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Review

The economic impact of antimicrobial stewardship programmes in hospitals: a systematic literature review

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SUMMARY

Background: Antimicrobial stewardship programmes (ASPs) include strategies that enable sustainable management of rational anti-infective treatment in the clinical setting. The successful introduction of ASPs requires close interdisciplinary collaboration among various health professionals, including the hospital management. So far, ASPs have been evaluated mainly from a clinical–pharmacological and infectious disease perspective.
Aim: To identify and evaluate parameters with decisive significance for the economic impact of ASPs.
Methods: A systematic literature search for peer-reviewed health-economic studies associated with antimicrobial stewardship programmes was performed. Primary outcomes included savings in drug costs and lower revenue losses for hospitals.
Findings and conclusions: A total of 16 studies met all inclusion criteria. Most of the evidence from published clinical trials demonstrated savings through reduced direct cost of antibiotics. However, there are also studies that prove revenue effects of ASPs through decreases in length of stay and readmission rates.

Introduction

It is undisputed that inappropriate or incorrect use of antimicrobial agents favours the emergence and spread of antimicrobial resistance, which have not only clinical but also health economic consequences. In comparison with hospital infections caused by susceptible bacteria, those caused by multidrug-resistant bacteria are associated with a higher comorbidity and mortality [1]. Due to inadequate empirical therapy and primary treatment failure, more antibiotics will be consumed overall and reserve antibiotics will have to be resorted to. This leads to increased antibiotic costs [2]. Additional costs arise from hygiene measures, diagnostics, and bed closures due to isolation of patients with multidrug-resistant bacteria [3]. Furthermore, length of hospital stay is often extended, which is not completely covered by lump-sum remuneration systems such as the German DRG system and therefore also a cost factor for hospitals [4]. Altogether, this results in a high motivation for the development of antimicrobial stewardship programmes (ASPs), because only the responsible use of antimicrobials can address this problem effectively.

Antimicrobial stewardship programmes

The term 'antimicrobial stewardship' is widely used in the literature [5]. Whereas no single definition exists, most explanations state that antimicrobial stewardship encompasses co-ordinated efforts to promote the appropriate use of antibiotics to improve patient outcomes, reduce microbial resistance, as well as decrease the spread of multidrug-

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resistant organisms and unnecessary costs [6]. In other words, ASPs can be described as a systematic effort to educate and convince prescribers to use an appropriate antimicrobial therapy, i.e. the patient receives the right drug in the right dose and over the right duration with the fastest possible de-escalation of initial broad-spectrum antibiotics [7].

Antimicrobial stewardship programmes are an inter-disciplinary approach in which members of various disciplines work together as a team. Most stewardship teams include an infectious disease physician, a pharmacist, and often an infection preventionist. There should also be a close collaboration with the staff in the microbiology laboratory, infection surveillance report system, and the hospital management [8].

There are several basic approaches of antibiotic stewardship in healthcare settings. In 2007, the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) published guidelines for developing institutional programmes to enhance antimicrobial stewardship [9]. This publication provides a template for several (European) guidelines, such as the German S3 guideline: 'Strategies for ensuring a rational use of antibiotic in hospitals' [10].

Not infrequently, a combination of different interventions within ASPs are used. In 2013, Davey *et al*. classified three ASP intervention types in a Cochrane review (Table I). The persuasive intervention type aims to provide information for prescribers and includes audit, educational programmes, reminders, or feedback. Restrictive type interventions (e.g. formulary restrictions, authorization, antibiotic cycling) ensure the prescription of antibiotics only by ASP-trained persons and set rules. The structural type has a supporting and controlling function and includes, for example, computerization of records or decision support systems.

So far, ASPs have been evaluated mainly from a clinical—pharmacological or microbiological point of view [11]. The implementation of intervention measures, however, can entail high investment costs. Therefore, it seems legitimate for the hospital management to know whether these investments will be monetized by corresponding cost savings. However, few studies can be found in the literature on the cost-effectiveness of ASPs [12—15]. The purpose of this study was to identify and evaluate parameters with decisive significance for the economic impact of ASPs.

