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ORIGINAL PAPER

Prescriptions of Broad-Spectrum Antibiotics to Outpatients do not Match Increased Prevalence and Antibiotic Resistance of Respiratory Pathogens in Bavaria

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Abstract

In this study we present an analysis of prescription numbers of various antibiotic classes to Bavarian (Southern Germany) outpatients between 2000 and 2006 compared to fluctuating resistance patterns in representative respiratory pathogens. Prescriptions of "narrow-spectrum" antibiotics (*e.g.* penicillins, macrolides) decreased by 39% while prescriptions of "broad-spectrum" antibiotics increased by 38%. The most prominent increase was for quinolones and cephalosporines class II. Prescriptions of these antibiotics exhibited prominent seasonal alterations suggesting that these drugs had been used for treatment of respiratory infections. In contrast, the numbers of *S. pneumoniae* and *H. influenzae* detected in respiratory specimen decreased. Almost constant resistance rates of *S. pneumoniae* for first line antibiotics do not justify an increased use of cephalosporins class II and quinolones. Compared to Europe and Germany in general, consumption of antibiotics is low in Bavaria. Even at this low level we propose an education of physicians treating outpatients in a way to avoid an excessive use of antimicrobials.

Key words: *H. influenzae*, *S. pneumoniae*, antibiotic prescription, respiratory infection,

Introduction

Increasing resistances of pathogens are an emerging problem in the treatment of bacterial infections (Goosseens *et al.*, 2005). Knowledge about international as well as regional antibiotic prescription habits are essential for the assessment of epidemiological trends, *i.e.* increased finding numbers or altering antibiotic susceptibilities of bacterial pathogens. Until recently, data about antibiotic consumption were collected by different, non-standardized methods providing only limited information. Starting 2001 the European Surveillance of Antimicrobial Consumption (ESAC) began to collect and provide important data about the use of antibiotics in Europe.

According to a recent report of the German Ministry of Health (www.bmg.bund.de) studies analysing the interaction of antibiotic consumption and bacterial resistances in outpatients are scarce (Schröder and Kern, 2008; Van der Linden *et al.*, 2008; Kresken *et al.*, 2008).

Due to legal restrictions, consumption of antibiotics in Germany ranks lowest in Europe, especially in Bavaria (Ferech *et al.*, 2006; Goosseens *et al.*, 2006; Muller *et al.*, 2007; Kern *et al.*, 2006).

Our laboratory located in Bavaria enables us to perform microbiological analyses for more than 10% of Bavarian physicians treating outpatients allowing epidemiological analyses of antibiotic consumption and alterations in resistances in this region.

In the present study we present data about the course of antibiotic prescriptions between 2000 and 2006. Also we compare data for alterations in prescription rates to the finding numbers and antibiotic susceptibilities of indicator bacteria in respiratory samples (*S. pneumoniae*, *H. influenzae*).

Experimental

Materials and Methods

Antibiotics prescriptions data. In Bavaria a population of 12493000 inhabitants has been registered in 2007 among which about 83% are members of the statutory health insurances. Prescription data for the

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years 2000–2006 were calculated by ATC/WHO procedure (http://www.whocc.no). This analysis focuses on two prescription periods (one year/three months). For better discrimination of antibiotic consumption within these periods prescriptions in defined daily dosages (DDD) per patient per one year/three months were used instead of the commonly used DDD per 1000 inhabitants per day.

The following antibiotic classes were defined: First-generation cephalosporines (cephalosporines class I [Ceph I]; J01DB), second-generation cephalosporines (cephalosporines class II [Ceph II]; J01DC), combinations of sulfonamides and trimethoprim including derivatives (folic acid antagonists [FA ant]; J01EE), macrolides ([Macro]; J01FA), beta-lactamase sensitive penicillins ([Pen]; J01CE), combinations of penicillins including β-lactamase inhibitors ([Pen/Inhib]; J01CR) and quinolones ([Quin]; J01M).

In our analysis we used data from patients registered at statutory health insurances in Bavaria. Data were obtained from the AOK Research Institute (WidO; http://www.wido.de).

Health care system and laboratory setting. In 2006 23 419 physicians working in ambulatory settings were registered at the Bavarian Medical Council. Approximately 30% were general practitioners (7206); 55% were consultants in other fields (12 917). About 14% (3296) were physicians in postgraduate professional education or physicians employed at ambulatory settings (http://www.blaek.de/ >> Mitglieder >> Mitglieder Jahresstatistik >> 2006).

