Surgical site infection and costs in low- and middle-income countries: A systematic review of the economic burden

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Abstract

Background

Surgical site infection (SSI) is a worldwide problem which has morbidity, mortality and financial consequences. The incidence rate of SSI is high in Low- and Middle-Income countries (LMICs) compared to high income countries, and the costly surgical complication can raise the potential risk of financial catastrophe.

Objective

The aim of the study is to critically appraise studies on the cost of SSI in a range of LMIC studies and compare these estimates with a reference standard of high income European studies who have explored similar SSI costs.

Methods

A systematic review was undertaken using searches of two electronic databases, EMBASE and MEDLINE In-Process & Other Non-Indexed Citations, up to February 2019. Study characteristics, comparator group, methods and results were extracted by using a standard template.

Results

Studies from 15 LMIC and 16 European countries were identified and reviewed in full. The additional cost of SSI range (presented in 2017 international dollars) was similar in the LMIC ($174—$29,610) and European countries ($21—$34,000). Huge study design heterogeneity was encountered across the two settings.
Discussion

SSIs were revealed to have a significant cost burden in both LMICs and High Income Countries in Europe. The magnitude of the costs depends on the SSI definition used, severity of SSI, patient population, choice of comparator, hospital setting, and cost items included. Differences in study design affected the comparability across studies. There is need for multi-centre studies with standardized data collection methods to capture relevant costs and consequences of the infection across income settings.

Introduction

Mortality within 30 days of surgery is the third largest contributor to global deaths [1]. Surgical Site Infection (SSI) is linked to 38% of deaths in patients with SSI [2]. SSI is common, associated with increased patient morbidity and mortality [3, 4], recognised globally as a problem and shown to represent a substantial financial burden [5, 6]. In comparison to the relatively high income countries (HIC) of Western Europe, the incidence rate of SSIs is much greater in Low- and Middle-Income Countries (LMIC) [7, 8] and here the majority of the hospital care cost is borne by the patient [9]. In the LMIC setting, the risk of acquiring an SSI substantially increases the overall risk of financial catastrophe- a situation in which health care spending on this event exceeds 10% of annual household expenditure [10].

Identifying appropriate solutions to combat SSI is of global interest [6, 11, 12]. Recently completed and ongoing research studies to find the most cost-effective prevention strategies for SSI, are having mixed success [13, 14]. The majority of this research is randomised controlled trials (RCTs) with a parallel economic evaluation based in HIC [15, 16]. Plans are in place to carry out similar studies exploring cost-effective strategies to combat SSI in the LMIC setting [17]. Significant challenges hamper clinical trials in LMICs relating to lack of infrastructure and limited human resources [18]. This limits the data that can be feasibly collected in contrast to trials in HICs settings.

A cost of illness (COI) study quantifies how much society is spending on a particular disease and represents the cost burden averted if the disease was eradicated [19]. Understanding the additional cost burden imposed by the complications of surgery such as those caused by an SSI, helps to strengthen the case for identifying interventions to reduce such complications [20]. This in turn provides the justification for undertaking economic evaluations to present relevant evidence to inform the prioritization of resource allocation decisions for interventions to reduce SSI complications."

We identified five main challenges in measuring the additional costs associated with an SSI. First, different definitions of an SSI affects which patients are considered to have an SSI [21]. Second, as an SSI can manifest beyond hospital discharge, approaches for post-discharge SSI confirmation will impact SSI detection rate [22, 23]. Follow-up difficulties can be exacerbated for surgical patients in low income settings due to high out-of-pocket transportation costs in accessing healthcare [24].

Third, estimating the additional cost of SSI relies on the choice of the comparator, which is patients without SSI. Studies with a case-control design try to address potential confounding with an adjusted comparison where each of the exposure and control patients have matching confounding variables (e.g. same age, gender, surgical procedure). Yet, the choice of matching
variables should be considered carefully in case-control studies because of its impact on the efficiency and validity of the results [25].

Fourth, SSI costs are only as representative as the hospital settings used. Resource use and costs are known to differ across urban and rural settings and different patient population mixes from different surgical procedures can influence the cost of SSI, limiting the generalisability across procedures. Finally, SSIs vary in severity, and those SSIs that are severe can substantially increase costs and inpatient length of stay [26]. However, the distinction between SSI severity levels is open to subjective interpretation by the attending physician [27].

The objective of this study is to critically appraise and assess how the cost of SSI has been estimated in a range of LMIC studies and compare with a selection of high income European studies which explored similar SSI costs. European studies are included in the review to provide a reference standard for the LMIC studies. The aim of the comparison is to examine the costs associated with SSI (presented in international dollars) across the different settings and identify potential data gaps, and methodological considerations in each setting.

This paper is structured so that the review of the selection of European studies is presented in Part 1. An analogous review of the LMIC studies is presented in Part 2. Part 3 presents a comparison between the main finding of the reviews for the HIC and LMIC settings before the main discussion.

Materials and methods

The review followed the UK Centre for Review and Dissemination [28] guidelines and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [29].

Search strategy

The following electronic databases were searched from inception to 20th February 2019: EMBASE and MEDLINE In-Process & Other Non-Indexed Citations. Additional references were found using hand searching of relevant journal articles and Google scholar searches. Search terms used for each database are detailed in S1–S4 Files

Eligibility criteria

Studies were included if they considered the costs associated with SSIs in European Organisation for Economic Co-operation and Development (OECD) countries [30]. For the analogous review of LMIC, studies were included if they considered the economic impact of SSIs in LMICs. For both settings costs could be borne by the healthcare providers, patients, wider community and/or society. Eligible articles included cost analysis, partial or full economic evaluations (trial-based and model-based) and cost of illness studies in a European country or LMIC setting. Multi-country studies were included if at least one eligible country was included and the study’s findings were reported separately for that country. Non-eligible studies were those that were not published in English, conference proceedings, protocols, commentaries, and editorials.