Methods

Data sources and search strategy

A systematic review of literature regarding the economic impact of ASPs in hospitals was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The search terms included 'antibiotic' OR 'antimicrobial' AND 'stewardship' AND 'hospitalization' OR 'readmission' OR 'drug' OR 'mortality' AND 'costs' OR 'economics' OR 'impact' OR 'burden'. The electronic databases PubMed and MedPilot were searched systematically for studies published in German and English between 1995 and June 2018. The search was carried out twice by two different persons. Additional records were added through screening of reference lists by hand.

Study selection

Figure 1 presents the study selection process using the PRISMA flowchart. Full text articles reporting on the economic aspect of implementing antimicrobial stewardship programmes in hospitals were included. In particular, studies evaluating the antibiotic consumption rates and costs as well as length of hospital stays, and studies providing information on infection rates and mortality, were included. The study design should include a control group, or changes in output parameters between pre- and post-ASP implementations should be comprehensible.

Exclusion criteria applied to all studies retrieved by the search were established. Duplicate records or double-published studies and articles published before 1995 were excluded. The selection was limited to studies written in English or German. No limitations were placed on geographical location. Studies were excluded afterwards if they were expert opinions, case reports, or studies that did not report on ASPs because of obviously irrelevant titles and abstracts. For the remaining potentially eligible articles, full text papers were obtained for a more detailed assessment. Full text articles with absence of clinical data or cost information were excluded. The remaining eligible articles were included in the qualitative summary. Relevant data were extracted from all studies meeting the eligibility criteria.

Outcome parameters

The data extraction of economic outcome parameters related to direct cost effects of antibiotic management (antibiotic consumption and total antibiotic costs) as well as to the revenue effects of changes in length of hospital stay and readmissions. In addition, data on clinical output parameters, mortality, and rates of healthcare-associated infections were extracted. Extracted data were recorded for respective groups (control and ASP interventions) or periods. For better comparability of the study results, data on antibiotic consumption were standardized as defined daily dose (DDD) per 100 patient-days and on antibiotic costs in US dollars ($) per 100 patient-days. Pre—post deviations were reported both as absolute difference values and as relative percentages. ASP effects on

Table I
Antimicrobial stewardship intervention types, defined by Cochrane review groupings [6]

Type of intervention	Aim	Examples
Persuasive	Provide information for prescribers	Educational programmes, reminders, audit, feedback
Restrictive	Set rules, implement standards	Formulary restrictions, authorization requirements, antibiotic cycling
Structural	Give support and control	Computerization of records, rapid diagnostics, decision support systems

