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REVIEW

Costs of hospital-acquired infection and transferability of the estimates: a systematic review

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Abstract Hospital-acquired infections (HAIs) present a substantial problem for healthcare providers, with a relatively high frequency of occurrence and considerable damage caused. There has been an increase in the number of cost-effectiveness and cost-savings analyses of HAI control measures, and the quantification of the cost of HAI (COHAI) is necessary for such calculations. While recent guidelines allow researchers to utilize COHAI estimates from existing published literature when evaluating the economic impact of HAI control measures, it has been observed that the results of economic evaluations may not be directly applied to other jurisdictions due to differences in the context and circumstances in which the original results were produced. The aims of this study were to conduct a systematic review of published studies that have produced COHAI estimates from 1980 to 2006 and to evaluate the quality of these estimates from the perspective of transferability. From a total of 89 publications, only eight papers (9.0%) had a high level of transferability in which all components of costs were described, data for costs in each component were reported, and unit costs were estimated with actual costing. We also did not observe a higher citation level for studies with high levels of transferability. We feel that, in order to ensure an appropriate contribution to the infection control program decision-making process, it is essential for researchers who estimate COHAI, analysts who use COHAI estimates for decision-making, as well as relevant journal reviewers and editors to recognize the importance of a transferability paradigm.

Keywords Hospital-acquired infection · Costs · Transferability · Costing method

Introduction

Hospital-acquired infections (HAIs) present a substantial problem for healthcare providers, as these infections occur with relatively high frequency [1] and each case may result in considerable damage [2]. There has been a recent increase in the frequency of published studies analyzing the incremental cost of HAIs at the hospital level, with many studies reporting quantified estimates. The driving force behind this recent increase in the number of cost of HAI (COHAI)-related research is the rationale that at least 20% of HAIs have been shown to be preventable [3].

In this way, COHAI research serves the following two purposes. Firstly, the quantification of COHAI can highlight the necessity of HAI control measures. As the containment of rising healthcare costs is a common goal among industrialized nations, the prevention of HAIs could be expected to curtail unnecessary costs. Secondly, COHAI quantifications can contribute to elucidating the savings effect necessary in the calculation of cost-effectiveness and cost-savings of HAI control measures. The rising importance of investigating the economic evaluations of HAI measures has been accelerated by the decision of Medicare

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in the US to withhold reimbursement to healthcare providers for preventable errors, which includes HAIs. Recent guidelines permit researchers to utilize COHAI estimates from existing published literature when evaluating the economic impacts of control measures [2], and some studies have been previously shown to use existing estimates [4].

In recent years, discussions concerning the external validity of economic evaluations have gained momentum within medical circles, with the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) using the term "transferability". The ISPOR task force has acknowledged that cost-effectiveness results may not be directly applied to other jurisdictions due to major differences with the context and circumstances in which the original results were produced, and that, when applying results to other jurisdictions, it is vitally important to account for differences in unit costs and clinical practice variations [5]. It has also been suggested that the high level of diversity in economic evaluations are due primarily to dissimilarities in unit costs, followed by variations in clinical practice [6]. Furthermore, the BMJ checklist [7], various national guidelines [5], two seminal texts for economic evaluation research [8, 9], and other researchers [10] have also emphasized the importance of reporting both resource consumption quantities and unit costs separately in order to improve the transferability of economic research.

The aims of this study were to conduct a systematic review of published studies that have produced COHAI estimates and to evaluate the quality of these estimates from the perspective of transferability. Also, we sought to investigate if studies evaluated as possessing high transferability are correspondingly well regarded by other researchers by analyzing the number of citations.

Methods

Study selection

We conducted a systematic review of published articles that had produced estimates of incremental COHAI (not including *length of stay*). This systematic review was conducted according to the general principles of the Cochrane Collaboration framework. The selection criteria for candidate studies were those that produced original COHAI estimates that were published in English from 1980 to 2006. We excluded review papers, editorials, meta-analyses, and decision analyses. The following keywords were used in a MEDLINE search to extract candidate publications: *["economics"(Subheading) OR "Hospital Costs"(MeSH)] AND ["Cross Infection"(MeSH) OR "Surgical Wound Infection"(MeSH) OR "Bacteremia"(MeSH) OR "Bacterial Infections"(MeSH) OR "Sepsis"(MeSH) OR "Staphylococcal Infections"(MeSH) OR "Pseudomonas Infections"(MeSH) OR "Pneumonia" (MeSH) OR "Urinary Tract Infections"(MeSH)]*. Studies that fulfilled the aforementioned criteria were then subjected to a two-step review process: first, an abstract review, followed by a full-paper review, before the decision to include them in the final assessment was made. The initial abstract review was conducted to identify: (1) studies that produced original cost estimates for treatment instead of those that used published cost estimates and (2) studies focusing on healthcare-acquired infections versus those that focused on or included community-acquired infections. Studies included in the subsequent full-paper review were those that had produced original estimates of costs of treating HAIs and those that could not be properly evaluated on the basis of the abstract alone. In the full-paper review, the estimates of the COHAI were evaluated, and the transferability of each paper was investigated. Both the abstract review and the full-literature review were conducted independently by two evaluators (HF and JL) whom possess backgrounds in economic evaluations and infectious diseases. Non-congruent evaluations were discussed before decisions were made. Additionally, we included publications cited within the extracted publications that produced original cost estimates of COHAI.

Study assessment

All selected papers were assessed for: (1) estimates of cost attributable to HAI, (2) transparency of cost estimates, (3) costing methods, and (4) record of the number of citations between publication and the year 2009. The citation record, obtained from the ISI Web of Science, was used to investigate if studies evaluated as possessing high transferability are correspondingly well regarded by other researchers. The transparency of cost estimates and costing methods were evaluated based on the two evaluation axes as described below.

Evaluation criteria for transferability: evaluation axis 1

The first axis of evaluation assesses the clarification of the scope of costing, i.e., the level of transparency on the reporting of items included in the estimates and how the estimates were calculated. Without clarifying the scope of costing, such as detailed description of costing components and data for both quantity and unit price of resources in each cost component, readers would be unable to judge the potential applicability to their own analyses. Therefore, our first axis assesses whether estimates have clarified scopes of costing, and we have established a hierarchy of four levels of transparency as follows:

- Level A: all components of costs were described and data for both quantity and unit price of resources were reported for each component.
- Level B: all components of costs were described and data for costs in each component were reported. This included studies that used graphical presentations of the aforementioned data.
- Level C: all components of costs were described but data for costs in each component were not reported.
- Level D: only the scope of costing was described but the components of costs were not described. For example, studies that only reported terms such as "hospital stay" or "direct costs" without further exposition were evaluated at Level D.

When there were studies that used two or more costing methods to produce COHAI estimates, we categorized these studies into the higher level of costing method.

Evaluation criteria for transferability: evaluation axis 2

However, differences in the methods used to calculate unit costs in the first evaluation axis may result in large variations in COHAI estimates, thereby, affecting the transferability of these estimates. Therefore, the second axis of evaluation was used to identify costing methodologies. The optimal choice of costing methods is the use of micro-costing or quasi-micro-costing, i.e., activity-based costing, in which the measurement of actual resource consumption is attempted. The second costing method involves the use of relative value units (RVUs). The next costing method uses charge data based on the ratio of costs to charges (RCCs). The difference with the use of RVUs is that RCCs utilize cost data at the hospital, medical department, and diagnostic categories (such as the diagnosis-related group [DRG]) levels, using ratios against charge data at each level, and is, therefore, intrinsically reliant on charge data. In general, cost estimates based on the use of RVUs are considered to be more accurate than those based on RCCs, as the former directly applies relative cost information on each item consumed [11]. The fourth costing method involves the use of unmodified charge data. As there is a strong political dimension in the determination of charge data, the external validity of such estimates to different contexts is drastically reduced. The final category of the evaluation of the method of cost estimation includes studies that offer no information to readers about the methodology used.

Statistical analysis

In recent years, discussions concerning the external validity of economic evaluations have gained momentum in healthcare research. As such, changes in proportions of the transferability of COHAI estimates by year of publication were analyzed using Fisher's exact test. Also, COHAI estimates provide a foundation for the quantification of additional resources attributable to HAIs, and as these estimates can be used in the calculations of cost-effectiveness and cost-savings analyses of infection control measures, there are many chances for such studies to be cited by other researchers. With the purpose of verifying whether studies that have been assessed as having a higher level of transferability are more frequently used by other researchers, we studied the post-publication number of citations per year for each paper, calculated the median of this citation record categorized by the two evaluation axes of transferability, and compared them using a Kruskal–Wallis test.