Study selection. The titles and abstracts of the databases’ search results were screened against the eligibility criteria. A three stage categorisation process was used to determine relevant studies appropriate for inclusion, using methods described elsewhere [31]. Two investigators carried out study screening and data extraction for the LMIC search (MM & ZA). One investigator (MM) carried out all study screening and data extraction for the European literature search, and another investigator (ZA) undertook screening of a random 20% to assess agreement. Disagreements were resolved through discussion, a third independent investigator (TR) was sought where agreement could not be reached.
For each included study, data were extracted on the study characteristics, country setting, costs and resource use included, use of adjusted analyses, and the main results reported. The information was tabulated, and the issues faced by the individual studies in estimating the additional costs of SSI were compared narratively. For consistency across studies, costs were converted to international dollars and inflated to 2017, where appropriate. To improve comparability of cost findings, costs were adjusted by their country’s Purchasing Power Parity (PPP) conversion factor [32]. Where a country did not have a PPP conversion factor, an implied PPP conversion factor from the IMF was used instead [33]. For inflation purposes, studies without a specified cost year were assumed to be the last year of data collection.

All included studies were assessed by a modified reporting Müller checklist (translated into English) for COI studies and scored by their inclusion of relevant items [34]. A study scored one on each aspect they had described or justified out of a possible maximum score of 36. The checklist for each study is available upon request.

Results and discussion

Part 1: European literature search

The electronic database search for the European studies yielded 588 citations. Fig 1 presents a flow diagram of the selection process. Sixteen studies met the inclusion criteria.

General study characteristics. The sixteen studies were published from 1992 to 2018 and data collection spanned 1987 to 2016. Studies were based in England (n = 6) [35–40], Spain (n = 2) [41, 42], Scotland (n = 2) [43, 44], Finland (n = 1) [45], France (n = 1) [46], Switzerland (n = 1) [47], Belgium (n = 1) [48], Denmark (n = 1) [49] and Germany (n = 1) [50]. Table 1 shows general characteristics of each study included in the review.

Definition of SSI. SSI was defined using the Center of Disease Control (CDC) guidelines in most of the studies [35, 37, 38, 41, 42, 45, 46, 50]. Other strategies for SSI confirmation included using a microbiological test [36, 39] or if a patient required antibiotic treatment for wound problems [40, 49]. Lynch et al [43] defined an SSI based on pus discharge or a wound with a score of greater than ten on ASEPSIS, a scoring mechanism for postoperative SSI [51]. Reilly et al [44] defined an SSI as pus or painful skin inflammation indicative of cellulitis.

Patients were followed-up for the occurrence of SSI for at least 30 days [35, 41, 43, 44] with two studies following up SSI patients until the wound had healed [37, 45]. Approaches to diagnose post-discharge SSI included outpatient clinics or primary care visits [41, 44, 45], surveys/questionnaires, [35, 43] or a home visit [37].

Patient matching. An imbalance of patient characteristics can bias and confound the cost calculation of SSI patients. This is analogous to an observational non-RCT setting where the difference in outcomes may be partially or wholly explained by factors other than the presence of SSI. Some form of patient matching in the analysis to adjust for confounding variables was used in most studies [35, 36, 38, 39, 41, 42, 46–48, 50]. However, justification for the selected matching variables was given in less than half of these studies [36, 38, 39, 41, 48].

Setting & procedure. Public teaching hospitals [35–37, 39–43, 46, 47, 50] were the setting for majority of the studies with one hospital setting unclear [44], and another study referring to unspecified referral hospitals [45]. Study settings were mostly restricted to a single site with only four studies involving multiple hospitals [38, 45, 48, 49]. Surgical procedures ranged from general surgery or multiple surgery categories (n = 8), cardiothoracic (n = 1), colorectal (n = 2), gynaecological (n = 1), and orthopaedic (n = 4). The patient population were all adult patients.

Half the studies that assessed SSI across surgical categories reported surgery category-specific costs associated with SSI [35, 43, 44, 47]. All of these studies showed variation of SSI costs
across surgical categories. Severity of SSI was always associated with increased costs. A deep SSI was more costly compared to a superficial SSI in all studies that had severity-specific SSI costs [39, 47, 49]. Yet, the stated approaches to classify the superficial versus deep SSI differed. Approaches to define superficial SSI included CDC criteria [49], or a treatment for an
Table 1. European study characteristics.

