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Dynamics between antibiotic drug use and resistance – An economic approach

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Dynamics between antibiotic drug use and resistance – An economic approach

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Abstract

In Europe, the emergence and spread of antibiotic resistance (AMR) has become a serious public health threat. Rational antibiotic policy, combined with enforcement of infection control practices are key strategies to combat AMR in the hospital setting. Using time-series analysis, we calculated potential savings resulting from changes in prescribing behaviour and improved compliance with hand hygiene. According to our calculations, a saving of 14 € would be achieved by reducing use of third-generation cephalosporins by one defined daily dose and further savings of almost 60 € would be achieved by increasing hospital-wide use of alcohol-based hand rub by one litre.

Keywords: Economic model, Externality, Antibiotics use, MRSA

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Introduction

In the past decades, antibiotic resistance (AMR) in pathogenic bacteria has been a growing problem both in Europe and worldwide. The race against resistance began soon after penicillin was developed. When with the emergence and spread of resistant organisms penicillin began to lose effectiveness, scientists dealt with the problem by developing methicillin, a synthetic penicillin; however, that agent, too, soon began to lose effectiveness.[1] Thus, new classes of antimicrobial agents were developed to replace methicillin. Now, as development has slowed down the effectiveness of antibiotics in general is beginning to decline.[2;3]

From a public health perspective, the effectiveness of antibiotic agents in hospital settings may be seen as a natural resource that is (1) protected by infection control practices implemented to prevent cross-transmission of resistant bacteria and (2) exploited by the use of antibiotics. Antibiotic use gives antibiotic-resistant bacterial strains a comparative advantage to spread, resulting in a direct correlation between the volume of antibiotic consumption and the spread of resistance in hospital settings, as 3 recent studies using time-series analysis have shown.[4-6]

Studies using time-series analyses on a hospital-wide level have shown that temporal increases (decreases) in the use of some classes of antibiotics are followed by temporal increases (decreases) in the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA), the most prominent multi-drug resistant pathogen. Furthermore, these studies have also shown that infection control practices such as hand disinfection are able to decrease MRSA incidence.[4-6]

Loss of antibiotic activity as a direct result of antibiotic consumption can be modelled on the approach of a negative externality. According to this concept, the cost of resistance is considered to be a negative externality of antibiotic use.[7;8] The study-objective was to determine the externalities of four classes of antibiotics which scientifically influence the occurrence of MRSA in hospital setting.[5]

Methods

The model

The externality determines the level of the cost of resistance that is caused by use of one defined daily dose (DDD) of a selected antibiotic. Therefore, knowledge of the extent to which an antibiotic may have contributed to the emergence of resistance and what costs are incurred by which type of resistant infection is imperative.

Following existing approaches, the probability of the failure of antibiotic treatment due to a resistant organism is termed *R*, while the additional cost of infections caused by resistant bacteria are represented by ΔV. The impact parameter between antibiotic use and the occurrence of resistance ε is called dose-response rate of drug use – drug resistance and may be described as the percentage change in the incidence of resistance following a 1% change in the level of antibiotic use.[8] The externality *E* of the use of antibiotic *q* is then given by

(1) $$E_q = \varepsilon_q R_q \Delta V ,$$

where the negative externality is determined by the linear relationship between antibiotic use and the occurrence of resistance ε, the probability of the acquisition of a resistant infection *R* and the constant costs of an infection caused by a resistant pathogen ΔV.

The data

In one of our previous studies, the impact of antibiotic use on the incidence of nosocomial MRSA infections was determined using a multivariate linear regression model.[5] There was a positive impact for the use of second-generation cephalosporins (coeff.= 1.41, p = 0.023), third-generation cephalosporins (coeff.= 1.03, p = 0.051), fluoroquinolones (coeff.= 1.12, p = 0.01) and lincosamides (coeff.= 0.42, p = 0.05). Since logarithmically transformed variables were used in the regression, the dose-response rates ε equaled the resulting coefficients, which means that a one percent increase in third-generation cephalosporin use was followed by a 1.03 percent increase in the number of nosocomial MRSA infections. The linear assumptions made in the model made a constant dose-response relationship probable.[9]