Results

The search of MEDLINE using our criteria returned 3,069 distinct results, and after conducting abstract and full-paper reviews, we identified 79 studies that estimated incremental COHAI. In addition, we identified 110 other publications cited by these 79 studies. Of these 110 publications, ten fulfilled our criteria for inclusion in our analysis. There were, therefore, a total of 89 publications included in our final assessment [12–100].

The characteristics of the studies included in the sample are shown in Table 1. With regard to the types of infections targeted in these studies, there were 28 COHAI estimates that targeted surgical site infections (SSI), 19 estimates for bloodstream infections (BSI), 12 estimates for pneumonia and ventilator-associated pneumonia (VAP), ten estimates for urinary tract infection (UTI), five estimates for respiratory tract infection (RTI), and 39 estimates for unspecified HAIs. Forty-one of the studies were conducted in the US, six studies in Turkey, five studies in the UK and France, and four in Taiwan. There were ten studies in the 1980s, 21 publications in the 1990s, and a steep increase to 58 studies from 2000 to 2006. Clarification of the scope of costing was graded from Levels A to D. There was only one study graded at Level A (1.1%), 35 studies graded at Level B (39.3%), 16 studies graded at Level C (18.0%), and 37 studies graded at Level D (41.6%). Variations in costing methods showed that the most frequent method was the use of charges as proxy, with 30 studies (33.7%). This was followed by 28 studies with unknown methods of costing (31.5%), 18 studies that used actual costs (20.2%), 11 studies with RCCs (12.4%), and two studies with RVUs (2.2%). There were three studies that used multiple costing methods to produce COHAI estimates, consisting of one study using actual costs and charges, one study using actual

Table 1 Characteristics of papers which estimated the additive cost of hospital-acquired infection (HAI) ($n = 89$)

Paper characteristics	*n*	%
Site of infection		
Surgical	28	31.5
Bloodstream	19	21.3
Pneumonia/VAP	12	13.5
Urinary tract	10	11.2
Respiratory tract	5	5.6
Unspecified	39	43.8
Country		
US	41	46.1
Europe	26	29.2
Asia	13	14.6
Other	9	10.1
Year of publication		
1980–1984	7	7.9
1985–1989	3	3.4
1990–1994	9	10.1
1995–1999	12	13.5
2000–2004	35	39.3
2005–2006	23	25.8
Clarification of scope of costing (level)		
A	1	1.1
B	35	39.3
C	16	18.0
D	37	41.6
Costing method		
Actual costing	18	20.2
Relative value units (RVUs)	2	2.2
Ratio of costs to charges (RCCs)	11	12.4
Charge	30	33.7
Unknown	28	31.5

Europe includes the UK (5), France (5), Belgium (4), Germany (3), Spain (3), the Netherlands (2), Ireland (1), Italy (1), Scotland (1), and Switzerland (1)

Asia includes Turkey (6), Taiwan (4), India (1), Thailand (1), and China (1)

Others include Canada (2), Argentina (2), Mexico (1), Trinidad and Tobago (1), Australia (1), New Zealand (1), and multi-country study (1)

costs and an unknown method, and the final study using charges and an unknown method. The first two studies were categorized as actual costs, while the third was included with the studies that utilized charges.

The results of the evaluation of the transferability of the COHAI by infection route are shown in Table 2. As shown in the table, there are very large variations observed in the cost estimates among the publications. These variations could be attributed to differences in the items included in costing, clinical practice patterns for HAIs, unit costs, difference between actual costs and charges, and cost estimation methods. As there is, therefore, no real discernable meaning to the aggregation of COHAI estimates by infection type, this study presents the estimates by publication, country of origin, type of hospital used in the sample, type of patients used in the sample, additional cost estimates to HAI, clarification of the scope of costing, and costing methods. The only study that reported both quantities of resources consumed and unit costs for each costing component used for the cost estimates was Coello et al. [12].

The clarification of scope and costing methods by year of publication are shown in Table 3. As there was only one study [12] that reported both the quantities of resources consumed and unit costs and, therefore, could be evaluated as Level A, this study was included together with Level B studies. We observed no change and an increase from the 1990s to post-2000 in the proportions of studies that were evaluated as A/B or C, respectively. Contemporaneously, the proportion of studies evaluated as Level D, in which the cost estimation methods were unclear, had decreased in the same time period. However, we did not find a statistical significance associated with this change in proportions. The use of charge data was categorized separately in costing methods. We observed a trend in which the proportion of studies that utilized actual costing or RVU methods, and not charge data, had increased since the 1980s to the present. There was a reduction of studies that used charge data to estimate costs from the 1980s to the 1990s, and after 2000, these comprised approximately 50% of reports. On the other hand, studies which used unknown cost estimation methods had reduced in 2000. The changes in cost estimation methods by year of publication have been shown to be marginally significant ($P = 0.039$).

The post-publication numbers of citations per year by evaluation of transferability are shown in Table 4. With respect to the clarification of scope, there was no statistical difference ($P = 0.278$) in the median number of citations among studies evaluated at Level A or B (median = 2.86), Level C (median = 3.93), and Level D (median = 3.83). With regard to costing methods, however, we found a significant difference ($P = 0.025$) in the number of citations between studies that used cost estimates without charge data (median = 4.87), cost estimates with charge data (median = 3.48), and unknown methods (median = 2.45).

Discussion

As the concept of transferability is still burgeoning, there is a possibility that the existence of COHAI estimates with little or no transferability may detrimentally influence the decision-making process in developing infection control

Table 2 Impact of hospital-acquired infection on hospital cost and results of the assessment of transferability

Authors	Year	Country	Type of setting	Patients studied	Additional cost to HAI, if stated (infected cost vs. uninfected cost) (*P*-value)	Axis 1	Axis 2
Surgical site infection							
Coello et al. [12]	1993	UK	General hospital	Surgical	Mean: +GBP1,456	A	Actual cost
Plowman et al. [13]	2001	UK	General hospital	Mixed	Regression: +GBP1,594 ($P < 0.05$)	B	Actual cost
Zoutman et al. [14]	1998	Canada	University hospital	Surgical	Mean: +CAD3,937 Median: +CAD1,737	B	Actual cost
Boyce et al. [15]	1990	US	University hospital	Surgical	Mean: +USD13,162 (25,957 vs. 12,795) ($P = 0.0002$)	B	RCC
Sheng et al. [16]	2005	Taiwan	University hospital	Admissions	Median: +TWD117,802 (357,013 vs. 126,519) ($P < 0.001$)	B	Charge
Hollenbeak et al. [17]	2001	US	Mixed: three hospitals	Surgical	Regression: +USD131,276 ($P < 0.001$)	B	Charge
Fabry et al. [18]	1982	France	Teaching hospital	Surgical	Mean: +FRF4,258	B	Charge
Wilson et al. [19]	2006	UK	University hospital	Surgical	Mean: +GBP4,018 (7,718 vs. 3,700)	B	Unknown
Coskun et al. [20]	2005	Turkey	University hospital	Surgical	<deep sternal>Mean: +USD6,851 <superficial sternal>Mean: +USD3,741	B	Unknown
Mugford et al. [21]	1989	Several	Mixed: several	Surgical	Mean: +GBP716 (1,435 vs. 719)	B	Unknown
Whitehouse et al. [22]	2002	US	University hospital	Surgical	Median: +USD27,969 (38,640 vs. 10,671) ($P < 0.001$)	C	Actual cost
Scheckler [23]	1980	US	Teaching hospital	Admissions	Mean: +USD1,329	C	Charge
Gavaldà et al. [24]	2006	Spain	Teaching hospital	Mixed	Mean: +EUR3,816	C	Unknown
VandenBergh et al. [25]	1996	Netherlands	University hospital	Surgical	Median: +USD9,320 (14,560 vs. 5,240) ($P < 0.001$)	C	Unknown
Lynch et al. [26]	1992	Scotland	Teaching hospital	Surgical	Mean: +GBP1,072 (2,680 vs. 1,607)	C	Unknown
Reilly et al. [27]	2001	UK	Not stated	Surgical	Mean: +GBP1,743	C	Unknown
Kirkland et al. [28]	1999	US	Community hospital	Surgical	Median: +USD3,089 (7,486 vs. 3,842) ($P < 0.05$)	D	Actual cost
Herwaldt et al. [29]	2006	US	Mixed: two hospitals	Surgical	<Nonfatal>Regression: +USD1,574 (3,473 vs. 1,899) ($P < 0.001$) <Fatal>Regression: +USD2,005 (3,904 vs. 1,899) ($P < 0.001$)	D	RCC
Hollenbeak et al. [30]	2000	US	Community hospital	Surgical	Regression: +USD18,938 ($P < 0.001$)	D	RCC
Vogel et al. [31]	2006	US	University hospital	Surgical	Regression: +USD94,331 (264,778 vs. 170,447) ($P < 0.001$)	D	Charge
Kasatpibal et al. [32]	2005	Thailand	University hospital	Surgical	Mean: +THB43,658 (75,544 vs. 31,886) ($P < 0.001$) Median: +THB31,140 (50,951 vs. 24,568) ($P < 0.001$)	D	Charge
McGarry et al. [33]	2004	US	Mixed: two hospitals	Surgical	Mean: +USD41,117 ($P < 0.001$)	D	Charge
Hollenbeak et al. [34]	2003	US	Mixed: three hospitals	Surgical (children)	+USD132,507 ($P < 0.05$)	D	Charge
Engemann et al. [35]	2003	US	Mixed: two hospitals	Surgical	<MSSA>Median: +USD23,336 (52,791 vs. 29,455) ($P < 0.001$) <MRSA>Median: +USD62,908 (92,363 vs. 29,455) ($P < 0.001$)	D	Charge
Apisarnthanarak et al. [36]	2003	US	Community hospital	Surgical	Mean: +USD12,477	D	Unknown