| Lead author (Year) | Country    | Patient population                         | Setting                           | Study aim                                                                                                                                                                                                 | Type of study                  | Number of SSI & Comparator | Period of data collection |
|-------------------|------------|---------------------------------------------|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|---------------------------|---------------------------|
| **Cardiothoracic surgery** |            |                                             |                                   |                                                                                                                                                                                                         |                               |                          |                           |
| Graf (2010) [50]  | Germany    | CABG patients                               | University hospital               | Calculate the costs of deep sternal wound infection                                                                                                                                                    | Case-control study            | 17 SSI/ 34 Non-SSI        | 2006–2008                |
| **Colorectal surgery** |            |                                             |                                   |                                                                                                                                                                                                         |                               |                          |                           |
| Tanner (2009) [37] | England    | Adult colorectal patients                   | University hospital               | Provide an accurate cost for treating patients with SSI                                                                                                                                               | Surveillance study             | 29 SSI/ 76 Non-SSI        | 2008                     |
| Turtiainen (2010) [45] | Finland    | Vascular surgery patients                   | Four secondary referral hospitals | Calculate the extra cost of services needed to treat SSI                                                                                                                                               | Prospective observational study | 49 SSI /136 Non-SSI      | 2007–2008                |
| **Multiple surgical categories** |            |                                             |                                   |                                                                                                                                                                                                         |                               |                          |                           |
| Alfonso (2007) [41] | Spain      | Adult patients                              | General, tertiary hospital        | To identify overall costs generated by SSI patients                                                                                                                                                  | Cost of illness study         | 30 SSI/ 52 non-SSI        | 2001–2005                |
| Defez (2008) [46]  | France     | Acute care patients                         | University hospital               | Calculate the additional costs of nosocomial infection:                                                                                                                                              | Prospective cohort study      | 21 SSI/21 non-SSI         | 2001–2003                |
| Jenks (2014) [35]   | England    | Patients who underwent major surgical procedures | University hospital              | Determine the clinical and economic burden of SSI                                                                                                                                                  | Cost analysis                 | 282 SSI/ 14,018 non-SSI  | 2010–2012                |
| Lynch (1992) [43]   | Scotland   | Adult surgical patients                     | Teaching hospital                 | Study the cost of SSI                                                                                                                                                                                | Cost analysis                 | 513 SSI/ 2969 non-SSI    | 1987–1989                |
| Reilly (2001) [44]  | Scotland   | Surgery patients                            | Unspecified hospital              | Quantify the cost of SSI to the hospital, community, and patient                                                                                                                                     | Prospective cohort study      | 220 SSI/1982 non-SSI     | 1995–1999                |
| Vegas (1993) [42]   | Spain      | General surgery and digestive surgery patients | University hospital              | Estimate the length of stay of SSI patients                                                                                                                                                         | Prospective cohort study      | 106 SSI/ 212 non-SSI     | 1990                     |
| Vrijens (2012) [48] | Belgium    | Acute care patients                         | Acute care hospitals in Belgium   | Estimate the total economic cost of infection to the public healthcare provider                                                                                                                          | Retrospective cohort study    | 77 SSI/ 261 non-SSI      | 2007                     |
| Weber (2008) [47]   | Switzerland | Traumatology, visceral and vascular surgery patients | University hospital              | Quantify the economic burden of SSI                                                                                                                                                                  | Retrospective cohort study    | 168 SSI/168 non-SSI      | 2000–2001                |
| **Gynaecological surgery** |            |                                             |                                   |                                                                                                                                                                                                         |                               |                          |                           |
| Hyldig (2018) [49]  | Denmark    | Obese women after caesarean section         | 5 obstetric departments across 2 tertiary & 3 teaching hospitals | Evaluate the cost-effectiveness of incisional negative pressure wound therapy in preventing SSI                                                                                                         | Within trial cost effectiveness analysis | 57 SSI/780 non-SSI        | 2013–2016                |
| **Orthopaedic surgery** |            |                                             |                                   |                                                                                                                                                                                                         |                               |                          |                           |
| Edwards (2008) [40] | England    | Hip fracture patients                       | University hospital               | Estimate the cost of treating SSI                                                                                                                                                                     | Retrospective cohort study    | 80 SSI/ 80 non-SSI        | 1999–2004                |
| Pollard (2006) [36] | England    | Proximal femoral fracture surgery patients over 65 years | Tertiary teaching hospital | Assess the financial burden of deep SSI after surgery                                                                                                                                               | Retrospective cohort study    | 61 SSI/ 122 non-SSI      | 1998–2003                |
| Parker (2018) [38]  | England    | Lower limb open fracture patients           | 24 specialist trauma hospitals    | Estimate economic outcomes associated with deep SSI                                                                                                                                                 | Costing analysis of a prospective RCT | 35 SSI/ 423 non-SSI      | 2012–2015                |
| Thakar (2010) [39]  | England    | Proximal femoral fracture patients          | Tertiary teaching hospital        | Calculate the additional hospital costs due to complications                                                                                                                                         | Prospective cohort study      | 46 SSI/ 92 non-SSI       | 2003–2008                |

All costs were inflated and converted to 2017 international dollars where appropriate

NNIS, Nosocomial Infection Surveillance System risk index; SSI, Surgical Site Infection;
infection at the surgical site within 30 days postoperatively [47], or were not defined [39]. Approaches to classify a deep SSI included a microbiological confirmation of tissue from a further surgery [39], or an SSI requiring surgery [47] or using CDC criteria [49]. The sample size of SSI patients in the European studies ranged from as low as 17 patients to as high as 513 patients.

Cost components. The type of costs included and considered in each of the studies is shown in Table 2 and S1 Table. All studies considered at least some form of direct medical costs in their cost calculations. However, there was a considerable variation in the description and the number of direct medical cost items included in each study. In terms of the costs arising from the initial hospitalization of patients, the description of the included cost components ranged from an unspecified cost per bed day to a comprehensive bottom up costing of the hospital length of stay, consumables, diagnostics, overhead, reoperation and staffing costs. Non-hospital costs were also considered in some of the studies including post-discharge costs from general practitioner/nurse visits [37, 41, 43, 44], and patient/community costs of wound dressings.

To facilitate a cost comparison across studies a specified year for which the costs are applicable allows for the findings to be inflated correctly. The cost year was not stated in six studies [35, 40, 43, 45, 46, 50]. Transparency on the amount that each cost component is contributing to the additional cost of SSI clarifies which aspects of medical care are driving the additional cost burden. However, the additional cost of SSI was not broken down into their cost components in seven studies [36, 38, 42, 45, 47, 49].

All but one study restricted costs to the perspective of the health care payer. Alfonso et al [41] widened the perspective to societal and looked at direct and indirect costs associated with SSI including hospital, primary care, informal care, and productivity loss.

Resource use. The reporting of resource use of SSI and non-SSI patients was inconsistent across studies. Beyond the main resource item of hospital length of stay, there was little detail on the differential resource use of SSI and non-SSI patients. Alfonso et al [41] (Spain) reported that patients with an SSI had significantly longer durations of use for hospital consumables (catheters, and antibiotics) compared with patients without an SSI. However, resource use details were omitted on general practitioner/nurse visits and the level of informal care needed. Reilly et al [44] (UK) presented a breakdown of resource use for SSI patients only.

Cost of surgical site infection. Overall there was a lack of detail in the reporting of costs for SSI and non-SSI patients. Average costs of both the respective SSI and non-SSI patients groups were omitted for the majority of studies [37, 41, 42, 44–49].

