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RESEARCH ARTICLE

The cost associated with the development of the antimicrobial stewardship program in the adult general medicine setting in Qatar

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ABSTRACT

Objective: To estimate the economic impact of the developed antimicrobial stewardship program (ASP) versus the preliminary ASP use, in the adults' general medicine settings in Qatar.

Methods: Patient records were retrospectively reviewed during two periods: preliminary ASP was defined as the 12 months following ASP implementation (i.e. May 2015-April 2016), and developed ASP was defined as the last 12 months of a 5-year ASP implementation in Hamad Medical Corporation (HMC) (i.e. February 2019-January 2020). The economic impact was the overall cost savings in resource use, including operational costs, plus the cost avoidance associated with ASP.

Results: A total of 500 patients were included in the study. The operational costs decreased with the developed ASP. Whereas antimicrobial consumption and resource utilisation, and their associated costs, appear to have declined with the developed ASP, with a cost saving of QAR458 (US$125) per 100-patient beds, the avoided cost was negative, by QAR4,807 (US$1,317) per 100-patient beds, adding to a total QAR4,224 (US$1,160) increase in the 100-patient beds cost after ASP development.

Conclusions: Despite that the developed ASP attained a total cost saving QAR458 (US$125) per 100-patient beds, the avoided cost was QAR-4,807 (US$ −1,317) per 100-patient beds, which exceeded the cost savings achieved.

KEYWORDS Antimicrobial; Stewardship; General medicine; Cost; Economic impact; Service

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Introduction

Globally, it is estimated that half of all antimicrobial agents prescribed are either unnecessary or inappropriately used (Davey et al., 2017; Schuts et al., 2016). In 2016, nearly 30% of antimicrobials prescribed in the United States (US) were deemed unnecessary, according to the Centers for Disease Control and Prevention (CDC) (2022). In Qatar, a survey revealed that approximately 82% of people used antibiotics without a prescription, 37% of whom used antibiotics that were prescribed for another family member, and 27% used antibiotics that were prescribed to them for a previous medical condition with a similar symptom (Aljayyousi et al., 2019). Additionally, 45% did not complete their antibiotic courses once they started feeling better or assuming that the antibiotic is not effective in treating the disease, which may expose the patients to antimicrobial resistance (Aljayyousi et al., 2019). Such rampant use has been associated with adverse events, increased healthcare costs and, importantly, the spread of multidrug-resistant organisms, which are, in turn, associated with higher comorbidity and mortality (Holmes et al., 2016). Globally, around five million deaths occurred in 2019, of which one million were attributed to antimicrobial resistance (Roth et al., 2017). It is undisputed that the emergence of antimicrobial resistance is detrimental to patients' health and well-being and the healthcare system (Coast et al., 1996; Hübner et al., 2014; Hübner & Flessa, 2016; Ojeniran et al., 2010). At present resistance rates, the Organization for Economic Cooperation and Development (OECD) countries projected that healthcare expenditures would amount to US$2.9 trillion by 2050 (Organisation for Economic Co-operation and Development, 2016).

In response to the issue of antimicrobial resistance and inappropriate use of antimicrobials, several regulatory bodies mandated the employment of antimicrobial stewardship programs (ASPs). ASP refers to pragmatic interventions by an interdisciplinary team to ensure the optimisation of antimicrobials, including patient-level stewardship (i.e. optimising antimicrobials for an individual according to microbiology results and clinical condition) and population-level stewardship (i.e. decreasing consumption of antimicrobials) (Davey et al., 2017). In most relevant literature, ASPs have been evaluated mainly from a clinical, pharmacological, or microbiological point of view (Pogue et al., 2015). The implementation of intervention measures, however, can entail high investment costs. Therefore, it seems legitimate for the hospital management to know whether corresponding cost savings will monetise these investments. Several studies were reported in the literature to document the economic impact of ASPs in their local settings. Studies come from the European Union, the US, Asia, and Canada (Borde et al., 2014; Boyles et al., 2013; COVID-19 rapid guideline: Managing COVID-19, 2022; Dik et al., 2015; Lin et al., 2013; Malani et al., 2013; Miyawaki et al., 2010; Ng et al.,

2008; Palmay et al., 2014; Standiford et al., 2012; Yu et al., 2014). The extent of the economic value of the reduced consumption of antimicrobials was different in different studies, and, in contrast to reductions in antimicrobial consumption, the effects of ASPs on length of stay and readmissions were not apparent, with studies varying between showing reductions and increases. Few studies did not demonstrate a significant reduction in antimicrobial costs following ASP implementation (Apisarnthanarak et al., 2006; Bruno-Murtha et al., 2005; Ho et al., 2005; Hurst et al., 2016; Krivoy et al., 2007; Lee et al., 2014; Lin et al., 2013; Oosterheert et al., 2005; Taggart et al., 2015) due to inappropriate metrics used for measuring antimicrobial use, increased use of expensive antimicrobials that are more effective in decreasing antimicrobial resistance, and the lack of adherence to ASP policies (Lee et al., 2014). In studies where hospital stay increased following ASP implementation (Cook et al., 2004; Hohn et al., 2015; Martínez et al., 2000; Nowak et al., 2012; Palmay et al., 2014; Smith et al., 2014), an extended use of antimicrobials due to patients' comorbidities or disease severity could be a factor. Such examples emphasise the local specificity of the economic impact of ASP, varying from one setting to another.

In the leading and public healthcare provider in Qatar, i.e. the Hamad Medical Corporation (HMC), an ASP was implemented in April 2015. It was implemented as a guideline to all HMC healthcare professionals in delivering appropriate antimicrobial management, in line with Qatar National Health Strategy 2018–2022, which addresses the need to reduce antimicrobial resistance (Ministry of Public Health, 2019). In Qatar, two studies revealed that ASPs minimised antimicrobial utilisation and enhanced the timely administration and proper discontinuation of antibiotics used for surgical prophylaxis (Garcell et al., 2016; Garcell et al., 2017). Based on the spectrum of activity, risk of misuse, and cost, the ASP in HMC only targets 18 antimicrobial agents. It aims to curb the overutilisation of antimicrobials and minimise antimicrobial resistance and healthcare costs. However, there is a lack of solid evidence to adequately inform decision-makers seeking optimal allocation of resources with ASP. Funders seek economic evaluations for a more accurate estimate of country-specific economic benefits. Further, to ensure the sustainability of practices, including the utilisation of resources and the hiring of personnel in practice sites, healthcare systems must demonstrate the return on the investments made in their services. In HMC, adhering to best international practices, the question around ASP is not about if it is a practice to implement, but it is about whether the cumulative experiences and improvement in the ASP practices towards development, since its inception in 2015, affected the economic impact of the ASP. Therefore, we aimed to estimate the economic impact of the 'developed ASP' use, after five years of implementation, versus the 'preliminary ASP' use, upon implementation, in the adults' general medicine settings at three central hospitals within HMC in Qatar.

Materials and methods

Economic analysis plan

The overall change in the economic consequences asscociated with the developed ASP was calculated as the sum of the cost savings and the cost avoidance associated with the service, in addition to the change in the operational cost of the service.

The study is a retrospective review of the patients who received any of the targeted antimicrobials by the HMC's ASP during two 12-month periods: 'preliminary ASP' use versus 'developed ASP' use.

The required ethics approval was obtained from the Medical Research Center, HMC (MRC-01-20-213).

Study population

The targeted antimicrobial use in this study is based on that performed in a cohort of general medicine inpatients during the study follow-up durations. The ASP in HMC, based on the spectrum of activity, risk of misuse, and cost, only targets 18 agents of antibiotics and antifungals. These are: cefepime, linezolid, teicoplanin, tigecycline, ertapenem, amikacin, colistin, ciprofloxacin, moxifloxacin, aztreonam, ceftazidime, daptomycin, anidulafungin, fluconazole, amphotericin, caspofungin, posaconazole, and voriconazole.

Inclusion criteria

Patients admitted to, and stayed at general medicine wards within the targeted study periods, who received any of the 18 antimicrobials targeted by the ASP, patients of whom antimicrobials were started within three days of admission, and who received the same antimicrobial for 48 h consecutively.

Exclusion criteria

We excluded critically ill patients who received any of the 18 antimicrobial therapies This is as the critical care protocol in HMC does not constrain decision-making and does not necessarily look to optimise antimicrobials use, but rather focuses a clinician's attention on the severity of illness. Protocol-driven care does not eradicate the need for clinical judgment, particularly in critical care settings. It also requires constant attention to the patient's illness and may demand deviations from the protocols. Pediatric patients were also excluded as HGH, AKH, and AWH are designed to provide care to adults only.