Table 2 continued

Authors	Year	Country	Type of setting	Patients studied	Additional cost to HAI, if stated (infected cost vs. uninfected cost) (*P*-value)	Axis 1	Axis 2
Hollenbeak et al. [37]	2002	US	Community hospital	Surgical	Unmatched mean: +USD20,012 ($P < 0.001$) Matched mean: +USD19,579 ($P < 0.001$) Linear regression: +USD20,103 ($P < 0.001$) Heckman's model: +USD14,211 ($P = 0.055$)	D	Unknown
Jenney et al. [38]	2001	Australia	Tertiary hospital	Surgical	Mean: +AUD12,419 (20,888 vs. 8,468) ($P = 0.001$)	D	Unknown
Vegas et al. [39]	1993	Spain	Tertiary hospital	Surgical	Mean: +USD4,449 ($P < 0.01$)	D	Unknown
Bloodstream infection							
Plowman et al. [13]	2001	UK	General hospital	Mixed	Regression: +GBP6,209 ($P < 0.05$)	B	Actual cost
Laupland et al. [40]	2006	Canada	Mixed: three hospitals	Intensive care	Median: +CAD12,321 (85,137 vs. 67,879) ($P < 0.05$) Mean: +CAD16,867 (103,987 vs. 87,120)	B	RVU
Blot et al. [41]	2005	Belgium	University hospital	Intensive care	<CABSI>Regression: +EUR 16,814 ($P < 0.001$) <CABSI>Median: +EUR13,585 (51,405 vs. 37,820) ($P < 0.001$)	B	Charge
Sheng et al. [16]	2005	Taiwan	University hospital	Admissions	Median: +TWD101,536 (323,479 vs. 199,365) ($P < 0.001$)	B	Charge
Slonim et al. [42]	2001	US	Children's hospital	Admissions—PICU	Mean: +USD58,344 (99,177 vs. 45,038) ($P < 0.001$)	B	RCC
Dimick et al. [43]	2001	US	Tertiary hospital	Surgical—ICU	<CABSI>Regression: +USD56,167 (102,973 vs. 46,806) ($P = 0.001$)	B-	RCC
Elward et al. [44]	2005	US	Tertiary hospital	Admissions—PICU	Regression: +USD39,219 (45,615 vs. 6,396) ($P < 0.001$)	B	Mixed
Warren et al. [45]	2006	US	Suburban hospital	Patients with CVC—ICU	<CABSI>Regression: +USD11,971 (29,256 vs. 17,285) ($P < 0.05$) <CABSI>Median: +USD26,241 (54,242 vs. 26,001)	C	Actual cost
Payne et al. [46]	2004	US	Mixed: 17 hospitals	Inborn and outborn infants	Mean: +USD5,875 (128,887 vs. 123,012) ($P = 0.141$) ~ +USD12,480 (94,060 vs. 81,580) ($P = 0.009$)	C	Charge
Orsi et al. [47]	2002	Italy	University hospital	Admissions	Mean: +EUR16,356	C	Unknown
Digiovine et al. [48]	1999	US	University hospital	Medical—ICU	Median: +USD15,965 (60,650 vs. 36,899) ($P < 0.001$)	D	RVU
Herwaldt et al. [29]	2006	US	Mixed: two hospitals	Surgical	<UTI and RTI and BSI> <Nonfatal>Regression: +USD6,536 (8,435 vs. 1,899) ($P < 0.001$) <Fatal>Regression: +USD3,249 (5,148 vs. 1,899) ($P < 0.001$)	D	RCC
Rosenthal et al. [49]	2003	Argentina	Mixed: three hospitals	Patients with CVC—ICU	<CVC-associated BSI>Mean: +USD4,888 (7,972 vs. 3,083)	D	RCC
Vogel et al. [31]	2006	US	University hospital	Surgical	Regression: +USD86,500 (247,440 vs. 160,940) ($P < 0.001$)	D	Charge
Rello et al. [50]	2000	Spain	Tertiary hospital	Admissions—ICU	Mean: +EUR3,124 (10,052 vs. 6,914)	D	Charge
Wisplinghoff et al. 51]	2003	Germany	University hospital	Patients with a hematologic malignancy	Mean: +USD3,170	D	Mixed
Liu et al. [52]	2002	Taiwan	Tertiary hospital	Surgical	Median: +TWD66,302 (131,584 vs. 65,282) ($P < 0.001$)	D	Unknown
Abramson and Sexton [53]	1999	US	University hospital	Admissions	<MSSA>Median: +USD9,661 ($P < 0.01$) <MRSA>Median: +USD27,083 ($P < 0.01$)	D	Unknown

Table 2 continued

Authors	Year	Country	Type of setting	Patients studied	Additional cost to HAI, if stated (infected cost vs. uninfected cost) (*P*-value)	Axis 1	Axis 2
Pittet et al. [54]	1994	US	University hospital	Surgical intensive care	Mean: +USD33,268 (91,241 vs. 57,973) ($P < 0.01$)	D	Unknown
Pneumonia and VAP							
Cocanour et al. [55]	2005	US	Tertiary hospital	Ventilated patients—ICU	<VAP>Mean: +USD57,158 (82,195 vs. 25,037) ($P < 0.05$)	B-	Actual cost
Hugonnet et al. [56]	2005	Switzerland	University hospital	Ventilated patients—ICU	<VAP>Mean: +USD10,450 (24,727 vs.17,438) ($P < 0.05$)	B-	Actual cost
Warren et al. [57]	2003	US	Tertiary hospital	Ventilated patients—ICU	<VAP>Regression: +USD11,897 (27,033 vs. 15,136) ($P < 0.05$)	B-	Actual cost
van Nieuwenhoven et al. [58]	2004	Netherlands	University hospital	Intensive care	<VAP>Mean: +USD15,623 (29,360 vs. 13,737)	C	Actual cost
Dietrich et al. [59]	2002	Germany	University hospital	Admissions	<Pneumonia>Mean: +DEM29,610	C	Actual cost
Scheckler [23]	1980	US	Teaching hospital	Admissions	<Pneumonia>Mean: +USD878	C	Charge
Gavaldà et al. [24]	2006	Spain	Teaching hospital	Mixed	<Pneumonia and RTI>Mean: +EUR358	C	Unknown
Rosenthal et al. [60]	2005	Argentina	Mixed: three hospitals	Intensive care	<Pneumonia>Mean: +USD2,253 (4,946 vs. 2,694) ($P < 0.001$)	D	RCC
Vogel et al. [31]	2006	US	University hospital	Surgical	<VAP>Regression: +USD89,187 (232,080 vs. 142,893) ($P < 0.001$)	D	Charge
Thompson et al. [61]	2006	US	Mixed: 994 hospitals	Surgical	<Pneumonia>Regression: +USD28,161 ($P < 0.05$)	D	Charge
Merchant et al. [62]	1998	India	Teaching hospital	Admissions	<Pneumonia>Mean: +USD496	D	Unknown
Kappstein et al. [63]	1992	Germany	University hospital	Ventilated patients—ICU	<VAP>Mean: +DEM14,253	D	Unknown
Urinary tract infection							
Coello et al. [12]	1993	UK	General hospital	Surgical	Mean: +GBP467	A	Actual cost
Tambyah et al. [64]	2002	US	University hospital	Admissions	<CAUTI>Mean: +USD589	B	Actual cost
Plowman et al. [13]	2001	UK	General hospital	Mixed	Regression: +GBP1,122 ($P < 0.05$)	B	Actual cost
Sheng et al. [16]	2005	Taiwan	University hospital	Admissions	Median: +TWD114,662 (354,608 vs. 159,953) ($P < 0.001$)	B	Charge
Lai and Fontecchio [65]	2002	US	University hospital	Admissions	<CAUTI>Mean: +USD1,214 <CAUTI>Median: +USD614	B	Charge
Fabry et al. [18]	1982	France	Teaching hospital	Surgical	Mean: +FRF2,726	B	Charge
Scheckler [23]	1980	US	Teaching hospital	Admissions	Mean: +USD146	C	Charge
Gavaldà et al. [24]	2006	Spain	Teaching hospital	Mixed	Mean: +EUR1792	C	Unknown
Herwaldt et al. [29]	2006	US	Mixed: two hospitals	Surgical	<UTI and RTI and BSI> <Nonfatal>Regression: +USD6,536 (8,435 vs. 1,899) ($P < 0.001$) <Fatal>Regression: +USD3,249 (5,148 vs. 1,899) ($P < 0.001$)	D	RCC
Givens and Wenzel [66]	1980	US	Teaching hospital	Surgical	<CAUTI>Mean: +USD558	D	Unknown
Respiratory tract infection							
Plowman et al. [13]	2001	UK	General hospital	Mixed	Regression: +GBP2,080 ($P < 0.05$)	B	Actual cost