Lynch et al [43] had the lowest relative magnitude of cost difference with SSI costs being 1.73 times higher than non-SSI costs. The authors had estimated the costs of SSI and non-SSI patients as $3,678 and $2,116 respectively [43].

Pollard et al [36] reported the highest relative magnitude of cost difference with SSI costs being 3.39 times higher than non-SSI costs. For elderly proximal femoral fracture surgery patients, they had estimated the costs of SSI and non-SSI patients to be $44,157 and $13,043 respectively. Their inclusion criteria meant that the SSI patients were those who specifically needed further surgery, representing an upper estimate of the additional costs of an SSI.

While all eligible studies had to present a cost difference between SSI and non-SSI patients, there was a lack of reporting of the average costs for the SSI and non-SSI patient groups used to calculate the difference (Table 2). All studies showed an elevated cost of SSI relative to non-SSI patients. The additional medical costs of SSI, which included costs incurred by the hospital and health system, ranged from $21 to $34,001 per patient.

The lowest additional cost associated of SSI was estimated in a Danish study assessing the cost-effectiveness of incisional negative pressure wound therapy in obese women after
## Table 2. Costs of SSI in European studies.

| Lead author (Year) | Adjusted group comparison | Costs included | Average cost | Average costs | Additional cost | Length of Stay |
|-------------------|---------------------------|----------------|--------------|---------------|----------------|----------------|
| **Cardiothoracic surgery** | | | | | | |
| Graf (2010) [50] | Age, sex, DRG, preoperative LOS | Surgery, lab tests, hospital LOS | $50,912 | $18,751 | $32,161 | SSI: 34.4 days  
Non-SSI: 16.5 days |
| **Colorectal surgery** | | | | | | |
| Tanner (2009) [37] | Unadjusted analysis | Hospital stay, nurse & GP visits, outpatient clinic, wound dressing, readmissions, antibiotics, wound swab | Not reported | Not reported | $18,101 | SSI: Extra 22.72 days  
Non-SSI not reported |
| Turtiainen (2010) [45] | Unadjusted analysis | LOS, Outpatient clinic and rehabilitation | Not reported | Not reported | $4,237 | Not reported |
| **Multiple surgical categories** | | | | | | |
| Alfonso (2007) [41] | Age, sex, diagnosis, surgery duration, comorbidity, and procedure | Hospital Stay, readmission, diagnostics, antibiotics informal care, primary care, productivity loss | Not reported | Not reported | Health care costs: $15,263 | SSI pre-discharge: 23.73 days  
Informal care: $15,734  
SSI post-discharge: 12.99 days  
Societal costs: $145,336  
No SSI: 9.45 days |
| Defez (2008) [46] | Age, sex, ward type, principal diagnosis | Hospital stay, laboratory tests, radiology, surgery, diagnostics, & antibiotics | Not reported | Not reported | $2,780 | Not reported |
| Jenks (2014) [35] | Surgery, age and NNIS risk index | Overhead, staffing costs, readmission, reoperation, hospital stay, diagnostics, consumables | $12,928 | $5,837 | $5,239 | SSI: 19 days  
Non-SSI 5 days |
| Lynch (1992) [43] | Unadjusted comparison | GP visits, wound dressings, antibiotic costs, hospital stay | $3,678 | $2,116 | $1,563 | No overall figures reported |
| Reilly (2001) [44] | Unadjusted comparison | Hospital stay, readmissions, GP and nurse visits, wound dressings, antibiotic prescriptions | Not reported | Not reported | $541 | Not reported |
| Vegas (1993) [42] | Diagnosis, procedure, age | Hospital stay | Not reported | Not reported | $10,688 | SSI: extra 14.33 days |
| Vrijens (2012) [48] | Destination after discharge, hospital, comorbidity, ward, Age, DRG | Hospital stay | Not reported | Not reported | $3,149 | SSI: 35.2 days  
Non-SSI: 29.2 days |
| Weber (2008) [47] | Age, procedure, and NNIS risk | Antibiotic use, postoperative LOS, hospital costs and patient charges | Not reported | Not reported | Overall: $17,060  
Superficial $2,226  
Deep incisional: $3,801  
Organ space: $34,001  
Non-SSI: 12.3 days | |
| **Gynaecological surgery** | | | | | | |
| Hyldig (2018) [49] | Unadjusted analysis | Inpatient stays, outpatient care, antibiotic treatment, postoperative dressing, primary care visits | Not reported | Not reported | Superficial SSI: $21  
Deep SSI: $9,527 | Not reported |
| **Orthopaedic surgery** | | | | | | |
| Edwards (2008) [40] | Unadjusted analysis | Inpatient stay, equipment, surgery consumables and staff salaries, investigations, medication, antibiotics | $49,290 | $17,060 | $32,229 | SSI: 76 days  
Non-SSI not reported |

(Continued)
caesarean section. In addition to the cost-effectiveness results, the study also provided a per-patient cost of superficial SSI and deep SSI compared with patients who did not suffer an SSI. The superficial SSI was defined as requiring antibiotic treatment for an infection at the surgical site within the first 30 days after the caesarean section and not requiring further surgery. The highest additional health care cost associated with SSI was estimated by Weber et al [47]. While the average additional cost of all SSI patients was $17,060, an organ space SSI approximately doubled the additional cost of an SSI in their case-control designed study.

Alfonso et al [41] (Spain) was the only study to adopt a broader societal perspective and included the cost of productivity loss, informal care and health care costs. They estimated the cost associated with SSI to be an additional $145,366 per patient. This estimate comprised productivity costs (78.7%) with carer costs (10.8%) and health costs (10.5%) making up the remainder. Including only the health care costs made the additional cost of SSI $15,733 per patient.