The Synlab Medical Care Service Centre Weiden, located in Bavaria analyzes laboratory samples from about 40 hospitals and over 2000 physicians serving outpatients. In 2006 a total of 161000 microbiological samples have been examined. In 2006 about half of them have been performed for either general physicians (1294) or consultants in other fields (1262).

Epidemiological and statistical analyses. Epidemiologic analysis was performed as described recently (Borgmann 2008). In brief, the Hybase system (Cymed AG, Bochum, Germany) linked to the laboratory data system "promed open" (mcs, Eltville, Germany) was used to calculate numbers of *S. pneumoniae* and *H. influenzae* in respiratory samples. Numbers were normalized for patients per period.

Bravais-Pearson (r) and Spearman (r_s) correlation coefficients (including p-value for r_s that variables are independent) and linear regression models were calculated by using STATA Version 9.2 (StataCorp, College Station, Texas, USA).

Bacterial culture and antibiotic susceptibility testing. Respiratory samples (sputum, bronchoalveolar lavages, throat swabs) were cultured on Columbia-Agar containing 5% sheep blood (Becton Dickinson, Heidelberg, Germany) and *Haemophilus*-Chocolat-2-Agar (BioMerieux, Nürtingen, Germany) for 48 h. Bacterial growth was examined after 24/48 hours.

Pneumococci were identified by characteristic morphology and susceptibility to optochin according to manufacturers instructions (BioMerieux, Nürtingen, Germany). Antibiotic susceptibility was examined by agar diffusion testing on Müller-Hinton-Agar containing 5% sheep blood (BD, Heidelberg, Germany).

H. influenzae was identified by growth of typical colonies on Trycase-Soy-Agar (BioMerieux, Nürtingen, Germany) overlaid with two disks containing factor V or X. Antibiotic susceptibility was examined by agar diffusion testing on *Haemophilus*-Test-Medium (HTM) (BD, Heidelberg, Germany).

Results

Prescriptions of antibiotics. Alterations of antibiotic treatment regimens in our region from 2000 to 2006 were followed *via* prescription rates of various antibiotic classes (penicillines, penicillins + β-lactamase inhibitors, macrolides, cephalosporines class I and II, folic acid antagonists, quinolones). Cumulative prescription rates of these antibiotics decreased from 2.83 DDD in 2000 to 2.16 DDD in 2001 (–23,6%) and stayed low at 2.24 DDD up to 2006. A transient increase to 2.44 DDD was noticeable in 2005 (Fig. 1. A left).

While the volume of penicillines, macrolides, cephalosporines class I, and folic acid antagonists from all prescribed antibiotics decreased from 2000 to 2006 that of penicillins + β-lactamase inhibitors, cephalosporines class II, and quinolones increased during this period (Fig. 1 A right). Regarding penicillins combined with beta-lactamase inhibitors, cephalosporines class II, and quinolones as broad-spectrum antibiotics their proportion increased from 22% to 38%.

Comparing prescription rates from 2000 to 2006 the largest decrease was observed for penicillins (0.77 *vs.* 0.38 DDD/member) while quinolones exhibited the strongest increase (0.34 *vs.* 0.46 DDD/member; Fig. 1 A right).

Data for seasonal prescription numbers of antibiotic classes used for treatment of respiratory infections are shown in Fig. 1 B. Prescripions of macrolides, cephalosporines class II and quinolones show prominent seasonal alterations.

A peak of "respiratory antibiotics" (macrolides, quinolones, cephalosporines class II) is obvious during the winter of 2004/2005.

Finding numbers of *S. pneumoniae* and *H. influenzae.* Changes in the occurrence of bacterial infections of the respiratory tract due to antibiotic prescriptions were followed by recording finding numbers of indicator bacteria (*S. pneumoniae* and

