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Surgical site infection and costs in low- and middle-income countries

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1 **Surgical Site Infection and Costs In Low- and Middle-**
2 **Income Countries: A Systematic Review Of The Economic**
3 **Burden**

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20

21 **Abstract:**

22 Background:

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

27 Objective

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

31 Methods

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

36 Results:

37 Studies from 15 LMIC and 16 European countries were identified and reviewed in full. The
38 additional cost of SSI range (presented in 2017 international dollars) was similar in the LMIC
39 (\$174 - \$29,610) and European countries (\$21 - \$34,000). Huge study design heterogeneity
40 was encountered across the two settings.

41 Discussion:

42 SSIs were revealed to have a significant cost burden in both LMICs and High Income
43 Countries in Europe. The magnitude of the costs depends on the SSI definition used, severity

44 of SSI, patient population, choice of comparator, hospital setting, and cost items included.
45 Differences in study design affected the comparability across studies. There is need for
46 multicentre studies with standardized data collection methods to capture relevant costs and
47 consequences of the infection across income settings.

48 Other:

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53 Department of Health and Social Care.

54

55 **Introduction**

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

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

73 A cost of illness (COI) study quantifies how much society is spending on a particular disease
74 and represents the cost burden averted if the disease was eradicated[19]. Understanding the
75 additional cost burden imposed by the complications of surgery such as those caused by an
76 SSI, helps to strengthen the case for identifying interventions to reduce such
77 complications[20]. This in turn provides the justification for undertaking economic

78 evaluations to present relevant evidence to inform the prioritization of resource allocation
79 decisions for interventions to reduce SSI complications.”.

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

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

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

99 The objective of this study is to critically appraise and assess how the cost of SSI has been
100 estimated in a range of LMIC studies and compare with a selection of high income European
101 studies which explored similar SSI costs. European studies are included in the review to

102 provide a reference standard for the LMIC studies. The aim of the comparison is to examine
103 the costs associated with SSI (presented in international dollars) across the different settings
104 and identify potential data gaps, and methodological considerations in each setting.

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

109 **Materials and methods**

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

112 ***Search Strategy***

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

117 ***Eligibility criteria***

118 Studies were included if they considered the costs associated with SSIs in European
119 Organisation for Economic Co-operation and Development (OECD) countries[30]. For the
120 analogous review of LMIC, studies were included if they considered the economic impact of
121 SSIs in LMICs. For both settings costs could be borne by the healthcare providers, patients,
122 wider community and/or society. Eligible articles included cost analysis, partial or full
123 economic evaluations (trial-based and model-based) and cost of illness studies in a European

124 country or LMIC setting. Multi-country studies were included if at least one eligible country
125 was included and the study's findings were reported separately for that country. Non-eligible
126 studies were those that were not published in English, conference proceedings, protocols,
127 commentaries, and editorials.

128 *Study Selection*

129 The titles and abstracts of the databases' search results were screened against the eligibility
130 criteria. A three stage categorisation process was used to determine relevant studies
131 appropriate for inclusion, using methods described elsewhere[31]. Two investigators carried
132 out study screening and data extraction for the LMIC search (MM & ZA). One investigator
133 (MM) carried out all study screening and data extraction for the European literature search,
134 and another investigator (ZA) undertook screening of a random 20% to assess agreement.
135 Disagreements were resolved through discussion, a third independent investigator (TR) was
136 sought where agreement could not be reached.

137 For each included study, data were extracted on the study characteristics, country setting,
138 costs and resource use included, use of adjusted analyses, and the main results reported. The
139 information was tabulated, and the issues faced by the individual studies in estimating the
140 additional costs of SSI were compared narratively. For consistency across studies, costs were
141 converted to international dollars and inflated to 2017, where appropriate. To improve
142 comparability of cost findings, costs were adjusted by their country's Purchasing Power
143 Parity (PPP) conversion factor[32]. Where a country did not have a PPP conversion factor, an
144 implied PPP conversion factor from the IMF was used instead[33]. For inflation purposes,
145 studies without a specified cost year were assumed to be the last year of data collection.

146 All included studies were assessed by a modified reporting Müller checklist (translated into
147 English) for COI studies and scored by their inclusion of relevant items[34]. A study scored

148 one on each aspect they had described or justified out of a possible maximum score of 36.
149 The checklist for each study is available upon request.