Checklist. All studies were compared against a modified reporting Müller COI study checklist (see S1 Table for scores). Alfonso et al [41] achieved the highest number of items (23 points) in the checklist with detailed descriptions of the methods used to estimate the additional costs of SSI. Turtainen et al [45] achieved the lowest score (11 points) in the checklist with little to no description in the study on what was included in the SSI cost estimate and how it was derived. In general, studies scored relatively poorly in the evaluation methods and presentation of results section of the checklist but highly in the discussion and conclusions sections.
Part 2: LMIC literature search

The LMIC studies electronic database search yielded 2,557 citations. Five additional records were identified through hand searching references of included papers. Fig 2 presents a flow diagram of the selection process. Fifteen studies met the inclusion criteria.

General study characteristics. The fifteen studies were published from 2003 to 2018 and data collection spanned 1999 to 2015. Studies were based in Turkey (n = 3) [52–54], China (n = 2) [55, 56], Jordan (n = 2) [57, 58], Thailand (n = 2) [59, 60], Brazil (n = 1) [61], Egypt
(n = 1) [62], India (n = 1) [63], Mexico (n = 1) [64], Rwanda (n = 1) [65], and South Africa (n = 1) [66]. According to the World Bank classifications, the studies were part of the following income groups: Low Income Country (n = 1) [65], Lower Middle Income (n = 2) [62, 63] and Upper Middle Income (n = 12) [52–61, 64, 66]. Table 3 shows general characteristics of each study included in the review.

**Definition of SSI.** The Center of Disease Control guidelines were used in the majority of the studies to define an SSI [52–57, 61–64, 66]. However, three studies lacked a definition of what constituted a SSI [59, 60, 65]. One study classified a SSI based on the wound discharge culture or other SSI suggestive signs and symptoms but these were not elaborated further [58].

Post-discharge SSIs cannot be detected where there is no follow-up. In this review, patients were not followed up after hospital discharge or it was not indicated in many of the studies [55, 56, 58–61, 63, 65, 66]. Where follow-up was specified, it was only recorded if the patient happened to return to the index hospital in two studies [54, 57]. The only specified method of follow-up in the studies was attendance of an outpatient clinic attendance a month after the patient’s operation [52, 54, 62, 64].

**Patient matching.** When estimating the additional cost burden of SSI, most of the studies did not make any adjustments in the comparison with non-SSI patients or it was unclear if adjustment had been used (Table 3). Justification on the inclusion of the patient matching variables was only given in one of the six studies where patient matching was utilised [56].

**Setting & procedure.** The setting where the findings are derived from were mainly public teaching hospitals [41, 52, 57–64, 66] with three based in private hospitals [53–55, 63]. All the studies were based in single centres. Surgical procedures ranged from general surgery or multiple surgical categories (n = 5), oncological procedures (n = 4), cardiothoracic (n = 2), orthopaedic (n = 1), gastric (n = 1), general, cardiac and neurosurgery (n = 2). The patient population was broader in the LMIC studies and varied from children (n = 2), adults (n = 12) and pregnant women (n = 1). For the studies with SSI patients taken from multiple surgical categories, none reported costs of SSI by surgical category. SSI severity increased the additional cost of SSI [54, 56]. A subgroup analysis of one study had low sample sizes for the superficial (n = 13), subcutaneous (n = 6) and deep soft SSIs (n = 1) [53]. Another study compared the severity of infections in three different types of surgical procedure, however, the reported cost was for all cases [64].

In general, studies tended to have a low number of SSI patients with the sample size of SSI patients in each study ranging from 4 patients [60, 63] to 106 patients [57]. Six studies had twenty or fewer SSI patients [52, 53, 56, 59, 60, 63].

**Cost components.** All studies estimated direct medical costs (Table 4). The lack of follow-up of patients beyond discharge limited most of the studies to report only inpatient hospital costs. One study had attempted to measure the direct non-medical costs, however the authors did not report it as a cost of an SSI [65]. Most studies did not report the relevant year for the cost estimation (S2 Table). The majority of studies did not break down the extent to which each cost component makes up the costs of SSI and non-SSI patients. Where cost components were reported in studies, it either included both SSI and non-SSI patients [55, 59, 65] or was limited to only SSI patients [53, 54, 61].

**Resource use.** There was no reporting of resource use of SSI and non-SSI patients beyond hospital length of stay in any of the studies. There was partial reporting on the additional procedures or investigations for SSI [54, 61] but no detail on the total resource use by SSI and non-SSI patients.

**Cost of surgical site infection.** The additional cost of SSI varied considerably across the studies. All but one study showed an elevated cost of SSI relative to non-SSI patients. The study by Özmen et al [52] (Turkey) study looked at outcomes of patients after elective gastric...
### Table 3. LMIC study characteristics.