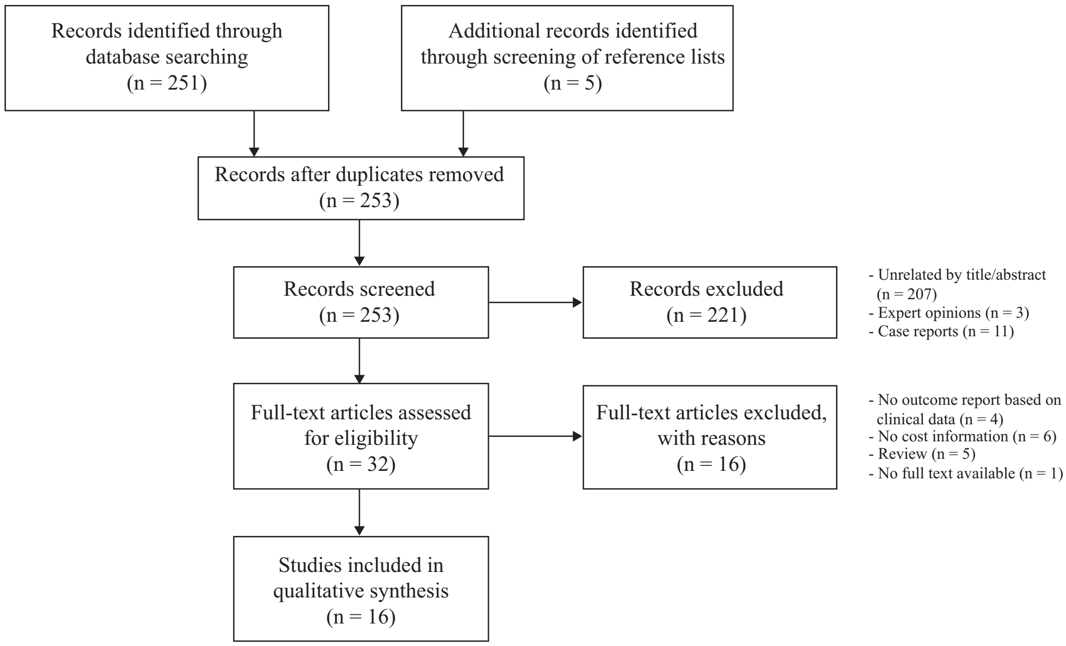

Figure 1. PRISMA flowchart.

the length of hospital stay (LOS) were illustrated by forest plot. All results were documented from the perspective of the hospital.

Results

Description of studies

In total, 16 studies were eligible for extraction and included in the qualitative analysis. Five studies came from the European Union (Germany (three), the Netherlands (one), and Ireland (one)). Another five studies came from the USA, two from Japan, and one each from Canada, South Africa, Taiwan, and Hong Kong. The majority of studies (69%) used a controlled, non-randomized study design that retrospectively included data from the control group. In three studies, the data were collected entirely retrospectively [13,16,17]. One study applied a descriptive cost analysis [18], one an interrupted time-series analysis [12], and one an analysis with a randomized step-wedge design [19]. All studies implemented reporting and feedback systems as part of the ASP interventions. In 13 studies (81%), further interventions were used (training, guidelines, restrictions, or computerization), partly in combination. The survey periods varied widely, between three months and seven years. The studies were published between 2008 and 2015.

Direct cost effects due to antibiotic management

Effects of ASP interventions on consumption of antibiotics were described in eight studies whereas total cost effects were reported in 15 studies (Table II). All eight studies showed a decrease in antibiotic consumption. The reduction varied between the studies but was on average −162 DDD per 100 patient-days or −16%, respectively. In four studies, the reduction due to the implementation of ASPs was considered statistically significant ($P < 0.05$) [12,15,23,24].

Total antibiotic cost savings were reported in all 15 studies. However, there were also large differences between the analyses. On average, the antibiotic costs after the ASP interventions were $1630.66 per 100 patient-days compared to $2078.91 per 100 patient-days in the control data. This corresponds to an average cost reduction of $448.25 per 100 patient-days or 25 %, respectively. In four studies, the saving effect was statistically significant ($P < 0.05$) [13,14,24,26].

Revenue effects due to changes in length of hospital stay and readmissions

Twelve studies reported results on changes in the length of hospital stay (Table III). On average, the mean LOS of 12.8 days in the control group decreased to 11.9 days in the intervention group (−0.90583 days or 7% in average). However, in three studies an increase in LOS was reported [19,21,24]. Figure 2 shows a forest plot of the difference between control and intervention (ASP) groups.

Five studies showed effects on readmission rates (Table III). On average, a decline of 0.19 percentage points or 4% could be determined. Nevertheless, only three studies demonstrated reductions in readmissions [16,20,26], compared with two studies indicating an increase [15,18]. Only Ng *et al.* reported the effect as statistically significant [15].

Effects on mortality and rates of healthcare-associated infections

Table IV presents extracted results of the clinical outcome rates of mortality and healthcare-associated infections. Eight studies reported mortality effects. On average, mortality decreased by 3.33 percentage points or by −7.7%, respectively.

Table II
Overview of studies with results on antibiotic consumption and antibiotic costs