Study setting

The study was conducted in the adult general medicine wards of Al-Wakra Hospital (AWH), Hamad General Hospital (HGH), and Al Khor Hospital (AKH) in HMC. HGH provides comprehensive clinical services to patients of all ages, including internal medicine, trauma, emergency medicine, pediatrics, critical care, and specialised and subspecialized surgery, with 603 beds. AWH is a general hospital that offers a wide range of medical services, from emergency care to general medicine and surgery, with 325 beds. AKH is a 115-bed general hospital delivering care in the northern region of Qatar (Hamad Medical Corporation, 2023).

Comparators

The two comparators in this study, namely 'preliminary ASP' versus 'developed ASP', are based on two different periods of ASP use. The preliminary ASP period was defined as the 12 months immediately upon ASP implementation (i.e. May 1, 2015 to April 30, 2016), and developed ASP period was defined as the last 12 months of a 5-year ASP implementation (i.e. February 1, 2019 to January 31, 2020).

Perspective

The study objective about the economic value of resource use was from the viewpoint of the service provider, i.e. HMC and, hence, the study adopted the perspective of the hospital.

Sample size and time horizon

Based on successful examples in the literature (Al et al., 1998; Branham et al., 2013; Gallagher et al., 2014; Malani et al., 2013; Miyamoto et al., 2021; Sebaaly et al., 2015), the current study's population was based on a 1-year duration or 500 individuals, whichever comes first. Our targeted sample of 500 patients aligns with relevant studies in the literature, which varied from less than 100 to less than 1,000 (Branham et al., 2013; Gallagher et al., 2014; Malani et al., 2013; Sebaaly et al., 2015). Hence, in our study, patient recruitment in any of the recruitment periods, at the general medicine sites, was planned based on the preliminary ASP use within 1-year duration (i.e. May 1, 2015, to April 30, 2016) versus the developed ASP use within 1-year duration (i.e. February 1, 2019, to January 31, 2020). Because cost-analysis studies are about making a cost estimation and are not concerned with hypothesis testing like clinical research, even if a cost-analysis is underpowered, it still provides important information for guiding decision-makers in healthcare systems.

Outcome measures

Primary outcome: the change in the monetary value of resource use between the developed state of ASP practices and the preliminary state of ASP practices in the general medicine wards of HMC. The change in the monetary of value of resource use was measured within the context of cost-savings, cost-avoidance, and operational cost measures.

Secondary outcomes: all-cause death within 30 days of hospitalisation, infection-related death within 30 days of hospitalisation, hospital readmission within 30 days of discharge for infection-related indication, development of hospital-onset Clostridium difficile infection (CDI), length of hospital stay due to infection-related indication, adverse drug events (ADEs) associated with antimicrobials, and development of antimicrobial resistance during hospitalisation.

All clinical data were obtained from each patient record in the Cerner electronic medical database.

Valuation of economic outcomes

Cost savings

The cost savings value was the reduced cost of therapy associated with an assumed reduction in defined daily dose (DDD) and resource utilisation with of the developed ASP.

Cost avoidance

Cost avoidance was the cost avoided by reducing hospital readmission, length of hospitalisation, development of CDIs, and ADEs due to inappropriate use of antimicrobials.

Operational cost

The cost of the ASP was represented by the operational cost of running the ASP. Operational costs included the monetary value of the time spent in data collection by the pharmacists and physicians, attending daily clinical rounds, and attending monthly committee meetings.

Measurement of resources and costs

Cost savings

In line with relevant studies in the literature that used a similar approach, analysis of medication utilisation and cost of drug utilisation was undertaken using the Anatomical Therapeutic Chemical (ATC)/Defined Daily Doses (DDD) method (World Health Organization, 2023), which is the internationally accepted method for measuring medicines utilisation, and has been used

to measure medications utilisation patterns between different geographical regions and healthcare facilities. DDDs are defined as the doses of medications most commonly used for the most common indication in adults. Data were expressed as DDD per 100 patient beds for respective antimicrobial agents, in line with similar literature (Huebner et al., 2019). The differences in resource cost between preliminary ASP use and developed ASP use were calculated based on the decrease in culture, laboratory, and diagnostic tests performed, and on switching from intravenous (IV) to oral therapy in the first three days of antibiotic therapy. The cost of resources was calculated via a microeconomic analysis of resource use in patient management at the individual level. For a patient, the total monetary value of the resource used was calculated based on the identified resource's unit cost and frequency.

Cost avoidance

The length of hospitalisation and the hospital readmission of interest in the study were those deemed infection-related and/or relevant to antimicrobials. The total monetary value of the length of hospitalisation was based on the daily hospitalisation cost and the number of hospitalisation days. The number of hospitalisation and readmission days was calculated at the individual patient level. For a patient, the total monetary value of CDI was calculated based on the cost unit of the CDI diagnosis and management. Consistent with international practices, we assumed that any patient with CDI had a CDI culture performed and was treated with the standard therapy that included vancomycin 125 mg orally, four times daily, for ten days (Johnson et al., 2021). Based on expert consensus in the current study and relevant previous literature studies (Abushanab et al., 2023; Chen et al., 2017; Classen et al., 1997; Weiss & Elixhauser, 2006), the additional length of hospital stay attributable to an ADE ranged between 1 and 2 days. Therefore, the cost of an ADE was calculated on the conservative assumption that any injectable and non-injectable antimicrobial will lead to an additional two days and one day of hospital stay in the relevant unit, respectively.

Operational cost

For the operational resources during the preliminary period, there was no official ASP committee, but there were one physician and one clinical pharmacist spending five hours monthly in ASP meetings. Furthermore, one clinical pharmacist and one physician spent three hours daily on data collection, and one physician spent one hour daily on clinical rounds. For the operational resources during the ASP development, an ASP committee became operative, compromising one infectious disease physician, one clinical pharmacist, one clinical microbiologist, one infection control practitioner, and one nurse, meeting ten hours monthly. Furthermore, one physician and one clinical

pharmacist spent three hours daily on data collection and one hour daily in clinical rounds.

For all economic outcomes in the study, only direct medical costs were considered in the analysis, as the perspective adopted in the cost analysis was that of the hospital.

Currency and price data

All costs were in Qatari Riyal, adjusted for the financial year 2023/24, utilising the Qatari Health Consumer Price Index as appropriate. All costs were also presented in United States dollars (US$). The unit costs of identified resources as part of patient admission in the hospital were obtained from the finance and costing department at HMC. For the antimicrobials, the unit costs of drugs were derived from the pharmacy department of HMC.

Statistical analysis

Data were tabulated for each patient and analysed using the IBM SPSS (Statistical Package for the Social Sciences) version-24. For categorical variables, data were presented as numerical and percentage measures and as mean and standard deviation measures for continuous variables. Because the two study periods are over four years apart, we needed to confirm the homogeneity of treated patients and that no considerable demographic shifts may affect ASP outcomes. Demographic and outcome variables were compared between periods using the student-*t* test or Mann–Whitney test for continuous data, while the X^2 test or Fisher tests were used for categorical variables. Binary logistic and linear regression analyses were performed to determine whether covariates were associated with an outcome. The following variables were considered as covariates: age, gender, nationality, class of antimicrobial, number of antimicrobials received, type of pathogen, location of infection, CCI score, and periods of receiving antimicrobial. Statistical significance was set at $P < 0.05$.

Sensitivity analysis

Sensitivity analyses were conducted to improve the study's reliability and generalizability of findings.

One-way sensitivity analysis. The values of uncertain input variables were altered, one at a time, with a range of new values of the input variables, to analyse the effect on the study conclusion. This uncertainty range in the base-case value of a variable was ±10% for the cost of hospitalisation, length of hospital stay during initial admission, and length of hospital stay during readmission, and ±20% for the additional stay in hospital due to ADEs.

Multivariate uncertainty analysis. Multivariate uncertainty analysis was performed by targeting several underlying uncertain inputs (concurrently) before rerunning the analysis several times. Inputs of interest were the cost of hospitalisation, length of hospital stay during initial admission, length of hospital stay during readmission, and time spent by HMC staff performing ASP tasks. The value of these was each associated with a ± 10% uncertainty range.

Both one-way and multivariate probabilistic analyses were conducted via Monte Carlo simulation, using @Risk-7.6 (Palisade Corporation, NY). In this method, the value of any targeted input is 'randomly' sampled from the uncertainty range assigned to the input. This random sampling of the input value, which can amount to thousands, occurs in every iteration of the analysis. In the current study, a triangular type of random input selection from the uncertainty range based on 1,000 iterations was used.

Results

Characteristics of patients

A total of 500 patients were included in the study; 250 for the period of preliminary ASP use and 250 for the period of developed ASP use. Patients in the developed ASP group were older, with a mean age of 60.39 ± 19.08 years versus 54.12 ± 20.64 years in the preliminary ASP use group ($p < 0.001$). Gender distribution was also statistically different between both groups ($p < 0.001$), with men accounting for 63.2% of the study population in the preliminary ASP group and women accounting for 56.6% in the mature ASP group. Also, the most participants in both groups received at least one antimicrobial, with 86.4% and 70% doing so, respectively ($p = 0.69$). Furthermore, patients in the mature ASP group were more likely to have a severe Charlson Comorbidity Index (CCI) score than in the preliminary APS group ($p < 0.001$). Further details about the demographic characteristics are presented in Table 1.