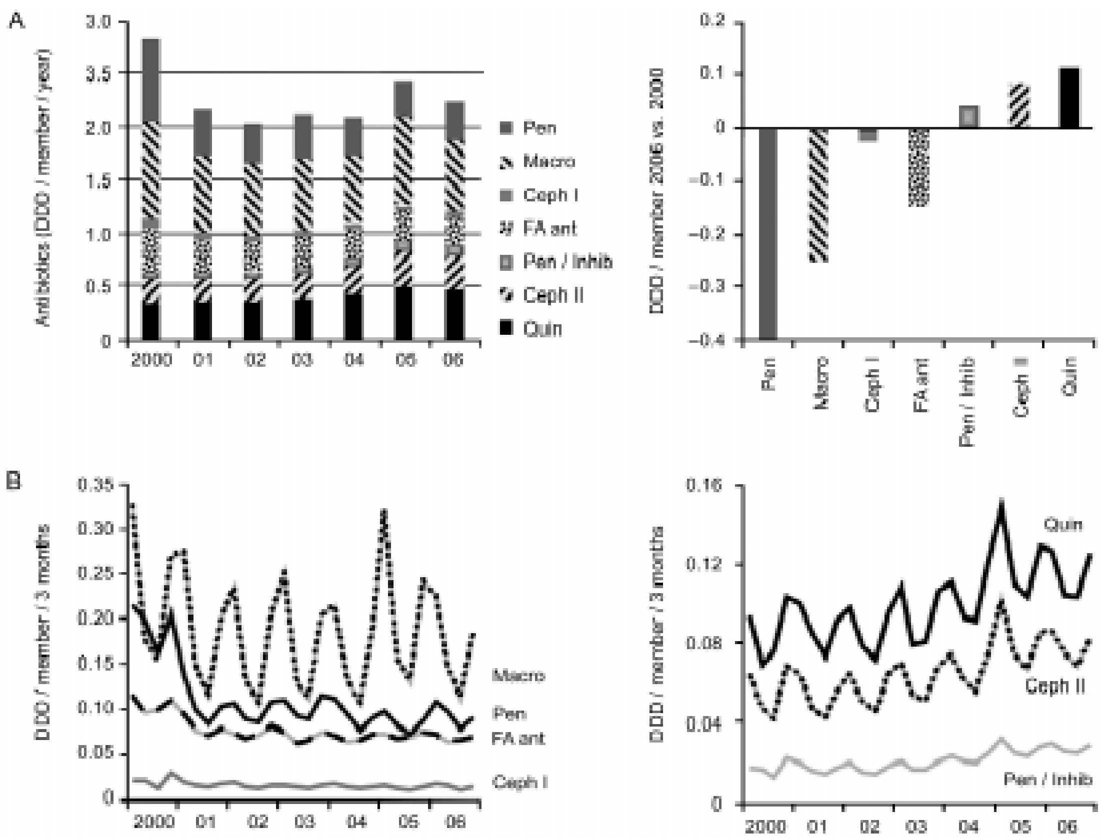


Fig. 1. Prescriptions of various antibiotic classes to Bavarian out-patients (2000–2006).
Prescriptions are given in defined daily dosages (DDD) per member of legal (statutory) health insurances. A: Antibiotic prescriptions per patients per year. Absolute DDD per member per year (left panel) and differences of prescription numbers of 2000 and 2006 (right panel). B: Antibiotic prescriptions per three months of narrow-spectrum (left panel) and broad spectrum (right panel). Definition of antibiotic classes [abbreviations]: refer to section Materials and Methods.

H. influenzae) from various respiratory samples from 2000 to 2006.

The findings of *S. pneumoniae* and *H. influenzae* in respiratory secretions showed defined seasonal trends (Fig. 2). Use of antibiotics reached a maximum during the first three months of 2005 (Fig. 1 B). Nevertheless the number of *S. pneumoniae* and *H. influenzae* findings in respiratory secretions and the proportion of positive samples were relatively low suggesting that the increase of antibiotic prescriptions did not count for increased numbers of bacterial respiratory infections.

Antibiotic resistances of *S. pneumoniae* and *H. influenzae.* Resistance rates of *S. pneumoniae* and *H. influenzae* were studied to examine, if upcoming antibiotic resistances of respiratory pathogens may have lead physicians to prescribe broad-spectrum antibiotics. The proportion of cefaclor and penicillin resistant pneumococci remained in the range of 0–4% indicating no increase of bacterial resistance to first line antibiotics. In contrast, the proportion of erythromycin resistant *S. pneumoniae* obviously had increased from 15% to 20%. However, a linear trend model revealed no significant increase of the proportion of erythromycin resistant pneumococci per three month intervals (Table I). No positive correlations were observed between prescription numbers of first line antibiotics and the percentage of *S. pneumoniae* resistant to them (Table II).