150

151 **Results and Discussion**

152 *Part 1: European Literature search*

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

155

156

157 **Fig 1. PRISMA diagram of European Search.**

158

159

160

161 *General Study Characteristics*

162 The sixteen studies were published from 1992 to 2018 and data collection spanned 1987 to
163 2016. Studies were based in England (n=6)[35-40], Spain (n=2)[41, 42], Scotland (n=2)[43,
164 44], Finland (n=1)[45], France (n=1)[46], Switzerland (n=1)[47], Belgium (n=1)[48],
165 Denmark (n=1)[49] and Germany (n=1)[50]. Table 1 shows general characteristics of each
166 study included in the review.

167 **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
Cardiothoractic 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

Lead author (Year)	Country	Patient population	Setting	Study aim	Type of study	Number of SSI & Comparator	Period of data collection
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

Lead author (Year)	Country	Patient population	Setting	Study aim	Type of study	Number of SSI & Comparator	Period of data collection
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;							

168 ***Definition of SSI***

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

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

179 ***Patient matching***

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

186 ***Setting & Procedure***

187 Public teaching hospitals[35-37, 39-43, 46, 47, 50] were the setting for majority of the studies
188 with one hospital setting unclear[44], and another study referring to unspecified referral
189 hospitals[45]. Study settings were mostly restricted to a single site with only four studies
190 involving multiple hospitals[38, 45, 48, 49]. Surgical procedures ranged from general surgery

191 or multiple surgery categories (n=8), cardiothoracic (n=1), colorectal (n=2), gynaecological
192 (n=1), and orthopaedic (n=4).The patient population were all adult patients.

193 Half the studies that assessed SSI across surgical categories reported surgery category-
194 specific costs associated with SSI [35, 43, 44, 47]. All of these studies showed variation of SSI
195 costs across surgical categories Severity of SSI was always associated with increased costs.
196 A deep SSI was more costly compared to a superficial SSI in all studies that had severity-
197 specific SSI costs[39, 47, 49]. Yet, the stated approaches to classify the superficial versus
198 deep SSI differed. Approaches to define superficial SSI included CDC criteria[49], or a
199 treatment for an infection at the surgical site within 30 days postoperatively[47], or were not
200 defined[39] . Approaches to classify a deep SSI included a microbiological confirmation of
201 tissue from a further surgery[39]; or an SSI requiring surgery[47] or using CDC
202 criteria[49]The sample size of SSI patients in the European studies ranged from as low as 17
203 patients to as high as 513 patients.

204 ***Cost components***

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

215 **Table 2. Costs of SSI in European 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
Cardiothoractic 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 Informal care: \$15,734 Societal costs: \$145,336	SSI pre-discharge: 23.73 days SSI post-discharge: 12.99 days No SSI: 9.45 days

Lead author (Year)	Adjusted group comparison	Costs included	Average cost SSI patients	Average costs Non-SSI patients	Additional cost of SSI	Length of Stay
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

Lead author (Year)	Adjusted group comparison	Costs included	Average cost SSI patients	Average costs Non-SSI patients	Additional cost of SSI	Length of Stay
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	SSI: 29 days 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

Lead author (Year)	Adjusted group comparison	Costs included	Average cost SSI patients	Average costs Non-SSI patients	Additional cost of SSI	Length of Stay
Parker (2018)[38]	Age, sex, trial site, wound grade, diabetes, height, weight, and smoking status	Hospital inpatient & outpatient services, community health & social care, medication, aids and adaptations	\$22,255 (complete case analysis)	\$20,429 (complete case analysis)	SSI (multiple imputation) \$2,866 SSI (complete case analysis): \$1,825	Not reported
Pollard (2006)[36]	Sex, age, fracture type, ASA grade, pre-fracture residence type, operation, social dependency & mobility scores	Hospital stay, Antibiotics, outpatient treatment, theatre time, prosthetic costs, radiology, physiotherapy	\$44,157	\$13,043	\$31,114	SSI: 80 days (median) Non-SSI: 28 days (median)
Thakar (2010)[39]	Sex, age, fracture type, ASA grade, operation, pre-fracture residence type, social dependency & mobility	Theatre time, prosthetic costs, radiology and pharmaceuticals	Superficial SSI: \$30,193 Deep SSI: \$39,299	Superficial SSI control: \$13,987 Deep SSI control: \$13,631	Superficial SSI: \$16,206 Deep SSI: \$25,669	Superficial SSI: 62.5 days Superficial SSI control: 35 days Deep SSI: 79.3 days Deep SSI matched control: 34.3 days