Description of antimicrobials and pathogens

One of the most used ASP antimicrobials was ciprofloxacin (n = 77, 30.8%), followed by cefepime (n = 70, 28%), comprised the majority of antimicrobials with the preliminary ASP, compared to ertapenem (n = 95, 38%) followed by ciprofloxacin (n = 49, 19.6%) with the developed ASP. For the second and third antimicrobials administered, ertapenem (n = 9, 30%) and moxifloxacin (n = 2, 50%) were mainly used with the preliminary ASP, compared to cefepime (n = 8, 23.5%) and tigecycline (n = 2, 33.3%) with the developed ASP. Further details about the antimicrobials administered to the study population are shown in Appendix 1.

Table 1. Patient demographics in the preliminary and developed ASP groups.

Variable	Preliminary ASP ($n = 250$)	Developed ASP ($n = 250$)	*p*-value
Gender, n (%)			
Male	158 (63.2)	108 (43.4)	<0.001
Female	92 (36.8)	141 (56.6)	
Age, mean ± SD	54.12 ± 20.64	60.39 ± 19.08	<0.001
Weight, mean ± SD	72.46 ± 21.78	76.84 ± 18.64	<0.001
Nationality, n (%)			
Arab	149 (59.6)	198 (79.5)	<0.001
Asian (non-Arab)	90 (36)	48 (19.3)	
Western	6 (2.4)	3 (1.2)	
African (non-Arab)	5 (2)	0 (0)	
Allergy, n (%)			
Yes	61 (24.4)	73 (29.3)	0.22
No	189 (51.8)	176 (70.7)	
Class of medications, n (%)			
Antibacterial	242 (96.8)	233 (93.6)	0.09
Antifungal	8 (3.2)	16 (6.4)	
Number of medications received n (%)			
1	216 (86.4)	210 (70)	0.69
2	30 (12)	34 (13.6)	
3 or more	4 (1.6)	6 (2.4)	
Type of pathogen, n (%)			
Bacteria	242 (96.8)	233 (93.6)	0.03
Fungal	8 (3.2)	16 (6.4)	
Location of infection, n (%)			
Central nervous system	3 (1.2)	2 (0.8)	<0.001
Eye	2 (0.8)	8 (3.2)	
Ear	0 (0)	1 (0.4)	
Esophagus	3 (1.2)	0 (0)	
Neck	2 (0.8)	0 (0)	
Skin and soft tissue	1 (0.4)	2 (0.8)	
Respiratory	76 (30.4)	66 (26.6)	
Heart	0 (0)	1 (0.4)	
Gastrointestinal	0 (0)	16 (6.5)	
Abdomen	55 (22)	26 (10.5)	
Genitourinary	81 (32.4)	107 (43.1)	
Liver	1 (0.4)	0 (0)	
Thigh	1 (0.4)	0 (0)	
Knee	3 (1.2)	1 (0.4)	
Blood	1 (0.4)	6 (2.4)	
Back	0 (0)	2 (0.8)	
Lower extremity infection	19 (7.6)	12 (4.8)	
Charlson Comorbidity Index score, n (%)			
0	79 (31.6)	42 (16.9)	<0.001
Mild	25 (10)	23 (9.2)	
Moderate	42 (16.8)	40 (16.1)	
Severe	104 (41.6)	144 (57.8)	

*ASP: antimicrobial stewardship programme.

The most common pathogens before receiving the initial antimicrobials were *Escherichia coli* (n = 21 versus 51, 8.4% versus 20.4%), *Klebsiella pneumonia* (n = 17 versus 24, 6.8% versus 9.6%), and *Pseudomonas aeruginosa* (n = 14 versus 25, 5.6% versus 10%), with preliminary ASP versus developed ASP, respectively. In the preliminary ASP cohort, and among those who received second antimicrobials, the most common pathogens identified were *Klebsiella*

pneumonia and *Staphylococcus aureus*, n = 3, 13.6%, each. In the developed ASP cohort, *Pseudomonas aeruginosa* (n = 9, 34.6%) and *Klebsiella pneumonia* (n = 2, 7.7%) were the commonly identified pathogens (Appendix 2).

Economic analysis

Cost saving: impact of developed ASP on DDDs

There was a decrease in antimicrobials consumption (DDDs) by over 50% with the developed ASP compared to the preliminary ASP (31,599 versus 64,819 per 100 patient beds). This is associated with total costs of QAR 3,801 (US$ 1,041) versus QAR 3,866 (US$ 1,059) per 100 patient beds, resulting in an antimicrobial-consumption-based saving of QAR 65 (US$ 18) per 100 patient beds. A trend of decreased antimicrobial use was observed in different types of antimicrobials, including antifungals and cephalosporins, and less used carbapenems and fluoroquinolones. The antimicrobials use and total cost of DDDs for antimicrobials during the preliminary and developed ASP stages are shown in Appendix 3.

Cost saving: impact of the developed ASP on resource utilisation

The total cost of resource utilisation dropped by nearly 15% with the developed ASP (QAR 2,149, (US$ 589) versus QAR 2,541 (US$ 696)), relative to the preliminary ASP, per 100 patient beds. This is a cost-saving, resulting from the reduced utilisation of culture, laboratory, and diagnostic tests, that was QAR 392 (US$ 107) per 100 patient beds. Costs associated with resource utilisation in both groups are summarised in Table 2.

Table 2. Resource utilisation during preliminary and developed ASP stages per 100 patient beds.

Resource	Preliminary ASP	Developed ASP
Cost saving with resource utilisation (QAR, US$)		
Culture performance before receiving therapy	172 (47)	183 (50)
Laboratory test performance before receiving therapy	1,191 (326)	986 (270)
Biopsy performance before receiving therapy	0	0
Culture performance after receiving therapy	78 (21)	62 (17)
Laboratory test performance after receiving therapy	1,097 (306)	911 (250)
Biopsy performance after receiving therapy	0	0
Switching from IV to oral	3 (0.8)	8 (2)
Total	**2,541 (696)**	**2,149 (589)**
Resource-use-based cost saving, in favour of developed ASP	***392 (107)***	
Cost avoidance (QAR, US$)		
Hospitalisation	52,689 (14,435)	44,409 (12,167)
Clostridium difficile infection diagnosis and management	19 (5)	155 (42)
Rehospitalization within 30 days	2,371 (650)	14,860 (4,071)
Adverse drug events	8,538 (2,339)	8,710 (2,386)
Total	**63,618 (17,430)**	**68,424 (18,746)**
Cost avoided, in favour of preliminary ASP	***−4,807 (−1,317)***	

*ASP: antimicrobial stewardship programme, QAR: Qatari Riyal, US$: United States dollar.

The total cost savings attributed to a reduction in DDDs and resource utilisation with the developed ASP is QAR 458 (US$ 125) per 100 patient beds.

Cost avoidance

The total cost of hospital readmission, length of hospitalisation, development of Clostridioides difficile infections (CDIs), and additional stay due to ADEs, as a consequence of inappropriate use of antimicrobials in the ASP development cohort, was QAR 68,424 (US$ 18,746) compared to QAR 63,618 (US$ 17,430) per 100 patient beds in the preliminary cohort, resulting in avoided cost of QAR −4,807 (US$ −1,317) per 100 patient beds in favour of the preliminary period. Table 2 summarises the cost associated with each category of cost avoidance.

Operational cost saving

The total operational cost during the preliminary ASP period was higher than during the developed ASP (QAR 742 (US$ 203) versus QAR 617 (US$ 169)), at a reduced cost of QAR 125 (US$ 34) with the latter.

Net change in cost

The net change in cost associated with ASP development was QAR −4,224 (US$ – 1,160) per 100 patient beds. The results of the cost analysis are summarised in Table 3.

Sensitivity analysis

One-way sensitivity analyses indicated that the study outcome was insensitive to most input uncertainties. Results of one-way sensitivity analyses, their input uncertainties, and their sampling distributions are presented in Table 4 and Figure 1.

Multivariate sensitivity analysis demonstrated that there is a 99% probability for the developed ASP to be less costly than the preliminary, with an average of QAR172 (US$47), 95% CI QAR-33–380 (US$−9–104), Figure 2.

Table 3. Cost analysis with the development of antimicrobial stewardship programme per 100 patient beds

Parameter	Value (QAR, US$), in favour of developed ASP
Cost saving in terms of DDDs	65 (18)
Cost saving in terms of resource utilisation	392 (107)
Total cost saving	458 (125)
Cost avoidance	−4,807
Operational cost saving	125 (34)
Net change in cost	−4,224 (−1,160)

*DDD: defined daily dose, QAR: Qatari Riyal, US$: United States dollar, ASP: antimicrobial stewardship.