Table 2 continued

Authors	Year	Country	Type of setting	Patients studied	Additional cost to HAI, if stated (infected cost vs. uninfected cost) (*P*-value)	Axis 1	Axis 2
Sheng et al. [16]	2005	Taiwan	University hospital	Admissions	Median: +TWD117,100 (368,435 vs. 180,059) ($P < 0.001$)	B	Charge
Fabry et al. [18]	1982	France	Teaching hospital	Surgical	Mean: +FRF2,060	B	Charge
Gavaldà et al. [24]	2006	Spain	Teaching hospital	Mixed	<Pneumonia and RTI>Mean: +EUR358	C	Unknown
Herwaldt et al. [29]	2006	US	Mixed: two hospitals	Surgical	<UTI and RTI and BSI> <Nonfatal>Regression: +USD6,536 (8,435 vs. 1,899) ($P < 0.001$)	D	RCC
Unspecified infection							
Plowman et al. [13]	2001	UK	General hospital	Mixed	Regression: +GBP2,917 ($P < 0.05$)	B	Actual cost
Shulkin DJ [67]	1993	US	University hospital	Surgical	<RCC>Regression: +USD12,542 ($P < 0.01$) <Charge>Regression: +USD32,383 ($P < 0.01$)	B	RCC and charge
Sheng et al. [16]	2005	Taiwan	University hospital	Admissions	Median: +TWD127,354 (363,425 vs. 165,965) ($P < 0.001$)	B	Charge
Sheng et al. [68]	2005	Taiwan	Mixed: three hospitals	Admissions	<Hospital 1>Mean: +USD5,335 (13,426 vs. 8,092) ($P < 0.001$) <Hospital 2>Mean: +USD5,058 (8,014 vs. 2,955) ($P < 0.001$)	B	Charge
Mahieu et al. [69]	2001	Belgium	University hospital	Neonates in NICU	Mean: +EUR11,750 (24,722 vs. 12,972) ($P < 0.001$)	B	Charge
Khan and Celik [70]	2001	Turkey	Tertiary hospital	Admissions	Mean: +USD442 (2,419 vs. 1,977) (*P*: not significant)	B	Charge
Leroyer et al. [71]	1997	France	Pediatric hospital	Neonates	Mean: +FRF52,192 (502,837 vs. 450,645) ($P = 0.03$)	B	Charge
Li and Wang [72]	1990	China	Specialized hospital	Surgical	Mean: +GBP290 (717 vs. 427) ($P < 0.001$)	B	Charge
Haley et al. [73]	1981	US	Mixed: three hospitals	Admissions	<Hospital A>Mean: +USD680 <Hospital B>Mean: +USD721 <Hospital C>Mean: +USD671	B	Charge
Girard et al. [74]	1983	France	University hospital	Neonates hospitalized	Mean: +FRF6,038 (25,170 vs. 19,132) ($P < 0.001$)	B	Charge
Piednoir et al. [75]	2003	France	University hospital	Child admissions	Mean: +EUR1,930 (3,097 vs. 1,167)	B	Mixed
Esatoğlu et al. [76]	2006	Turkey	Clinics	Not stated	Mean: +USD2,027 (3,907 vs. 1,524) ($P < 0.001$)	B	Unknown
Oncul et al. [77]	2002	Turkey	Teaching hospital	Burned admissions	Mean: +USD502 (579 vs. 77) ($P = 0.001$)	B	Unknown
Onen et al. [78]	2002	Turkey	Surgery clinic	Child admissions	Mean: +USD452 (963 vs. 511) ($P < 0.001$)	B	Unknown
Yalçin et al. [79]	1997	Turkey	University hospital	Not stated	Mean: +USD1,582 (2,280 vs. 698) ($P < 0.001$)	B	Unknown
Wilcox et al. [80]	1996	UK	Teaching hospital	Admissions	Mean: +GBP4,107	B	Unknown
de Clercq et al. [81]	1983	Belgium	Not stated	Admissions–ICU	Mean: +BEF1,639 (3,442 vs. 1,803)	B	Unknown
Wakefield et al. [82]	1988	US	University hospital	Admissions	Mean: +USD3,198 Median: +USD1,058	B	Unknown
Chen et al. [83]	2005	Taiwan	Tertiary hospital	Intensive care	Regression: +USD3,306 ($P < 0.05$)	C	Actual cost
Roberts et al. [84]	2003	US	Teaching hospital	Admissions	Regression: +USD15,275 ($P < 0.001$)	C	Actual cost
Noskin et al. [85]	2005	US	Mixed: 986–994 hospitals	Admissions	Regression: +USD32,856 ($P < 0.001$) Matched mean: +USD36,119 ($P < 0.001$)	C	Charge
Scheckler [23]	1980	US	Teaching hospital	Admissions	Mean: +USD636	C	Charge

Table 2 continued

Authors	Year	Country	Type of setting	Patients studied	Additional cost to HAI, if stated (infected cost vs. uninfected cost) (*P*-value)	Axis 1	Axis 2
Song et al. [86]	2003	US	University hospital	Admissions	Median: +USD81,208	C	Charge
Gray et al. [87]	1995	US	Mixed: two hospitals	Admissions—NICU	Regression: +USD25,090	C	Charge
Gavaldà et al. [24]	2006	Spain	Teaching hospital	Mixed	Mean: +EUR2,730	C	Unknown
Upton et al. [88]	2005	NZ	Specialized hospital	Surgical	Mean: +NZD45,577 (76,104 vs. 30,527) ($P < 0.001$)	D	Actual cost
Lazarus et al. [89]	2005	US	Teaching hospital	Trauma admissions	2.04 times	D	Actual cost
Dominguez et al. [90]	2001	US	Tertiary hospital	Admissions—PICU	Regression: +USD50,362 ($P < 0.001$) Matched mean: +USD32,040 (63,971 vs. 32,291)	D	RCC
Macartney et al. [91]	2000	US	Children's hospital	Child admissions	Mean: +USD45,335	D	RCC
Nelson and Dries [92]	1986	US	Not stated	Surgical	Mean: +USD6,605 (14,443 vs. 7,838)	D	RCC
Pirson et al. [93]	2005	Belgium	General hospital	Admissions	Mean: +EUR12,853 (18,288 vs. 5,440) ($P < 0.001$)	D	Charge
Watters et al. [94]	2004	Ireland	Tertiary hospital	Surgical	Mean: +GBP8,955 (11,795 vs. 2,840)	D	Charge
Taylor et al. [95]	1990	US	Teaching hospital	Surgical	Regression: +USD41,559 ($P < 0.001$)	D	Charge
Zhan and Miller [96]	2003	US	Mixed: 994 hospitals	Not stated	<Postoperative sepsis>Mean: +USD57,727 ($P < 0.001$) <Selected infection>Mean: +USD38,656 ($P < 0.001$)	D	Charge
Haley et al. [97]	1980	US	General hospital	Admissions	Mean: +USD1,018 (1,733 vs. 714)	D	Charge
Sánchez-Velázquez et al. [98]	2006	Mexico	National hospital	Intensive care	Median: +USD12,155	D	Unknown
Chaix et al. [99]	1999	France	University hospital	Medical—ICU	Mean: +USD9,275 (30,225 vs. 20,950) ($P = 0.004$) Median: +USD5,885 (24,525 vs. 17,105) ($P = 0.003$)	D	Unknown
Orrett et al. [100]	1998	Trinidad and Tobago	Tertiary hospital	Admissions	Mean: +USD1,910	D	Unknown
Vegas et al. [39]	1993	Spain	Tertiary hospital	Surgical	Mean: +USD2,850 ($P < 0.01$)	D	Unknown

