCTION

Lower respiratory tract infections (LRTIs), in particular community-acquired pneumonia (CAP), are a cause of considerable morbidity and mortality in young children and adults, especially in the elderly and in COPD patients. LTRIs were the fourth cause of adult death worldwide in 2014 (1), and the second cause of death in children under five in 2015 (2). In Europe, the overall annual incidence of CAP in adults ranges between 1.07 and 1.7 per 1,000 person-years (3). Elderly are more susceptible for LRTIs, with an incidence rate of up to 14 per 1,000 person-years for adults aged ≥65y (3). *Streptococcus pneumoniae* is the most common cause of CAP, as confirmed in several epidemiological studies (4,5), accounting for approximately 22% of LRTI deaths (6). Furthermore, pneumococci can cause invasive pneumococcal disease (IPD), such as meningitis, sepsis or bacteraemia. Most data on LRTIs, CAP and aetiology are collected in hospitals. Data in ambulatory patients are limited because diagnostic tools such as chest radiography or sputum are usually not carried out in primary care, underestimating the incidence and burden of pneumococcal disease and LRTIs in general practice (5). Flamaing et al. (7) conducted a multicentre prospective observational study in Belgium to assess the proportion of *S. pneumoniae* in LTRIs during two winter seasons (2011-2013). Using urinary antigen detection, 5% of LTRIs were caused by *S. pneumoniae*. Moreover, pneumococcal infection was associated with a significant increase in morbidity (7).

S. pneumoniae is a common part of the human nasopharyngeal flora. Many individuals in a population are colonised with *S. pneumoniae* at any given time, and probably all individuals have been colonised at least once during the first two years of life (8,9). Carriage rates are particularly high in children attending day care centres due to crowding (10,11). Other places where transmission of the pathogen is facilitated are hospitals and prisons (12,13). Nevertheless, nasopharyngeal carriage of *S. pneumoniae* is considered to be a major factor in the horizontal transmission of the pathogen. In addition, Gray et al. performed a longitudinal study on carriage patterns of *S. pneumoniae* and they pointed out that infections generally occur after preceding nasopharyngeal colonisation with a newly-acquired strain (14). Besides age and crowding, several other risk factors seem to influence carriage. Those independent variables for pneumococcal colonisation are ethnicity, sex, family size (having siblings), smoking, recent antibiotic use and socioeconomic status (11,15-17). Due to the lack of diagnostic tests in primary care as mentioned above, antibiotic treatment is initiated empirically when a bacterial LTRI is presumed. These antimicrobials must tackle *S. pneumoniae* as most common pathogen. Therefore, resistance patterns of *Streptococcus pneumoniae* in community are useful to decide what type of antibiotic treatment is chosen (18).

Antimicrobial resistance (AMR) is increasing worldwide and has become a global public health concern. The most important reasons for the growing resistance are the excessive use of antibiotics by humans, mostly inappropriate (19,20), and the excessive antibiotic use in livestock breeding (21). Most studies investigating resistance are carried out in hospitals. Nevertheless, 90% of antibiotics are used in primary care and resistance patterns probably differ between general population and hospitalized patients. So identifying the prevalence and resistance in community samples is important to adapt guidelines, to promote appropriate use of antibiotics and to prevent the development of further AMR (22,23). Given the horizontal transmission of *S. pneumoniae*, nasopharyngeal carriage of resistant strains can serve as an indicator of the prevalence of resistance in the community. This approach has been used in several populations (10,24-25).

In this context, the APRES-study (Appropriateness of Prescribing Antibiotics in Primary Health Care in Europe with Respect to Antibiotic Resistance) (26,27) was conducted in 2010. The objective of this EU-study was to identify the prevalence and resistance pattern of commensal *S. aureus* and *S.*

pneumoniae in a healthy community-based population in nine European countries with different rates and patterns of antibiotic prescription behaviour.

The present study aimed to evaluate the antibiotic prescription behaviour for LRTIs in adults in Flemish primary care between 2001 and 2015 based on the Intego-data collection system (Intego: integrated computerized network https://intego.be/nl) (28). Type of antimicrobial and co-variables such as gender, age, pneumococcal vaccination and comorbidity were taken into account. Additionally, the Belgian results of the APRES-study were investigated. We aimed to interpret these results together with the antibiotic prescription behaviour and to formulate implications for the future.

MATERIALS AND METHODS

General methods of Intego

Data were obtained from Intego, a Flemish general practice-based morbidity registration network. Currently 111 General Practitioners (GP), all using the medical software program Medidoc®, are collaborating in the Intego project. These GPs work in 44 practices evenly spread throughout Flanders, the northern part of Belgium. The Intego GPs prospectively and continuously register all new diagnoses together with new drug prescriptions, laboratory test results, vaccinations and some sociodemographic information (including sex and year of birth) using computer-generated keywords linked to international codes (ICD-10, ICPC2, ATC). The participating GPs receive yearly quality checks based on peer comparison and feedback on the quality of their data. Using specially framed extraction software, new data are collected from the computers of the participating GPs and entered into a central database. Registered data are continuously updated, accumulating a history for each patient.

Data selection

Between 2001 and 2015, all cases of acute pneumonia (ICPC2 R81) and acute bronchitis (ICPC2 R78) in adults (≥18y) were extracted from Intego and divided into 5-year periods. For all cases, relevant co-variables were checked: age, gender, pneumococcal vaccination (ATC J07AL) and comorbidity. For relevant morbidities, we categorized patients into 3 categories with increasing risk: immuno-compromising conditions, immunocompetent adults with chronic medical conditions and adults without these conditions (29) (see Addendum 1).

Furthermore, we evaluated the percentage of LRTIs where an antimicrobial therapy was initiated. Only the first antimicrobial product for a newly diagnosed LRTI was selected. We determined the prescription percentage of tetracyclines (ATC J01AA), amoxicillin (ATC J01CA04), amoxicillin-clavulanate (ATC J01CR02), beta-lactamase sensitive penicillins (ATC J01CE), beta-lactamase resistant penicillins (ATC J01CF), second-generation cephalosporins (ATC J01DC), ceftazidime (ATC J01DD02), neo-macrolides (ATC J01FA), clindamycin (ATC J01FF01), cotrimoxazole (ATC J01EE01) and fluoroquinolones (ATC J01MA).

APRES study design

The European APRES study assessed the prevalence of *S. aureus* and *S. pneumoniae* carriage in healthy primary care patients in nine European countries (26,27). The study design is described elsewhere (30). Briefly, 17-27 GP practices in each country were recruited, representative for the GP population in that country. All participating practices were members of national General

Practitioners Networks; in Belgium the GPs were recruited among members participating in Intego. Between November 2010 and July 2011, they were asked to collect a nasal swab from 200 patients, aged 4 or older, who consulted for a non-infectious disorder. Patients with recent antimicrobial therapy or hospital admission (previous 3 months), immunocompromised patients (e.g. diabetes mellitus) and patients in nursing homes were excluded.

In Belgium, a charcoal swab (Transystem, 114 C; Copan Italia, Brescia, Italy) of both anterior nares was taken from each subject and sent to the microbiological laboratory of the University Hospital of Antwerp within 48 hours. When *S. pneumoniae* was isolated, the sample was sent to the central APRES laboratory of the Maastricht University Centre, The Netherlands. There the samples were tested for antibiotic resistance according to the EUCAST standard (31). The examined antibiotics were: penicillin, amoxicillin, amoxicillin-clavulanate, cefaclor, ceftazidime, cefuroxime, ciprofloxacin, moxifloxacin, clarithromycin, clindamycin, tetracycline and cotrimoxazole. Multidrug resistance was defined as a strain resistant to three or more antibiotic classes.

Furthermore, subjects had to complete a questionnaire, providing sociodemographic information (sex, age, educational level, profession and location of residence) and assessing possible risk factors for *S. pneumoniae* or *S.aureus* carriage: having young children (<5 years) in the family, keeping cattle, having a chronic skin condition (e.g. eczema, psoriasis, furunculosis) and working in nursery, health care or livestock breeding. Additionally, the number of GP visits in the last year, and vaccination status of pneumococci and influenza was assessed.