Results

The study was conducted at University Medical Center Freiburg, a 1600 bed tertiary care teaching hospital. During the study period (January 2003 through October 2007), the mean monthly number of episodes of nosocomial infection was identified as being 2.69. Monthly antibiotic use is shown in Table 1. The probability of treatment-failure due to a resistant organism was calculated by using the monthly number of nosocomial MRSA infections in relation to the amount of antibiotics used.($\sum \text{MRSA} / \sum \text{DDD}$; see Table 1).

Presuming that the additional cost of an MRSA-patient is significantly higher (8198€) than that of a non-MRSA patient,[10] the calculations shown in Table 1 demonstrate the extent of the external cost of antibiotic consumption from promoting resistance.

(Insert Table 1 here)

Equally, equation (1) can be used to determine the positive effect of hand disinfection. Using existing data,[5] we integrated the series of alcohol-based hand rub use into our multivariate model (coeff.= -5.37, $p < 0.001$). The negative coefficient estimated in the model shows the preventive impact of alcohol-based hand rub use on the incidence of MRSA. The results obtained from including alcohol-based hand rub use in equation (1) is shown in Table 1 and may be seen as the potential costs prevented by use of one litre of alcohol-based hand rub solution for hand disinfection. In other words, using only 3ml alcohol-based hand rub solution for hand disinfection, saves 0.18€ of the potential cost incurred by MRSA-related infections.

Discussion

As of yet, there are few studies demonstrating that use of antibiotics leads to indirect external costs by promoting resistance.[7;8]

Although, the estimates presented here for the externality of antibiotic use are crude, they demonstrate that antibiotic consumption does from the perspective of a hospital, at least, substantially affect the cost of resistance. An externality of around 10 € per DDD is a small amount of money compared to the overall per diem cost of hospitalization, but is a significant amount compared to the direct cost of the antibiotic.

According to our calculations, a saving of approximately 14 € would be achieved by reducing use of third-generation cephalosporins by a single DDD. Increasing hospital-wide use of alcohol-based hand rub by one litre would give a saving of approximately 60 €. The emergence and spread of resistance in hospital settings is a multifactor process. Thus, prevention of AMR in the hospital can be only achieved by taking a multifactor approach in changing the major variables antibiotic use and infection control practice, especially hand hygiene. Both variables were tested in the multivariate time-series analysis.[5]

Demonstrating the net benefit of preventing AMR may lead to changes in prescribing behaviour and increase compliance with infection control practices.

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Transparency declarations

No conflicts of interest.

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Table 1: Characteristics of the parameters used for the determination of the externality

q[a]	Mean use of q[b]	$R= \sum \text{MRSA} / \sum \text{DDD}$ [c]	ε [d]	ΔV [e]	E[f]
second-generation cephalosporins	6544	0.0004111	1.41	8 198 €	4.75 €
third-generation cephalosporins	1627	0.0016534	1.03	8 198 €	13.96 €
fluoroquinolones	2352	0.0011437	1.12	8 198 €	10.50 €
lincosamides	840	0.0032024	0.42	8 198 €	11.03 €
alcohol-based hand rub	1991	0.0013511	-5.37	8 198 €	-59.45 €[g]

[a]Uses of antibiotics and alcohol-based hand rub solution as included in the multivariate analysis.
[b]Monthly amounts of antibiotic use (in DDD) and alcohol-based hand rub use (in litres) during the study period (01/2003 – 10/2007).
[c]The probability of the acquisition of a resistant infection.
[d]Dose-response rate of drug use – drug resistance as determined in the multivariate analysis.
[e]The additional costs of an Infection due to MRSA according to a recent study in 11 German hospitals.[10]
[f]The externality E of the use of one unit of q according to equation $E_q = \varepsilon_q R_q \Delta V$.
[g]The externality of alcohol-based hand rub use may be seen as potential costs prevented by one litre of alcohol-based hand rub use for hand disinfection.

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