Between 2000 and 2005 a slight increase in the proportion of cefaclor resistant *H. influenzae* was noticed while the proportion of amoxcicillin resistant

Table I
Linear trend for consumption of first line antibiotics per three month intervals.

Resistance	Slope	Lower 95 % CI	Upper 95 % CI	Adj. R^2
S.p. – Penicillin	0.040	–0.015	0.095	0.04
S.p. – Erythromycin	0.212	–0.039	0.464	0.07
S.p. – Cefaclor	0.065	0.012	0.117	0.17
H.i. – Amoxicillin	0.226	0.015	0.437	0.12
H.i. – Cefaclor	0.436	0.231	0.641	0.40
H.i. – Amoxicillin (2000–2005)	0.002	–0.192	0.196	–0.05
H.i. – Cefaclor (2000–2005)	0.297	0.056	0.537	0.19

S.p.: *S. pneumoniae*, H.i.: *H. influenzae*, βLS: Beta-lactamase-sensitive, ceph. I: Cephalosporin class I, CI: Confidence interval, Adj.: Adjusted

Table II
Correlation coefficients between resistance in indicator bacteria and consumption of first line antibiotics per three month intervals

Resistance	Consumption	r	r_s	p-value
S.p. – Penicillin	Penicillins (βLS)	–0.435	–0.543	< 0.01
S.p. – Erythromycin	Makrolids	–0.364	–0.334	0.08
S.p. – Cefaclor	Ceph. I	–0.472	–0.511	< 0.01
H.i. – Amoxicillin	Penicillins (βLS)	–0.079	0.032	0.87
H.i. – Cefaclor	Ceph I	–0.324	–0.338	0.08

abbreviations: see Table I and methods section

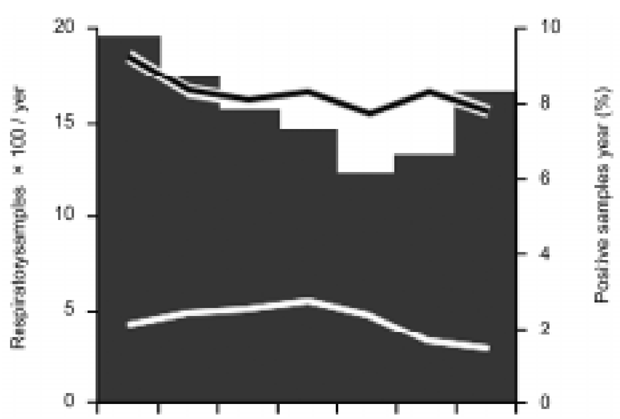
H. influenzae remained constant (Fig. 3). However, in 2006 proportion of *H. influenzae* being resistant to amoxicillin and/or cefaclor markedly increased.

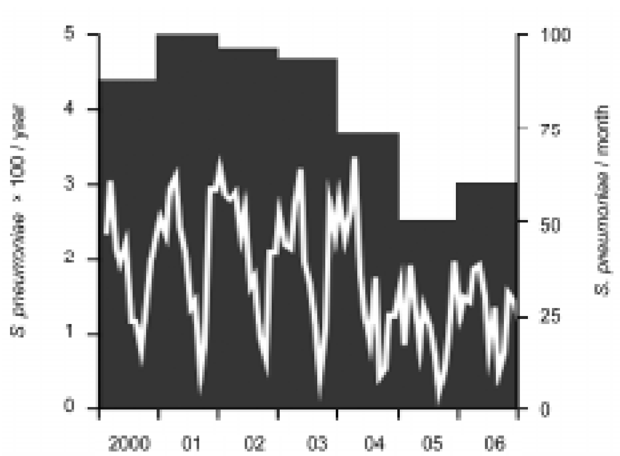
Regarding 2000–2005 there was a significant linear trend for an increase of resistance to amoxicillin and cefaclor. However, this trend disappeared for amoxicillin and diminished considerably for cefaclor when analysis was restricted to the years 2000–2005 (Table I). Resistances to quinolones were not observed. No significant correlation between antibiotic prescriptions and antibiotic resistances of *H. influenzae* was noticed (Table II).

