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Antibiotic usage and resistance — trends in Estonian University Hospitals

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Abstract

The use of antibiotics, type of infections and resistance of prevalent bacteria was surveyed in Tartu University hospitals. The data from two ICUs (1995 and 1998), surgical and internal medicine departments (1998) were compared. Overall antibiotic usage in the ICUs and in the hospital as a whole had increased. There was a significant increase in Gram-positive bacterial infections and a decrease in Gram-negative infections in the ICUs. At the same time, susceptibility to several antibiotics decreased in most of the prevalent Gram-negative aerobes in the ICUs (*Acinetobacter* spp., *Pseudomonas* spp., *Klebsiella* spp.). Exceptions to this were the greater susceptibility of *Pseudomonas* spp. to gentamicin and *Acinetobacter* spp. to imipenem. Some changes in the predominant bacterial populations did not correlate to changes in antibiotic use.

Keywords: Antibiotic use; Antibiotic resistance; Infections in ICU

1. Introduction

Increasingly rapid emergence and dissemination of antimicrobial-resistant bacteria has become a world wide problem during the last decades. The unpredictability of the consequences of this increase have produced speculations such as 'end of the antibiotic era', 'crisis of modern medicine' and the application of the chaos theory to medicine but some doctors still believe in the possibilities of controlling or even reducing the spread of antibiotic resistance [1–6]. The Nordic countries have a low incidence of resistance and reports of resistance reduction by prudent antibiotic use supports their policies [7].

Knowledge about putative factors accelerating or preventing the spread of resistance and their importance in different settings is an essential prerequisite for rational policy to control antibacterial resistance. As antibiotic pressure has been supposed a major force for selection and spread of resistant strains, several projects have been conducted for surveillance of trends in antibiotic use and resistance patterns [2,8–11]. The end objectives of these studies are to make evidence based recommendations to reduce the emergence and spread of antimicrobial resistant pathogens. Because of differences in local resistance patterns and modes of antibiotic usage, local and hospital surveillance programmes are needed for elaboration of local directives for rational antibiotic use and hospital infection control.

Great changes in antibiotic usage have been taking place in Estonia during the last decade. Following the improved economical situation, total consumption of antibiotics has risen in hospital as well as in the community [12,13]. The spectrum of antibiotics use has changed dramatically: consumption of some drugs have been reduced significantly while broader spectrum antibiotics have been introduced. Until recently there were no official restrictions or guidelines for antibacterial prophylaxis and therapy in most hospitals. This unique situation gives us an opportunity to analyse the changes in resistance patterns together with changes in antibiotic use. The present study analyses this situation in one of the largest hospitals of Estonia.

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2. Material and methods

2.1. Study plan

The study included the following objectives: (1) to compare antibiotic use, type of prevalent bacteria and their susceptibility in departments with different types of patient; (2) to compare the changes in two different intensive care units over two 1-year periods; (3) to seek correlation between antibiotic consumption and resistance patterns; and (4) to evaluate implications for antibiotic policy.

The study was carried out in Tartu University Hospitals with 1381 beds in 1999. Antibiotic consumption and resistance was surveyed over two periods: years 1995 and 1998. In 1995, two intensive care units were included: ICU A, as a general surgical ICU and ICU B, as a neurosurgical ICU. These ICUs are compared in Table 1. In 1998, surgical and internal medicine departments were also included. The total number of beds of the departments included in the study in 1998 was 647.

During the study period no official external or internal guidelines for antibacterial prophylaxis or therapy were used in the departments under surveillance. The level of hospital hygiene and measures for infection control were the same in the ICUs under study. No special interventions to change the hospital hygiene were made during the study period.

2.2. Microbiology and pharmacy data

Non-duplicate isolates considered to be pathogens, from routine clinical samples were studied. A duplicate isolate was defined as an isolate of the same species of bacteria with the same antimicrobial susceptibility pattern isolated form the same patient and site within 2 weeks. Obligate anaerobes were not included in this study.

Susceptibility testing was performed by a disc diffusion method according NCCLS guidelines [14,15]. The same breakpoints were used in 1995 and 1998. The percentage of sensitive strains includes only these that were categorised as sensitive.

Susceptibility data was compared for predominant bacteria: *Pseudomonas* spp., *Acinetobacter* spp., *Klebsiella* spp., *E. coli*, total coliforms, *S. aureus* and coagulase negative staphylococci (CONS).