Table 4. Sensitivity analyses, their uncertainty distributions, and outcomes.

One-way sensitivity analysis						
		PreliminaryASP		DevelopedASP		Outcomes
Variable	Distribution	Point estimate	Variation range	Point estimate	Variation range	Net cost change, in favour of developed ASP, (95% CI QAR (US$))
Cost of hospitalisation, QAR (US$)	Triangular	1,718 (471)	1,374 (376), 1,718 (471), 2,062 (565)	1,718	1,374 (376), 1,718 (471), 2,062 (565)	−17,980 (−4,926) (−4,219 (−1,156), 8,766 (2,402))
Length of hospital stay (Days, per 100 patient beds)	Triangular	31	25, 31, 37	26	21, 26, 31	−12,566 (−3,443), (−12,419 (−3,402), −12,246 (−3,355))
Length of re-hospital stay (Days, per 100 patient beds)	Triangular	2	1.6, 2, 2.4	9	7, 9, 11	8,224 (2,253), (8,265 (2,264), 8,305 (2,275))
Additional hospital stay due to ADEs (days)	Triangular	1 for non-injectable medications and 2 for injectable medications	1.6, 2, 2.4 0.8, 1, 1.2	1 for non-injectable medications and 2 for injectable medications	1.6, 2, 2.4 0.8, 1, 1.2	−4,344 (−1,190), (−4,224 (−1,157), −4,042 (−1,107))
Multivariate sensitivity analysis						
Variable	Distribution	Point estimate	Variation range	Point estimate	Variation range	Net cost change, in favour of developed ASP, (95% CI QAR (US$))
Cost of hospitalisation QAR (US$)	Triangular	1,718 (471)	1,546 (424), 1,718 (471), 1,890 (518)	1,718 (471)	1,546 (424), 1,718 (471), 1,890 (518)	−33 (−9), 172 (47), 380 (104)
Length of hospital stay (Days, per 100 patient beds)	Triangular	31	27, 31, 34	26	23, 26, 29	
Length of re-hospital stay (Days, per 100 patient beds)	Triangular	2	1.8, 2, 2.2	9	8, 9, 10	
Additional hospital stay due to ADEs (days)	Triangular	1 for non-injectable medications and 2 for injectable medications	1.6, 2, 2.4 0.8, 1, 1.2	1 for non-injectable medications and 2 for injectable medications	1.6, 2, 2.4 0.8, 1, 1.2	

*ADE: adverse drug event, CI: confidence interval, QAR: Qatari Riyal, US$: United States dollar.

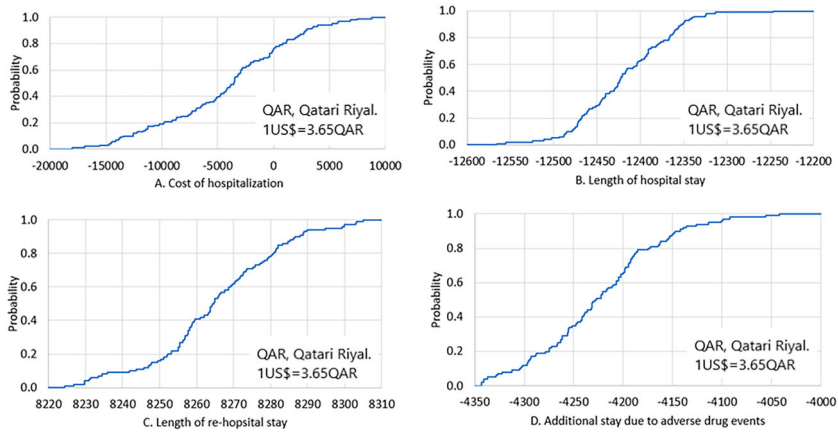

Figure 1. The probability curve of net cost difference in favour of developed ASP, one-way sensi-tivity analysis.

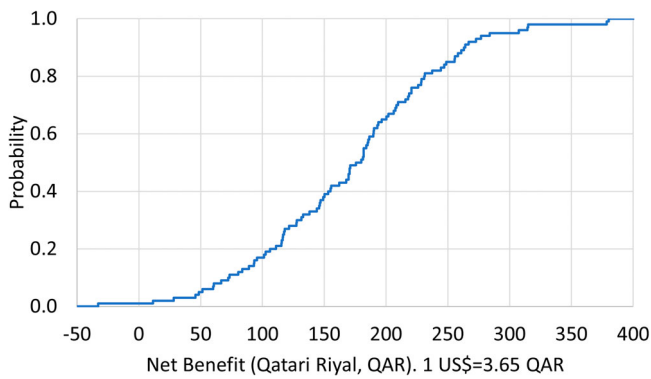

Figure 2. The probability curve of change in cost in favour of developed ASP, multi-variate sensi-tivity analysis.

Results of multivariate sensitivity analysis, input uncertainties, and sampling distributions are presented in Table 4.

A regression Tornado analysis revealed that the main driver of the net benefit outcome was the length of hospital stay, followed by the cost of hospitalisation, Figure 3.

Secondary outcomes (clinical outcomes)

While the length of hospital stay (initial disposition) was statistically significantly shorter during the developed ASP, with nearly 12 days versus ten days, hospital stay during readmission was significantly more extended

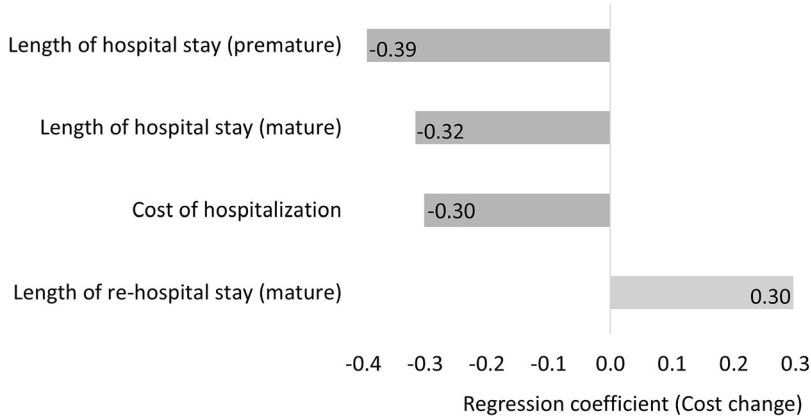

Figure 3. Effect of input variables on the change in cost outcome.

during the developed ASP group, with three days versus one day. The developed ASP use was also associated with higher cases of antimicrobial resistance and CDI (122 versus 32, and 16 versus 2, respectively, $p < 0.001$). There were no significant differences between the two groups with regard to all-cause death, death due to infection, and ADEs. Only one patient in the preliminary ASP group developed peripheral neuropathy ADE due to linezolid, which was resolved without introducing medications. Table 5 shows the clinical outcomes of the study patients.

Table 5. Clinical outcomes.

Variable	PreliminaryASP ($n = 250$)	DevelopedASP ($n = 250$)	p-value
Length of hospital stay (initial disposition), *mean ± SD*	12.27 ± 23.41	10.34 ± 9.07	<0.001
Readmission, *n (%)*			
Length of hospital stay (second disposition), *mean ± SD*	0.55 ± 2.90	3.46 ± 9.46	<0.001
All-cause death, *n (%)*			
Yes	10 (4)	7 (2.8)	0.46
No	240 (96)	242 (97.2)	
Infection-related death, *n (%)*			
Yes	4 (1.6)	4 (1.6)	1
No	246 (98.4)	246 (98.4)	
Antimicrobial resistance, *n (%)*			
Yes	32 (12.8)	122 (48.8)	<0.001
No	218 (87.2)	128 (51.2)	
Clostridioides difficile, *n (%)*			
Yes	2 (0.8)	16 (6.4)	<0.001
No	248 (99.2)	234 (93.6)	
Adverse drug events, *n (%)*			
Yes	1 (0.4)	0 (0)	1
No	249 (99.6)	250 (100)	

*ASP: antimicrobial stewardship programme, SD: standard deviation.

Effect of variables on outcomes

The binary logistic and linear regression analyses show that age was significantly associated with all-cause death, and the number of antimicrobials received was associated with infection-related death. Additionally, periods of receiving antimicrobials were associated with hospitalisation, rehospitalization, and CDI, while the CCI score and periods of receiving antimicrobials were associated with antimicrobial resistance. The findings of regression analysis are shown in Appendix 4.

Discussion

While several ASPs focus on improving antimicrobial use practices in terms of improved health outcomes, the effects of ASPs also include resource utilisation and associated costs (Nathwani et al., 2019). To the best of our knowledge, this is the first comprehensive cost analysis estimating the change in cost associated with a revised ASP version compared to it upon inception. There are no available electronic medical records in HMC before 2015, noting that the ASP was implemented in HMC in 2015. Therefore, creating a no-ASP relative control group was not possible.

