Economic Evaluations on Antimicrobial Stewardship Programme: A Systematic Review

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Received, October 22, 2017; Revised, November 6, 2017; Accepted, November 7, 2017; Published, November 7, 2017.

ABSTRACT - Purpose: To systematically review studies on cost-effectiveness of implementing Antimicrobial stewardship programmes (ASP) in the hospital setting. **Methods**: A systematic literature search was performed using electronic databases, such as EMBASE, PubMed/Medline, CINAHL, NHS and CEA Registry from 2000 until 2017. The quality of each included study was assessed using Joanna Briggs Institute Critical Appraisal Checklist for Economic Evaluations and Consolidated Health Economic Evaluation Reporting Standards Statement checklist. **Results**: Of the 313 papers retrieved, five papers were included in this review after assessment for eligibility. The majority of the studies were cost-effectiveness studies, comparing ASP to standard care. Four included economic studies were conducted from the provider (hospital) perspective while the other study was from payer (National Health System) perspective. The cost included for economic analysis were as following: personnel costs, warded cost, medical costs, procedure costs and other costs. **Conclusions**: All studies were generally well-conducted with relatively good quality of reporting. Implementing ASP in the hospital setting may be cost-effective. However, comprehensive cost-effectiveness data for ASP remain relatively scant, underlining the need for more prospective clinical and epidemiological studies to incorporate robust economic analyses into clinical decisions.

INTRODUCTION

Antimicrobial resistance is a growing public health threat. It has been associated with high mortality, with more than one million people die from drug-resistant infections over the last two years [1]. Managing antimicrobial resistance is a costly exercise; in the United States alone, an excess cost of 20 billion USD was spent to treat these drug-resistant infections annually [2]. Resistance to new superbugs has reached an alarming level and more importantly, no major new types of antibiotics have been developed in the past three decades [3]. This looming public health threat has attracted the attention of various governments and global organisations, and thus, numerous strategies, including antimicrobial stewardship programmes (ASP), have been deliberated to combat antimicrobial resistance.

ASP aims to improve antimicrobial use (i.e. optimal selection, dosage, and duration of antimicrobial treatment) to optimise clinical outcomes and patient safety, reduce resistant infections, and minimise costs [4]. Two core strategies, which involves (1) prospective audit with intervention and feedback, and (2) formulary restriction and pre-authorisation, are identified as the foundation of ASP [4]. Davey *et al.* classified the antimicrobial stewardship intervention types into three: persuasive (e.g. audit, educational programmes, reminders, feedback), restrictive (e.g. formulary restrictions, authorisation, antibiotic cycling) and structural (e.g. computerisation of records, decision support system) [5]. Numerous studies [6-8] have shown the effectiveness of ASP and its interventions; and recently, there is an

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increasing emphasis in evaluating cost-effectiveness upon implementation of these interventions. The recent reviews involved a large variation in the method and depth of ASP being economically evaluated (i.e. included predominantly costing studies [9], focused mainly on the clinical outcomes [10] or a narrative review with only one database was search [11]). The studies, therefore, were limited by substantial inter-study methodological heterogeneity, hindering meaningful conclusion to be drawn. Partial economic evaluations that took only drug acquisition cost of antimicrobial agents into consideration would have underestimated cost advantage and health benefit of ASP. Accordingly, the aim of the current study was to systematically review the economic evaluations of ASP in the hospital setting, facilitating informed decision making by policy makers and healthcare providers, in particular the countries with budget constraint.

METHODS

Search Strategy

A systematic search of electronic databases, including EMBASE, PubMed/Medline, CINAHL, NHS and CEA Registry website from year 2000 to 2017, was performed by two independent authors (KM and NHI). The combinations of search terms, together with MESH terms, employed in this review were as follow: "(Antimicrobial OR antibiotic) AND stewardship AND (economics OR cost). These included ((""anti-bacterial agents""[Pharmacological Action] OR ""anti-bacterial agents""[MeSH Terms] OR (""anti-bacterial""[All Fields] AND ""agents""[All Fields]) OR ""anti-bacterial agents""[All Fields] OR ""antibiotics""[All Fields]) AND ""cost""[All Fields] OR ""costs and cost analysis""[MeSH Terms] OR (""costs""[All Fields] AND ""cost""[All Fields] AND ""analysis""[All Fields]) OR ""costs and cost analysis""[All Fields])) AND stewardship [All Fields]. The final search was done in October 2017.