Consumption of antibiotics was calculated as defined daily doses per 100 bed days (DDD/100) as described previously [13,16]. Data of antibacterial drugs active only against obligate anaerobes such as metronidazole were not included.

2.3. Statistics

The prevalence of bacterial groups and susceptible strains was compared using Fischer or χ^2 test using Jandel SigmaStat 2.0 program.

3. Results

3.1. Use of antibiotics

Total consumption of antibiotics in the university hospitals increased from 47.6 DDD/100 in 1995 to 62.1 DDD/100 in 1998. The increase was observed in both ICUs, consumption rising by 44% in ICU A and by 24.5% in ICU B (Fig. 1). This increase was across all groups of antibiotics but was greatest with cephalosporins (87% increase in ICU A and a seven-fold increase in ICU B), amikacin (from 0 to 8.2 and 10.2 DDD/100 respectively) and fluoroquinolones (3- and 2.5-fold increase, respectively). While use of gentamicin remained unchanged, neomycin, streptomycin and kanamycin were replaced totally with amikacin in 1998. New antibiotics such as carbapenems, aztreonam and β-lactam/β-lactamase inhibitor combinations were introduced in 1998.

Comparing antibiotic use in different groups of departments in 1998 we found that total antibiotic consumption in the ICUs was three-fold higher than in general surgical departments and five-fold higher than in medical departments (Fig. 2).

3.2. Aetiology of infections in the ICU

In 1995 483 non duplicate aetiological agents were isolated from ICUs; 139 from ICU A and 344 from ICU B. In 1998, the numbers of isolates were: ICUs

Table 1
Comparison of facilities, length of stay and outcome in ICU A and ICU B

ICU	Year	Number of beds	Number of patients treated	Average stay in ICU (days)	Mortality (%)
ICU A	1995	12	389	5.9	18.8
	1998	12	400	6.4	21.7[a]
ICU B	1995	10	395	8.3	16.2
	1998	10	451	5.3	15.7[a]

[a] $P < 0.05$.

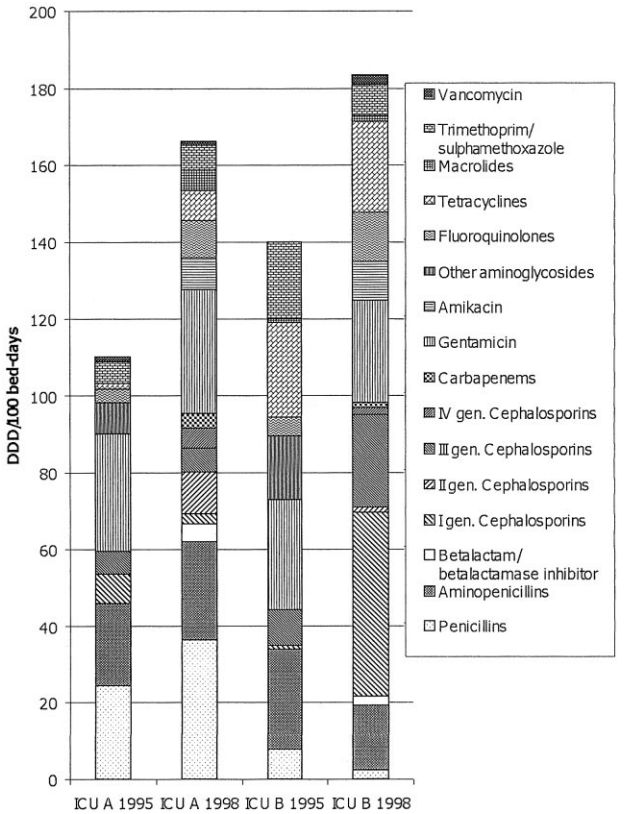

Fig. 1. Usage of antibiotics in ICUs A and B in 1995 and 1998.

A — 339 and B — 317, general surgical departments — 837 and general medical departments — 493.