| Lead author (Year) [Income Group] | Country | Patient population | Setting | Study aim | Type of study | Number of SSI & Comparator | Period of data collection |
|-----------------------------------|---------|---------------------|---------|-----------|--------------|---------------------------|--------------------------|
| **Cardio-thoracic surgery**       |         |                     |         |           |              |                           |                          |
| Al-Zaru (2011) [57] [Upper Middle Income] | Jordan | CABG adult patients | Teaching hospital | Assess clinical & economic impact of SSIs | Retrospective comparative study, cost estimation | 106 SSI/ 525 Non-SSI | 2005–2008 |
| Coskun (2005) [54] [Upper Middle Income] | Turkey | CABG adult patients referred back with Sternal SSI | Private hospital | Evaluate costs & outcomes for Sternal SSI | Prospective surveillance | 88 SSI/88 Non-SSI | 1999–2002 |
| **General Surgery or multiple surgical categories** |         |                     |         |           |              |                           |                          |
| Dramowski (2016) [66] [Upper Middle Income] | South Africa | Paediatric surgery, orthopaedics and urology patients | Teaching hospital | Investigate burden & risk factors of HAI | Prospective surveillance | 21 SSI/ 1022 Non-SSI | 2014–2015 |
| Galal (2011) [62] [Lower Middle Income] | Egypt | Surgery patients 21–60 years | Teaching hospital | Compare different sutures for SSI reduction | Prospective randomised double blind study | 50 SSI/400 Non-SSI | Not reported |
| Porras-Hernández (2003) [64] [Upper Middle Income] | Mexico | Neurological, cardiovascular & general surgery patients, younger than 18 years | Tertiary teaching paediatric hospital | Determine the incidence of SSI | Prospective study | 80 SSI / 348 Non-SSI | 1998–1999 |
| Siribumrungrongwong (2015) [60] [Upper Middle Income] | Thailand | Varicose Vein patients | Teaching hospital | Economic evaluation of interventions for great saphenous vein ablation | Prospective cohort study / economic analysis | 4 SSI / 73 Non-SSI | 2011–2013 |
| Tiwari (2013) [63] [Lower Middle Income] | India | Adult patients with at least 48 hours hospital stay | Private tertiary care hospital | Assess the costs associated with HAI | Retrospective comparative study / cost analysis | 4 SSI / 104 Non-SSI | 2008–2009 |
| **Gastrointestinal surgery**      |         |                     |         |           |              |                           |                          |
| Liu (2018) [56] [Upper Middle Income] | China | Colorectal cancer adult patients who had tumour surgically removed | Tertiary public hospital | Economic burden caused by HAI | Retrospective surveillance / cost analysis | 20 SSIs/ 38 Non-SSI | 2015 |
| Özmen (2016) [52] [Upper Middle Income] | Turkey | Elective gastric surgery cancer patients | Teaching hospital | Factors affecting SSI rate after elective gastric cancer surgery | Prospective observational cohort study | 10 SSI / 42 Non-SSI | 2013 |
| Phothong (2015) [59] [Upper Middle Income] | Thailand | Patients with sigmoid cancer | Teaching hospital | Outcomes and treatment costs following a sigmoidectomy | Retrospective review / Economic analysis | 6 SSI / 44 Non-SSI | 2008–2013 |
| Silverstein (2016) [65] [Low Income] | Rwanda | Biliary disease surgery patients | Referral military hospital, secondary and tertiary care | Laparoscopic cholecystectomy versus an open approach | Economic analysis / Cohort study | Not reported | Not reported |
| **Gynaecological Surgery**        |         |                     |         |           |              |                           |                          |
| Kösüş (2009) [53] [Upper Middle Income] | Turkey | Women who had caesarean surgery | Private hospital | Trial on the prevention of post-caesarean wound infection | Randomised prospective study | 38 SSI / 76 Non-SSI | 2004–2007 |
| **Cardio & Neurological surgery** |         |                     |         |           |              |                           |                          |
| Zhou (2015) [55] [Upper Middle Income] | China | Patients who had a cranioencephalic operation | Tertiary care hospital | Cost-benefit analysis of SSI control | Prospective study / economic analysis | 12 SSI / 588 Non-SSI | 2009–2012 |
| Hweidi (2018) [58] [Upper Middle Income] | Jordan | Adult patients who had a cranioencephalic operation | Teaching hospital | Estimate the additional healthcare costs attributable to SSI | Retrospective case control study | 32 SSI / 32 NonSSI | 2009–2015 |
| **Orthopaedic surgery**           |         |                     |         |           |              |                           |                          |
| Dal-paz (2010) [61] [Upper Middle Income] | Brazil | Total knee arthroplasty patients | Tertiary level teaching hospital | Estimate the additional cost of nosocomial infections | Retrospective observational cohort study / cost analysis | 34 SSI / Non-SSI cases not reported | 2006–2007 |

All costs were inflated and converted to 2017 international dollars where appropriate.

CABG, Coronary Artery Bypass Graft; HAI, Hospital Acquired Infection; SSI, Surgical Site Infection;

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Table 4. Costs of SSI in LMIC studies.

| Lead author (Year) | Adjusted group comparison | Costs included | Average cost SSI patients | Average costs Non-SSI patients | Additional cost of SSI | Length of Stay |
|--------------------|---------------------------|----------------|---------------------------|-------------------------------|-----------------------|----------------|
| **Cardio-thoracic surgery** | | | | | | |
| Al-Zaru (2011) [57] | Unadjusted comparison | Hospital stay, medications, radiology, microbiological & lab tests | $31,666 | $22,329 | $9,337 | SSI: 16.7 days Non-SSI: 7.8 days |
| Coskun (2005) [54] | Age & sex | Medication, examination and lab test, hospital stay, additional operation | Not reported | Not reported | Deep: $23,408 Superficial: $12,782 | Deep SSI: Extra 35 days Superficial SSI: Extra 21 days |
| **General surgery** | | | | | | |
| Dramowski (2016) [68] | Age, ward, preoperative length of stay | Hospital length of stay, laboratory investigations, radiology and pharmacy cost | Not reported | Not reported | $1,546 | SSI median excess days: 4 days Non-SSI: not reported |
| Galal (2011) [62] | Unadjusted comparison | Hospital stay | $2,465 | $610 | $1,855 | SSI: 7.10 days Non-SSI: 3.39 days |
| Porras-Hernández (2003) [64] | Unadjusted comparison | Hospital stay (excluding antibiotics) | Not reported | Not reported | $2,164 | SSI: 13 days Non-SSI: 6 days |
| Siribumrungwong (2015) [60] | Not reported | Unspecified hospital costs | Not reported | Not reported | $174 | Not reported |
| Tiwari (2015) [63] | Matched groups of HAI and non-HAI by age, diagnosis, illness severity | Consumables, hospital room, medications, investigations, blood components, consultation | $37,295 | $7,685 | $29,610 | SSI: Not reported Non-SSI: 9 days |
| **Gastrointestinal surgery** | | | | | | |
| Liu (2018) [58] | Age, sex, comorbidity, disease, and prior surgeries | Medication, equipment & supplies, diagnostics | Not reported | $11,691 | Overall: $1,410 Superficial: $462 Subcutaneous SSI: $2,386 Deep soft SSI: $17,094 | SSI: Not reported Non-SSI: 22 days (median) |
| Özmén (2016) [52] | Unadjusted comparison | Hospital stay | $4,195 | $4,872 | SSI patients had lower costs | SSI: 5.27 days Non-SSI: 5.40 days |
| Phothong (2015) [59] | Unadjusted comparison | Room charges, theatre time, medication, anaesthesia, equipment & laboratory charges & nursing | $12,109 | $5,960 | $6,149 | SSI: 23.5 days Non-SSI: 9.8 days |
| Silverstein (2016) [65] | Not reported | Unclear | Not reported | Not reported | $16,676 | Not reported |
| **Cardio & Neurological surgery** | | | | | | |
| Zhou (2015) [55] | Age, sex, operation type, incision type, operation date, & physical status | Medication, equipment, lab test, treatment, exams and additional surgeries | $16,979 | $10,240 | $6,739 | SSI: 29 days Non-SSI: 17.25 days |
| Hweidi (2018) [58] | Age, sex, index diagnosis, admission month | Length of stay, antibiotics, reoperation | $15,247 | $19,574 | $4,329 | SSI: 30.15 days Non-SSI: 6.98 days |
| **Gynaecological surgery** | | | | | | |
| Koçüş (2009) [53] | Unadjusted comparison | Preventative antibiotics, hospital readmission and outpatient | $1,736 | $0 | $1,736 | Two SSI patients had 7 days readmission. None for Non-SSI patients |
| **Orthopaedic surgery** | | | | | | |
| Dal-paz (2010) [61] | Unadjusted comparison | Hospital stay, lab and imagining test, additional operations and antibiotics | Not reported | Not reported | $3,865 | SSI: Extra 29.7 days Non-SSI not reported |