Study Selection

Economic evaluations [i.e. cost-effectiveness analysis (CEA), cost-utility analysis or cost-benefit analysis] of ASP were included in this systematic review. The exclusion criteria were as follow: studies that included only direct cost of antimicrobial agents, studies presented only as abstracts with no full reporting of findings, review papers, editorial letter, non-English literatures, studies involving ASP in the outpatient setting, studies comparing the effectiveness of different antibiotic regimens and studies before year 2000 were all excluded. Partial economic evaluations were excluded due to the fact that the lack of information for performing an in-depth quality assessment while studies before year 2000 were excluded due to the rapid advancement in ASP. The eligibility of all potential economic studies identified for inclusion was independently assessed by two review authors (KH and NHI). Any discrepancies on study inclusion were resolved through discussion and consensus.

Data Extraction and Collection

A standardised, electronic form was used to extract data from each economic study. Data (e.g. country, type of economic analysis, year of costing, perspective, time horizon, comparators, cost components, outcome measure, sensitivity analysis, economic findings) obtained from the included studies were independently extracted by two authors (KH and NHI).

Assessment of Methodological Quality

Quality assessment for all included economic studies were independently assessed (KM and NHI) using criteria as outlined in the Joanna Briggs Institute Critical Appraisal Checklist for Economic Evaluations [12]. The quality of reporting was evaluated using the Consolidated Health Economic Evaluation Reporting Standards checklist [13]. Any disagreement was resolved by discussion between the authors.

RESULTS

Description of Included Studies

A total of 313 studies was identified via the search. After removal of duplicates (n=34), 244 studies were excluded based on the pre-specified criteria (Figure 1). A total of five economic studies investigating the cost-effectiveness of ASP in the hospital setting were included in the qualitative synthesis. Four studies were published within the past five years and were from Western countries. All studies were carried out in the different settings of hospital, with two studies conducted in both general and critical care units [14, 15], one study in critical care unit only [16], one in urology ward [17] and one in surgical and non-surgical wards and emergency department [18].