Comparing prevalent bacteria in ICUs in 1995 and 1998 several changes could be seen. In both ICUs the percentage of Gram-positive organisms increased significantly: from 21% of isolates in A and 10.5% in B to 30 and 38.5%, respectively ($P < 0.001$). There was a significantly increased proportion of CONS ($P < 0.05$) in ICU A and, *S. aureus* ($P < 0.05$), CONS ($P < 0.001$) and *S. pyogenes* ($P < 0.05$) in ICU B (Fig. 3). Despite a reduction in the total Gram-negative organisms isolated, the proportion of *Klebsiella* spp. increased in both ICUs ($P < 0.001$). In ICU A, the greatest reduction was observed in the percentage of *Acinetobacter* spp. ($P < 0.001$) but in ICU B, a decrease in *Pseudomonas* spp. occurred ($P < 0.001$). Because of these changes *Pseudomonas* spp. became the most common bacterial genus in ICU A (29.5% versus 14% in ICU B, $P < 0.001$) and *Acinetobacter* spp. in ICU B (31% versus 10% in ICU A, $P < 0.001$) in 1998.

The aetiology of infections in the ICUs, and in the surgical and internal medicine departments in 1998 was different. In the surgical departments Gram-positive bacteria were significantly more frequent (54.5%) compared with the ICUs (34%, $P < 0.001$) and internal medicine departments (38%, $P < 0.001$). In the ICUs *Acinetobacter* spp. and *Pseudomonas* spp. (Fig. 4) were the predominant bacteria and were significantly more common than in other departments ($P < 0.001$). *Klebsiella* spp. were also more common in ICUs than in surgical departments ($P < 0.01$). *E. coli* was the predominant species in internal medicine departments ($P < 0.001$ versus ICUs and surgical departments). In the surgical departments Gram-positive cocci were dominant and the percentage of *S. aureus* was higher than in all other types of departments ($P < 0.001$); CONS and streptococci occurrence was higher than in the ICUs ($P < 0.001$ and 0.05, respectively).

3.3. Antibacterial susceptibility

No significant differences were found in the susceptibility of ICU isolates of Gram-positive bacteria in 1995 and 1998. The percentage of methicillin resistant *S. aureus* (MRSA) was 10% in 1995 and 9% in 1998. The susceptibility of *S. aureus* to erythromycin was 79.5 and 80%, respectively.No vancomycin resistant enterococci were found during the study.

In contrast to Gram-positives, the susceptibility of Gram-negative bacteria to most of the relevant antibi-

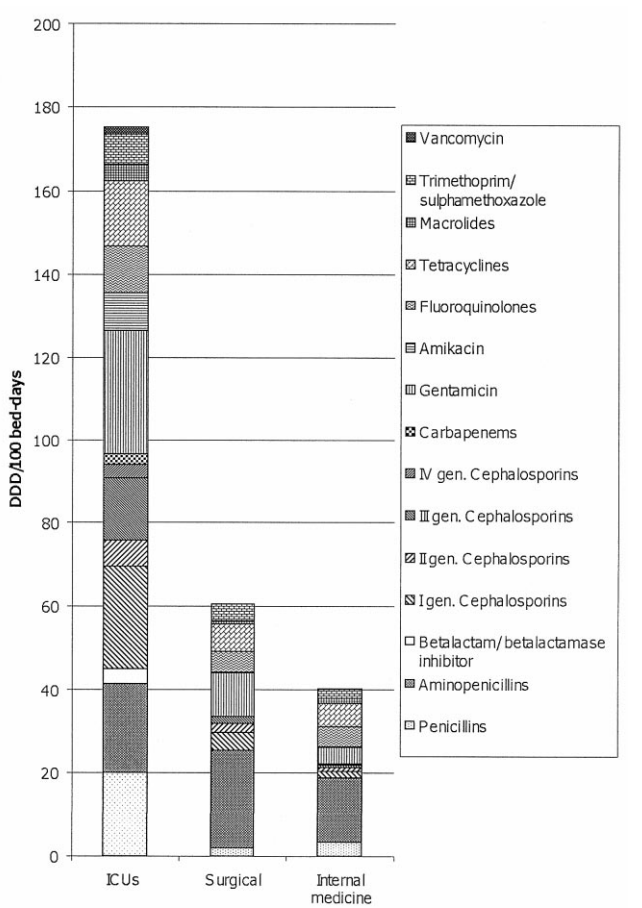

Fig. 2. Usage of antibiotics in ICUs, surgical and internal medicine departments in 1998.