Statistical analysis

Data were presented as numbers and frequencies. Comparisons between two categories of subjects were performed using the Chi-Square Independency or Fisher's Exact test for categorical variables. *P*-values of < 0.05 were considered significant. The statistical analyses were performed using Stata 11 (StataCorp, College Station, TX).

Ethical considerations

All subjects provided written informed consent. For children, both child and parents gave their approval. In Belgium, the study was approved by the Medical Ethics Committee of the University Hospitals of KU Leuven.

RESULTS

During the period 2001-2015, 88,340 events of lower respiratory tract infections (LRTIs) were registered in Intego. Most infections occurred in low-risk patients (57.7%) followed by medium-risk patients (36.4%) and high-risk patients (5.9%)(Table 1). Over the 15-year period, pneumococcal vaccination coverage was 16.8%. Vaccination rate in high-risk patients was higher than in low-risk patients (27.7% vs. 4.3% resp.; $p<0.0001$; RR 6.47, 95% CI [6.10-6.87]) and a steady increase of vaccination rate was observed (14.6% in 2001-2005 vs. 19% in 2011-2015; $p<0.0001$).
Antibiotics were prescribed in 80.6% of all cases, with a slightly higher antibiotic prescription rate in high-risk patients compared to low-risk patients (83.3% vs. 81.5% resp.; $p=0.005$). Antibiotic prescription for LRTIs declined from 84.1% in 2001-2005 to 78.1% in 2011-2015 ($p<0.0001$). High-risk patients more often needed more than 1 different antibiotic per event of LRTI (10.1% vs. 7.5% for high-risk and low-risk respectively; $p<0.0001$).

Table 1. Results of the Intego data collection system.

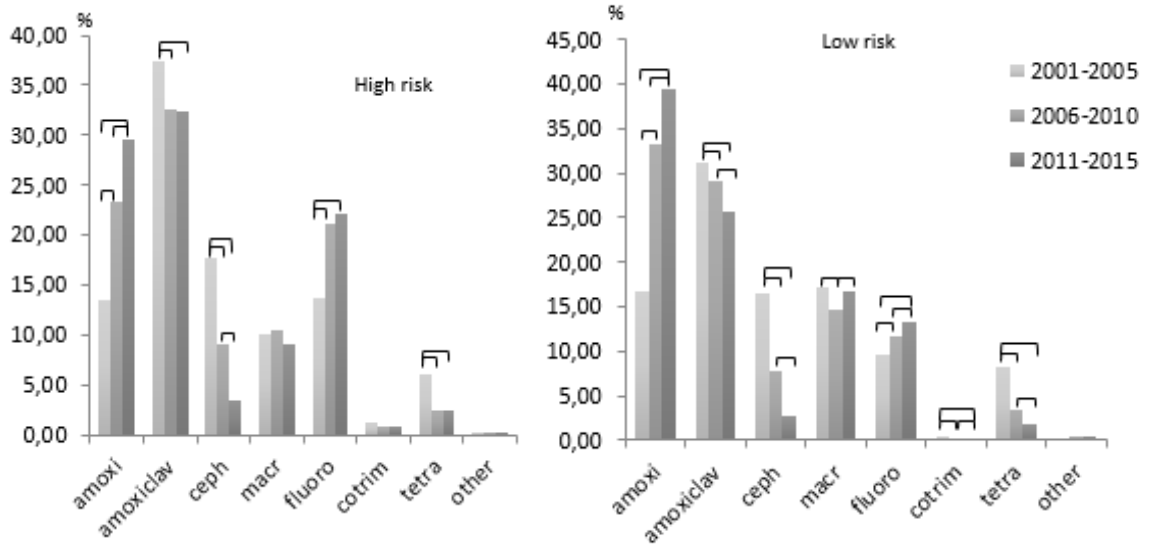
Risk group	N of patients with LRTI	Percentage	Pneumococcal vaccination (%)	Antibiotic prescription (%)	> 1 AB (%)
High	5242	5.9%	1454 (27.6%)	4357 (83.3%)	528 (10.1%)
Medium	32114	36.4%	5912 (18.4%)	24657 (76.8%)	2446 (7.6%)
Low	50984	57.7%	2185 (4.3%)	41569 (81.5%)	3839 (7.5%)

AB: antibiotic

The choice of antibiotic varied across the risk groups with more amoxicillin and macrolides prescribed in low-risk patients, and more amoxicillin-clavulanate and fluoroquinolones in high-risk patients (Figure 1). Furthermore, during the study period, an evolution was seen in prescription behaviour in favour of amoxicillin and fluoroquinolones and at the expense of amoxicillin-clavulanate and macrolides.

Amoxicillin was prescribed in 22.7% of all cases, while amoxicillin-clavulanate accounted for 24.0% of all antibiotic prescriptions. Results of the stratified analysis are listed in Table 2. In 2011-2015, amoxicillin was significantly more prescribed in non-vaccinated persons in all risk groups while in 2001-2005 this was also the case except in the low-risk group where vaccinated people were more often prescribed amoxicillin. Amoxicilline-clavulanate was statistically more often prescribed in vaccinated people although not consistently in all risk groups and over time. (Table 2)

Figure 1. Choice of antibiotic prescription in high-risk (left) and low-risk patients (right) between 2001-2015.



Amoxi: amoxicillin; amocla: amoxicillin-clavulanate; ceph: cephalosporins; macr: macrolides; fluoro: fluoroquinolones; cotrim : co-trimoxazole; tetra : tetracyclines. Intervals marked by brackets are significant (p <0.05).

Table 2. Stratified analysis of amoxicillin (top) and amoxicillin-clavulanate (bottom) prescription per risk group and vaccination status.

	Total		**2001-2005 N antibiotic prescriptions (% amoxi)**			**2011-2015 N antibiotic prescriptions (% amoxi)**		
Risk group	**N Antibiotic prescription (% amoxi)**	***p*-value RR (95% CI)**	**Vaccina-ted**	**Not vaccina-ted**	***p*-value RR (95%CI)**	**Vaccina-ted**	**Not vaccina-ted**	***p*-value RR (95%CI)**
High	2799 (22.15)	*High vs. medium* *p*<0.0001 1.06 (1.03-1.08)	347 (8.07)	956 (15.59)	*p*= 0.0007 0.52 (0.35-0.76)	474 (19.41)	1022 (34.34)	*p*<0.0001 0.57 (0.46-0.69)
Medi um	16073 (26.32)	*Medium vs. low* *p*=0.04 1.01 (1.00-1.02)	1371 (13.20)	6825 (15.88)	*p*= 0.01 0.83 (0.72-0.96)	1735 (30.32)	6142 (39.71)	*p*<0.0001 0.76 (0.71-0.83)
Low	27351 (27.25)	*High vs. low* *p*<0.0001 1.07 (1.05-1.09)	481 (20.79)	14103 (16.46)	*p*= 0.01 1.26 (1.07-1.51)	751 (34.49)	12016 (39.71)	*p*=0.005 0.86 (0.79-0.96)

	Total		**2001-2005 N antibiotic prescriptions (% amocla)**			**2011-2015 N antibiotic prescriptions (% amocla)**		
Risk group	**N Antibiotic prescription (% amocla)**	**p-value RR (95% CI)**	**Vaccina-ted**	**Not vaccina-ted**	***p*-value RR (95%CI)**	**Vaccina-ted**	**Not vaccina-ted**	***p*-value RR (95%CI)**
High	2799 (34.73)	*High vs. medium* *p*=0.0001 0.95 (0.92-0.97)	347 (41.79)	956 (35.88)	*p*= 0.06 1.16 (1.00-1.35)	474 (36.50)	1022 (30.43)	*p*=0.02 1.20 (1.03-1.39)
Medi um	16073 (31.07)	*Medium vs. low* *p*<0.0001 0.97 (0.95-0.98)	1371 (35.81)	6825 (33.44)	*p*= 0.1 1.07 (0.99-1.16)	1735 (30.78)	6142 (27.47)	*p*=0.007 1.12 (1.03-1.22)
Low	27351 (38.64)	*High vs. low* *p*<0.0001 0.91 (0.89-0.94)	481 (27.03)	14103 (31.38)	*p*= 0.048 0.86 (0.74-1.00)	751 (26.23)	12016 (25.63)	*p*=0.75 1.02 (0.9à-1.16)

Amoxi: amoxicillin; Amocla: amoxicillin-clavulanate.