Publication	Consumption of antibiotics			Total costs of antibiotics				
	DDD per 100 patient-days		Difference in DDD per 100 patient-days (%)	As shown in the original publication		Standardized in US$ per 100 patient-days		Difference in US$ per 100 patient-days (%)
	Control	ASP interventions		Control	ASP interventions	Control	ASP interventions	
Borde *et al.* [12]	110.5	94.8	−15.7 (−14%)	€1,038,648	€594,684	981.48	561.95	−419.53 (−43%)
Boyles *et al.* [20]	59.20	47.58	−11.62 (−20%)	R1,068,325	R694,705	246.17	166.06	−80.11 (−33%)
Dik *et al.* [13]	n.p.	n.p.	n.p.	€17.42 per patient	€13.35 per patient	261.96	245.16	−16.80 (−6%)
Dunn *et al.* [21]	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.
Huebner *et al.* [22]	n.p.	n.p.	n.p.	€76,835	€29,315	835.91	316.89	−519.02 (−62%)
Lin *et al.* [14]	899	705	−194 (−22%)	$21,139 per 1000 patient-days	$11,851 per 1000 patient-days	2113.9	1185.1	−928.8 (−44%)
Malani *et al.* [16]	n.p.	n.p.	n.p.	$1,503,748	$1,274,837	166.25	125.85	−40.40 (−24%)
Miyawaki *et al.* [17]	n.p.	n.p.	n.p.	¥359,169	¥262,528	1.02	0.78	−0.24 (−24%)
Ng *et al.* [15]	1507	1410	−970 (−6%)	$1,458,593	$1,104,694	1083.52	817.39	−266.13 (−25%)
Niwa *et al.* [23]	21.03	19.26	−17.7 (−8%)	$2,023,344	$1,858,954	2697.36	2597.14	−100.22 (−4%)
Palmay *et al.* [19]	n.p.	n.p.	n.p.	$11.73 per patient-day	$11.33 per patient-day	1173	1133	−40 (−3%)
Pate *et al.* [24]	91.4	72.1	−19.3 (−21%)	$26.9 per patient-day	$18.2 per patient-day	2690	1820	−870 (−32%)
Rimawi *et al.* [25]	n.p.	n.p.	n.p.	$63,364	$40,878	2891.00	2466.78	−424.22 (−15%)
Standiford *et al.* [18]	117.4	85.1	−32.3 (−28%)	$3,503,878	$3,183,232	2003.72	1596.88	−406.84 (−20%)
Weber *et al.* [26]	n.p.	n.p.	n.p.	€108,379	€94,628	1457.48	1249.11	−208.37 (−14%)
Yu *et al.* [27]	504.8	460.4	−44.4 (−9%)	$125,808 per 1000 patient-days	$101,778 per 1000 patient-days	12,580.8	10,177.8	−2403.0 (−19%)

DDD, defined daily dose; ASP, antibiotic stewardship programme; n.p., data not presented in article; R, South African rand; ¥, Japanese yen.

Table III
Overview of studies with results on mean length of stay and readmission rate

Publication	Mean length of stay in days					No. of readmissions (% of patients within 30 days)		
	Control	ASP interventions	Difference in days (%)	95% CI	*P*-value	Control	ASP interventions	Difference in percentage points (%)
Borde *et al.* [12]	n.p.	n.p.	n.p.	n.p.		n.p.	n.p.	n.p.
Boyles *et al.* [20]	n.p.	n.p.	n.p.	n.p.		226 (9.3%)	213 (8.5%)	−0.8 (−9%)
Dik *et al.* [13]	7.57	6.2	−1.37 (−18%)	0.62	0.012	n.p.	n.p.	n.p.
Dunn *et al.* [21]	9 (median)	10 (median)	1 (11%)	n.p.		n.p.	n.p.	n.p.
Huebner *et al.* [22]	8.87	8.13	−0.74 (−8%)	n.p.		n.p.	n.p.	n.p.
Lin *et al.* [14]	10.6–12.2	10.6–12.2	n.p.	n.p.		n.p.	n.p.	n.p.
Malani *et al.* [16]	8 (median)	7 (median)	−1 (−13%)	0.5	0.44	76 (20%)	69 (20%)	0
Miyawaki *et al.* [17]	24.9	19.9	−5	n.p.		n.p.	n.p.	n.p.
Ng *et al.* [15]	7.46	6.97	−0.49 (−7%)	0.1489	<0.001	2897 (17.6%)	3322 (18.7%)	1.1 (6%)
Niwa *et al.* [23]	12	11	−1 (−8%)	0.5	0.0001	n.p.	n.p.	n.p.
Palmay *et al.* [19]	9.5	10.3	0.8 (8%)	0.377	0.003	n.p.	n.p.	n.p.
Pate *et al.* [24]	23 (median)	26 (median)	3 (13%)	1.183	<0.001	n.p.	n.p.	n.p.
Rimawi *et al.* [25]	10.29	7.78	−2.51 (−24%)	1.166	0.0188	n.p.	n.p.	n.p.
Standiford *et al.* [18]	6.1	5.54	−0.56 (−9%)	n.p.		1.533 (5.3%)	2.218 (6.15%)	0.85 (16%)
Weber *et al.* [26]	26.6	23.6	−3 (−11%)	1.275	0.81	20 (6.2%)	13 (4.1%)	−2.1 (−34%)
Yu *et al.* [27]	n.p.	n.p.	n.p.	n.p.		n.p.	n.p.	n.p.