At a national level, antimicrobial utilisation has been used as a surrogate outcome measure for policy strategies, assuming that decreased antimicrobial consumption will result in reduced future resistance rates and improved clinical and economic outcomes. Our findings showed that the development of an ASP was associated with a decrease in total antimicrobial consumption by almost one-half, and the use of restricted antimicrobial agents was further reduced during the developed ASP period. Decreasing unnecessary DDD of antifungals, cephalosporins, carbapenems, and fluoroquinolones was associated with the most significant cost savings increase. This is mainly driven by the restrictive prescribing of these antimicrobials to the infectious disease team in HMC.

In our analysis, however, the utilisation of ASP failed to maintain an overall positive monetary value over five years of implementation. While the development of the ASP was associated with a reduced cost due to a reduction in antimicrobial consumption and resource use, it was also associated with increased cost due to an increase in readmission and antimicrobial resistance. Here, it is important to note that the measured at the respective time points of the cohorts was the resource use and not the monetary value of these resources. The economic value of the resource use was only assigned to the resource use at the time of the analysis, based on the similar monetary values of resources based on the same financial year, regardless of the cohort. Medical inflation, therefore, is not a counfounder in the current study. It is also very essential to note that it is impossible to assume that

this latter increase is because of a decreased effectiveness with the developed ASP relative to the preliminary. All that we can conclude from this study is that there is an increased cost associated with the developed ASP, without necessarily associating this with a lack of developed ASP performance. After all, the increase in hospital readmission following ASP development can be influenced by reasons beyond antibiotic use, including comorbidities and disease severity or factors such as antimicrobial resistance. Indeed, in our study, the developed ASP cohort had a significantly greater number of patients with a severe CCI score (57.8%) compared to the preliminary ASP cohort (41.6%), together with an antimicrobial resistance that was statistically significantly higher with the developed ASP cohort. Our regression analysis supported this, which demonstrated that the CCI score was associated with antimicrobial resistance. Unsurprisingly, patients with a higher CCI score may be expected to be associated with worse outcomes more often as a more significant number of comorbidities are generally found in sicker individuals who would be more prone to die or require frequent hospital admissions (Charlson et al., 1987; Hoyer et al., 2018).

Antimicrobial resistance is also largely attributable to factors such as an increase in the use of broad-spectrum antimicrobials, poor access to adequate and affordable medicines, vaccines, genetics, unknown adherence to management guidelines, lack of awareness and knowledge, lack of an automated alert system for IV to PO antibiotic switching eligibility, and lack of information technology, as well as poor communication between ASP committee members (Hurst et al., 2016; Liew et al., 2015; Nasr et al., 2021). Direct communication between infectious diseases and other units has been shown to engage discussion among healthcare providers, promote education of the medical team, improve antibiotic prescribing, and minimise antimicrobial consumption and resistance, accordingly (Hurst et al., 2016; Nasr et al., 2021). Additionally, if the consumption of only certain antimicrobials is restricted, a significant decrease in resistance cannot be expected (Hagert et al., 2012). It is also likely that resistant strains are not related to changes made in hospitals, as it is difficult to distinguish community-acquired resistance from those in the hospital (Bruno-Murtha et al., 2005; Cook et al., 2004).

Our findings are consistent with a 2017 Cochrane review that found that ASP decreased antimicrobial therapy consumption by nearly 19% following implementation of ASP but did not increase mortality (Davey et al., 2017).

Several studies found that patient death increased following ASP implementation, noting that the majority of these studies did not report statistical significance (Hohn et al., 2015; Mach et al., 2007; MacVane & Nolte, 2016; Nilholm et al., 2015; Palmay et al., 2014; Pate et al., 2012; Wenzler et al., 2016). In contrast, all-cause death rates in our patients were lower in the developed ASP group but not statistically significant. While not

significant, this could be due to lower and appropriate consumption of antimicrobials, immediate administration of antimicrobials when required, and enhanced communication between ASP staff committee members regarding optimum antimicrobials during the ASP development period.

While in our study we illustrated that a total positive cost saving with the ASP development at QAR 458 (US$125), a few economic studies did not demonstrate a significant reduction in antimicrobial costs following ASP implementation (Apisarnthanarak et al., 2006; Bruno-Murtha et al., 2005; Ho et al., 2005; Hurst et al., 2016; Krivoy et al., 2007; Lee et al., 2014; Lin et al., 2013; Oosterheert et al., 2005; Taggart et al., 2015). This could be due to inappropriate metrics for measuring antimicrobial use, increased use of expensive antimicrobials that are more effective in decreasing antimicrobial resistance, and the lack of adherence to ASP policies (Lee et al., 2014). Further, in contrast to our findings, prior studies found that hospital stays increased following ASP implementation (Cook et al., 2004; Hohn et al., 2015; Martínez et al., 2000; Nowak et al., 2012; Palmay et al., 2014; Smith et al., 2014). The reason behind this could be affected by the extended use of antimicrobials due to patients' comorbidities or disease severity.

Notwithstanding, the literature studies and their results are generally not comparable to our results because, in this study, we report the impact of the developed use of ASP compared to its use during the preliminary period. In addition, the comparison with prior studies is difficult due to variations in resource utilisation, the overall nature of the healthcare system, and the wide range of years between when the studies were published.

Also, a potential confounder is that the impact of an antimicrobial shortage and subsequent conservation efforts on antimicrobial use and expenditure were not considered in our study.

Despite a decrease in the cost of antimicrobial consumption and resource utilisation, cost avoidance in terms of readmission and antimicrobial resistance increased over a 5-year implementation timeframe. Practitioners at the study site, similar to the international audience, can benefit here from the recognising the fact that an implemented ASP is not necessarily associated with similar or reduced spending over time, and in addition to recognising factors that contribute the value of resource use the most in relevance to an ASP, inlcuding pitfalls to try to avoide. Measures that can be taken to remedy the study's outcome are the ones that fixes current pitfalls that the ASP has in Qatar. The lack of prioritising of specific interventions aimed at reducing antimicrobial resistance is a pitfall. In internal medicine facilities, focusing on the most commonly prescribed antimicrobials with the potential of the emergence of resistance would be a critical targeted intervention. Many studies showed that ASPs have the potential to restrict the emergence and spread of resistance (Hwang & Kwon, 2021). ASPs have demonstrated a link between

antimicrobial use and the emergence of resistance. For instance, fluoroquinolone use has been associated with Methicillin-resistant Staphylococcus aureus (Madaras-Kelly et al., 2006), cephalosporin with cephalosporin-resistant Enterobacteriaceae (Rohde et al., 2018), teicoplanin with Coagulase-Negative Staphylococci (Balasiu & MacKenzie, 2023), and carbapenem with carbapenem-resistant Acinetobacter, Pseudomonas, and Enterobacteriaceae (Tomczyk et al., 2019). Another pitfall could be the lack of restricting antimicrobial formulary use. Restricting antimicrobial use has been shown to reduce the spread of antimicrobial resistance (Obolski et al., 2015). Hence, a strategy for ASP in internal medicine settings could include efforts to restrict antimicrobials, which may yield the most significant increases in benefits. Formulary restriction is particularly considered as the critical strategy in the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) guidelines (Johnson et al., 2021). Another pitfall where a strategy could be suggested, is to include reviewing broad-spectrum empirical antimicrobials and then de-escalating or discontinuing therapy based on antimicrobial susceptibility test findings and clinical response. For instance, switching from a broad-spectrum cephalosporin to cefazolin, in a patient with an infection caused by cefazolin-susceptible gram-negative bacteria, would be considered a type of de-escalation or discontinuation of cefazolin when not indicated (Krivoy et al., 2007; Wenzler et al., 2016). One of the most frequent reasons for unnecessary use of cefazolin exposure is in the management of a presumed skin and soft tissue infection that, in fact, is not a true infection. ASPs could, consequently, also focus on educational efforts pertaining to the diagnose and manage skin and soft tissue infections using local consensus protocols. Coupled with interventions such as restrictions or reviewing broad-spectrum antimicrobials, ASPs are based primarily on education. Including the above, the following interventions can also be considered to remedy possible pitfalls by ASP clinicians: (1) education of prescribers about microbial virulence, immunological and genetic host factors; (2) formulary restriction; (3) antimicrobial susceptibility testing for a rapid and reliable prediction of antimicrobial success; (4) accurate organism-identification; (5) understanding pharmacokinetic and pharmacodynamic properties of antimicrobials which aids choosing optimal dose and duration of antimicrobials; and (6) development of protocols for de-escalation of antimicrobials.