Concerning carriage, 3132 nose swabs were collected in Belgium. Of those, 3025 were eligible for analysis, because 101 patients had incomplete or mismatch data and 6 patients were less than 4 years old. Of all subjects, 54.2% were women. With respect to age distribution, 4.66 % were aged 4-18 y., 58.34% were aged 19-64 y. and 36.93% were aged ≥65y. Sociodemographic characteristics are shown in Table 3.

Table 3. Sociodemographic characteristics of the APRES-study population

	N (%)		**N (%)**
Study population	3025	Employment	
Men	1379 (45.6)	Livestock	45 (1.49)
Aged 4-18y	141 (4.66)	Healthcare	139 (4.60)
Aged 19-39y	531 (17.55)	Nursery	67 (2.21)
Aged 40-64y	1234 (40.79)	Other	2774 (91.70)
Aged ≥ 65y	1117 (36.93)	Living with children (0-5y)	306 (10.12)
Vaccination		Nasal carriage of	
Pneumococci	493 (16.3)	*S. pneumoniae*	44 (1.45)
Influenza 2009-2010	1486 (49.12)	*S. aureus*	582 (19.30)
Influenza 2010-2011	1376 (45.49)	*MRSA*	12 (0.4)

S. pneumoniae was present in 44 swabs (1.45%). Resistance patterns are listed in Table 4. Highest resistance was found for cefaclor (77.27%), followed by cefuroxime and penicillin (both 25%). No resistance was shown for fluoroquinolones. Of the 44 swabs, 13 swabs (29.55%) showed multidrug resistance and 9 swabs (20.45%) were susceptible for all antibiotics tested (see Addendum 2).

Table 4. Resistance of *S. pneumoniae* isolates (n=44)

Antibiotic	**Percent (n)**	**Antibiotic**	**Percent (n)**
Penicillin	25 (11)	Cefaclor	77.27 (34)
Amoxicillin	15.91 (7)	Ceftazidime	22.73 (10)
Amoxicillin/clavulanate	6.82 (3)	Cefuroxime	25 (11)
Cotrimoxazole	20.45 (9)	Clarithromycin	22.73 (10)
Clindamycin	18.18 (8)	Ciprofloxacin	0 (0)
Tetracycline	20.45 (9)	Moxifloxacin	0 (0)

Results of univariate analysis are shown in Table 5. Having a younger age (< 18y) and living with little children were significantly associated with carriage of *S. pneumoniae*, while a trend was observed towards a higher risk of carriage when working in nursery. Furthermore, carriers of *S. pneumoniae* visited their GPs significantly less often in the past year than non-carriers. No variables were significantly associated with any resistance or multi-drug resistance.

Table 5. Regression model for carriers of *S. pneumoniae*, carriers with any resistance and multi-drug resistant carriers.

Variable	**Subvariable**	***S. pneumoniae* carrier**		**Carrier with resistance against one or more AB**		**MDR carrier**	
		OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**	**OR (95% CI)**	***p*-value**
Sex	Male	1.56 (0.86-2.85)	0.170	1.07 (0.24-4.66)	1.000	2.11 (0.53-8.32)	0.335
	Female	1.0		1.0			
Age	Child (4-18y)	3.33 (1.38-8.00)	0.015	1.33 (0.14-13.09)	1.000	1.23 (0.20-7.70)	1.000
	Adult (> 18y)	1.0		1.0			
Job	Healthcare	1.53 (0.47-5.01)	0.454	/	1.000	5.45 (0.45-66.31)	0.204
	Nursery	3.34 (1.01-11.05)	0.072	/	1.000	0	0.544
	Other	1.0		1.0		1.0	
Vaccination	Pneumococci	0.94 (0.42-2.12)	1.000	1.66 (0.17-15.82)	1.000	0.95 (0.16-5.63)	1.000
	Influenza 2009	0.64 (0.35-1.18)	0.173	2.63 (0.48-14.49)	0.445	0.62 (0.16-2.44)	0.735
	Influenza 2010	0.61 (0.33-1.14)	0.130	1.04 (0.22-4.93)	1.000	0.25 (0.05-1.33)	0.162
Environment	Living with children 0-5y	3.39 (1.73-6.66)	0.001	3.67 (0.41-33.02)	0.405	2.14 (0.53-8.68)	0.295
	Chronic skin disease	1.00 (0.24-4.19)	1.000	/ (n=1)		/	
Living in country	<3years	2.31 (0.31-17.31)	0.364	/ (n=2)		/	
	≥ 3 years	1.0		/		/	
Number of GP visits last year	None	1.0		1.0		1.0	
	1-4	0.33 (0.12-0.89)	0.040	4.50 (0.60-33.71)	0.287	0.39 (0.05-3.04)	0.569
	≥5	0.22 (0.08-0.61)	0.018	6.00 (0.67-53.68)	0.131	0.55 (0.07-4.56)	0.613

AB: antibiotics; MDR: multi-drug resistance; OR: odds ratio; CI: confidence-interval

DISCUSSION

To our knowledge, our study is the first study on this scale that investigated antibiotic prescription behaviour for LRTIs in adults in primary care. Our results indicated that for 80.6% of LRTIs an antimicrobial therapy was initiated. The choice of the antibiotic differed depending on comorbidity. Over the 15-year period, a slightly positive evolution was observed towards fewer antibiotic prescriptions and more compliance to guidelines, but there is clearly room for further improvement.

Previous studies showed remarkable differences throughout Europe with respect to antibiotic prescribing for LRTIs (32-34). In a 13-country cross-sectional prospective observational study in 14 primary care research networks, 3,368 adults in primary care with a newly diagnosed LRTI were recruited and followed for 28 days (35). Overall antibiotic prescription was 52.7%, ranging from 20.6% to 88%, with a wide variation in antibiotic classes prescribed. In that study Belgium, represented by a GP network in Antwerp, showed an antibiotic prescription rate of 30%, which was among the lowest in the 13 countries. These results are in high contrast with the 80.6% prescribing rate observed in the present study, which clearly positions Belgium among the largest prescribers. This difference might be on the one hand the consequence of regional differences and on the other hand the consequence of the prospective nature of the European study, which may have influenced prescribing behaviour. Also the GPs in the present study may handle a different case definition for LRTI selecting a population with more severe cases of LRTI. However, in 2015 the incidence of LRTI as recorded in Intego was 50.5 per 1,000 persons per year, which is in line with the reported incidence of acute bronchitis and CAP among adults in general practice in Europe: 30-50 per 1,000 people per year and 1.7-11.6 cases per 1,000 people per year respectively (36).

Data from ESAC-Net (European Surveillance of Antimicrobial Consumption Network) further support our findings of a high antibiotic consumption in Belgium (37). In 2012 Belgium was ranked third in Europe in terms of antibiotic consumption after Greece and Romania. Antibiotic consumption in the community rose from 25.4 DDD/1,000/D in 1997 to 29.8 DDD/1,000/D in 2012, despite public campaigns aiming to sensitize the population. The increase was driven mostly by the expanded use of beta-lactam antibiotics (37). Between 2008 and 2012, Belgium was one of the five European countries that showed a significant increase in antibiotic consumption. This is in sharp contrast with its neighbouring country, The Netherlands, where the lowest antibiotic prescription of Europe was found with a DDD of 11.3 DDD/1,000/D in 2012 (37). Needless to mention there is still a long way to go in Belgium.