USD US dollar, *EUR* Euro, *GBP* British Pound, *THB* Thai Baht, *TWD* New Taiwan dollar, *AUD* Australian dollar, *CAD* Canadian dollar, *FRF* French franc, *DEM* Deutsche Mark, *NZD* New Zealand dollar, *BEF* Belgian franc

Table 3 Number of published papers by the clarification of scope and costing method by publication year

	Publication year			*P*-value
	1980–1989 ($n = 10$)	1990–1999 ($n = 21$)	2000–2006 ($n = 58$)	
Clarification of scope				$P = 0.761$*
A and B	6 (60.0%)	8 (38.1%)	22 (37.9%)	
C	1 (10.0%)	3 (14.3%)	12 (20.7%)	
D	3 (30.0%)	10 (47.6%)	24 (41.4%)	
Costing methods				$P = 0.039$**
Cost estimates without charge data	0 (0.0%)	4 (19.0%)	16 (27.6%)	
Actual cost	0 (0.0%)	3 (14.3%)	15 (25.9%)	
RVU	0 (0.0%)	1 (4.8%)	1 (1.7%)	
Cost estimates with charge data	6 (60.0%)	6 (28.6%)	29 (50.0%)	
RCC	1 (10.0%)	2 (9.5%)	8 (13.8%)	
Charge	5 (50.0%)	4 (19.0%)	21 (36.2%)	
Unknown	4 (40.0%)	11 (52.4%)	13 (22.4%)	

* Fisher's exact test for the independence of the row of clarification of scope and publication year (3×3). The row is A and B, C, and D

** Fisher's exact test for the independence of the row of costing methods and publication year (3×3). The row is cost estimates without charge data, cost estimates with charge data, and unknown

Table 4 Times of citations per passed year by the clarification of scope and costing method by publication year

	Publication year; median (min–max)			
	1980–1989 ($n = 6$)	1990–1999 ($n = 20$)	2000–2006 ($n = 50$)	Total ($n = 76$)
Clarification of scope				
A and B	1.81 (0.25–7.14)	2.58 (0.25–8.36)	3.44 (0.63–18.86)	2.86 (0.25–18.86)
C	–	3.75 (2.64–4.87)	4.20 (1.78–12.20)	4.20 (1.78–12.20)
D	2.54 (2.54–2.54)	10.19 (0.42–40.38)	3.20 (0.60–37.00)	3.83 (0.42–40.38)
Costing methods				
Cost estimates without charge data	–	10.35 (3.17–21.55)	4.63 (0.60–18.86)	4.87 (0.60–21.55)
Actual cost	–	4.88 (3.17–21.55)	4.86 (0.60–18.86)	4.87 (0.60–21.55)
RVU	–	15.82 (15.82–15.82)	4.00 (4.00–4.00)	9.91 (4.00–15.82)
Cost estimates with charge data	1.62 (0.25–7.14)	2.58 (0.25–5.65)	3.94 (1.20–37.00)	3.48 (0.25–37.00)
RCC	2.54 (2.54–2.54)	2.58 (2.35–2.80)	4.50 (1.89–10.56)	3.30 (1.89–10.56)
Charge	0.70 (0.25–7.14)	3.59 (0.25–5.65)	3.89 (1.20–37.00)	3.53 (0.25–37.00)
Unknown	2.43 (1.81–3.05)	3.24 (0.42–40.38)	2.20 (0.63–6.25)	2.45 (0.42–40.38)

Kruskal–Wallis (A and B vs. C vs. D): $P = 0.278$

Kruskal–Wallis (cost estimates without charge data vs. cost estimates with charge data vs. unknown): $P = 0.025$

measures. The following three conclusions were derived from this study: (1) there is a large degree of variation in COHAI estimates among publications, (2) there is a large degree of variation in the transferability of these COHAI estimates among publications, and (3) there is no significant difference in citation frequency between COHAI estimates with high transferability and COHAI estimates with low transferability. In order to scientifically implement infection control measures, it is necessary to conduct cost-effectiveness and cost-saving analyses on various control measure programs. However, as this study shows the existence of variations in these estimates, on which the calculated incremental cost-effectiveness ratios (ICERs) for infection control programs are heavily dependent, this may incorporate citation bias. In the current situation where tests for the transferability of estimates are not required [2], analysts are freely allowed to cite COHAI data. As such, there is the danger that the credibility of ICERs calculated for these infection control programs may be severely compromised. As such, we feel that, in order to ensure an appropriate contribution to the infection control program decision-making process, it has become essential for researchers who estimate COHAI, analysts who use COHAI estimates for decision-making, as well as relevant journal reviewers and editors to recognize the importance of a transferability paradigm.

Various publications have previously identified barriers to the external validity of economic evaluations. Sculpher et al. [6] and O'Brien [101] identified the following factors that hinder generalizability based on data from previous studies: (1) clinical factors, (2) healthcare system factors, and (3) patient factors. Clinical factors represent the problems associated with variations among healthcare providers with regard to processes of care. As variations in clinical practice are affected by country, community, and individuals [102], economic evaluations of practice should not be directly extrapolated to other jurisdictions. However, by using the evaluation axis of the clarification of the scope of costing that we have proposed, it becomes possible to judge whether there is sufficient information necessary to evaluate the transferability of the estimates. For example, in the case of COHAI clarification of scope, descriptions in detail of the medical resource consumption amounts by processes of care (e.g., the different mean values or standard errors of the groups) between infected and uninfected groups allows readers to comparatively evaluate the process of care in their own institution with the process of care in the institution where the original evaluation was produced. It, therefore, is possible to adjust for the intrinsic differences and allow for transferability to a reader's own institution. Healthcare system factors could affect both unit costs and clinical practice. In our evaluation axis of the clarification of the scope of costing, therefore, we included not only resource consumption amounts in detail, but the unit costs as well. By specifying the unit costs used by the sample institution, readers can compare and appropriately adjust for the differences with their own institution, thereby, increasing the study's usefulness as a reference or source of applicable data. Patient factors may also influence COHAI estimates, particularly in severity biases or selection biases. While this represents an important issue in COHAI research, it is distinct from transferability, which is the focus of this paper.

In general, it is desirable for cost estimates to fulfill the Level A criteria of providing precise reports of unit costs and resource loading amounts. However, in the field of cost of illness estimates, we believe that it is more realistic to accept estimates that attain the standards of Level B, where all components of costs were described and data for costs in each component were reported. This is because providing precise data on unit costs and resource amounts used for all medications, tests, and manpower involved in medical treatment would be prohibitively extensive. Also, even in cases where medication costs are summarized in a consolidated amount, and not broken down by individual items, the inclusion of detailed information on medications would severely hamper efforts to describe unit costs and resource amounts. On the other hand, if the cost items were not sufficiently clear, other researchers would be unable to evaluate transferability. Therefore, it is essential to provide the clarification of Level B. While only one of the studies in our sample, that of Coello et al. [12], fulfilled the standards of Level A, 40% of the papers sampled were able to fulfill Level B standards, which may point to its practical usability. When elucidating the details of cost estimates, in cases subject to the limitations of space, the use of journal web sites should be maximized [103].

With regard to costing methods, it is advisable for estimates published in international journals to be based on either actual costing or RVUs. According to Shwartz et al. [11], by providing the means of individual patient cost estimates by each DRG category based on RCCs categorized by department, the errors between cost estimates based on the RVU method would be minimized, and, therefore, may secure an acceptable level of accuracy. However, as COHAI are focused on the individual costs per patient, and not per department, the accuracy of the RCC method may not be sufficient. As such, the use of RCCs and charge data to calculate estimates could be thought to be appropriate for domestic journals. According to Howard et al., while estimates based on RCCs are acceptable [104], charges are determined politically and, therefore, have high usability for other researchers in the same country using the same payment systems. On the other hand, descriptions of costing methods used were markedly scarcely, as studies whose costing methods could not be determined comprised 31.8% of the sample, which highlights a serious issue in the quality of economic evaluations. The simple reporting of "costs" without further exposition would make it difficult for readers to determine if actual costing or charges had been used. As providing the necessary details would be easy on the part of the reporting analyst, this would appear to be a negative effect caused by their insufficient recognition. After 2000, while there was a reduction in the proportion of publications with an unknown method of costing, the complete elimination of this type of study may be the most important step to increase the overall quality of economic evaluation studies.