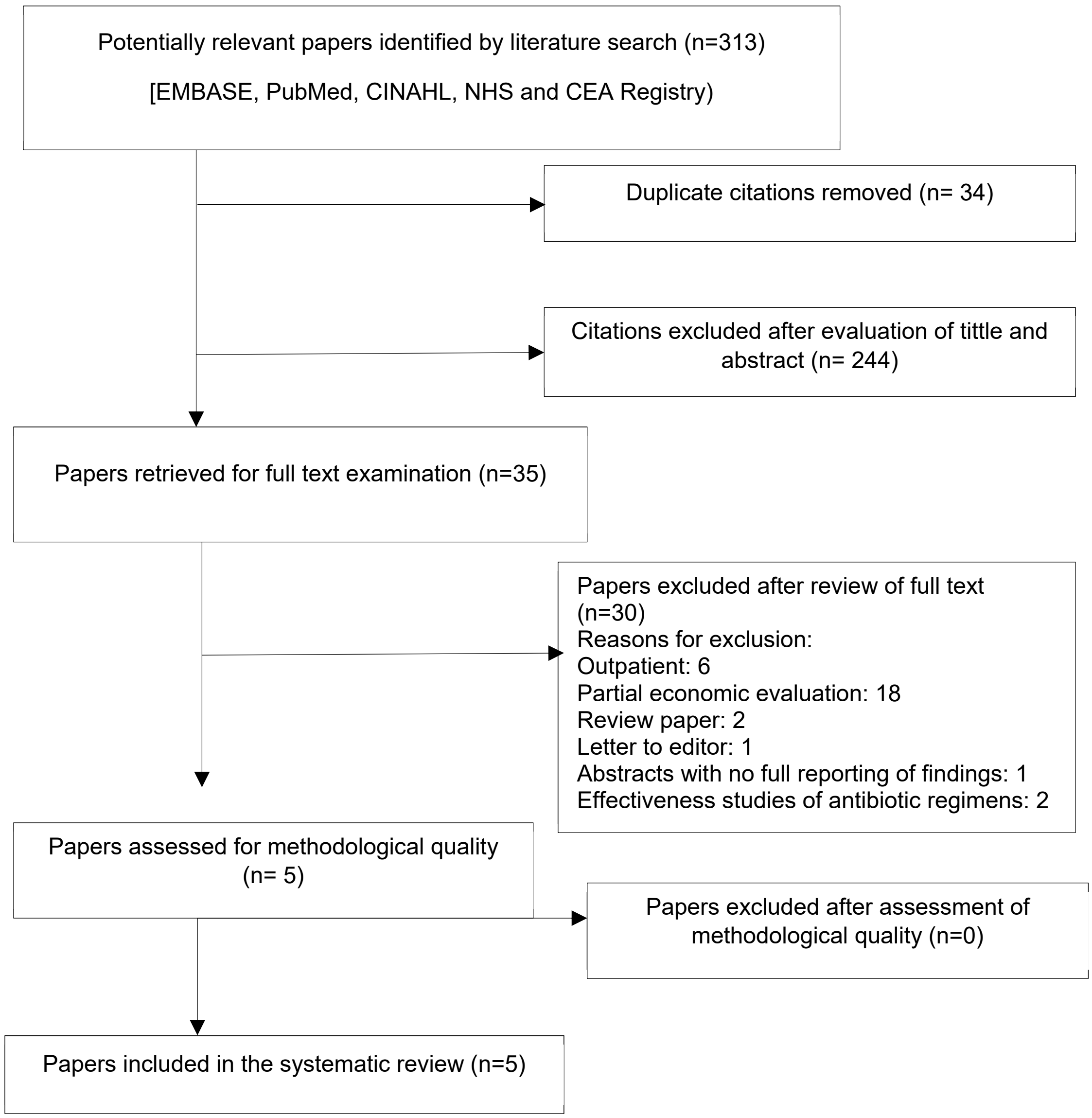

Figure 1. Flow chart of the search method

All included papers were CEA [14-16, 18], except one was cost-benefit analysis [17] (Table 1). The majority of them were conducted from provider (hospital) perspective [14, 15, 17, 18] with only one study was from a payer (i.e. National Health System) perspective [16]. Hence, only direct medical costs were taken into account, which comprised of hospitalisation, healthcare providers and drug costs. Apart from that, additional cost such as computerised clinical decision support system was included in the study by Scheetz *et al.* [14] while Okumura *et al.* included research cost in the analysis [15]. Development costs of antibiotic checklist, implementation costs (i.e. web site, e-learning, briefing, posters and laminated pocket version) and operational costs were included in the study by Van Daalen *et al.* [18]. All costs were obtained retrospectively in all studies except one study [16] obtained the average cost from the published literature.

Four studies compared ASP to standard care [14, 16-18] while the other study compared the two different types of ASP strategies (i.e. bundled ASP versus conventional strategy) [15]. In the study by

Okumura *et al.* [15], bundle ASP consisted of prospective auditing and local education about prescription of antibiotics therapy, microbiological data discussion with laboratory personnel to guide empirical or pre-emptive treatment and face-to-face interventions to enhance antimicrobial drug therapy. On the other hand, conventional ASP strategy included a clinical pharmacist screening for antimicrobial drug-related problem, case discussions with infectious disease physicians and telephone-based interventions [15]. Wide variation in the type and depth of ASP intervention(s) was noted in the other four studies that compared ASP to standard care. For instance, Scheetz *et al.* [14] evaluated Antibiotic Stewardship Team (A-ST) that included expert opinion decision for active treatment of BSI and implementing a computerised clinical decision support system in their strategies (i.e. structural intervention) while Dik *et al.* [17] applied day-2 case audit after initiation of antimicrobial therapy (i.e. persuasive intervention). Van Daalen *et al.* [18] developed and implemented the use of antibiotic checklist (i.e. persuasive intervention) in nine Dutch hospitals and evaluated the cost-effectiveness of checklist usage as ASP intervention. Antimicrobial stewardship interventions in the study by Ruiz-Ramos *et al.* [16] was comprehensive, which included antimicrobial restriction (both antibiotics and antifungals), formal consultation, implementation of protocols for de-escalation and guidelines for antibiotic prophylaxis or treatment, formal reassessment of antimicrobials and implementation of computer-assisted decision support (i.e. persuasive, restrictive and structural interventions).