Belgian and Dutch guidelines, along with British and most other guidelines, state that no antibiotic treatment is needed for an acute uncomplicated LRTI (38,39). In a randomised controlled trial, 2,061 adults with an acute LRTI were randomly assigned to receive either amoxicillin (1g three times a day for 7 days) or placebo (40). The results indicated that in case pneumonia was not suspected clinically, amoxicillin provided little benefit for acute lower-respiratory-tract infection in primary care but caused more side effects (40,41). These findings further question the need for prescribing antibiotics in uncomplicated LRTI in adults. An important question in the light of antibiotic prescription is the aetiology of LRTI. In primary care, few studies have been done, partly due to a lack of diagnostic tests. A study in Denmark in 364 adults showed radiographic signs of pneumonia in 13% and bacterial growth out of sputa in 19% (42). Creer et al. (43) investigated 80 adults with LRTI in primary care in UK, and they found a bacterial cause in 26% of cases. This percentage was also estimated by an American study in patients with acute respiratory tract infections who seek medical attention (44). Given the average European prescription rate of 52.7% for LRTI (35), there is still a lot of space for further improvement.

When pneumonia is suspected, the Belgian guideline (BAPCOC) (2012) recommends amoxicillin as first choice for lower respiratory infections in low-risk adults, while amoxicillin-clavulanate is preferred in adults with comorbidity (38). This is in contrast with the Dutch guideline (NHG) (2010) where amoxicillin is preferred for all adults independent of comorbidities (39). The NICE guideline (45) (2014) has yet another recommendation, more specifically amoxicillin for low-severity CAP, dual therapy with amoxicillin and macrolide for moderate-severity CAP and amoxicillin-clavulanate for high-severity CAP. However, in Belgium the most common used guidelines are the Belgian and Dutch guidelines. Noteworthy is that both the Belgian and Dutch guidelines were published in the second half of the investigated period. In our study, the overall antibiotic of choice was amoxicillin-clavulanate in 24.0% of all cases, while amoxicillin accounted for 22.7% of all antibiotic prescriptions. Other common prescribed antibiotics were macrolides for 11.3% and fluoroquinolones for 10.4% of all cases. Furthermore, a remarkable evolution was seen for amoxicillin and amoxicillin-clavulanate, for which prescription rate rose from 20.3% to 36.6% and declined from 27.1% to 20.9% respectively. In the GRACE-study (35), amoxicillin was the most common prescribed antibiotic for the treatment of LRTI, accounting for 29% of all prescriptions. Macrolides were prescribed for 26% of patients, followed by amoxicillin-clavulanate for 15% and tetracyclines for 14%. It should be noted though that marked differences existed between the GP networks participating in the study with for example amoxicillin accounting for 3% to 83% of antibiotic prescriptions (35).

From the present study it seems that GPs with regard to their choice of antibiotic indeed differentiate between patients without and with comorbidity as recommended by the BAPCOC guideline. However, the choice of antibiotic is in the majority of cases not in line with the recommendations. From the patients who were prescribed an antimicrobial therapy, a bit less than one third of low-risk patients were prescribed amoxicillin, while amoxicillin-clavulanate was prescribed for 31.4% and 33.0% for medium-risk and high-risk patients respectively. Also the frequency of other commonly prescribed antibiotics differed in function of comorbidity. For example, macrolides were prescribed in 9.8 % of high-risk patients, 11.4% of medium-risk patients and 16.1% of low-risk patients. In contrast, fluoroquinolones were prescribed in 19.2% of high-risk patients, 14.9% of medium-risk patients and 11.4% of low-risk patients. Furthermore an association between vaccination status and choice of antibiotic was demonstrated. Amoxicillin was more given in non-vaccinated patients while vaccinated patients were more often prescribed amoxicillin-clavulanate. This could be explained by the observation that the pneumococcal vaccination rate rose together with the risk status of patients. So patients more at risk are more likely to be vaccinated and to receive a broad-spectrum antibiotic.
Previous studies already confirmed that comorbidity is an independent factor in deciding whether or not to prescribe an antimicrobial therapy (46-50). Besides comorbidity, other co-variables were also found to have an influence on antibiotic prescribing. For example, Stanton et al. (51) demonstrated that smoking is an independent factor to decide whether or not to prescribe an antibiotic (RR 1.44; p =0.005).

Furthermore, in this study the Belgian results of the APRES-project were evaluated. Overall carriage of *S. pneumoniae* in Belgium was 1.45%, and carriage in men was more prevalent than carriage in women (1.81% vs. 1.17% resp.). These results are comparable with the European results of the APRES-project, where the prevalence of carriage ranged between 1.2% and 4.4%, and occurred more often in men compared to women (3.7% vs. 2.7% resp.) (27). In the European study, carriage in children under ten was more prevalent than carriage in older children and adults (27.2% vs. 1.9% resp.). In Belgium, children had only a slightly higher carriage rate (4.58% and 1.31% for children <18y and adult population respectively). Reasons therefore are unclear, but can be related to the small study population and the organization of health care in Belgium, where a lot of children visit a

paediatrician and not their GP. Having a younger age (≤ 18y) and living with little children were significantly associated with carriage. This is most likely a consequence of the higher carriage in children as described above. Multiple studies confirmed the importance of horizontal transmission and intra-familiar spreading (52-56). However, other studies found conflicting results and questioned those intra-familiar spreading (17,57). A surprising finding was that carriers visited less frequently their GP compared to non-carriers. The explanation for this observation is unclear.

The highest resistance observed in Belgium was to cefaclor (77.27%), as found in most other European countries. Other antibiotics with a quite high percentage of resistance in Belgium were penicillin, cefuroxime (both 25%), ceftazidime and clarithromycin (both 22.73%). European results showed a high variability between countries with most of the lowest resistances found in Sweden and most of the highest resistances found in Spain (27). Tetracyclines showed the highest intercountry variability ranging between 1.9% and 29.9%. For most antibiotics - with the exception of clindamycin- Belgium is one of the worst students of the class with resistances found above 20% (27). An important remark is that amoxicillin and amoxicillin-clavulanate have not been investigated in the European study. In the present study, the resistance against amoxicillin in Belgium was almost 16%. This is surprisingly high, since 20% resistance is considered to be a threshold for empirical therapy and guideline recommendations. When resistance rates are too high, risk of failure is higher, along with morbidity and mortality (58,59). These finding highlights the importance of antibiotic resistance surveillance to adapt local recommendations when necessary.

Several studies have demonstrated a link between antibiotic consumption and resistance patterns (60-62). However, no causal effects could be proved. Malhotra-Kumar et al. (63) were one of the first to confirm the causal effect between antibiotic use and the development of resistance. In a double-blind, randomized trial of healthy volunteers, macrolide use (azithromycin of clarithromycin) for 7 days was associated with a 50% increase (p<0.0001) in macrolide resistance in the nasopharyngeal streptococcal flora. The resistance remained significantly higher than in the placebo group until 180 days (63). The same authors performed a similar study with amoxicillin versus placebo during 7 days in patients with confirmed uncomplicated LRTI during winter 2009-2010 (64). Immediately after treatment, amoxicillin resistance increased 11-fold (0.5% to 10.4%) and amoxicillin non-susceptibility increased 2.5-fold (17.9% to 66.2%) in the treatment group. However, these differences were no longer present 4 weeks post-treatment, although the mean proportion of amoxicillin non-susceptibility remained significantly higher than at day 0 (64). The modest and short-lived emergence of resistance to amoxicillin compared with macrolides further supports the guidelines that recommend amoxicillin as first choice in LRTI (64).

The high level of multidrug resistance, with almost three in ten swabs demonstrating resistance against three of more antibiotic classes, was quite surprising. Nevertheless, this finding is compatible with the European results, where an average MDR of 33.9% was found (27). Multi-drug resistance varies widely in Europe, with the lowest prevalence found in Sweden (3.8%) and the highest prevalence found in Spain (50.4%)(27). However, differences in antibiotic consumption between the participating countries might not be fully explaining that variability. For example, beta-lactam consumption in Sweden was higher than in The Netherlands (7.0 DDD/1,000/D vs. 4.5 DDD/1,000/D) (37) but the resistance rate in Sweden was the lowest. This might be explained by the great use of narrow spectrum penicillins in Sweden, congruent with the Swedish guidelines. For tetracyclines, the highest resistance was found in Spain whereas Sweden had a more than four-fold consumption of this agent (0.7 DDD/1,000/D vs. 3.4DDD/1,000/D) (37) but the lowest resistance. Other factors, such as socioeconomic and cultural determinants and health care policy probably may also influence antibiotic resistance prevalence.