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

ASA grade, American Society of Anaesthesiologists; DRG, Diagnosis-related group; GP, General Practitioner; HAI, Hospital Acquired Infection; LOS, Length of stay; NNIS, Nosocomial Infection Surveillance System risk index; SSI, Surgical Site Infection

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

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

226 ***Resource use***

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

234 ***Cost of Surgical Site Infection***

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

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

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

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

251 The lowest additional cost associated of SSI was estimated in a Danish study assessing the
252 cost-effectiveness of incisional negative pressure wound therapy in obese women after
253 caesarean section. In addition to the cost-effectiveness results, the study also provided a per-
254 patient cost of superficial SSI and deep SSI compared with patients who did not suffer an
255 SSI. The superficial SSI was defined as requiring antibiotic treatment for an infection at the
256 surgical site within the first 30 days after the caesarean section and not requiring further
257 surgery. The highest additional health care cost associated with SSI was estimated by Weber
258 et al[47]. While the average additional cost of all SSI patients was \$17,060, an organ space
259 SSI approximately doubled the additional cost of an SSI in their case-control designed study.

260 Alfonso et al[41] (Spain) was the only study to adopt a broader societal perspective and
261 included the cost of productivity loss, informal care and health care costs. They estimated the

262 cost associated with SSI to be an additional \$145,366 per patient. This estimate comprised
263 productivity costs (78.7%) with carer costs (10.8%) and health costs (10.5%) making up the
264 remainder. Including only the health care costs made the additional cost of SSI \$15,733 per
265 patient.

266 *Checklist*

267 All studies were compared against a modified reporting Müller COI study checklist (see
268 Table S1 for scores). Alfonso et al[41, 52] achieved the highest number of items (23 points)
269 in the checklist with detailed descriptions of the methods used to estimate the additional costs
270 of SSI. Turtainen et al[45] achieved the lowest score (11 points) in the checklist with little to
271 no description in the study on what was included in the SSI cost estimate and how it was
272 derived. In general, studies scored relatively poorly in the evaluation methods and
273 presentation of results section of the checklist but highly in the discussion and conclusions
274 sections.

275 **PART 2: LMIC LITERATURE SEARCH**

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

279

280

281 **Fig 2. PRISMA Diagram of LMIC search.**

282 ***General Study Characteristics***

283 The fifteen studies were published from 2003 to 2018 and data collection spanned 1999 to
284 2015. Studies were based in Turkey (n=3)[53-55], China (n=2)[56, 57], Jordan (n=2)[58, 59],
285 Thailand (n=2)[60, 61], Brazil (n=1)[62], Egypt (n=1)[63], India (n=1)[64], Mexico
286 (n=1)[65],Rwanda (n=1)[66], and South Africa (n=1)[67]. According to the World Bank
287 classifications, the studies were part of the following income groups: Low Income Country
288 (n=1) [66], Lower Middle Income (n=2)[63, 64] and Upper Middle Income (n=12)[53-62, 65,
289 67]. Table 3 shows general characteristics of each study included in the review.

290 **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)[58] [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)[55] [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)[67] [Upper Middle Income]	South Africa	Paediatric surgery, orthopaedics and urology patients	Teaching Children hospital	Investigate burden & risk factors of HAI	Prospective surveillance	21 SSI/ 1022 Non-SSI	2014 -2015
Galal (2011)[63] [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)[65] [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

Lead author (Year) [Income Group]	Country	Patient population	Setting	Study aim	Type of study	Number of SSI & Comparator	Period of data collection
Siribumrungwong (2015)[61] [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)[64] [Lower Middle Income]	India	Adult patients with at least 48 hours hospital stay	Private tertiary care hospital	Assess the costs associated with HAIs	Retrospective comparative study / cost analysis	4 SSI/ 104 Non-SSI	2008-2009
Gastrointestinal surgery							
Liu (2018)[57] [Upper Middle Income]	China	Colorectal cancer adult patients who had tumour surgically removed	Tertiary public hospital	Economic burden caused by HAIs	Retrospective surveillance / cost analysis	20 SSIs/ 38 Non-SSI	2015
Özmen (2016)[53] [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)[60] [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)[66] [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