While we observed a low citation level for studies that scored highly on the clarification of the scope of costing evaluation axis, there was a statistically higher citation level for studies that used cost estimates without charge data, which were evidently usable to other researchers. As discussions on the topic of transferability has recently started to gain momentum [5, 6, 10, 101], it is likely that its importance was not previously well understood among researchers. On the other hand, costing methods had been addressed by Finkler in his forward-thinking paper in a high-impact medical journal [105], as well as emphasized by Gold et al. [9] in their economic evaluation study, which may have had a large impact on improving the costing methods of researchers.

While there have been previous review studies focused on COHAI, this is the first paper to address the issues of the possibility of the utilization of COHAI estimates from the point of view of other researchers. Some researchers had reviewed COHAI publications and calculated the mean additional costs by infection type [2, 106]. While these studies used this data to appeal for the necessity for infection control measures, taking into account the differences among target samples, estimation methods, items included in costing, unit costs, and clinical practice leads to the conclusion that there is very little meaning in the simple aggregation and comparison among existing COHAI studies. These reviews, therefore, did not provide enough information to allow for other researchers to identify which COHAI estimates could be used in their own analyses. Few review studies have elucidated the estimation methods in COHAI. In this study, we present information to allow other researchers to identify the transferability of each paper, as well as a guide to assist researchers who intend to conduct economic evaluation studies for infection controls and decision-makers for infection control policies. In addition, our evaluation axis has a further characteristic in that it has a framework that allows for the four-layered evaluation of the degree of clarification of the scope of costing for each economic evaluation study. We believe that this will assist other researchers in gaining a greater understanding of transferability.

This evaluation of transferability was conducted based on the reported methods in each study in the sample. However, there is the possibility that the description in the methods had been simplified due to space limitations, resulting in the study being evaluated at a lower level than in reality. However, while this possibility may exist, we are convinced of the appropriateness of basing our evaluation on the reported information in this study, as other readers would only have access to the reported information. The current environment of many medical journals is such that there is a trend towards simplifying studies for the convenience of readers. However, in the case of economic evaluations, information regarding transferability would influence the value of the research, and should, therefore, be reported in greater detail.

While the Cochrane Collaboration generally advocates the use of multiple databases for searches, Sassi et al. have argued that the use of MEDLINE is the key source for reviewers of economic evaluations, and searches of other databases produces "limited additional yield" [107]. We have, therefore, decided to utilize the MEDLINE database solely in this review. Furthermore, a citation search using the ISI Web of Science database only revealed duplicates of the papers that were already identified by the MEDLINE search, thereby, supporting the use of MEDLINE as the sole database for review analysis searches. We also only included English language studies in our review. However, because of the large number of studies evaluated, we believe that our results of the evaluation of the transferability of COHAI reflect the actual stature.

As this study is an evaluation of transferability based on judgment criteria, a study which scores highly in this investigation will not necessarily score highly according to the evaluation framework for economic evaluation research developed by Drummond et al. [8]. An important component of Drummond et al.'s framework is the inclusion of an estimation sample in the evaluation sample. However, this would seem to be more related to internal validity than external validity. In contrast, the framework used in this study would result in a favorable evaluation of a study if the estimation sample has a high level of transparency, even if it did not include important costing components. Therefore, our framework alone is insufficient for evaluating the quality of economic evaluation studies, and should be used in conjunction with the guidelines as presented by Drummond et al.'s group.

This study evaluated the transferability of published studies that estimated COHAI, and the evaluation axes used here are applicable and encouraged for future use in general economic evaluation research. By improving the transferability of economic evaluations, it becomes possible to apply knowledge from each country and institution to a researcher's own country and institution, and increase the efficiency and effectiveness of related decision-making processes.

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References

1. Klevens RM, Edwards JR, Richards CL Jr, Horan TC, Gaynes RP, Pollock DA, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. Public Health Rep. 2007;122:160–6.
2. Perencevich EN, Stone PW, Wright SB, Carmeli Y, Fisman DN, Cosgrove SE. Raising standards while watching the bottom line: making a business case for infection control. Infect Control Hosp Epidemiol. 2007;28:1121–33.

3. Harbarth S, Sax H, Gastmeier P. The preventable proportion of nosocomial infections: an overview of published reports. J Hosp Infect. 2003;54:258–66.
4. Fukuda H, Imanaka Y. Assessment of transparency of cost estimates in economic evaluations of patient safety programmes. J Eval Clin Pract. 2009;15:451–9.
5. Drummond M, Barbieri M, Cook J, Glick HA, Lis J, Malik F, et al. Transferability of economic evaluations across jurisdictions: ISPOR Good Research Practices Task Force report. Value Health. 2009;12:409–18.
6. Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, et al. Generalisability in economic evaluation studies in healthcare: a review and case studies. Health Technol Assess. 2004;8:1–192.
7. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ. 1996;313:275–83.
8. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. Methods for the economic evaluation of health care programmes. New York: Oxford University Press; 2005.
9. Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine. New York: Oxford University Press; 1996.
10. Heyland DK, Kernerman P, Gafni A, Cook DJ. Economic evaluations in the critical care literature: do they help us improve the efficiency of our unit? Crit Care Med. 1996;24:1591–8.
11. Shwartz M, Young DW, Siegrist R. The ratio of costs to charges: how good a basis for estimating costs? Inquiry. 1995–1996; 32:476–81.
12. Coello R, Glenister H, Fereres J, Bartlett C, Leigh D, Sedgwick J, et al. The cost of infection in surgical patients: a case–control study. J Hosp Infect. 1993;25:239–50.
13. Plowman R, Graves N, Griffin MA, Roberts JA, Swan AV, Cookson B, et al. The rate and cost of hospital-acquired infections occurring in patients admitted to selected specialties of a district general hospital in England and the national burden imposed. J Hosp Infect. 2001;47:198–209.
14. Zoutman D, McDonald S, Vethanayagan D. Total and attributable costs of surgical-wound infections at a Canadian tertiary-care center. Infect Control Hosp Epidemiol. 1998;19:254–9.
15. Boyce JM, Potter-Bynoe G, Dziobek L. Hospital reimbursement patterns among patients with surgical wound infections following open heart surgery. Infect Control Hosp Epidemiol. 1990;11:89–93.
16. Sheng WH, Chie WC, Chen YC, Hung CC, Wang JT, Chang SC. Impact of nosocomial infections on medical costs, hospital stay, and outcome in hospitalized patients. J Formos Med Assoc. 2005;104:318–26.
17. Hollenbeak CS, Alfrey EJ, Souba WW. The effect of surgical site infections on outcomes and resource utilization after liver transplantation. Surgery. 2001;130:388–95.
18. Fabry J, Meynet R, Joron MT, Sepetjan M, Lambert DC, Guillet R. Cost of nosocomial infections: analysis of 512 digestive surgery patients. World J Surg. 1982;6:362–5.
19. Wilson AP, Hodgson B, Liu M, Plummer D, Taylor I, Roberts J, et al. Reduction in wound infection rates by wound surveillance with postdischarge follow-up and feedback. Br J Surg. 2006;93: 630–8.
20. Coskun D, Aytac J, Aydinli A, Bayer A. Mortality rate, length of stay and extra cost of sternal surgical site infections following coronary artery bypass grafting in a private medical centre in Turkey. J Hosp Infect. 2005;60:176–9.
21. Mugford M, Kingston J, Chalmers I. Reducing the incidence of infection after caesarean section: implications of prophylaxis with antibiotics for hospital resources. BMJ. 1989;299:1003–6.
22. Whitehouse JD, Friedman ND, Kirkland KB, Richardson WJ, Sexton DJ. The impact of surgical-site infections following orthopedic surgery at a community hospital and a university hospital: adverse quality of life, excess length of stay, and extra cost. Infect Control Hosp Epidemiol. 2002;23:183–9.
23. Scheckler WE. Hospital costs of nosocomial infections: a prospective three-month study in a community hospital. Infect Control. 1980;1:150–2.
24. Gavaldà L, Masuet C, Beltran J, Garcia M, Garcia D, Sirvent JM, et al. Comparative cost of selective screening to prevent transmission of methicillin-resistant *Staphylococcus aureus* (MRSA), compared with the attributable costs of MRSA infection. Infect Control Hosp Epidemiol. 2006;27:1264–6.
25. VandenBergh MF, Kluytmans JA, van Hout BA, Maat AP, Seerden RJ, McDonnel J, et al. Cost-effectiveness of perioperative mupirocin nasal ointment in cardiothoracic surgery. Infect Control Hosp Epidemiol. 1996;17:786–92.
26. Lynch W, Malek M, Davey PG, Byrne DJ, Napier A. Costing wound infection in a Scottish hospital. Pharmacoeconomics. 1992;2:163–70.
27. Reilly J, Twaddle S, McIntosh J, Kean L. An economic analysis of surgical wound infection. J Hosp Infect. 2001;49:245–9.
28. Kirkland KB, Briggs JP, Trivette SL, Wilkinson WE, Sexton DJ. The impact of surgical-site infections in the 1990s: attributable mortality, excess length of hospitalization, and extra costs. Infect Control Hosp Epidemiol. 1999;20:725–30.
29. Herwaldt LA, Cullen JJ, Scholz D, French P, Zimmerman MB, Pfaller MA, et al. A prospective study of outcomes, healthcare resource utilization, and costs associated with postoperative nosocomial infections. Infect Control Hosp Epidemiol. 2006;27: 1291–8.
30. Hollenbeak CS, Murphy DM, Koenig S, Woodward RS, Dunagan WC, Fraser VJ. The clinical and economic impact of deep chest surgical site infections following coronary artery bypass graft surgery. Chest. 2000;118:397–402.
31. Vogel TR, Diaz JJ, Miller RS, May AK, Guillamondegui OD, Guy JS, et al. The open abdomen in trauma: do infectious complications affect primary abdominal closure? Surg Infect (Larchmt). 2006;7:433–41.
32. Kasatpibal N, Thongpiyapoom S, Narong MN, Suwalak N, Jamulitrat S. Extra charge and extra length of postoperative stay attributable to surgical site infection in six selected operations. J Med Assoc Thai. 2005;88:1083–91.
33. McGarry SA, Engemann JJ, Schmader K, Sexton DJ, Kaye KS. Surgical-site infection due to *Staphylococcus aureus* among elderly patients: mortality, duration of hospitalization, and cost. Infect Control Hosp Epidemiol. 2004;25:461–7.
34. Hollenbeak CS, Alfrey EJ, Sheridan K, Burger TL, Dillon PW. Surgical site infections following pediatric liver transplantation: risks and costs. Transpl Infect Dis. 2003;5:72–8.
35. Engemann JJ, Carmeli Y, Cosgrove SE, Fowler VG, Bronstein MZ, Trivette SL, et al. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with *Staphylococcus aureus* surgical site infection. Clin Infect Dis. 2003;36:592–8.
36. Apisarnthanarak A, Jones M, Waterman BM, Carroll CM, Bernardi R, Fraser VJ. Risk factors for spinal surgical-site infections in a community hospital: a case–control study. Infect Control Hosp Epidemiol. 2003;24:31–6.
37. Hollenbeak CS, Murphy D, Dunagan WC, Fraser VJ. Nonrandom selection and the attributable cost of surgical-site infections. Infect Control Hosp Epidemiol. 2002;23:177–82.
38. Jenney AW, Harrington GA, Russo PL, Spelman DW. Cost of surgical site infections following coronary artery bypass surgery. ANZ J Surg. 2001;71:662–4.