We believe our study has some strengths. First, the population of Intego is believed to be representative for the whole Flemish population. Second, this study has a large statistical power due to the large number of events (almost 90,000!). Third, the Intego data collection system is used in a retrograde way. This has the advantage that GPs are not influenced in their prescription behaviour. Concerning the APRES-study, nasopharyngeal swabs were taken, which is considered the best method for detecting pneumococci in children and, to a lesser extent, in adults (65). Another important advantage is that the prevalence of carriage and resistance on the one hand and antibiotic prescription behaviour on the other hand were investigated in the same GP practices. This personal prescribing information is far more reliable than ecological data on antibiotic consumption expressed in DDD.

We are aware that this study has some limitations. The general practitioners in the Intego data collection system are not representative for all GPs in Belgium. It may be possible that the participating GPs are more interested in evidence-based medicine and have a more scientific background. Furthermore, the GPs are checked on quality indexes and are willing to register all diagnoses. We can assume that for all Belgian GPs, the results concerning guidelines compliance are worse than observed in this study. In the APRES-study, the number of pneumococcal carriers was scarce (n=44). This group is too small to detect significant associations with carriage or resistance and has not enough power to be meaningful. Future studies are necessary to replicate the results in a larger population. Secondly, asymptomatic carriage in a healthy population was investigated. Therefore, these results cannot be extrapolated to high-risk population or to ill subjects. However, asymptomatic carriage is indicative of the resistance circulating in community.

CONCLUSION

In Flemish primary care, too many antibiotics are still prescribed for LRTIs. Despite several campaigns, little is changing. More and multifaceted interventions are needed to further reduce antibiotic consumption.

As recommended in the Belgian guideline, we found an antibiotic prescription behaviour dependent of comorbidity. Nevertheless, guideline compliance is scarce for all risk groups. Furthermore guidelines are conflicting further impeding better adherence.

The choice to recommend amoxicillin for LRTIs in Belgium is still reliable, but can become a problem in future due to growing resistance of *S. pneumoniae*. Therefore, continuously monitoring of resistance in primary care is recommended to adapt guidelines in function of resistance patterns.

REFERENCES

1. **WHO (World Health Organization).** Top ten causes of death. Available on: http://www.who.int/mediacentre/factsheets/fs310/en/
2. **WHO (World Health Organization).** Causes of child mortality. Available on: http://www.who.int/gho/child_health/mortality/causes/en/
3. **Torres A, Peetermans WE, Viegi G, Blasi F.** Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax*. 2013;68:1057–65.
4. **Guthrie R.** Community-acquired lower respiratory tract infections: etiology and treatment. *Chest.* 2001;120:2021–34.
5. **Holm A, Nexoe J, Bistrup LA, Pedersen SS, Obel N, Nielsen LP, et al.** Aetiology and prediction of pneumonia in lower respiratory tract infection in primary care. *Br J Gen Pract.* 2007;57:547–54.
6. **GBD 2013 Mortality and Causes of Death Collaborators.** Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015; 385(9963): 117-171.
7. **Flamaing J, De Backer W, Van Laethem Y, Heijmans S, Mignon A.** Pneumococcal lower respiratory tract infections in adults: an observational case–control study in primary care in Belgium. *BMC Fam Pract*. 2015;16:66.
8. **Bogaert D, De Groot R, Hermans PWM**. *Streptococcus pneumoniae* colonisation: the key to pneumococcal disease. Lancet Infect Dis 2004; 4: 144–154.
9. **Bogaert D, Engelen MN, Timmers-Reker AJM et al.** Pneumococcal carriage in children in the Netherlands: a molecular epidemiological study. *J Clin Microbiol* 2001; 39:3316–3320.
10. **Malfroot A, Verhaegen J, Dubru JM, Van Kerschaver E, Leyman S**. A cross-sectional survey of the prevalence of *Streptococcus pneumoniae* nasopharyngeal carriage in Belgian infants attending day care centers. *Clin Microbiol Infect* 2004; 10: 797–803.
11. **Principi N, Marchisio P, Schito GC, Mannelli S.** Risk factors for carriage of respiratory pathogens in the nasopharynx of healthy children. Ascanius Project Collaborative Group. *Pediatr Infect Dis J* 1999; 18:517–23.
12. **Hoge CW, Reichler MR, Dominguez EA, et al.** An epidemic of pneumococcal disease in an overcrowded inadequately ventilated jail. *N Engl J Med* 1994; 331: 643–48.
13. **Mandigers CM, Diepersloot RJ, Dessens M, Mol SJ, van Klingeren B**. A hospital outbreak of penicillin-resistant pneumococci in The Netherlands. *Eur Respir J* 1994; 7: 1635–39.
14. **Gray BM, Converse GM 3rd, Dillon HC Jr.** Epidemiologic studies of *Streptococcus pneumoniae* in infants: acquisition, carriage, and infection during the first 24 months of life. *J Infect Dis* 1980; 142: 923–33.
15. **Petrosillo N, Pantosti A, Bordi E, et al.** Prevalence, determinants, and molecular epidemiology of *Streptococcus pneumoniae* isolates colonizing the nasopharynx of healthy children in Rome. *Eur J Clin Microbiol Infect Dis* 2002; 21: 181–88.
16. **Cardozo DM, Nascimento-Carvalho CM, Andrade AL, Silvany-Neto AM, Daltro CH, Brandão AP, et al.** Prevalence and risk factors for nasopharyngeal carriage of *Streptococcus pneumoniae* among adolescents. *J Med Microbiol.* 2008;57:185–189.
17. **Regev-Yochay G, Raz M, Dagan R, Porat N, Shainberg B, et al.** Nasopharyngeal carriage of Streptococcus pneumoniae by adults and children in community and family settings. *Clin Infect Dis*.2004;38:632–639.

18. **Cardozo DM, Nascimento-Carvalho CM, Souza FR, Silva NM.** Nasopharyngeal colonization and penicillin resistance among pneumococcal strains: a worldwide 2004 update. *Braz J Infect Dis.*2006;10:293–304
19. **Goossens H, Ferech M, Vander Stichele R, Elseviers M;** ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet.* 2005; 365:579– 87.
20. **Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M**. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis.* 2014; 9(14): 13.
21. **Prescott JF**. Antimicrobial use in food and companion animals. *Anim. Health Res*. 2008; Rev. 9, 127–133.
22. **Carrie AG, Zhanel GG.** Antibacterial use in community practice: assessing quantity, indications and appropriateness, and relationship to the development of antibacterial resistance. *Drugs.* 1999; 57:871–81
23. Communication from the Commission to the European Parliament and the Council. Action plan against the rising threats from Antimicrobial Resistance. Available on: http://ec.europa.eu/dgs/health_food-safety/docs/communication_amr_2011_748_en.pdf
24. **Chiu SS, Ho PL, Chow FKH, Yuen KY, Lau YL**. Nasopharyngeal Carriage of Antimicrobial-resistant *Streptococcus pneumoniae* among Young Children Attending 79 Kindergartens and Day Care Centers in Hong Kong. *Antimicrobial Agents and Chemotherapy*. 2001;45(10):2765-2770.
25. **Marchisio P, Esposito S, Schito GC, et al.** Nasopharyngeal Carriage of *Streptococcus pneumoniae* in Healthy Children: Implications for the Use of Heptavalent Pneumococcal Conjugate Vaccine. *Emerging Infectious Diseases*. 2002;8(5):479-484.
26. **den Heijer CD, van Bijnen EM, Paget WJ, Pringle M, Goossens H, Bruggeman CA, et al.** Prevalence and resistance of commensal Staphylococcus aureus, including methicillin-resistant S aureus, in nine European countries: a cross-sectional study. *Lancet Infect Dis.* 2013;13(5):409–15.
27. **Yahiaoui RY, den Heijer CDj, van Bijnen EM, Paget WJ,Pringle M, Goossens H, Bruggeman CA, Schellevis FG, Stobberingh EE; APRES Study Team**. Prevalence and antibiotic resistance of commensal Streptococcus pneumoniae in nine European countries. *Future Microbiol.* 2016 Jun;11:737-44.
28. **Truyers C, Goderis G, Dewitte H, Vanden Akker M, Buntinx F**. The Intego database: background, methods and basic results of a Flemish general practice-based continuous morbidity registration project. *BMC Med Inform Decis Mak*. 2014;14:48.
29. **Shea KM, Edelsberg J, Weycker D, Farkouh RA, Strutton DR, Pelton SI.** Rates of pneumococcal disease in adults with chronic medical conditions. *Open Forum Infect Dis*. 2014;1(1):ofu024.
30. **Van Bijnen EM, den Heijer CD, Paget WJ, et al.** The appropriateness of prescribing antibiotics in the community in Europe: study design. *BMC Infect Dis* 2011; 11: 293.
31. **European Committee on Antimicrobial Susceptibility Testing**. Determination of minimum inhibitory concentrations (MICs) of antibacterial agents by agar dilution. EUCAST definitive document E.DEF 3.1. *Clin Microbiol Infect*. 2000;6:509–15.
32. **Godycki-Cwirko M, Hood K, Nocun M, Muras M, Goossens H, Butler CC.** Presentation, antibiotic management and associated outcome in Polish adults presenting with acute cough/LRTI. *Fam Pract* 2011; 28: 608-14.