Lead author (Year) [Income Group]	Country	Patient population	Setting	Study aim	Type of study	Number of SSI & Comparator	Period of data collection
Gynaecological Surgery							
Köşüş (2009)[54] [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)[56] [Upper Middle Income]	China	Patients who had a craniocerebral operation	Tertiary care hospital	Cost-benefit analysis of SSI control	Prospective study / economic analysis	12 SSI/ 588 Non-SSI	2009-2012
Hweidi (2018)[59] [Upper Middle Income]	Jordan	Adult patients who had a craniocerebral operation	Teaching hospital	Estimate the additional healthcare costs attributable to SSI	Retrospective case control study	32 SSI/ 32 Non-SSI	2009- 2015
Orthopaedic surgery							
Dal-paz (2010)[62] [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;							

291

292

293 ***Definition of SSI***

294 The Center of Disease Control guidelines were used in the majority of the studies to define an
295 SSI[53-58, 62-65, 67]. However, three studies lacked a definition of what constituted a
296 SSI[60, 61, 66]. One study classified a SSI based on the wound discharge culture or other SSI
297 suggestive signs and symptoms but these were not elaborated further[59].

298 Post-discharge SSIs cannot be detected where there is no follow-up. In this review, patients
299 were not followed up after hospital discharge or it was not indicated in many of the
300 studies[56, 57, 59-62, 64, 66, 67]. Where follow-up was specified, it was only recorded if the
301 patient happened to return to the index hospital in two studies[55, 58]. The only specified
302 method of follow-up in the studies was attendance of an outpatient clinic attendance a month
303 after the patient's operation[53, 55, 63, 65].

304 ***Patient matching***

305 When estimating the additional cost burden of SSI, most of the studies did not make any
306 adjustments in the comparison with non-SSI patients or it was unclear if adjustment had been
307 used (Table 3). Justification on the inclusion of the patient matching variables was only given
308 in one of the six studies where patient matching was utilised[57].

309

310 ***Setting & Procedure***

311 The setting where the findings are derived from were mainly public teaching hospitals[41, 53,
312 58-63, 65, 67] with three based in private hospitals[54-56, 64]. All the studies were based in
313 single centres. Surgical procedures ranged from general surgery or multiple surgical
314 categories (n=5), oncological procedures (n=4), cardiothoracic (n=2), orthopaedic (n=1),

315 gastric (n=1), general, cardiac and neurosurgery (n=2).The patient population was broader in
316 the LMIC studies and varied from children (n=2), adults (n=12) and pregnant women (n=1).
317 For the studies with SSI patients taken from multiple surgical categories, none reported costs
318 of SSI by surgical category.

319 SSI severity increased the additional cost of SSI[55, 57]. A subgroup analysis of one study
320 had low sample sizes for the superficial (n=13), subcutaneous (n=6) and deep soft SSIs
321 (n=1)⁵³. Another study compared the severity of infections in three different types of surgical
322 procedure, however, the reported cost was for all cases[65].

323 In general, studies tended to have a low number of SSI patients with the sample size of SSI
324 patients in each study ranging from 4 patients[61, 64] to 106 patients[58]. Six studies had
325 twenty or fewer SSI patients[53, 54, 57, 60, 61, 64].

326 ***Cost components***

327 All studies estimated direct medical costs (Table 4). The lack of follow-up of patients beyond
328 discharge limited most of the studies to report only inpatient hospital costs. One study had
329 attempted to measure the direct non-medical costs, however the authors did not report it as a
330 cost of an SSI[66]. Most studies did not report the relevant year for the cost estimation (S2
331 Table). The majority of studies did not break down the extent to which each cost component
332 makes up the costs of SSI and non-SSI patients. Where cost components were reported in
333 studies, it either included both SSI and non-SSI patients[56, 60, 64] or was limited to only
334 SSI patients[54, 55, 62].

335 **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)[58]	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)[55]	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)[67]	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)[63]	Unadjusted comparison	Hospital stay	\$2,465	\$610	\$1,855	SSI: 7.10 days Non-SSI: 3.39 days
Porrás-Hernández (2003)[65]	Unadjusted comparison	Hospital stay (excluding antibiotics)	Not reported	Not reported	\$2,164	SSI: 13 days Non-SSI: 6 days

Lead author (Year)	Adjusted group comparison	Costs included	Average cost SSI patients	Average costs Non-SSI patients	Additional cost of SSI	Length of Stay
Siribumrungwong (2015)[61]	Not reported	Unspecified hospital costs	Not reported	Not reported	\$174	Not reported
Tiwari (2013)[64]	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)[57]	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)
Özmen (2016)[53]	Unadjusted comparison	Hospital stay	\$4,195	\$4,872	SSI patients had lower costs	SSI: 5.27 days Non-SSI: 5.40 days
Phothong (2015)[60]	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)[66]	Not reported	Unclear	Not reported	Not reported	\$483	Not reported