Several modelling techniques were reported across the four included studies, including decision tree [14, 16], a 30-day Markov model [15] and cost-minimisation model [17]. Van Daalen *et al.* study [18] did not adopt any modelling techniques. Four studies employed incremental cost-effectiveness ratio (ICER) as model outcome [14-16, 18], except one used return on investment [17]. All included studies, except one [18], conducted both deterministic and probabilistic sensitivity analyses to compute the effect of uncertainty in input variables on model outcome. Only one study ran the subgroup analysis since the cohort were from two different groups of patients (i.e. one had infection-related indications and the other had severe underlying diseases such as cancer) [17]. All studies concluded that ASP was cost-effective in either short- or long-term setting.

Quality Assessment

The quality assessment and quality of reporting of the five studies were summarised in the Table 2 and Table 3, respectively. In general, most studies were able to adequately report at least 16 items that essential for performing an economic evaluation, indicating that these studies were of good quality of methodology.

DISCUSSION

Whilst the five economic evaluations included in the current review suggested that implementation of ASP was a cost-effective option in the hospital setting, these findings need to be interpreted with caution. The lack of standardisation in outcome measure of the economic evaluations in the ASP setting, in addition to the inconsistencies in the study design and depth of the ASP interventions employed, has hindered the usefulness of data on costs and benefits in the current evidence-based practice. It is important to note that there is a wide variation in the outcome measure reported among the economic studies in the current review [e.g. ICER per life-years gained, ICER per quality-adjusted life years (QALYs) gained or ICER per averted death in 30 days)]. In addition, return on investment was reported as an outcome measure in one of the studies [17]. Return on investment is a form of cost-benefit analysis that measures the cost of program versus the financial return from that programme, calculated as total benefit minus total cost (net benefit) over total cost [19]; the benefits of intervention are converted into monetary [20]. However, a return on investment analysis typically relies on short-term returns and often ignores the health of beneficiaries or patients [20]. Future studies should consider QALY, which takes into account the quality of life of those who experience the health outcomes, as a standardised outcome measure (effectiveness) [16] since it permits comparability across the economic analyses. The outcome probabilities (i.e. input variables for effectiveness data) for all included studies were mainly obtained from the published literatures [14, 16] or historical cohort studies [15, 17, 18]. These retrospective data could be subject to bias due to incomplete record and loss of follow up. Furthermore, estimation of the levels and long-term effects of antimicrobial resistance that will have on patient evolution as well as disease transmission are not being taken into consideration in these economic studies, and thus, underestimating the impact of ASP. All studies attained the cost inputs retrospectively and through gross costing except the study by Ruiz-Ramos *et al.* used average cost from published literatures in other countries to estimate antimicrobial cost per patient in critical care unit [16]; the appropriateness of adopting cost data from other countries into the analysis is a major consideration.

The included economic studies had high level of heterogeneity due to differences in the study setting, ASP strategies, clinical benefits and economic measurements. Therefore, it is difficult to determine which type of ASP strategies is the most cost-effective. This is further complicated by the dearth of economic evaluations in determining the cost-effectiveness of ASPs. The ASP interventions implemented in the economic studies included in the current review fulfilled most of the core elements of hospital ASP requirements set by Centers for Disease Control and Prevention, which includes leadership commitment, accountability, drug expertise, action, tracking, reporting and education [21]. Whilst multiple approaches in ASP interventions (i.e. bundled ASP strategy) are expected to provide better health outcomes, however, the driver of the cost-effectiveness cannot be distinguished and determined. Of note, none of these economic evaluations was conducted from societal perspective. Most economic studies were conducted from institutional (i.e. payer and provider) perspective given that the funding of ASP comes from the hospital administration; the societal benefits of ASP (e.g. loss of productivity due to multidrug resistant infections), however, should not be underestimated [14].