39. Vegas AA, Jodra VM, García ML. Nosocomial infection in surgery wards: a controlled study of increased duration of hospital stays and direct cost of hospitalization. Eur J Epidemiol. 1993;9:504–10.
40. Laupland KB, Lee H, Gregson DB, Manns BJ. Cost of intensive care unit-acquired bloodstream infections. J Hosp Infect. 2006;63:124–32.
41. Blot SI, Depuydt P, Annemans L, Benoit D, Hoste E, De Waele JJ, et al. Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. Clin Infect Dis. 2005;41:1591–8.
42. Slonim AD, Kurtines HC, Sprague BM, Singh N. The costs associated with nosocomial bloodstream infections in the pediatric intensive care unit. Pediatr Crit Care Med. 2001;2:170–4.
43. Dimick JB, Pelz RK, Consunji R, Swoboda SM, Hendrix CW, Lipsett PA. Increased resource use associated with catheter-related bloodstream infection in the surgical intensive care unit. Arch Surg. 2001;136:229–34.
44. Elward AM, Hollenbeak CS, Warren DK, Fraser VJ. Attributable cost of nosocomial primary bloodstream infection in pediatric intensive care unit patients. Pediatrics. 2005;115:868–72.
45. Warren DK, Quadir WW, Hollenbeak CS, Elward AM, Cox MJ, Fraser VJ. Attributable cost of catheter-associated bloodstream infections among intensive care patients in a nonteaching hospital. Crit Care Med. 2006;34:2084–9.
46. Payne NR, Carpenter JH, Badger GJ, Horbar JD, Rogowski J. Marginal increase in cost and excess length of stay associated with nosocomial bloodstream infections in surviving very low birth weight infants. Pediatrics. 2004;114:348–55.
47. Orsi GB, Di Stefano L, Noah N. Hospital-acquired, laboratory-confirmed bloodstream infection: increased hospital stay and direct costs. Infect Control Hosp Epidemiol. 2002;23:190–7.
48. Digiovine B, Chenoweth C, Watts C, Higgins M. The attributable mortality and costs of primary nosocomial bloodstream infections in the intensive care unit. Am J Respir Crit Care Med. 1999;160:976–81.
49. Rosenthal VD, Guzman S, Migone O, Crnich CJ. The attributable cost, length of hospital stay, and mortality of central line-associated bloodstream infection in intensive care departments in Argentina: a prospective, matched analysis. Am J Infect Control. 2003;31:475–80.
50. Rello J, Ochagavia A, Sabanes E, Roque M, Mariscal D, Reynaga E, et al. Evaluation of outcome of intravenous catheter-related infections in critically ill patients. Am J Respir Crit Care Med. 2000;162:1027–30.
51. Wisplinghoff H, Cornely OA, Moser S, Bethe U, Stützer H, Salzberger B, et al. Outcomes of nosocomial bloodstream infections in adult neutropenic patients: a prospective cohort and matched case–control study. Infect Control Hosp Epidemiol. 2003;24:905–11.
52. Liu JW, Su YK, Liu CF, Chen JB. Nosocomial blood-stream infection in patients with end-stage renal disease: excess length of hospital stay, extra cost and attributable mortality. J Hosp Infect. 2002;50:224–7.
53. Abramson MA, Sexton DJ. Nosocomial methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* primary bacteremia: at what costs? Infect Control Hosp Epidemiol. 1999;20: 408–11.
54. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. JAMA. 1994;271:1598–601.
55. Cocanour CS, Ostrosky-Zeichner L, Peninger M, Garbade D, Tidemann T, Domonoske BD, et al. Cost of a ventilator-associated pneumonia in a shock trauma intensive care unit. Surg Infect (Larchmt). 2005;6:65–72.
56. Hugonnet S, Eggimann P, Borst F, Maricot P, Chevrolet JC, Pittet D. Impact of ventilator-associated pneumonia on resource utilization and patient outcome. Infect Control Hosp Epidemiol. 2004;25:1090–6.
57. Warren DK, Shukla SJ, Olsen MA, Kollef MH, Hollenbeak CS, Cox MJ, et al. Outcome and attributable cost of ventilator-associated pneumonia among intensive care unit patients in a suburban medical center. Crit Care Med. 2003;31:1312–7.
58. van Nieuwenhoven CA, Buskens E, Bergmans DC, van Tiel FH, Ramsay G, Bonten MJ. Oral decontamination is cost-saving in the prevention of ventilator-associated pneumonia in intensive care units. Crit Care Med. 2004;32:126–30.
59. Dietrich ES, Demmler M, Schulgen G, Fekec K, Mast O, Pelz K, et al. Nosocomial pneumonia: a cost-of-illness analysis. Infection. 2002;30:61–7.
60. Rosenthal VD, Guzman S, Migone O, Safdar N. The attributable cost and length of hospital stay because of nosocomial pneumonia in intensive care units in 3 hospitals in Argentina: a prospective, matched analysis. Am J Infect Control. 2005;33: 157–61.
61. Thompson DA, Makary MA, Dorman T, Pronovost PJ. Clinical and economic outcomes of hospital acquired pneumonia in intra-abdominal surgery patients. Ann Surg. 2006;243:547–52.
62. Merchant M, Karnad DR, Kanbur AA. Incidence of nosocomial pneumonia in a medical intensive care unit and general medical ward patients in a public hospital in Bombay, India. J Hosp Infect. 1998;39:143–8.
63. Kappstein I, Schulgen G, Beyer U, Geiger K, Schumacher M, Daschner FD. Prolongation of hospital stay and extra costs due to ventilator-associated pneumonia in an intensive care unit. Eur J Clin Microbiol Infect Dis. 1992;11:504–8.
64. Tambyah PA, Knasinski V, Maki DG. The direct costs of nosocomial catheter-associated urinary tract infection in the era of managed care. Infect Control Hosp Epidemiol. 2002;23: 27–31.
65. Lai KK, Fontecchio SA. Use of silver-hydrogel urinary catheters on the incidence of catheter-associated urinary tract infections in hospitalized patients. Am J Infect Control. 2002;30:221–5.
66. Givens CD, Wenzel RP. Catheter-associated urinary tract infections in surgical patients: a controlled study on the excess morbidity and costs. J Urol. 1980;124:646–8.
67. Shulkin DJ, Kinosian B, Glick H, Glen-Puschett C, Daly J, Eisenberg JM. The economic impact of infections. An analysis of hospital costs and charges in surgical patients with cancer. Arch Surg. 1993;128:449–52.
68. Sheng WH, Wang JT, Lu DC, Chie WC, Chen YC, Chang SC. Comparative impact of hospital-acquired infections on medical costs, length of hospital stay and outcome between community hospitals and medical centres. J Hosp Infect. 2005;59:205–14.
69. Mahieu LM, Buitenweg N, Beutels P, De Dooy JJ. Additional hospital stay and charges due to hospital-acquired infections in a neonatal intensive care unit. J Hosp Infect. 2001;47:223–9.
70. Khan MM, Celik Y. Cost of nosocomial infection in Turkey: an estimate based on the university hospital data. Health Serv Manage Res. 2001;14:49–54.
71. Leroyer A, Bedu A, Lombrail P, Desplanques L, Diakite B, Bingen E, et al. Prolongation of hospital stay and extra costs due to hospital-acquired infection in a neonatal unit. J Hosp Infect. 1997;35:37–45.
72. Li LY, Wang SQ. Economic effects of nosocomial infections in cardiac surgery. J Hosp Infect. 1990;16:339–41.
73. Haley RW, Schaberg DR, Crossley KB, Von Allmen SD, McGowan JE Jr. Extra charges and prolongation of stay attributable to nosocomial infections: a prospective interhospital comparison. Am J Med. 1981;70:51–8.