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 & Neurological surgery						
Zhou (2015)[56]	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)[59]	Age, sex, index diagnosis, admission month	Length of stay, antibiotics, reoperation	\$34,872	\$15,974	\$18,899	SSI: 30.15 days Non-SSI: 6.98 days
Gynaecological surgery						
Köşüş (2009)[54]	Unadjusted comparison	Preventative antibiotics, hospital readmission and out-patient	\$1,736	\$0	\$1,736	Two SSI patients had 7 days readmission. None for Non-SSI patients
Orthopaedic surgery						
Dal-paz (2010)[62]	Unadjusted comparison	Hospital stay, lab and imaging 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;

337 ***Resource use***

338 There was no reporting of resource use of SSI and non-SSI patients beyond hospital length of
339 stay in any of the studies. There was partial reporting on the additional procedures or
340 investigations for SSI[55, 62] but no detail on the total resource use by SSI and non-SSI
341 patients.

342 ***Cost of Surgical Site Infection***

343 The additional cost of SSI varied considerably across the studies. All but one study showed
344 an elevated cost of SSI relative to non-SSI patients. The study by Özmen et al[53] (Turkey)
345 study looked at outcomes of patients after elective gastric cancer surgery and found that the
346 unspecified hospital costs were non-significantly lower for superficial SSI patients compared
347 to non-SSI patients. The calculations behind the lower SSI cost was unclear given that overall
348 hospital costs were higher than either of the mean costs of the patient groups (SSI and non-
349 SSI).

350 The additional cost of SSI ranged from \$174 (Thailand)[61] to \$29,610 (India)[64]. The
351 lowest additional cost of SSI was from a study by Siribumrungwong et al[61]. Their SSI cost
352 was made up of undefined hospital costs of four SSI patients with no detail of the non-SSI
353 comparator group. The highest additional cost of SSI was from a study by Tiwari et al[64].
354 For their four patients who suffered an SSI, drug acquisition costs, length of stay and
355 antimicrobial drugs were the main cost drivers.

356 Clarity on the relative magnitude of difference in cost between SSI and non-SSI patients was
357 mixed. Half of studies did not present average costs of both SSI and non-SSI patients. The
358 lowest relative magnitude of difference in reported costs was in Jordan where SSI costs were
359 1.4 times higher than non-SSI costs[58]. However, it is unclear what cost items are the major

360 contributors of the additional costs. They had estimated the costs of SSI and non-SSI patients
361 as \$31,666 and \$22,329, respectively. The highest relative magnitude of difference in costs
362 was in India where Tiwari et al[64] found that SSI costs were 4.8 times higher than non-SSI
363 costs[64]. The authors had estimated the costs of SSI and non-SSI patients as \$37,295 and
364 \$7,685 respectively.

365 ***Checklist***

366 For the COI checklist, the studies achieved on average a score of 11.07 out a maximum of
367 possible score of 36. The lack of a stated perspective and cost year reduced the scores of
368 many of the LMIC studies. Dramowski et al[67] scored the highest number of items (16) in
369 the discussion and conclusion. The lack of description of pertinent study items meant that
370 Porras-Hernández et al[65] scored the lowest (6).

371 **Part 3: Comparison between HIC European Countries** 372 **and LMICs**

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

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

385 ***Statement of principal findings***

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

388 For medical costs, the additional cost of SSI was \$21 to \$34,000 in European studies while
389 the additional cost attributed to SSI ranged from \$174 to \$29,610 in LMICs. The huge range
390 of costs in both settings reflects the difficulty associated with accurately estimating the costs
391 attributable to SSI and consequently limited cross-study comparability of findings. Five main
392 challenges to the estimation of the costs are summarised below:

- 393 1. Time horizon for capturing an SSI
- 394 2. Choice of comparator
- 395 3. Over reliance on single centre studies and small number of patients with SSI
- 396 4. Under representation of Low Income and Lower Middle Income Countries in the
397 literature
- 398 5. Inconsistency in consideration of costs and narrow cost perspective.