The difficulty in directly extrapolating the published economic findings to the appropriate patient populations that reflect the clinical caseload encountered in daily practice remains to be resolved since the economic studies included in the current review were conducted in critical care, urology wards, surgical and non-surgical wards and emergency department. Apart from that, other factors such as variability in healthcare systems and the resistance pattern which may differ according to the geographical areas pose great challenges to transfer cost-effectiveness data between countries.

The current review emphasises the need for research on a more systematic approach to evaluate the cost-effectiveness of individual ASP programmes. Robust health economic evaluations will provide a reasonable foundation for decision-making and thus, facilitating the ideal allocation for limited resources countries to fight against antimicrobial resistance. In general, the quality and execution of the included economic studies on economic evaluation were considered satisfactory. In the current review, the Joanna Briggs Institute Checklist for Economic Evaluation [12] was used to appraise the economic studies in addition to the Consolidated Health Economic Evaluation Reporting Standards checklist [13]. A 'YES' on the Consolidated Health Economic Evaluation Reporting Standards checklist may not adequately assess the quality of the criteria, but may only to indicate the completeness of the reporting rather than whether the choices were appropriate or justified. The present work, however, has shortcomings. Only studies published in English were included, and thus, leading to the small numbers of retrieved articles. The high level of the methodological heterogeneity, in terms of ASP interventions, that was noted in the current review is another limitation.

CONCLUSION

Although implementing ASP in the hospital setting is considered to be cost-effective, existing economic evaluations are limited by their great variation in the study design, outcome measure, types of ASP intervention and clinical settings. Therefore, future research evaluating the economic impact of ASP should consider using a standardised outcome measure with a longer time horizon of analysis. Robust economic studies to assess the cost-effective component of ASP across an extended clinical setting are anticipated.

TRANSPARENCY DECLARATIONS

All authors have no conflicts of interest to declare. This review was partially supported by UiTM internal grant (600-IRMI/DANA5/3/BESTARI (044/2017).

Table 1. *Economic Evaluations of Antimicrobial Stewardship Programmes*

Source	Type of analysis	Currency, year of costing	Perspective (Timeframe)	Comparator	Outcome measure(s)	Sensitivity Analysis (SA), (variable inputs)	Economic Findings	Conclusion
[14]	CEA	US$, 1999	Provider-Hospital (Not stated)	ASP versus Standard care	ICER/QALY	One-way SA (e.g. ability of ASP to transit patient to active treatment), multi-way SA and probabilistic SA (e.g. event likelihoods, cost ranges, utility ranges)	ICER was US$2,367 per QALY gained and more than 90% likelihood that ASP was cost effective at level of US$10,000 per QALY	Maintaining ASP to improve care of bacteraemia is cost-effective from the hospital perspective
[17]	Cost-benefit analysis	Euro €, 2013	Provider-Hospital (1 year)	ASP versus Standard care	Return on investment	Multi-variate SA (e.g. LOS, % primary admitted due to infection, cost for consultant, expected LOS due to antimicrobial resistance) and probabilistic SA (e.g. LOS, nursing time, antibiotic costs)	The model estimated total savings of €60,306 after one year for this single department, leading to a return on investment of 5.9	The implemented multi-discipli nary A-Team performing a day-2 case audit in the hospital had a positive return on investment caused by a reduced LOS due to a more appropriate antibiotic therapy
[15]	CEA	Brazilian Real and converted to US$, 2013	Provider-Southern Brazilian University Hospital (30 days)	Conventional ASP strategy versus Bundled ASP strategy	ICER/Averted death in 30 days	Deterministic SA (e.g. cost) and probabilistic SA (e.g. cost)	Bundled ASP was associated with an ICER of US$ 19 ,287.54 per averted death in 30 days	Bundled ASP was more cost-effective and also associated with higher probabilities of clinical success and at