Importantly, cost reduction or increase without regard to the clinical outcomes achieved is self-defeating. Thus, to ensure the sustainable success of an ASP, hospital ASPs should promote the efficient and judicious use of therapy to combat the rise in antimicrobial resistance. The consequences of ASP practices often yield effects that extend from antimicrobial use to improved or maintained patient outcomes, which drive down resource utilisation and associated costs.

Future work should extend the setting and measure the cost change associated with the development of ASP in other HMC clinical practice units such as cancer, cardiology, and women's health. As our multivariate sensitivity analysis showed that the developed ASP becomes cheaper in 99% of iterations, the economic impact would, to a substantial extent, be driven by the hospital bed day cost. For example, in Europe, the proportion of a bed day saved through the implementation of ASP represents 60–80% of the total hospital stay, while in the US, the proportion of a bed day saved was lower (∼ 32%) (Nathwani et al., 2019). These results align with our Tornado diagram findings, which depicted that the length of hospital stay was the main influential cost factor. The results of the Tornado diagram were further confirmed by the findings of one-way sensitivity analysis. Consistently with previous studies, a systematic review of studies conducted in the US, reported shorter hospital stay and higher cost savings per patient following ASP implementation, and this was mainly due to the high cost of a hospital bed day in the US (Nathwani et al., 2019).

The current study has some inherent limitations that should be acknowledged and considered when interpreting results. Generally, confounding and bias are typical issues that cannot be entirely avoided with this retrospective study design. Additionally, while only direct medical costs were included in the analysis, the economic implications of ASP are far more extensive and are influenced by many indirect costs and benefits. Productivity losses, such as lost wages resulting from premature death or absence from work due to reasons such as antimicrobial resistance, were not considered, and may underestimate the actual cost of ASP. Furthermore, we should have accounted for the long-term impact of ASP in reducing total healthcare costs, potentially underestimating the consequential cost of ASP. Long-term impact can be influenced by the unexpected emergence, spread of new antimicrobial-resistance genes, patient compliance with antimicrobial therapy, and compliance with infection control procedures. Moreover, the generalizability of results is limited by the fact that, compared to other medication use, antimicrobial treatment is unique in that its use might differ among different countries given the variations in antimicrobial resistance. In addition, varying compliance with preventive measures, such as focusing on limiting the patient-to-patient spread of multidrug-resistant organisms, which was not addressed in this study, would contribute substantially to wide-ranging improvement in the reduction of costs. In conclusion, in the adult general medicine settings in HMC, as per the study perspective and limitations, the total cost savings attributed to the reduction in DDDs and resource utilisation with the developed ASP is QAR 458 (US$ 125) per 100 patient beds. The total operational cost also achieved a cost saving of QAR 125 (US$ 34) with the developed ASP. Nevertheless, the total cost of hospital readmission, length of

hospitalisation, development of CDIs, and additional stay due to ADEs, as a consequence of inappropriate use of antimicrobials, resulted in an avoided cost of QAR −4,807 (US$ −1,317) per 100 patient beds in favour of the preliminary period. This was mainly due to increased hospital readmission and high antimicrobial resistance during the developed period. Overall, it seems that running the ASP programme for five years, with presumed development in its practices, was not associated with any similar or reduced monetary spending.

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

DA and DA-B conceived the study and led the analysis and interpretation of data. DA wrote the first draft of the manuscript. WA contributed to data collection. All authors reviewed the draft for content and accuracy. All authors approved the final version of the article.

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References

Abushanab, D., Gulied, A., Hamad, A., Abu-Tineh, M., Abdul Rouf, P. V., Al Hail, M., El-Kassem, W., El Hajj, M. S., & Al-Badriyeh, D. (2023). Cost savings and cost avoidance with the inpatient clinical pharmacist interventions in a tertiary cancer care hospital. *Journal of Oncology Pharmacy Practice*, 10781552231160276.

Al, M. J., van Hout, B. A., Michel, B. C., & Rutten, F. F. (1998). Sample size calculation in economic evaluations. *Health Economics*, *7*(4), 327–335. https://doi.org/10.1002/(SICI)1099-1050(199806)7:4<327::AID-HEC342>3.0.CO;2-U

Aljayyousi, G. F., Abdel-Rahman, M. E., El-Heneidy, A., Kurdi, R., & Faisal, E. (2019). Public practices on antibiotic use: A cross-sectional study among Qatar University students and their family members. *PLoS One*, *14*(11), e0225499. https://doi.org/10.1371/journal.pone.0225499

Apisarnthanarak, A., Danchaivijitr, S., Khawcharoenporn, T., Limsrivilai, J., Warachan, B., Bailey, T. C., & Fraser, V. J. (2006). Effectiveness of education and an antibiotic-control program in a tertiary care hospital in Thailand. *Clinical Infectious Diseases*, *42*(6), 768–775. https://doi.org/10.1086/500325

Balasiu, A. D., & MacKenzie, C. R. (2023). Teicoplanin-Resistant coagulase-negative staphylococci: Do the current susceptibility testing methods reliably detect this elusive phenotype? *Antibiot (Basel, Switzerland)*, *12*.

Borde, J. P., Kaier, K., Steib-Bauert, M., Vach, W., Geibel-Zehender, A., Busch, H., Bertz, H., Hug, M., de With, K., & Kern, W. V. (2014). Feasibility and impact of an intensified antibiotic stewardship programme targeting cephalosporin and fluoroquinolone use in a tertiary care university medical center. *BMC Infectious Diseases*, *14*(1), 201. https://doi.org/10.1186/1471-2334-14-201

Boyles, T. H., Whitelaw, A., Bamford, C., Moodley, M., Bonorchis, K., Morris, V., Rawoot, N., Naicker, V., Lusakiewicz, I., Black, J., Stead, D., Lesosky, M., Raubenheimer, P., Dlamini, S., & Mendelson, M. (2013). Antibiotic stewardship ward rounds and a dedicated prescription chart reduce antibiotic consumption and pharmacy costs without affecting inpatient mortality or re-admission rates. *PLoS One*, *8*(12), e79747. https://doi.org/10.1371/journal.pone.0079747

Branham, A. R., Katz, A. J., Moose, J. S., Ferreri, S. P., Farley, J. F., & Marciniak, M. W. (2013). Retrospective analysis of estimated cost avoidance following pharmacist-provided medication therapy management services. *Journal of Pharmacy Practice*, *26*(4), 420–427. https://doi.org/10.1177/0897190012465992

Bruno-Murtha, L. A., Brusch, J., Bor, D., Li, W., & Zucker, D. (2005). A pilot study of antibiotic cycling in the community hospital setting. *Infection Control & Hospital Epidemiology*, *26*(1), 81–87. https://doi.org/10.1086/502491

Centers for Disease Control and Prevention CDC: 1 in 3 Antibiotic Prescriptions Unnecessary. (2022). Retrived December 12, 2022 from: https://www.cdc.gov/media/releases/2016/p0503-unnecessaryprescriptions.html.

Charlson, M. E., Pompei, P., Ales, K. L., & MacKenzie, C. R. (1987). A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Diseases*, *40*(5), 373–383. https://doi.org/10.1016/0021-9681(87)90171-8

Chen, C.-C., Hsiao, F.-Y., Shen, L.-J., & Wu, C.-C. (2017). The cost-saving effect and prevention of medication errors by clinical pharmacist intervention in a nephrology unit. *Medicine*, *96*(34), e7883. https://doi.org/10.1097/MD.0000000000007883

Classen, D. C., Pestotnik, S. L., Evans, R. S., Lloyd, J. F., & Burke, J. P. (1997). Adverse drug events in hospitalized patients. Excess length of stay,: extra costs, and attributable

mortality. *JAMA: The Journal of the American Medical Association*, *277*(4), 301–306. https://doi.org/10.1001/jama.1997.03540280039031

Coast, J., Smith, R. D., & Millar, M. R. (1996). Superbugs: Should antimicrobial resistance be included as a cost in economic evaluation? *Health Economics*, *5*(3), 217–226. https://doi.org/10.1002/(SICI)1099-1050(199605)5:3<217::AID-HEC200>3.0.CO;2-S

Cook, P. P., Catrou, P. G., Christie, J. D., Young, P. D., & Polk, R. E. (2004). Reduction in broad-spectrum antimicrobial use associated with no improvement in hospital antibiogram. *Journal of Antimicrobial Chemotherapy*, *53*(5), 853–859. https://doi.org/10.1093/jac/dkh163

COVID-19 rapid guideline: Managing COVID-19. (2022). [Internet]. 2022. [cited 2022 Aug 14]. https://www.nice.org.uk/guidance/ng191/resources/covid19-rapid-guideline-managing-covid19-pdf-51035553326.