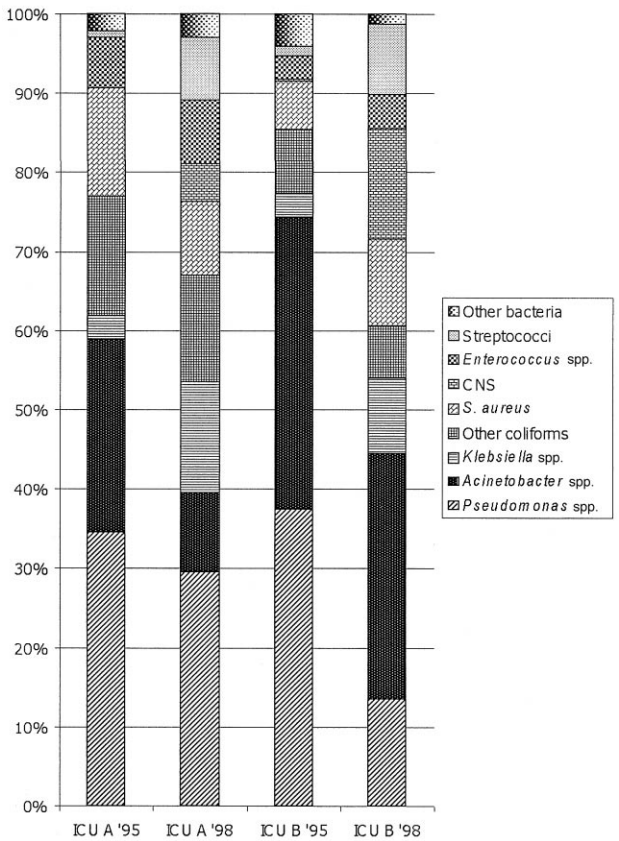

Fig. 3. Aetiology of infections in ICUs A and B in 1995 and 1998.

otics decreased (Table 2). Contrary to this trend *Pseudomonas* spp. became more sensitive to gentamicin and *Acinetobacter* spp. to imipenem. Similar trends occurred in both ICUs. The only difference between changes in ICU A and ICU B was in the susceptibility of *Pseudomonas* spp. to aztreonam: in ICU A susceptibility to aztreonam and some other β-lactams decreased while the percentage of sensitive strains in ICU B increased significantly (from 63 to 86%, $P = 0.01$). *Pseudomonas* spp. strains isolated from ICU B in 1998 were also significantly more sensitive to some other antibiotics (ceftazidime, cefepime, aztreonam and ciprofloxacin, $P < 0.05–0.001$) than *Pseudomonas* spp. isolates from ICU A.

Gram-negative bacteria in the ICUs were usually more resistant than in other departments (Table 3). An opposite trend was seen in case of ciprofloxacin resistance in coliforms. Imipenem-resistant *Acinetobacter* spp. and aztreonam-resistant coliforms were more frequent in surgical departments than in the ICUs and internal medicine departments.

The only significant difference in Gram-positive bacteria was in the proportion of oxacillin-resistant CONS which was higher in ICUs than other departments. There were no differences in the percentage of MRSA and macrolide-resistance among staphylococci in the departments studied.

4. Discussion

Our study shows that in this situation where there were no official limitations to antibacterial drug treatment, antibiotic pressure increased in ICUs. This was expressed in a rise in the total consumption of antibiotics in ICUs as well as in the hospital as a whole. There was a trend to replace narrow spectrum antibiotics with broader spectrum ones. Especially increased was the consumption of cephalosporins and fluoroquinolones and the new antibiotics such as amikacin, aztreonam, imipenem and β-lactams/β-lactamase inhibitor combinations which were unavailable in 1995. Thus the pressure increased on both Gram-positive as well as Gram-negative micro-organisms. The simultaneous changes in antibacterial susceptibility and the aetiology of infections were sometimes difficult to interpret. As expected, the sensitivity of prevalent Gram-negative bacteria to cephalosporins, amikacin, aztreonam and ciprofloxacin decreased significantly in the ICUs. Surprisingly the sensitivity of *Pseudomonas* spp. to gentamicin and *Acinetobacter* spp. to imipenem increased. As reported in other studies, Gram-negative