33. **Tell D, Engström S, Mölstad S.** Adherence to guidelines on antibiotic treatment for respiratory tract infections in various categories of physicians: a retrospective cross-sectional study of data from electronic patient records. *BMJ Open 2015*;5:e008096.
34. **Macfarlane J, Lewis SA, Macfarlane R, Holmes W.** Contemporary use of antibiotics in 1089 adults presenting with acute lower respiratory tract illness in general practice in the U.K.: implications for developing management guidelines. *Respir Med.* 1997;91:427–34.
35. **Butler CC, Hood K, Verheij T et al.** Variation in antibiotic prescribing and its impact on recovery in patients with acute cough in primary care: prospective study in 13 countries. *BMJ* 2009;338:b2242.
36. **European Respiratory Society.** European Lung White book; Part C Chapter 18: Acute lower respiratory infections. Available on: http://www.erswhitebook.org/chapters/acute-lower-respiratory-infections/
37. **European Centre for Disease Control and Prevention** (ECDC) Surveillance report. Surveillance of Antimicrobial Consumption in Europe 2012. Available on: http://ecdc.europa.eu/en/healthtopics/antimicrobial-resistance-and-consumption/antimicrobial-consumption/publications-documents/Pages/publications.aspx
38. **BAPCOC** (Belgian Antibiotic Policy Coordination Committee). Edition 2012. Available on: http://www.bcfi.be/legacy_assets/antibioticagids-nl.pdf
39. **NHG** (Dutch college of General Practitioners). Acute coughing. Revised 2010. Available on: https://www.nhg.org/standaarden/volledig/nhg-standaard-acuut-hoesten
40. **Little P, Stuart B, Moore M, et al**. Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. *Lancet Infect Dis* 2013;13:123–9.
41. **Moore M, Stuart B, Coenen S, Butler C, Goossens H, Verheij T, et al.** Amoxicillin for acute lower respiratory tract infection in primary care: subgroup analysis of potential high-risk groups. *Br J Gen Pract* 2014; 64: e75–e80.
42. **Holm A, Nexoe J, Bistrup LA, Pedersen SS, Obel N, Nielsen LP, et al**. Aetiology and prediction of pneumonia in lower respiratory tract infection in primary care. *Br J Gen Pract.* 2007;57(540):547–554.
43. **Creer DD, Dilworth JP, Gillespie SH, et al.** Aetiological role of viral and bacterial infections in acute adult lower respiratory tract infection (LRTI) in primary care. *Thorax*. 2006;61(1):75-79.
44. **Gonzales R, Malone D, Sande MA**. Estimating the amount and cost of ideal and excess antibiotic use for acute respiratory tract infections in the United States. *Clin Infect Dis.* 2001;33:757–62.
45. **NICE (National Institute for Health and Care Excellence)**. Pneumonia in adults: Diagnosis and management. Clinical guideline (CG191). Published Date 3 December 2014. Available on: https://www.nice.org.uk/guidance/cg191
46. **Shallcross L, Beckley N, Rait G, Hayward A, Petersen I**. Antibiotic prescribing frequency amongst patients in primary care: a cohort study using electronic health records. *J Antimicrob Chemother.* 2017 dkx048.
47. **Piccirillo JF, Mager DE, Frisse ME, Brophy RH, Goggin A.** Impact of first-line vs second-line antibiotics for the treatment of acute uncomplicated sinusitis. *JAMA*.2001;286:1849-1856.
48. **Steinman MA, Landefeld CS, Gonzales R.** Predictors of broad-spectrum antibiotic prescribing for acute respiratory tract infections in adult primary care. *JAMA*. 2003;289:719–25.
49. **Aspinall SL, Good CB, Metlay JP, Mor MK, Fine MJ**. Antibiotic prescribing for presumed nonbacterial acute respiratory tract infections. *Am J Emerg Med* 2009;27:544–51.

50. **Brookes-Howell L, Hood K, Cooper L, Coenen S, Little P, Verheij T, et al**. Clinical influences on antibiotic prescribing decisions for lower respiratory tract infection: a nine country qualitative study of variation in care. *BMJ Open* 2012;2**:**e000795.
51. **Butler CC, Simpson SA, Dunstan F, Rollnick S, Cohen D, Gillespie D, et al.** Effectiveness of multifaceted educational program to reduce antibiotic dispensing in primary care: practice based randomised controlled trial. *BMJ* 2012;344:d8173.
52. **Hendley JO, Sande MA, Stewart PM, Gwaltney JM**. Spread of *Streptococcus pneumoniae* in families. I. Carriage rates and distribution of types. *J Infect Dis.* 1975; 132:55–61.
53. **Leino T, Auranen K, Jokinen J, Leinonen M, Tervonen P, Takala AK.** Pneumococcal carriage in children during their first two years: important role of family exposure. *Pediatr Infect Dis J.* 2001; 20:1022–7.
54. **Hoshino K, Watanabe H, Sugita R, et al.** High rate of transmission of penicillin-resistant *Streptococcus pneumoniae* between parents and children. *J Clin Microbiol.* 2002; 40:4357–9.
55. **Shimada J, Yamanaka N, Hotomi M, et al.** Household transmission of *Streptococcus pneumoniae* among siblings with otitis media. *J Clin Microbiol.* 2002; 40:1851–3.
56. **Samore MH, Magill MK, Alder SC, Severina E, Morrison-De Boer L, Lyon JL, Carroll K, Leary J, Stone MB, Bradford D, et al.** High rates of multiple antibiotic resistance in streptococcus pneumoniae from healthy children living in isolated rural communities: association with cephalosporin use and intrafamilial transmission. *Pediatrics.* 2001;108(4):856–865.
57. **Borer A, Meirson H, Peled N, et al**. Antibiotic-resistant pneumococci carried by young children do not appear to disseminate to adult members of a closed community. *Clin Infect Dis.* 2001; 33:436–44.
58. **Lismond A, Carbonnelle S, Verhaegen J, et al.** Antimicrobial susceptibility of *Streptococcus pneumoniae* isolates from vaccinated and non-vaccinated patients with a clinically confirmed diagnosis of community-acquired pneumonia in Belgium. *Int J Antimicrob Agents.* 2012;39:206–216.
59. **Gupta K, Hooton TM, Naber KG, et al.** International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis*.2011;52(5):e103–e120.
60. **del Castillo F, Baquero-Artigao F, Garcia-Perea A.** Influence of recent antibiotic therapy on antimicrobial resistance of Streptococcus pneumoniae in children with acute otitis media in Spain. *Pediatr Infect Dis J* 1998;17: 94–7
61. **Bell BG, Schellevis F, Stobberingh E, Goossens H, Pringle M**. A systematic review and meta-analysis of the effects of antibiotic consumption on antibiotic resistance. *BMC Infect Dis.* 2014;14:13.
62. **Albrich WC, Monnet DL, Harbarth S.** Antibiotic Selection Pressure and Resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Emerging Infectious Diseases*. 2004;10(3):514-517.
63. **Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H.** Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet*.2007; 369:482–90.
64. **Malhotra-Kumar S, Van Heirstraeten L, Coenen S, et al, on behalf of the GRACE study group.** Impact of amoxicillin therapy on resistance selection in patients with community-acquired lower respiratory tract infections: a randomized, placebo-controlled study. *J Antimicrob Chemother* 2016; 71 (11): 3258-3267.