74. Girard R, Fabry J, Meynet R, Lambert DC, Sepetjan M. Costs of nosocomial infection in a neonatal unit. J Hosp Infect. 1983;4:361–6.
75. Piednoir E, Bessaci K, Bureau-Chalot F, Sabouraud P, Brodard V, Andréoletti L, et al. Economic impact of healthcare-associated rotavirus infection in a paediatric hospital. J Hosp Infect. 2003;55:190–5.
76. Esatoğlu AE, Agirbas I, Onder OR, Celik Y. Additional cost of hospital-acquired infection to the patient: a case study in Turkey. Health Serv Manage Res. 2006;19:137–43.
77. Oncul O, Yüksel F, Altunay H, Açikel C, Celiköz B, Cavuşlu S. The evaluation of nosocomial infection during 1-year-period in the burn unit of a training hospital in Istanbul, Turkey. Burns. 2002;28:738–44.
78. Onen A, Ciğdem MK, Geyik MF, Kökoğlu OF, Otçu S, Oztürk H, et al. Epidemiology and control of nosocomial infections in paediatric surgery. J Hosp Infect. 2002;52:166–70.
79. Yalçin AN, Hayran M, Unal S. Economic analysis of nosocomial infections in a Turkish university hospital. J Chemother. 1997;9:411–4.
80. Wilcox MH, Cunniffe JG, Trundle C, Redpath C. Financial burden of hospital-acquired *Clostridium difficile* infection. J Hosp Infect. 1996;34:23–30.
81. de Clercq H, De Decker G, Alexander JP, Huyghens L. Cost evaluation of infections in intensive care. Acta Anaesthesiol Belg. 1983;34:179–89.
82. Wakefield DS, Helms CM, Massanari RM, Mori M, Pfaller M. Cost of nosocomial infection: relative contributions of laboratory, antibiotic, and per diem costs in serious *Staphylococcus aureus* infections. Am J Infect Control. 1988;16:185–92.
83. Chen YY, Chou YC, Chou P. Impact of nosocomial infection on cost of illness and length of stay in intensive care units. Infect Control Hosp Epidemiol. 2005;26:281–7.
84. Roberts RR, Scott RD 2nd, Cordell R, Solomon SL, Steele L, Kampe LM, et al. The use of economic modeling to determine the hospital costs associated with nosocomial infections. Clin Infect Dis. 2003;36:1424–32.
85. Noskin GA, Rubin RJ, Schentag JJ, Kluytmans J, Hedblom EC, Smulders M, et al. The burden of *Staphylococcus aureus* infections on hospitals in the United States: an analysis of the 2000 and 2001 Nationwide Inpatient Sample Database. Arch Intern Med. 2005;165:1756–61.
86. Song X, Srinivasan A, Plaut D, Perl TM. Effect of nosocomial vancomycin-resistant enterococcal bacteremia on mortality, length of stay, and costs. Infect Control Hosp Epidemiol. 2003;24:251–6.
87. Gray JE, Richardson DK, McCormick MC, Goldmann DA. Coagulase-negative staphylococcal bacteremia among very low birth weight infants: relation to admission illness severity, resource use, and outcome. Pediatrics. 1995;95:225–30.
88. Upton A, Smith P, Roberts S. Excess cost associated with *Staphylococcus aureus* poststernotomy mediastinitis. N Z Med J. 2005;118:U1316.
89. Lazarus HM, Fox J, Burke JP, Lloyd JF, Snow GL, Mehta RR, et al. Trauma patient hospital-associated infections: risks and outcomes. J Trauma. 2005;59:188–94.
90. Dominguez TE, Chalom R, Costarino AT Jr. The impact of adverse patient occurrences on hospital costs in the pediatric intensive care unit. Crit Care Med. 2001;29:169–74.
91. Macartney KK, Gorelick MH, Manning ML, Hodinka RL, Bell LM. Nosocomial respiratory syncytial virus infections: the cost-effectiveness and cost-benefit of infection control. Pediatrics. 2000;106:520–6.
92. Nelson RM, Dries DJ. The economic implications of infection in cardiac surgery. Ann Thorac Surg. 1986;42:240–6.
93. Pirson M, Dramaix M, Struelens M, Riley TV, Leclercq P. Costs associated with hospital-acquired bacteraemia in a Belgian hospital. J Hosp Infect. 2005;59:33–40.
94. Watters K, O'Dwyer TP, Rowley H. Cost and morbidity of MRSA in head and neck cancer patients: what are the consequences? J Laryngol Otol. 2004;118:694–9.
95. Taylor GJ, Mikell FL, Moses HW, Dove JT, Katholi RE, Malik SA, et al. Determinants of hospital charges for coronary artery bypass surgery: the economic consequences of postoperative complications. Am J Cardiol. 1990;65:309–13.
96. Zhan C, Miller MR. Excess length of stay, charges, and mortality attributable to medical injuries during hospitalization. JAMA. 2003;290:1868–74.
97. Haley RW, Schaberg DR, Von Allmen SD, McGowan JE Jr. Estimating the extra charges and prolongation of hospitalization due to nosocomial infections: a comparison of methods. J Infect Dis. 1980;141:248–57.
98. Sánchez-Velázquez LD, Ponce de León Rosales S, Rangel Frausto MS. The burden of nosocomial infection in the intensive care unit: effects on organ failure, mortality and costs. A nested case–control study. Arch Med Res. 2006;37:370–5.
99. Chaix C, Durand-Zaleski I, Alberti C, Brun-Buisson C. Control of endemic methicillin-resistant *Staphylococcus aureus*: a cost–benefit analysis in an intensive care unit. JAMA. 1999;282:1745–51.
100. Orrett FA, Brooks PJ, Richardson EG. Nosocomial infections in a rural regional hospital in a developing country: infection rates by site, service, cost, and infection control practices. Infect Control Hosp Epidemiol. 1998;19:136–40.
101. O'Brien BJ. A tale of two (or more) cities: geographic transferability of pharmacoeconomic data. Am J Manag Care. 1997;3:S33–9.
102. Wennberg JE, Barnes BA, Zubkoff M. Professional uncertainty and the problem of supplier-induced demand. Soc Sci Med. 1982;16:811–24.
103. Jefferson T, Demicheli V, Vale L. Quality of systematic reviews of economic evaluations in health care. JAMA. 2002;287:2809–12.
104. Howard D, Cordell R, McGowan JE Jr, Packard RM, Scott RD 2nd, Solomon SL. Measuring the economic costs of antimicrobial resistance in hospital settings: summary of the Centers for Disease Control and Prevention-Emory Workshop. Clin Infect Dis. 2001;33:1573–8.
105. Finkler SA. The distinction between cost and charges. Ann Intern Med. 1982;96:102–9.
106. Stone PW, Larson E, Kawar LN. A systematic audit of economic evidence linking nosocomial infections and infection control interventions: 1990–2000. Am J Infect Control. 2002;30:145–52.
107. Sassi F, Archard L, McDaid D. Searching literature databases for health care economic evaluations: how systematic can we afford to be? Med Care. 2002;40:387–94.