All costs were inflated and converted to 2017 international dollars where appropriate.

CABG, Coronary Artery Bypass Graft; HAI, Hospital Acquired Infection; SSI, Surgical Site Infection;

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cancer surgery and found that the unspecified hospital costs were non-significantly lower for superficial SSI patients compared to non-SSI patients. The calculations behind the lower SSI cost was unclear given that overall hospital costs were higher than either of the mean costs of the patient groups (SSI and non-SSI).

The additional cost of SSI ranged from $174 (Thailand) [60] to $29,610 (India) [63]. The lowest additional cost of SSI was from a study by Siribumrungwong et al [60]. Their SSI cost was made up of undefined hospital costs of four SSI patients with no detail of the non-SSI comparator group. The highest additional cost of SSI was from a study by Tiwari et al [63]. For their four patients who suffered an SSI, drug acquisition costs, length of stay and antimicrobial drugs were the main cost drivers.

Clarity on the relative magnitude of difference in cost between SSI and non-SSI patients was mixed. Half of studies did not present average costs of both SSI and non-SSI patients. The lowest relative magnitude of difference in reported costs was in Jordan where SSI costs were 1.4 times higher than non-SSI costs [59]. However, it is unclear what cost items are the major contributors of the additional costs. They had estimated the costs of SSI and non-SSI patients as $31,666 and $22,329, respectively. The highest relative magnitude of difference in costs was in India where Tiwari et al [63] found that SSI costs were 4.8 times higher than non-SSI costs [63]. The authors had estimated the costs of SSI and non-SSI patients as $37,295 and $7,685 respectively.

Checklist. For the COI checklist, the studies achieved on average a score of 11.07 out a maximum of possible score of 36. The lack of a stated perspective and cost year reduced the scores of many of the LMIC studies. Dramowski et al [66] scored the highest number of items (16) in the discussion and conclusion. The lack of description of pertinent study items meant that Porras-Hernández et al [66] scored the lowest (6).

Part 3: Comparison between HIC European countries and LMICs

The CDC criteria were used for SSI diagnosis by most studies in both settings. The biggest methodological difference between the HIC and LMIC settings was the use of adjusted analyses for comparing SSI and non-SSI patients. Most European studies used patient matching while the opposite was true for LMIC studies. Multicentre study settings were only present in the European studies. Slightly more European studies had follow up beyond discharge but the follow-up methods varied. Sample sizes of SSI patients tended to be higher in the European studies. On the other hand, LMIC studies had marginally better reporting of the average costs of the SSI and non-SSI patient groups.

For the COI reporting checklist, the European studies achieved a higher score on average compared with the LMIC studies. In both settings, studies tended to score highly in the discussion and conclusion checklist but poorly on the evaluation methods and result presentation sections.

Statement of principal findings. This review assessed the estimated the cost burden of SSIs in the reported literature for both LMICs and a selection of European High Income Countries.

For medical costs, the additional cost of SSI was $21 to $34,000 in European studies while the additional cost attributed to SSI ranged from $174 to $29,610 in LMICs. The huge range of costs in both settings reflects the difficulty associated with accurately estimating the costs attributable to SSI and consequently limited cross-study comparability of findings. Five main challenges to the estimation of the costs are summarised below:
1. **Time horizon and follow-up**: Studies from both settings used the CDC criteria to define SSI, but the lack of follow-up in LMIC studies failed to meet the recommended time needed to detect an SSI. According to the CDC, the specified time horizon for an SSI to occur is up to 30 days post-surgery for non-implant operations and up to 12 months for implant operations. Where no follow-up exists, there is a risk of underestimating the true number of SSI patients and skewing the cost burden information to only patients with an inpatient SSI. The type of follow-up method will affect the detection rate but this was rarely mentioned in studies. Inadequate IT infrastructure in LMIC healthcare systems has been implicated as the cause of poor follow up through health care pathways [67].

2. **The choice of comparator** was important in the estimating the additional cost burden of SSI. Most LMIC studies did not use any adjustments for potential confounders which risked producing a false estimation (overestimate or underestimate) of SSI costs due to an imbalance in the characteristics of the comparators. For example, some of the differences in costs between SSI patients and non-SSI patients could be due to greater levels of comorbidity in one group, causing a higher estimated additional cost for SSI than may otherwise be true. In contrast, the majority of the European studies did make adjustments for potential confounders but few gave justification for the included matching variables. Proper consideration of matching variables can help avoid the problem of undermatching or overmatching in case-control studies [25].