Discussion

During 2000 to 2006 we analysed bacteriological specimen for more than 2 000, representing about 11% of physicians treating outpatients in Bavaria. The results were compared to antibiotic prescription data reported from Bavarian ambulance physicians. The Bavarian Medical Council (BMC) lists at least three categories of physicians working in ambulatory settings: general practitioners, consultants in other fields of profession and physicians in postgraduate professional training mainly in clinical settings. Our data allow distinction between general practitioners and consultants in other fields. Postgraduate training of general practitioners is usually performed at ambulances while that of consultants is occupied by hospitals. Therefore, the percentage of general practitioners cooperating with our laboratory was markedly higher than that published by BMC (49.4% vs. 30.6%). Taking this source of underestimation into account and looking at the proportion of consultants cooperating with our laboratory (50.6% vs. 55.2% BMC) we consider these data representative for the vast majority of Bavarian ambulance physicians.

The present study shows that prescription numbers of "narrow-spectrum" antibiotics in Bavaria have decreased from 2000 to 2006 while broad-spectrum antibiotics were prescribed more frequently. However, in-





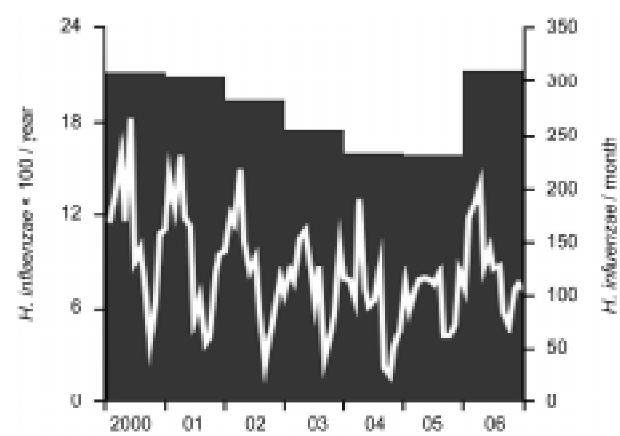


Fig. 2. Finding numbers of *S. peumoniae* and *H. influenzae* in respiratory samples between 2000 and 2006.

Top panel: Total number of respiratory samples examined per year (left scale, grey bars) and percentage of patients being positive for *H. influenzae* (black line) or *S. peumoniae* (white line). Bottom panels: Number of patients positive for *S. pneumoniae* (left panel) or *H. influenzae* (hight panel). Grey bars and the left scale represent finding numbers of *S. pneumoniae* and *H. influenzae* per year; white lines and the right scale represent the monthly distribution of finding numbers of *S. pneumoniae* and *H. influenzae*, respectively.

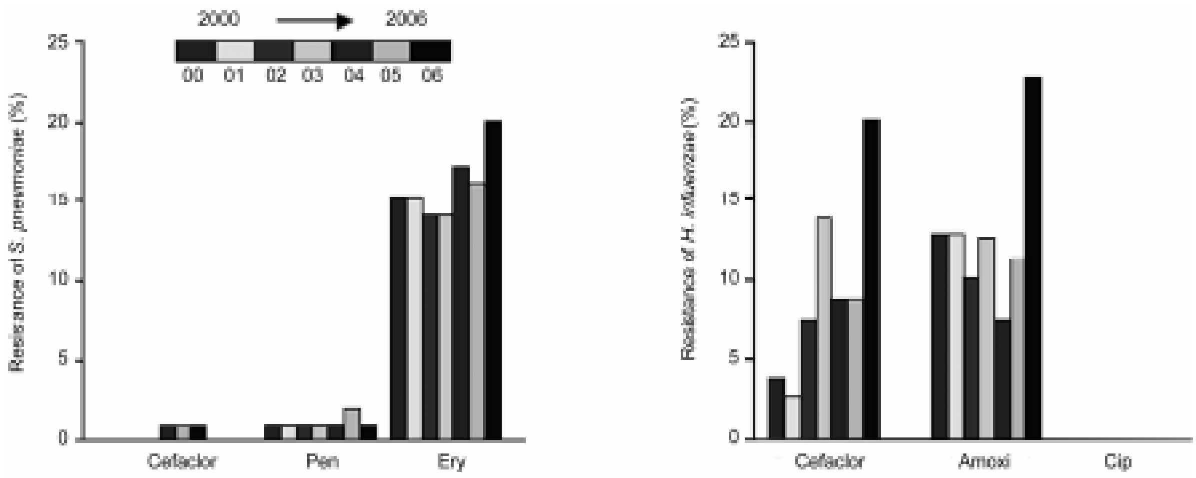


Fig. 3. Percentages of bacteria exhibiting resistance to indicated antibiotics.
Numbers are given for *S. pneumoniae* (left panel) and *H. influenzae* (right panel) in respiratory samples. Amoxi: amoxicillin; Cipro: ciprofloxacin; Ery: erythromycin; Pen: penicillin.

creased use of broad-spectrum antibiotics does not explain the upcoming of important infections reflected by the recognition of indicator bacteria or antibiotic susceptibilities.