65. **Satzke C, Turner P, Virolainen-Julkunen A, Adrian PV, Antonio M, Hare KM, et al**. Standard method for detecting upper respiratory carriage of *Streptococcus pneumoniae*: updated recommendations from the World Health Organization Pneumococcal Carriage Working Group. *Vaccine*. 2013;32(1):165–79.

ADDENDUM

ADDENDUM 1: selection of morbidities in the INTEGO-database (ICPC2-code)

High risk patients:	*AIDS (B90) *Lymphoma (B72) *Leukemia (B73) *Malignant neoplasm (B74) *Immunosuppressant (ATC L04) *Glucocorticoids (ATC H02AB)
Median risk patients:	*Chronic bronchitis (R79) *Congenital respiratory anomaly (R89) *COPD (R95) *Asthma (R96) *Congenital cardiovascular anomaly (K73) *Angina pectoris (K74) *Acute myocardial infarction (K75) *Chronic ischemic heart disease (K76) *Heart failure (K77) *Atrial fibrillation (K78) *Pulmonary heart disease (K82) *Heart valve disease (K83) *TIA (K89) *CVA (K90) *Peripheral arterial disease (K92) *Chronic liver disease (D97) *Chronic kidney disease eGFR< 60mL/min (ICPC2-PLUS U99023) *Chronic alcohol abuse (P15)
Low risk patients:	All other patients

ADDENDUM 2: Resistance patterns of *S. pneumoniae* isolates

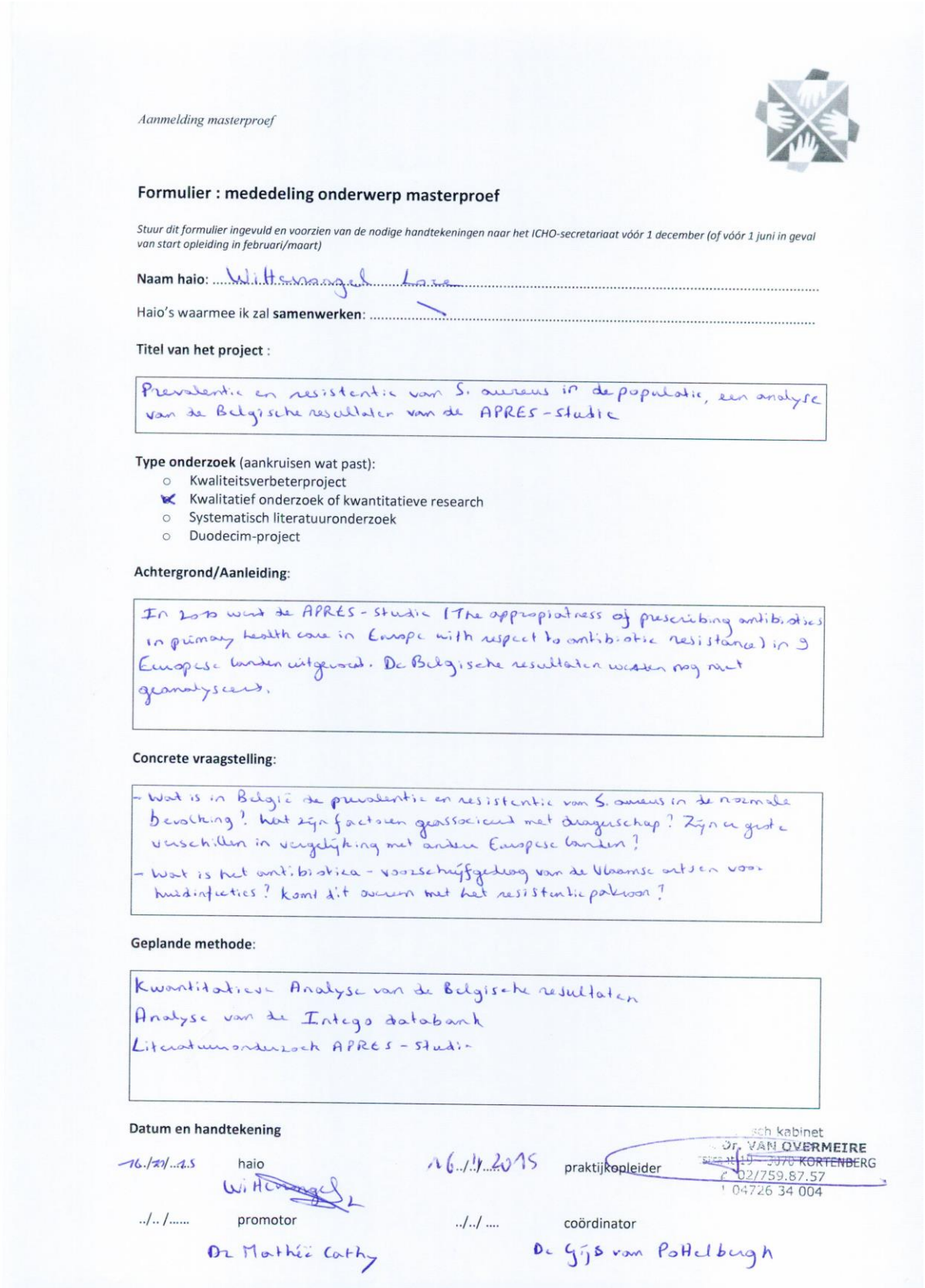
Number of resistances of *S. pneumoniae* against AB (n=44)

Nr of res.	Percent (n)	AB resistance ranked by frequency in percent (n)	Nr of res.	Percent (n)	AB resistance ranked by frequency in percent (n)
0	20.45 (9)		6	9.09 (4)	PENI 100.0 (4), CEFA 100.0 (4), CEFUR 100.0 (4), CEFTA 75.0 (3), COTRIM 50.0 2), TETRA 25.0 (1), AMOXI 50.0 (2), CLINDA 50.0 (2), CLARITHRO 50.0 (2)
1	47.73 (21)	CEFA 100.0 (21)	7	2.27 (1)	PENI 100.0 (1), CEFA 100.0 (1), CEFTA 100.0 (1), CEFUR 100.0 (1), TETRA 100.0 (1), CLARITHRO 100.0 (1), CLINDA 100.0 (1)
2	2.27 (1)	CEFA 100.0 (1), TETRA 100.0 (1)	8	2.27 (1)	PENI 100.0 (1), AMOXI 100.0 (1), CEFA 100.0 (1), CEFTA 100.0 (1), COTRIM 100.0 (1), CEFUR 100.0 (1), TETRA 100.0 (1), CLARITHRO 100.0 (1)
4	4.55 (2)	CLINDA 100.0 (2), TETRA 100.0 (2), CLARITHRO 100.0 (2), CEFA 50.0 (1), COTRIM 50.0 (1)	9	6.82 (3)	PENI 100.0 (3), AMOXI 100.0 (3), CEFA 100.0 (3), CEFTA 100.0 (3), CEFUR 100.0 (3), CLINDA 100.0 (3), COTRIM 100.0 (3), CLARITHRO 100.0 (3), TETRA 66.7 (2), AMOCLA 33.3 (1)
5	2.27 (1)	PENI 100.0 (1), CEFA 100.0 (1), CEFTA 100.0 (1), CEFUR 100.0 (1), COTRIM 100.0 (1)	10	2.27 (1)	PENI 100.0 (1), AMOXI 100.0 (1), AMOCLA 100.0 (1), CEFA 100.0 (1), CEFTA 100.0 (1), CEFUR 100.0 (1), COTRIM 100.0 (1), TETRA 100.0 (1), CLINDA 100.0 (1), CLARITHRO 100.0 (1)

Nr of res: number of resistances; AB: antibiotics. AMOXI: amoxicillin; AMOCLA: amoxicillin/clavulanate; CEFA: cefaclor; CEFTA: ceftazidime; CEFUR: cefuroxime; CLARITHRO: clarithromycin; CLINDA: clindamycin; COTRIM: cotrimoxazole; PENI: penicillin; TETRA : tetracycline.