ASP, antibiotic stewardship programme; CI, confidence interval; n.p., data not presented in article.

None of the studies rated the effects on mortality as statistically significant.

Nine studies included data on ASP influences on healthcare-associated infection rates, but documentation was variable. Five studies referred to *Clostridium difficile* infections (CDIs), with two studies [24,25] showing an increase and two studies [17,27] showing a decrease in the infection rate. Huebner *et al.* stated that there were no changes in the CDI rate but presented no supporting data [22]. Study results of Ng *et al.* and Malani *et al.* were statistically significant ($P < 0.05$) [15,16].

Discussion

Nearly all included studies reported cost savings in antibiotic therapy. This was accompanied by a reduction in antibiotic consumption compared to control as reported by more than half of the studies extracted. The effect is clearly due to targeted control of the selection of appropriate antimicrobial agents by ASPs. Inadequate initial therapies were avoided, resulting in faster treatment success with fewer comorbidities and mortalities. This correlates with the study results on effects on length of stay and readmissions. However, in contrast to reductions in antimicrobial consumption, the effects of ASPs on length of stay and readmissions were not so clear, with studies showing reductions as well as increases. Hence, evidence from included studies was still too vague to enable firm conclusions on revenue effects from length of stay and readmissions.

The current study has limitations that need to be considered when interpreting the data. First, study selection focused on publications connecting ASP interventions to economic outcome parameters. Therefore, publications reporting clinical effects but no economic endpoints of ASP interventions were

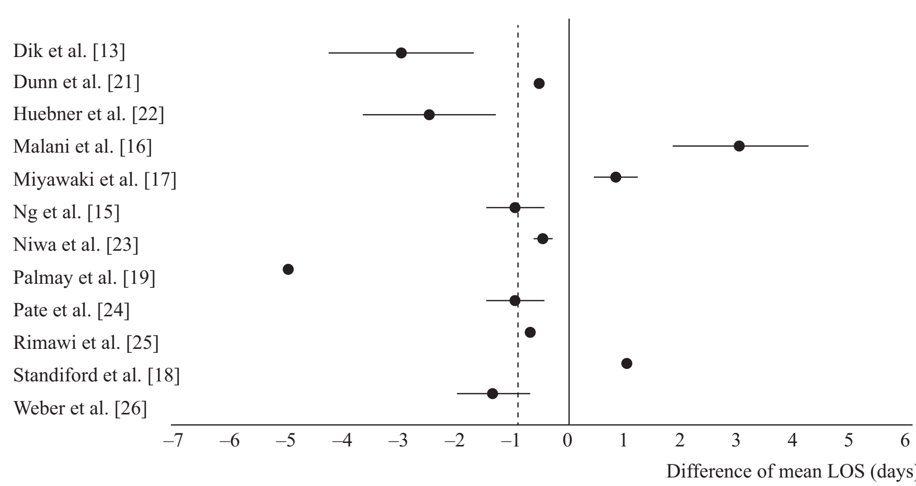

Figure 2. Forest plot of reported differences and 95% confidence intervals in hospital length of stay (LOS) between control and antibiotic stewardship programme groups; 12 studies included, mean difference −0.90583 days (dotted line).