Davey, P., Marwick, C. A., Scott, C. L., Charani, E., McNeil, K., Brown, E., Gould, I. M., Ramsay, C. R., & Michie, S. (2017). Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database of Systematic Reviews*, *2*, CD003543. https://doi.org/ 10.100214651858.CD003543.pub4

Dik, J.-W. H., Hendrix, R., Friedrich, A. W., Luttjeboer, J., Panday, P. N., Wilting, K. R., et al. (2015). Cost-minimization model of a multidisciplinary antibiotic stewardship team based on a successful implementation on a urology ward of an academic hospital. *PLoS One*, *10*(e0126106), e0126106.

Gallagher, J., Byrne, S., Woods, N., Lynch, D., & McCarthy, S. (2014). Cost-outcome description of clinical pharmacist interventions in a university teaching hospital. *BMC Health Services Research*, *14*(1), 177. https://doi.org/10.1186/1472-6963-14-177

Garcell, H. G., Arias, A. V., Fernandez, E. A., Guerrero, Y. B., & Serrano, R. N. A. (2016). Antibiotic consumption during a 4-year period in a community hospital with an antimicrobial stewardship program. *Oman Medical Journal*, *31*(5), 352–356. https://doi.org/10.5001/omj.2016.70

Garcell, H. G., Arias, A. V., Sandoval, C. P., Valle Gamboa, M. E., Sado, A. B., & Alfonso Serrano, R. N. (2017). Impact of a focused antimicrobial stewardship program in adherence to antibiotic prophylaxis and antimicrobial consumption in appendectomies. *Journal of Infection and Public Health*, *10*(4), 415–420. https://doi.org/10.1016/j.jiph.2016.06.006

Hagert, B. L., Williams, C., Wieser, C. M., Rohrich, M. A., Lo, T. S., Newman, W. P., & Koo, J. M. (2012). Implementation and outcome assessment of an inpatient antimicrobial stewardship program. *Hospital Pharmacy*, *47*(12), 939–945. https://doi.org/10.1310/hpj4712-939

Hamad Medical Corporation. (2023). https://www.hamad.qa/EN/Pages/default.aspx (accessed on 9 July 2023).

Ho, B. P., Lau, T. T. Y., Balen, R. M., Naumann, T. L., & Jewesson, P. J. (2005). The impact of a pharmacist-managed dosage form conversion service on ciprofloxacin usage at a major Canadian teaching hospital: A pre- and post-intervention study. *BMC Health Services Research*, *5*(1), 48. https://doi.org/10.1186/1472-6963-5-48

Hohn, A., Heising, B., Hertel, S., Baumgarten, G., Hochreiter, M., & Schroeder, S. (2015). Antibiotic consumption after implementation of a procalcitonin-guided antimicrobial stewardship programme in surgical patients admitted to an intensive care unit: A retrospective before-and-after analysis. *Infection*, *43*(4), 405–412. https://doi.org/10.1007/s15010-014-0718-x

Holmes, A. H., Moore, L. S. P., Sundsfjord, A., Steinbakk, M., Regmi, S., Karkey, A., Guerin, P. J., & Piddock, L. J. V. (2016). Understanding the mechanisms and drivers of antimicrobial resistance. *Lancet (London, England)*, *387*, 176–187. https://doi.org/10.1016/S0140-6736(15)00473-0

Hoyer, E. H., Brotman, D. J., Apfel, A., Leung, C., Boonyasai, R. T., Richardson, M., Lepley, D., & Deutschendorf, A. (2018). Improving outcomes after hospitalization: A prospective observational multicenter evaluation of care coordination strategies for reducing 30-day readmissions to Maryland hospitals. *Journal of General Internal Medicine*, *33*(5), 621–627. https://doi.org/10.1007/s11606-017-4218-4

Hübner, C., & Flessa, S. (2016). Reimbursement for hospital-acquired infections with multidrug resistant organisms in German DRG system. *Economics & Sociology*, *9* (3), 111e–1118. https://doi.org/10.14254/2071-789X.2016/9-3/10

Hübner, C., Hübner, N.-O., Hopert, K., Maletzki, S., & Flessa, S. (2014). Analysis of MRSA-attributed costs of hospitalized patients in Germany. *European Journal of Clinical Microbiology & Infectious Diseases*, *33*(10), 1817–1822. https://doi.org/10.1007/s10096-014-2131-x

Huebner, C., Flessa, S., & Huebner, N.-O. (2019). The economic impact of antimicrobial stewardship programmes in hospitals: A systematic literature review. *Journal of Hospital Infection*, *102*(4), 369–376. https://doi.org/10.1016/j.jhin.2019.03.002

Hurst, A. L., Child, J., Pearce, K., Palmer, C., Todd, J. K., & Parker, S. K. (2016). Handshake stewardship: A highly effective rounding-based antimicrobial optimization service. *Pediatric Infectious Disease Journal*, *35*(10), 1104–1110. https://doi.org/10.1097/INF.0000000000001245

Hwang, S., & Kwon, K. T. (2021). Core elements for successful implementation of antimicrobial stewardship programs. *Infection & Chemotherapy*, *53*(3), 421–435. https://doi.org/10.3947/ic.2021.0093

Johnson, S., Lavergne, V., Skinner, A. M., Gonzales-Luna, A. J., Garey, K. W., Kelly, C. P., & Wilcox, M. H. (2021). Clinical practice guideline by the Infectious Diseases Society of America (IDSA) and society for healthcare epidemiology of America (SHEA): 2021 focused update guidelines on management of clostridioides difficile infection in adults. *Clinical Infectious Diseases*, *73*(5), e1029–e1044. https://doi.org/10.1093/cid/ciab549

Krivoy, N., El-Ahal, W. A., Bar-Lavie, Y., & Haddad, S. (2007). Antibiotic prescription and cost patterns in a general intensive care unit. *Pharmacy Practice (Internet)*, *5*(2), 67–73. https://doi.org/10.4321/S1886-36552007000200003

Lee, T. C., Frenette, C., Jayaraman, D., Green, L., & Pilote, L. (2014). Antibiotic self-stewardship: Trainee-led structured antibiotic time-outs to improve antimicrobial use. *Annals of Internal Medicine*, *161*(1), S53–S58. https://doi.org/10.7326/M14-0820

Liew, Y. X., Lee, W., Kwa, A. L.-H., & Chlebicki, M. P. (2015). Cost effectiveness of an antimicrobial stewardship programme. *International Journal of Antimicrobial Agents*, 594–595. https://doi.org/10.1016/j.ijantimicag.2015.08.008

Lin, Y.-S., Lin, I.-F., Yen, Y.-F., Lin, P.-C., Shiu, Y.-C., Hu, H.-Y., & Yang, Y.-P. (2013). Impact of an antimicrobial stewardship program with multidisciplinary cooperation in a community public teaching hospital in Taiwan. *American Journal of Infection Control*, *41*(11), 1069–1072. https://doi.org/10.1016/j.ajic.2013.04.004

Mach, R., Vlcek, J., Prusova, M., Batka, P., Rysavy, V., & Kubena, A. (2007). Impact of a multidisciplinary approach on antibiotic consumption,: cost and microbial resistance in a Czech hospital. *Pharmacy World & Science*, *29*(5), 565–572. https://doi.org/10.1007/s11096-006-9059-x

MacVane, S. H., & Nolte, F. S. (2016). Benefits of adding a rapid PCR-based blood culture identification panel to an established antimicrobial stewardship program. *Journal of Clinical Microbiology*, *54*(10), 2455–2463. https://doi.org/10.1128/JCM.00996-16

Madaras-Kelly, K. J., Remington, R. E., Lewis, P. G., & Stevens, D. L. (2006). Evaluation of an intervention designed to decrease the rate of nosocomial methicillin-resistant

staphylococcus aureus infection by encouraging decreased fluoroquinolone use. *Infection Control & Hospital Epidemiology*, *27*(2), 155–169. https://doi.org/10.1086/500060

Malani, A. N., Richards, P. G., Kapila, S., Otto, M. H., Czerwinski, J., & Singal, B. (2013). Clinical and economic outcomes from a community hospital's antimicrobial stewardship program. *American Journal of Infection Control*, *41*(2), 145–148. https://doi.org/10.1016/j.ajic.2012.02.021

Martínez, M. J., Freire, A., Castro, I., Inaraja, M. T., Ortega, A., Del Campo, V., Rodriguez, I., Bardán, B., Morano, L. E., & Garcia, J. F. (2000). Clinical and economic impact of a pharmacist-intervention to promote sequential intravenous to oral clindamycin conversion. *Pharmacy World and Science*, *22*(2), 53–58. https://doi.org/10.1023/A:1008769204178

Ministry of Public Health. (2019). Qatar National Health Strategy 2018–2022. https://www.moph.gov.qa/HSF/Documents/short%20report%20eng%2020.03.2018.pdf/ (13 February 2020,: date last accessed).