3. **Over reliance on single centre studies**: Both settings had an overreliance on single centre studies and the lack of multi-centre settings affected the representativeness of the findings. Greater numbers of hospitals participating and more diversity in hospital settings for each study would help strengthen the applicability and robustness of any findings. Some studies with a patient population across multiple surgical categories indicated differential additional SSI costs by procedure. However, this was only reported in the European studies and there was no clear signal on which procedures would be the costliest across these studies. Some studies had low numbers of SSI patients; cost estimation with a small sample size are prone to unreliability and imprecision. This has an impact on the interpretation of the results given that the differences in costs between SSI patients and non-SSI patients could be driven by chance or extreme values. In general, the European studies had more patients, but this could be as a result of better SSI surveillance.

4. **Lack of studies in Low Income and Lower Middle Income countries**: The LMIC studies found in the review span across different continents, patient populations, surgical procedures, income levels, health systems and cultures. However, there was an underrepresentation of studies in Low Income countries and Lower Middle Income countries making the generalisability of the overall findings to these settings more difficult.

5. **Inconsistency in consideration of costs and narrow cost perspective**: The type of costs included will have a direct impact on the estimation of SSI costs. The cross-country cost comparison of SSI was hindered by the absence of a standardized approach in the basket of
cost items included. However, even when a standardized approach is adopted as in a multi-
national randomised control trial, costs and resource use will differ across countries [68].
Variations in clinical practice and relative prices across countries will affect the transferabil-
ity of healthcare resource use and costs [69]. Despite an SSI has far-reaching resource use
implications for the healthcare system, patient and community, costs from the patient’s per-
spective were not considered in any LMIC study. The absence of patient and societal costs
are concerning given the relatively high out of pocket expenditure faced by patients in
LMICs. Lack of consideration of these costs is likely to underestimate the true cost burden
of SSI, and one of the European studies found that the addition of informal care alone dou-
bled the costs associated with SSI [41].

Strengths and weaknesses. The strength of this study is that it is the first systematic
review to specifically investigate the economic impact of SSI in LMICs. By including a parallel
review of SSI with HICs in Europe, the review offers new insight into the methodological con-
siderations and the potential data gaps in SSI cost studies from the contrasting settings.
A limitation relates to the use of an implied PPP exchange rate for some of the LMIC set-
tings and the English language restriction for the article inclusion criteria. A PPP exchange
rate is used to adjust for the cost of living differences between countries. Relying on implied
PPP rates for adjusting the comparative cost results is likely to introduce measurement error
in the study findings compared to those using official PPP rates [70]. A previous study looking
at risk factors for child conduct problems and youth violence in LMICs reported that including
only English language studies was likely to have reduced the number of potentially relevant
articles by around 15% [71].

Comparison with other studies. Previous systematic reviews have looked at the costs of a
SSI, mainly in high income countries [5, 72, 73]. Similar issues were encountered on the lack
of standardized approach, insufficient detail on how costs were derived, and the failure to
include societal costs. To better articulate the first two study issues, the present review added
the use of a cost of illness reporting checklist to give an indication of the study transparency
and comparability. In contrast to the previous systematic reviews, the search criteria of the
present study were not limited by date to be as inclusive as possible. A previous systematic
review established that many essential surgical interventions are cost-effective in resource
poor countries [74]. However, complications such as SSI can impose unforeseen additional
costs in these countries, which are overlooked by most of the studies included in the paper.

Implications for practice. An SSI is the most common hospital acquired infection in
LMICs [75]. Preventing SSIs will decrease the financial burden of both the patient and health
system. Hospital bed overcrowding is problematic in LMICs [76–78] and any reduction in
SSIs would help to increase capacity in bed days.

There is need for multicentre studies with large number of SSI patients to capture relevant
costs and consequences of the infection across settings. The use of a standardized data collec-
tion pathway will help improve cross-study comparability. Future studies should include more
detailed information on analytic approaches in the methods along with rationale and discus-
sion of their likely impact on results. Ideally, reporting should include resource use, costs and
cost categories of SSI and non-SSI patients to give more context on the key influences for the
cost difference between patient groups. The identification, measurement and collection of
costs should as far as possible take a societal perspective to appropriately encompass all health-
care, patient and wider society costs that may be affected by an SSI. The costs of inpatient SSI
and outpatient SSI need to be differentiated given that the former is plausibly more expensive
from increased inpatient bed days. Subgroup analysis would allow the heterogeneity to be examined between these groups instead of being masked in overall figures.

Conclusions
An SSI represents a financial burden in both high income and LMICs settings. The magnitude of the cost difference depends on the SSI definition used, severity of SSI, patient population, choice of comparator, hospital setting, and cost items included. Huge heterogeneity in design and lack of transparency has made it difficult to draw meaningful comparison across studies and countries.

We suggest that future studies endeavour to achieve the most appropriate time horizon to include appropriate complications, focus on a comparator that has a degree of matching of patient characteristics, and researchers should limit their focus on single centre studies to increase generalisability. These three items are typically within the gift of researchers during the design stage. The impact of SSI in low-income countries is likely to be severe and more research in these setting is required with particular care on choosing the right perspective for the collection of cost data, which is key to ensuring the appropriate financial burden captured. Agreement on what would the composition of a standardised basket of items of costs to include would also be extremely helpful.

Supporting information
S1 Table. Cost information included in each European study.
(DOCX)
S2 Table. Cost information included in each LMIC study.
(DOCX)
S1 File. LMIC search strategy medline.
(DOCX)
S2 File. LMIC search strategy embase.
(DOCX)
S3 File. Europe search strategy medline.
(DOCX)
S4 File. Europe search strategy embase.
(DOCX)
S1 Checklist. PRISMA 2009 checklist.
(DOC)

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