Table IV
Overview of studies with results on mortality and infection rates

Publication	Mortality in cases (% of patients within 30 days)			Infections (% of patients or as indicated)		
	Control	ASP interventions	Difference in percentage points (%)	Control	ASP interventions	Difference (%)
Borde *et al.* [12]	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.
Boyles *et al.* [20]	311 (12.8%)	315 (12.5%)	−0.3 (−2%)	n.p.	n.p.	n.p.
Dik *et al.* [13]	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.
Dunn *et al.* [21]	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.
Huebner *et al.* [22]	n.p.	n.p.	n.p.	n.p.	n.p.	CDI showed no differences
Lin *et al.* [14]	2.6–3.9 per 100 admissions	2.6–3.9 per 100 admissions	n.p.	1.9 HAI per 1000 patient-days	1.3 HAI per 1000 patient-days	(−32%)
Malani *et al.* [16]	77 (21%)	55 (16%)	−5 (−24%)	46 CDI (12%)	20 CDI (6%)	(−5%)
Miyawaki *et al.* [17]	319 (2.4%)	306 (1.9%)	−0.5 (−21%)	(0.75%) HA-MRSA	(0.68%) HA-MRSA	(−9%)
Ng *et al.* [15]	(8.8%)	(8.4%)	−0.4 (−5%)	5301 RI (69.9%)	8251 RI (42.6%)	(+45%)
Niwa *et al.* [23]	n.p.	n.p.	n.p.	n.p.	n.p.	n.p.
Palmay *et al.* [19]	(3.2%)	(4.3%)	1.1 (34%)	1.06 CDI per 1000 patient-days	1.01 CDI per 1000 patient-days	(−5%)
Pate *et al.* [24]	n.p.	n.p.	n.p.	5.3 CDI per 10,000 patient-days	11.3 CDI per 10,000 patient-days	(+113%)
Rimawi *et al.* [25]	34 (28%)	29 (24%)	−4 (−12%)	7 CDI (6%)	9 CDI (7%)	(+17%)
Standiford *et al.* [18]	867 (3%)	983 (2.7%)	−0.3 (−10%)	n.p.	n.p.	n.p.
Weber *et al.* [26]	n.p.	n.p.	n.p.	205 HAI (63.9%)	184 HAI (58%)	(−9%)
Yu *et al.* [27]	85.65% HSMR	68.4% HSMR	−17.25 (−20%)	7.55 CDI per 10,000 patient-days	7.95 CDI per 10,000 patient-days	(−5%)

ASP, antibiotic stewardship programme; n.p., data not presented in article; CDI, *Clostridium difficile* infection; HAI, hospital-acquired infection; HA-MRSA, hospital-acquired meticillin-resistant *Staphylococcus aureus*; RI, respiratory infection.

not systematically included. Whereas including these studies could have strengthened our conclusions on effects on clinical endpoints such as infection rate or mortality, we deliberately focused on studies that reported economic endpoints in accordance with our research goal. Second, our analysis shows a great amount of overall heterogeneity in design, interventions, duration, targets, and reporting between the studies. Many studies relied on a non-randomized design with historical controls, thus limiting their value by possible bias. Generally speaking, confounding and bias are typical problems for this type of study that cannot be fully avoided, but authors should include data to control for them in the analyses. However, significant research is still needed to establish methods that lead to standardized reports and analyses, allowing better comparison of results between studies. Additionally, it is important to calculate and report the costs of different interventions and to contrast them with the determined effects for evaluation of the cost-effectiveness of ASPs. It must be noted also that in the analyses shown, only direct outcome parameters such as antibiotic prescriptions were addressed. However, the economic implications of nosocomial infections are far more extensive and are influenced by many other factors in addition to the choice of antimicrobial drugs [28,29]. This must be taken into greater account in the evaluation of ASPs in the future.

The strength of our review is the standardization and statistical presentation of extracted data wherever possible. This helps to quantify the (un)certainty of current evidence and helps to direct further research. In light of the heterogeneity and limited number of studies that could be included in this review and the possibly large effect of costs other than for antibiotic perceptions, the total economic effect of ASPs may be positive but is still uncertain from the hospital perspective. As economic effects are critical for sustained ASPs, further research is warranted.

In conclusion, although existing economic evaluations of implementing ASPs in the hospital setting are still limited, there is already evidence of positive health economic impact from various clinical trials. Most results point to the reduction of the direct cost of antibiotics. However, some references in the literature also consider length of hospitalization and readmission rates, which have an impact on hospital revenue. There is urgent need for further research in the field, which also includes other aspects of infection prevention besides pure medication of antibiotics.

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