APPENDIX

BIJLAGE 1. Goedgekeurd protocol



Aanmelding masterproef

Formulier : mededeling onderwerp masterproef

Stuur dit formulier ingevuld en voorzien van de nodige handtekeningen naar het ICHO-secretariaat vóór 1 december (of vóór 1 juni in geval van start opleiding in februari/maart)

Naam haio: Wittevrongel Lore

Haio's waarmee ik zal **samenwerken:** /

Titel van het project :

Prevalentie en resistentie van S. aureus in de populatie, een analyse van de Belgische resultaten van de APRES-studie

Type onderzoek (aankruisen wat past):

- ○ Kwaliteitsverbeterproject
- ✗ Kwalitatief onderzoek of kwantitatieve research
- ○ Systematisch literatuuronderzoek
- ○ Duodecim-project

Achtergrond/Aanleiding:

In 2010 werd de APRES-studie (The appropriateness of prescribing antibiotics in primary health care in Europe with respect to antibiotic resistance) in 9 Europese landen uitgevoerd. De Belgische resultaten werden nog niet geanalyseerd.

Concrete vraagstelling:

- Wat is in België de prevalentie en resistentie van S. aureus in de normale bevolking? Met zijn factoren geassocieerd met dragerschap? Zijn er grote verschillen in vergelijking met andere Europese landen?
- Wat is het antibiotica-voorschrijfgedrag van de Vlaamse artsen voor huidinfecties? Komt dit overeen met het resistentiepatroon?

Geplande methode:

Kwantitatieve Analyse van de Belgische resultaten
Analyse van de Intego databank
Literatuuronderzoek APRES-studie

Datum en handtekening

16./11./2015 haio Wittevrongel

16./11./2015 praktijkopleider

sch kabinet
Dr. VAN OVERMEIRE
[illegible] 3070 KORTENBERG
02/759.87.57
04726 34 004

../../..... promotor Dr Mathéi Cathy

../../.... coördinator Dr Gijs van Pottelbergh

Aanvraag Ethische begeleiding masterproeven "Prevalentie en resistentie van S. aureus in de Belgische populatie" (mp11053)

Gelieve in te loggen op http://gbiomed.kuleuven.be/apps/ec om deze aanvraag te controleren.

Samenvatting aanvraag

Prevalentie en resistentie van S. aureus in de Belgische populatie

Student(en):

Lore Wittevrongel

Faculteit:

Geneeskunde

Opleiding:

Master in de huisartsgeneeskunde (Leuven e.a.)

Het onderzoek is:

monocentrisch

De opdrachtgever is:

academisch (universiteit,...)

Het onderzoek is:

Het onderzoek is uitsluitend retrospectief.

Bijkomende gegevens:

Achtergrond:

In 2010 werd de APRES-studie (Appropriateness of prescribing antibiotics in primary health care in Europa with respect to antibiotic resistance) in 9 Europese landen uitgevoerd. De Belgische resultaten werden nog niet volledig geanalyseerd.

Vraagstelling:

Wat is in België de prevalentie en resistentie van S aureus in de populatie? Wat zijn factoren geassocieerd met dragerschap? Zijn er grote verschillen in vergelijking met andere Europese landen?

Wat is het antibiotica- voorschrijfgedrag van de Belgische artsen met betrekking tot huisinfecties? Komt dit overeen met het resistentiepatroon?

Methodologie:

Literatuuronderzoek ikv APRES-studie

Kwantitatieve analyse van de Belgische resultaten

Analyse van de Intego-databank

Referenties:

1. **Van Bijnen EM, den Heijer CD, Paget WJ, et al.** The appropriateness of prescribing antibiotics in the community in Europe: study design. *BMC Infect Dis* 2011; 11: 293.

2. den Heijer CDJ, van Bijnen EDE, Paget WJ, Pringle M, Goossens H, Bruggeman CA, et al. Prevalence and resistance of commensal *Staphylococcus aureus*, including meticillin-resistant *Staphylococcus aureus*: a European cross-sectional study. The Lancet Infectious Diseases, The Lancet Infectious Diseases, Early Online Publication, 6 March 2013; doi: 10.1016/S1473-3099(13)70036-7.

3. van Bijnen EM1, Paget J1, de Lange-de Klerk ES2, den Heijer CD3, Versporten A4, Stobberingh EE4, Goossens H4, Schellevis FG5; collaboration with the APRES Study Team. Antibiotic Exposure and Other Risk Factors for Antimicrobial Resistance in Nasal Commensal Staphylococcus aureus: An Ecological Study in 8 European Countries. PLoS One. 2015 Aug 11;10(8):e0135094. doi: 10.1371/journal.pone.0135094. eCollection 2015.

Informed consent / vragenlijsten / interviewprotocols:

Promotor:

Cathy Matheï (catharina.mathei@med.kuleuven.be - u0009104 - Acad. Centr. voor Huisartsgeneeskunde)

Registratienummer:

mp11053

BIJLAGE 2. Gunstig advies Ethisch comité

Gunstig advies van OBC

2016-03-24 17:46:45

Bekijk status geschiedenis

Student(en):	Lore Wittevrongel
Promotor:	Cathy Matheï (catharina.mathei@med.kuleuven.be - u0009104 - Acad. Centr. voor Huisartsgeneeskunde)
Faculteit:	Geneeskunde
Opleiding:	Master in de huisartsgeneeskunde (Leuven e.a.)
Het onderzoek is:	monocentrisch
De opdrachtgever is:	academisch (universiteit,...)
Het onderzoek is:	Het onderzoek is uitsluitend retrospectief.

BIJKOMENDE GEGEVENS:

Achtergrond:	In 2010 werd de APRES-studie (Appropriateness of prescribing antibiotics in primary health care in Europa with respect to antibiotic resistance) in 9 Europese landen uitgevoerd. De Belgische resultaten werden nog niet volledig geanalyseerd.
Vraagstelling:	Wat is in België de prevalentie en resistentie van S aureus in de populatie? Wat zijn factoren geassocieerd met dragerschap? Zijn er grote verschillen in vergelijking met andere Europese landen? Wat is het antibiotica- voorschrijfgedrag van de Belgische artsen met betrekking tot huisinfecties? Komt dit overeen met het resistentiepatroon?
Methodologie:	Literatuuronderzoek ikv APRES-studie Kwantitatieve analyse van de Belgische resultaten Analyse van de Intego-databank
Referenties:	1. **Van Bijnen EM, den Heijer CD, Paget WJ, et al.** The appropriateness of prescribing antibiotics in the community in Europe: study design. *BMC Infect Dis* 2011; 11: 293. 2. den Heijer CDJ, van Bijnen EDE, Paget WJ, Pringle M, Goossens H, Bruggeman CA, et al. Prevalence and resistance of commensal *Staphylococcus aureus*, including meticillin-resistant *Staphylococcus aureus*: a European cross-sectional study. The Lancet Infectious Diseases, The Lancet Infectious Diseases, Early Online Publication, 6 March 2013; doi: 10.1016/S1473-3099(13)70036-7. 3. van Bijnen EM1, Paget J1, de Lange-de Klerk ES2, den Heijer CD3, Versporten A4, Stobberingh EE4, Goossens H4, Schellevis FG5; collaboration with the APRES Study Team. Antibiotic Exposure and Other Risk Factors for Antimicrobial Resistance in Nasal Commensal Staphylococcus aureus: An Ecological Study in 8 European Countries. PLoS One. 2015 Aug 11;10(8):e0135094. doi: 10.1371/journal.pone.0135094. eCollection 2015.

Informed consent / vragenlij...