399

400 ***1. Time horizon and follow-up:*** Studies from both settings used the CDC criteria to define
401 SSI, but the lack of follow-up in LMIC studies failed to meet the recommended time
402 needed to detect an SSI. According to the CDC, the specified time horizon for an SSI to
403 occur is up to 30 days post-surgery for non-implant operations and up to 12 months for
404 implant operations. Where no follow-up exists, there is a risk of underestimating the true

405 number of SSI patients and skewing the cost burden information to only patients with an
406 inpatient SSI. The type of follow-up method will affect the detection rate but this was
407 rarely mentioned in studies. Inadequate IT infrastructure in LMIC healthcare systems has
408 been implicated as the cause of poor follow up through health care pathways[68].

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

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

430 European studies had more patients, but this could be as a result of better SSI
431 surveillance.

432 **4. Lack of studies in Low Income and Lower Middle Income countries:** The LMIC

433 studies found in the review span across different continents, patient populations, surgical
434 procedures, income levels, health systems and cultures. However, there was an
435 underrepresentation of studies in Low Income countries and Lower Middle Income
436 countries making the generalisability of the overall findings to these settings more
437 difficult.

438 **5. Inconsistency in consideration of costs and narrow cost perspective:** The type of costs

439 included will have a direct impact on the estimation of SSI costs. The cross-country cost
440 comparison of SSI was hindered by the absence of a standardized approach in the basket
441 of cost items included. However, even when a standardized approach is adopted as in a
442 multinational randomised control trial, costs and resource use will differ across
443 countries[69]. Variations in clinical practice and relative prices across countries will
444 affect the transferability of healthcare resource use and costs[70]. Despite an SSI has far-
445 reaching resource use implications for the healthcare system, patient and community,
446 costs from the patient's perspective were not considered in any LMIC study. The absence
447 of patient and societal costs are concerning given the relatively high out of pocket
448 expenditure faced by patients in LMICs. Lack of consideration of these costs is likely to
449 underestimate the true cost burden of SSI, and one of the European studies found that the
450 addition of informal care alone doubled the costs associated with SSI[41].

451

452 ***Strengths and weaknesses***

453 The strength of this study is that it is the first systematic review to specifically investigate the
454 economic impact of SSI in LMICs. By including a parallel review of SSI with HICs in
455 Europe, the review offers new insight into the methodological considerations and the
456 potential data gaps in SSI cost studies from the contrasting settings.

457 A limitation relates to the use of an *implied* PPP exchange rate for some of the LMIC settings
458 and the English language restriction for the article inclusion criteria. A PPP exchange rate is
459 used to adjust for the cost of living differences between countries. Relying on implied PPP
460 rates for adjusting the comparative cost results is likely to introduce measurement error in the
461 study findings compared to those using official PPP rates[71]. A previous study looking at
462 risk factors for child conduct problems and youth violence in LMICs reported that including
463 only English language studies was likely to have reduced the number of potentially relevant
464 articles by around 15%[72].

465 ***Comparison with other studies***

466 Previous systematic reviews have looked at the costs of a SSI, mainly in high income
467 countries[5, 73, 74]. Similar issues were encountered on the lack of standardized approach,
468 insufficient detail on how costs were derived, and the failure to include societal costs. To
469 better articulate the first two study issues, the present review added the use of a cost of illness
470 reporting checklist to give an indication of the study transparency and comparability. In
471 contrast to the previous systematic reviews, the search criteria of the present study were not
472 limited by date to be as inclusive as possible. A previous systematic review established that
473 many essential surgical interventions are cost-effective in resource poor countries[75].
474 However, complications such as SSI can impose unforeseen additional costs in these
475 countries, which are overlooked by most of the studies included in the paper.

476

477

478 ***Implications for practice***

479 An SSI is the most common hospital acquired infection in LMICs[76]. Preventing SSIs will
480 decrease the financial burden of both the patient and health system. Hospital bed
481 overcrowding is problematic in LMICs[77-79] and any reduction in SSIs would help to
482 increase capacity in bed days.

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

496 **Conclusions**

497 An SSI represents a financial burden in both high income and LMICs settings. The
498 magnitude of the cost difference depends on the SSI definition used, severity of SSI, patient
499 population, choice of comparator, hospital setting, and cost items included. Huge

500 heterogeneity in design and lack of transparency has made it difficult to draw meaningful
501 comparison across studies and countries.

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

511

512 **Supporting information**

513 S1 Table. Cost information included in each European study

514 S2 Table. Cost information included in each LMIC study

515 S1 File. LMIC Search strategy Medline

516 S2 File. LMIC Search strategy Embase

517 S3 File. Europe Search strategy Medline

518 S4 File. Europe Search strategy Embase

519

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