To assess trends in the consumption of antibiotics in Europe ESAC performed various analyses. (Ferech *et al.*, 2006; Kern *et al.*, 2006; Muller *et al.*, 2007). In Germany the Ministry of Health initiated the "Deutsche Antibiotika-Resistenzstrategie" (German Antibiotic Resistance Strategy) in order to expand surveillance systems for monitoring development of antibiotic resistances and changes in prescription standards (www.bmg.bund.de). Furthermore, the EVA project was initiated to study reasons influencing physicians' decisions for antibiotic prescriptions (Barger *et al.*, 2008).

In this study we compare the number of prescriptions of antibiotics to the number of indicator bacteria and to the occurrence of bacterial respiratory tract infections between 2000 and 2006 in a region with low prescription numbers compared to other European countries. Regarding prescriptions of the examined antibiotic classes the data of this study match those published elsewhere (Ferech *et al.*, 2006; Goosseens *et al.*, 2005; Goosseens *et al.*, 2006; Kern *et al.*, 2006; Muller *et al.*, 2007). A shift from conventional narrow-spectrum to modern broad-spectrum antibiotics has been noticed in Europe and has lead to a discussion about the use of broad-spectrum antibiotics for the treatment of respiratory infections (Goossens *et al.*, 2005).

Distinct seasonal differences leading to prescription peaks during cold seasons suggest that antibiotics are being used for treatment of respiratory infections. Within the observation period prescriptions of narrow-spectrum penicillins and macrolides showed a strong decrease. While seasonal variations for penicillins were relatively low those of macrolides were high. As prescriptions of broad-spectrum antibiotics also exhibited prominent seasonal alterations, it seems likely that treatment of respiratory infections had contributed to increased prescriptions of broad-spectrum antibiotics.

This context suggests that the number of bacterial infections and consequently the number of respiratory pathogens found in patients' samples should have increased. However the number of *S. pneumoniae* and *H. influenzae* findings declined during the observation period (Fig. 2). Since the proportion of positive respiratory samples also had decreased lower isolation counts of respiratory pathogens is a real phenomenon and not due to decreased case numbers. This discrepancy indicates that increased prescriptions of broad-spectrum antibiotics were performed without indication.

Regarding seasonal antibiotic use, the transient increase of prescriptions of macrolides, quinolones and cephalosporines group II in the first three months of 2005 may be due to treatment of increased respiratory infection numbers. Compared to other years, however, in this season isolation numbers of *S. pneumoniae* and *H. influenzae* were low while the number of persons affected by influenza virus was extremely high (www.influenza.rki.de/agi). Therefore, many prescriptions of broad-spectrum antibiotics were used to treat viral infections and therefore largely unnecessarily.

Although prescriptions of penicilins, macrolides and cephalosporines group II decreased within the observation period an increasing proportion of resistant *S. pneumococci* and *H. influenzae* were noticed. However, the percentages of resistant bacteria showed prominent fluctuations and the increases of *S. pneumoniae* were not significant. Therefore, at present it is not predictable if the proportion of resistant isolates will increase in the future. Recently, it was observed that in the past years the proportion of macrolide resistant pneumococci in Germany remained relatively constant (van der Linden et al. 2008).

In the present study, resistance of *H. influenzae* to amoxicillin and cefaclor significantly increased from 2000–2006. However, in 2006 an above-average increase was obvious and excluding 2006 from the statistical analysis the increase was no longer significant. On the other hand, in Germany the proportion of amoxicillin resistant *H. influenzae* continuously increased from 3.2% in 1999/2000 to 7.9% in 2007 (Kresken *et al.*, 2008). Therefore, increased antibiotic resistance of *H. influenzae* to amoxicillin might be a real phenomenon that has to be examined in future analyses.

In summary, here we show that between 2000 and 2006 broad-spectrum antibiotics were prescribed increasingly to Bavarian outpatients while consumption of narrow-spectrum antibiotics went down. Our data do not support the idea of using broad-spectrum antibiotics for curing respiratory infections.

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