Miyamoto, G. C., Ben, ÂJ, Bosmans, J. E., van Tulder, M. W., Lin, C.-W. C., Cabral, C. M. N., & van Dongen, J. M. (2021). Interpretation of trial-based economic evaluations of musculoskeletal physical therapy interventions. *Brazilian Journal of Physical Therapy*, *25*(5), 514–529. https://doi.org/10.1016/j.bjpt.2021.06.011

Miyawaki, K., Miwa, Y., Tomono, K., & Kurokawa, N. (2010). Impact of antimicrobial stewardship by infection control team in a Japanese teaching hospital. *Yakugaku Zasshi*, *130*(8), 1105–1111. https://doi.org/10.1248/yakushi.130.1105

Nasr, Z. G., Jibril, F., Elmekaty, E., Sonallah, H., Chahine, E. B., & AlNajjar, A. (2021). Assessment of antimicrobial stewardship programs within governmental hospitals in Qatar: A SWOC analysis. *International Journal of Pharmacy Practice*, *29*(1), 70–77. https://doi.org/10.1093/ijpp/riaa011

Nathwani, D., Varghese, D., Stephens, J., Ansari, W., Martin, S., & Charbonneau, C. (2019). Value of hospital antimicrobial stewardship programs [ASPs]: a systematic review. *Antimicrobial Resistance And Infection Control*, *8*(35), 35.

Ng, C. K., Wu, T. C., Chan, W. M. J., Leung, Y. S. W., Li, C. K. P., Tsang, D. N. C., & Leung, G. M. (2008). Clinical and economic impact of an antibiotics stewardship programme in a regional hospital in Hong Kong. *Quality and Safety in Health Care*, *17*(5), 387–392. https://doi.org/10.1136/qshc.2007.023267

Nilholm, H., Holmstrand, L., Ahl, J., Månsson, F., Odenholt, I., Tham, J., Melander, E., & Resman, F. (2015). An audit-based, infectious disease specialist-guided antimicrobial stewardship program profoundly reduced antibiotic use without negatively affecting patient outcomes. *Open Forum Infectious Diseases*, *2*(2), ofv042. https://doi.org/10.1093/ofid/ofv042

Nowak, M. A., Nelson, R. E., Breidenbach, J. L., Thompson, P. A., & Carson, P. J. (2012). Clinical and economic outcomes of a prospective antimicrobial stewardship program. *American Journal of Health-System Pharmacy*, *69*, 1500–1508.

Obolski, U., Stein, G. Y., & Hadany, L. (2015). Antibiotic restriction might facilitate the emergence of multi-drug resistance. *PLOS Computational Biology*, *11*(6), e1004340. https://doi.org/10.1371/journal.pcbi.1004340

Ojeniran, M., Shouval, R., Miskin, I. N., Moses, A. E., & Shmueli, A. (2010). Costs of appropriate and inappropriate use of antibiotics in the emergency department. *The Israel Medical Association Journal*, *12*, 742–746.

Oosterheert, J. J., van Loon, A. M., Schuurman, R., Hoepelman, A. I. M., Hak, E., Thijsen, S., Nossent, G., Schneider, M. M. E., Hustinx, W. M. N., & Bonten, M. J. M. (2005). Impact of rapid detection of viral and atypical bacterial pathogens by real-time

polymerase chain reaction for patients with lower respiratory tract infection. *Clinical Infectious Diseases*, *41*(10), 1438–1444. https://doi.org/10.1086/497134

Organisation for Economic Co-operation and Development. (2016). Antimicrobial resistance - Policy insights.

Palmay, L., Elligsen, M., Walker, S. A. N., Pinto, R., Walker, S., Einarson, T., Simor, A., Rachlis, A., Mubareka, S., & Daneman, N. (2014). Hospital-wide rollout of antimicrobial stewardship: A stepped-wedge randomized trial. *Clinical Infectious Diseases*, *59*(6), 867–874. https://doi.org/10.1093/cid/ciu445

Pate, P. G., Storey, D. F., & Baum, D. L. (2012). Implementation of an antimicrobial stewardship program at a 60-bed long-term acute care hospital. *Infection Control & Hospital Epidemiology*, *33*(4), 405–408. https://doi.org/10.1086/664760

Pogue, J. M., Kaye, K. S., Cohen, D. A., & Marchaim, D. (2015). Appropriate antimicrobial therapy in the era of multidrug-resistant human pathogens. *Clinical Microbiology and Infection*, *21*, 302–312.

Rohde, A. M., Zweigner, J., Wiese-Posselt, M., Schwab, F., Behnke, M., Kola, A., Obermann, B., Knobloch, J. K.-M., Feihl, S., Querbach, C., Gebhardt, F., Mischnik, A., Ihle, V., Schröder, W., Armean, S., Peter, S., Tacconelli, E., Hamprecht, A., Seifert, H., … Wolke, S. (2018). Incidence of infections due to third generation cephalosporin-resistant Enterobacteriaceae - a prospective multicentre cohort study in six German university hospitals. *Antimicrobial Resistance & Infection Control*, *7*(1), 159. https://doi.org/10.1186/s13756-018-0452-8

Roth, G. A., Johnson, C., Abajobir, A., Abd-Allah, F., Abera, S. F., Abyu, G., et al. (2017). Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. *Journal of the American College of Cardiology*, *70*(1), 1–25. https://doi.org/10.1016/j.jacc.2017.04.052

Schuts, E. C., Hulscher, M. E. J. L., Mouton, J. W., Verduin, C. M., Stuart, J. W. T. C., Overdiek, H. W. P. M., van der Linden, P. D., Natsch, S., Hertogh, C. M. P. M., Wolfs, T. F. W., Schouten, J. A., Kullberg, B. J., & Prins, J. M. (2016). Current evidence on hospital antimicrobial stewardship objectives: A systematic review and meta-analysis. *The Lancet Infectious Diseases*, *16*(7), 847–856. https://doi.org/10.1016/S1473-3099(16)00065-7

Sebaaly, J., Parsons, L. B., Pilch, N. A. W., Bullington, W., Hayes, G. L., & Easterling, H. (2015). Clinical and financial impact of pharmacist involvement in discharge medication reconciliation at an academic medical center: A prospective pilot study. *Hospital Pharmacy*, *50*(6), 505–513. https://doi.org/10.1310/hpj5006-505

Smith, T., Philmon, C. L., Johnson, G. D., Ward, W. S., Rivers, L. L., Williamson, S. A., & Goodman, E. L. (2014). Antimicrobial stewardship in a community hospital: Attacking the more difficult problems. *Hospital Pharmacy*, *49*(9), 839–846. https://doi.org/10.1310/hpj4909-839

Standiford, H. C., Chan, S., Tripoli, M., Weekes, E., & Forrest, G. N. (2012). Antimicrobial stewardship at a large tertiary care academic medical center: Cost analysis before: During, and after a 7-year program. *Infection Control & Hospital Epidemiology*, *33*(4), 338–345. https://doi.org/10.1086/664909

Taggart, L. R., Leung, E., Muller, M. P., Matukas, L. M., & Daneman, N. (2015). Differential outcome of an antimicrobial stewardship audit and feedback program in two intensive care units: A controlled interrupted time series study. *BMC Infectious Diseases*, *15*(1), 480. https://doi.org/10.1186/s12879-015-1223-2

Tomczyk, S., Zanichelli, V., Grayson, M. L., Twyman, A., Abbas, M., Pires, D., Allegranzi, B., & Harbarth, S. (2019). Control of carbapenem-resistant enterobacteriaceae, acinetobacter baumannii, and pseudomonas aeruginosa in healthcare facilities: A

systematic review and reanalysis of quasi-experimental studies. *Clinical Infectious Diseases*, *68*(5), 873–884. https://doi.org/10.1093/cid/ciy752

Weiss, A. J., & Elixhauser, A. (2006). *Characteristics of adverse drug events originating during the hospital stay, 2011*.

Wenzler, E., Goff, D. A., Mangino, J. E., Reed, E. E., Wehr, A., & Bauer, K. A. (2016). Impact of rapid identification of Acinetobacter Baumannii via matrix-assisted laser desorption ionization time-of-flight mass spectrometry combined with antimicrobial stewardship in patients with pneumonia and/or bacteremia. *Diagnostic Microbiology and Infectious Disease*, *84*(1), 63–68. https://doi.org/10.1016/j.diagmicrobio.2015.09.018

World Health Organization. (2023). The ATC/DDD Methodology. https://www.who.int/tools/atc-ddd-toolkit/methodology (accessed on 9 July 2023).

Yu, K., Rho, J., Morcos, M., Nomura, J., Kaplan, D., Sakamoto, K., Bui, D., Yoo, S., & Jones, J. (2014). Evaluation of dedicated infectious diseases pharmacists on antimicrobial stewardship teams. *American Journal of Health-System Pharmacy*, *71*, 1019–1028. https://doi.org/10.2146/ajhp130612