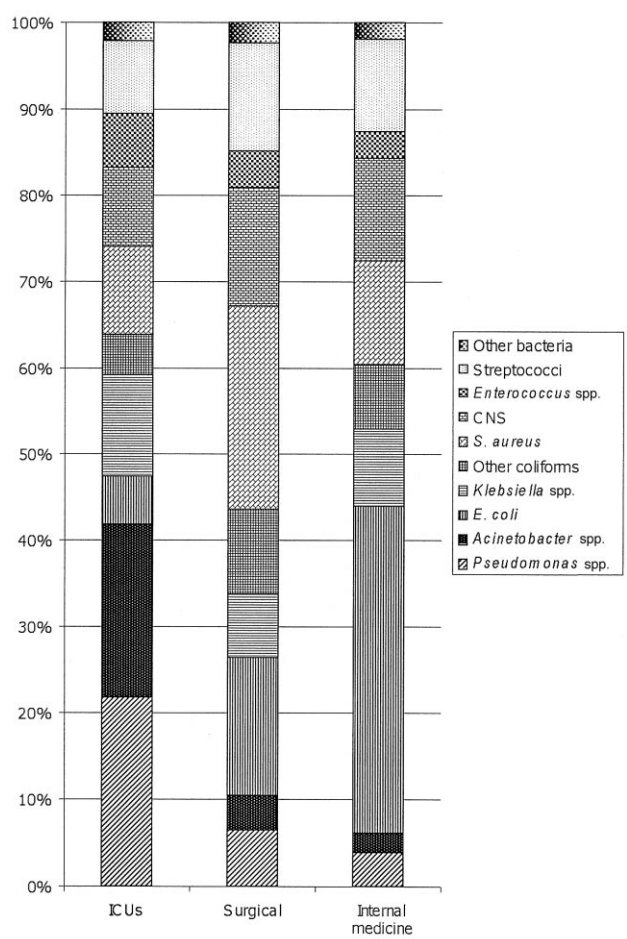

Fig. 4. Aetiology of infections in ICUs, surgical and internal medicine departments in 1998.

Table 2
Susceptibility of prevalent Gram-negative bacteria in ICUs[a]

	Percentage of sensitive strains in 1995/1998			
	Acinetobacter spp.	*Pseudomonas* spp.	*Klebsiella* spp.	Total coliforms
Ampicillin	NT[b]	NT	**21/2**[c]	**41/19**[d]
Cefalexin	NT	NT	**71/21**[c]	**66/30**[c]
Ceftazidime	**56/43**[c]	91/77	86/78	87/82
Cefepime	NT/47	NT/79	NT/80	NT/87
Imipenem	**93/99**[c]	87/90	NT	NT
Gentamicin	27/19	**52/83**[e]	**86/30**[e]	**80/52**[e]
Amikacin	**95/60**[e]	96/94	100/92	100/92
Aztreonam	14/9	**70/52**[d]	NT/67	NT/75
Ciprofloxacin	**67/33**[e]	**81/55**[e]	86/82	88/87

[a] Statistically significant differences between 1995 and 1998 are printed in bold.
[b] NT, not tested.
[c] $P<0.05$.
[d] $P<0.01$.
[e] $P<0.001$.

bacteria in the ICUs were usually more resistant than in other departments and was probably due to greater antibiotic use. However, higher ciprofloxacin resistance was found in coliforms isolated from patients outside ICUs than was found in ICU patients.

A clear relationship between antibiotic use and resistance of Gram-positive cocci was not very evident in our study. While the resistance of CONS to oxacillin was significantly higher in ICUs than in other departments, the proportion of MRSA did not differ outside and inside ICUs. Despite the increase in antibiotic use in the ICUs the prevalence of MRSA remained the same. However, because the proportions of staphylococci in ICU infections increased, the absolute number of infections caused by methicillin-resistant staphylococci increased.

As expected bacteria with high intrinsic resistance such as *Acinetobacter* spp. and *Pseudomonas* spp. caused infections in ICUs more frequently. Despite or because of the progressive antibiotic pressure with broad-spectrum antimicrobial drugs the proportion of these bacteria decreased in both ICUs. Furthermore, the remaining populations became more sensitive to some antibiotics. Despite a general positive relationship between antibiotic pressure and resistance some exceptions to this rule were seen.