								reasonable implementation costs
[16]	CEA	€, 2015	Payer-Spain National Health System (Not reported)	ASP versus Standard care	ICER/LYG	Univariate SA (e.g. reason for admittance to critical care, incidence of nosocomial infection, reduction in *Clostridium difficile* infection, ASP impact on average treatment cost) and probabilistic SA (e.g. short-term ASP benefit, incidence of nosocomial infection, percentage of multi-resistant species present in the unit, impact of ASP on the prevalence of infection by multi-resistant bacteria)	ASP was associated with an ICER of 9,788€/ LYG. More than 90% likelihood that an ASP would be cost-effective at a level of 8,000€ per LYG.	Implementing an ASP focusing on critical care patients is a long-term cost-effective tool.
[18]	CEA	€, 2015	Hospital Perspective (not reported)	ASP versus Usual care	ICER/extra patient receiving appropriate treatment, and ICER/day reduction in LOS	Not performed	ICERs of €54.01 per extra patient with appropriate treatment and €51.43 per day reduction in LOS were reported.	Implementation of this antibiotic checklist can be a cost-effective antimicrobial stewardship strategy

US = United States, LOS = Length of stay, ICER = Incremental cost-effectiveness ratio, ASP = Antimicrobial stewardship programme, QALY = Quality adjusted life-years, LYG = Life-year gained, SA = Sensitivity analysis, CEA = Cost-effectiveness analysis

Table 2. Joanna Briggs Institute Critical Appraisal Checklist for Economic Evaluations

ITEM	QUESTION	STUDIES				
		Sheetz *et. al.* (2009)	**Dik *et. al.* (2015)**	**Okumura *et. al.* (2016)**	**Ruiz-Ramos *et. al.* (2017)**	**Van Daalen *et. al.* (2017)**
1.	Is there a well-defined question/objective?	+	+	+	+	+
2.	Is there comprehensive description of alternatives?	+	+	+	-	+
3.	Are all important and relevant costs and outcomes for each alternative identified?	+	+	+	Unclear	+
4.	Has clinical effectiveness been established?	+	Unclear	+	+	+
5.	Are costs and outcomes measured accurately?	+	+	+	+	+
6.	Are costs and outcomes valued credibly?	+	+	Unclear	+	+
7.	Are costs and outcomes adjusted for differential timing?	-	+	+	+	Unclear
8.	Is there an incremental analysis of costs and consequences?	+	-	+	+	+
9.	Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	+	+	+	+	-
10.	Do study results include all issues of concern to users?	Unclear	Unclear	+	+	+
11.	Are the results generalizable to the setting of interest in the review?	Unclear	Unclear	+	+	+

+ = Yes
- = No

Table 3. Consolidated Health Economic Evaluation Reporting Standard (CHEERS CHECKLIST)

Section/Item	Study				
	Scheetz *et. al.* (2009)	**Dik *et. al.* (2015)**	**Okumura *et. al.* (2016)**	**Ruiz-Ramos *et. al.* (2017)**	**Van Daalen *et. al.* (2017)**
Title/Abstract/Introduction					
Title	A	A	A	A	A
Abstract	A	A	A	A	A
Background/objectives	A	A	A	A	A
Methods					
Target population/subgroups	A	A	A	A	A
Setting/location	A	A	A	A	A
Study perspective	A	A	A	A	A
Comparators	A	A	A	A	A
Time horizon	A	A	A	A	NA
Discount rate	A	NA	A	A	NA
Choice of health outcomes	A	A	A	A	A
Measurement of effectiveness	A	A	A	A	A
Estimating resources and costs	A	A	A	A	A
Currency, price date, conversion	PA	A	A	PA	PA
Choice of model	A	A	A	A	NA
Assumptions	A	A	A	A	A
Analytical model	A	A	A	A	NA
Results					
Study parameters	A	A	A	A	A
Incremental costs and outcomes	A	NA	A	A	A
Characterizing uncertainty	A	A	A	A	NA
Characterizing heterogeneity	A	A	A	A	NA
Discussion/Others					
Study findings, limitations, generalizability, current knowledge	A	A	A	A	A
Source of funding	A	A	A	A	A
Conflict of interest	A	A	A	A	A

A - Adequate (Information was explicitly presented in the text)
PA - Partially adequate (Information was NOT explicitly presented but it was suggested)
NA - Not adequate (No information about the matter was available in the text)

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