Several considerations should be taken into account to avoid oversimplification of the correlation between the use of a particular antibiotic and resistance of pathogens. Although antibiotic use is probably the most important factor in the selection of resistant bacteria in the ICU there are other factors influencing the bacteria in the selective environment [17]. Transfer of resistant or sensitive strains occurs between the community and the hospital, factors others than antibiotics influence bacterial transfer from patient to patient, there is enhanced susceptibility of ICU patients to infections and the pressure of disinfectants and several other factors are difficult to quantify [18,19]. The impact of these factors can explain the discrepancy between antibiotic use and resistance in these two ICUs in 1998. Despite higher antibiotic use in ICU B, several bacterial groups were more sensitive in this ward compared with ICU A. Also, it is known that patients admitted to ICU A had usually been treated in other departments prior to transfer and probably already were carrying resistant hospital strains. Patients were admitted more frequently directly from outside the hospital to ICU B. In ICU A patients stayed $\sim$1 day longer with higher risk of acquisition of hospital strains. Mortality in this ICU was significantly higher indicating a cohort of more seriously ill patients.

Another problem with these attempts to correlate resistance and antibiotic consumption is the fact that one antibiotic can select resistance to other unrelated types of drugs. This could happen by selection of multidrug resistance carrying plasmids or broad spectrum resistance mechanisms such as multidrug efflux [17,18]. Examples are amikacin and imipenem resistance detected in 1995 before the introduction of these drugs. Therefore, besides monitoring use of particular antibiotics, it is also important to survey the total consumption. On the other hand the introduction of a highly effective drug can reduce population of bacteria resistant to other antibiotics.

Quantification of antibiotic pressure by antibiotic usage is difficult since surveillance of defined daily doses per bed days did not give precise details of the practice of antibiotic administration in local institutions that might have had significant influence on the emergence of resistance. The use of sub-optimal doses, unreasonable duration of prophylaxis and the effect of

Table 3
Differences in sensitivity of prevalent bacteria in different hospital departments in 1998

Antibiotic	Group of bacteria	Percentage of sensitive strains			Statistical significance
		ICU	Surgical	Internal medicine	
Ampicillin	*Klebsiella* spp.	2[1]	11[2]	33[1,2]	[1]$P<0.001$, [2]$P=0.01$
	Total coliform	19[1,2]	37[1,3]	49[2,3]	[1,2]$P<0.001$, [3]$P<0.01$
Cefamandole	*Klebsiella* spp.	30[1]	46[2]	79[1,2]	[1]$P<0.001$, [2]$P<0.05$
	Total coliforms	47[1,2]	65[1,3]	86[2,3]	[1]$P=0.01$, [2]$P<0.001$, [3]$P<0.01$
Ceftazidime	*Pseudomonas* spp.	77[1]	96[1]	100	[1]$P<0.01$
Imipenem	*Acinetobacter* spp.	99[1]	75[1]	100	[1]$P<0.001$
Aztreonam	*Acinetobacter* spp.	9[1]	13[2]	83[1,2]	[1]$P<0.005$, [2]$P<0.001$
	Total coliforms	75[1]	50[1]	71	[1]$P=0.005$
Ciprofloxacin	*Klebsiella* spp.	82[1]	53[1]	71	[1]$P<0.05$
	Total coliforms	87[1]	67[1]	70	[1]$P=0.005$
Oxacillin	CONS	26[1,2]	60[1]	65[2]	[1,2]$P<0.001$

drug combinations are some examples of such practices on which we have no information. Evaluation of these factors in ICUs where patients simultaneously receive several different antibiotics is quite difficult. Our previous study carried out in ICU B in 1995, found that patients received from two to seven (median four) different types of antibiotics during their stay in the department [20].

We found that significant changes in resistance and prevalence of bacteria in ICUs took place during the 3 years separating the two periods of study. In some cases these shifts were independent of the different ICUs and did not correlate with antibiotic use. This indicates that unpredictable replacement of one dominating bacterial population with another can happen over a short time. Thus, continuous local monitoring of resistance patterns is needed for adequate empirical therapy.

Although the need for advisory guidelines for antibiotic use is evident, several problems arise with the introduction of these kinds of restrictions. Several studies have shown a decrease of resistance after limitation in the use of a particular antibiotic [7–9,21]. However restriction of use of some antibiotics can increase consumption of others, resulting in new, unexpected resistance problems [8,9,21]. While evaluating the success of antibiotic policies apart from cost-effectiveness and reduction of resistance the final endpoint should also include the reduction of mortality after intervention.

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