Gesundheitsökonomische Evaluation von Krankenhausinfektionen

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Abkürzungsverzeichnis

Abkürzung	Definition
AB	Antibiotika
ACCP/SCCM	American College of Chest Physicians/Society of Critical Care Medicine
AWI	Atemwegsinfektion
BSI	Primary blood stream infection
CABG	Coronary Artery Bypass Grafting
Carbapen	Carbapeneme
CBAs	Cost-benefit analyses
CCR	Cost-to-charge ratio
CDAD	Clostridium difficile-associated diarrhea
CDC	Centers for Disease Control and Prevention
CDI	*Clostridium difficile* infection
CEAs	Cost-effectiveness analyses
Cephalo2	Cephalosporine der 2. Generation
Cephalo3	Cephalosporine der 3. Generation
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHGIS	Chlorhexidine gluconate-impregnated sponge
CI	Confidence Interval
CMAs	Cost-minimization analyses
CUAs	Cost-utility analyses
CW	Cost-weight
DALY	Disability-adjusted Life Year
DRG	Diagnosis-related Groups
E.coli	*Escherichia coli*
ECDC	European Centre for Disease Prevention and Control

ESAC-Net	European Surveillance of Antimicrobial Consumption Network
Fluorchi	Fluorchinolone
GDP	Gross Domestic Product
GKV	Gesetzliche Krankenversicherung
GlycopAB	Glycopeptid-Antibiotika
HAIs	Health care-associated infections
HICP	Harmonized index of consumer prices
HR	Hazard ratio
HWI	Harnwegsinfektion
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICUs	Intensive Care Units
IfSG	Infektionsschutzgesetz
InEK	Institut für das Entgeltsystem im Krankenhaus
IQRs	Interquartile ranges
IQWIG	Institute for Quality and Efficiency in Health Care
ITS	Intensivstation
KISS	Krankenhaus-Infektions-Surveillance-System
LBFW	Landesbasisfallwert
LOS	Length of hospital stay
LRTI	Lower Respiratory Tract Infection
MICU	Medical Intensive Care Unit
MRSA	Methicillin-resistant *Staphylococcus aureus*
NHS EED	National Health Service Economic Evaluation Database
NI	Nosokomiale Infektion
NRZ	Nationale Referenzzentrum
OCEBM	Oxford Centre for Evidence-based Medicine

OECD	Organisation for Economic Co-operation and Development
P. aeruginosa	*Pseudomonas aeruginosa*
PenicBLI	Penicilline plus Beta-Lactamase-Inhibitoren
PeniciEW	Penicilline mit erweitertem Wirkungsspektrum
PICO	Population, Intervention, Comparison, and Outcomes
PPP	Purchasing Power Parity
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RG	Relativgewicht
RhAPC	Recombinant human activated protein C
RKI	Robert Koch Institut
S.aureus	*Staphylococcus aureus*
SD	Standard Deviation
SE	Standard Error
SEM	Standard Error of Measurement
SIGN	Scottish Intercollegiate Guidelines Network
SPP	Species
SSI	Surgical Site Infection
SulfoTri	Kombinationen von Sulfonamiden und Trimethoprim inkl. Derivate
USD	United States Dollar
UTI	Urinary Tract Infection
WBC	White Blood Cells
WHO	World Health Organization
WI	Wundinfektion
WOK	Web of Knowledge
WTP	Willingness-to-pay
ZVK	Zentralvenöser Katheter

1. Einleitung

1.1. Nosokomiale Infektion

Nosokomiale Infektionen oder Krankenhausinfektionen sind eine schwerwiegende Komplikation im Krankenhaus und erhöhen sowohl die Morbidität als auch die Mortalität (Klevens et al., 2007, Hagel et al., 2013). Sie führen zu zusätzlichen Behandlungen und Schmerzen, darüber hinaus verlängern sie die Verweildauer für die betroffenen Patienten (De Angelis et al., 2010, Manoukian et al., 2018). Weiterhin verursachen sie zusätzliche Kosten für den Krankenhausträger und für das Gesundheitssystem (Marchetti und Rossiter, 2013, Stone, 2009). Wenn eine Infektion bei Krankenhausaufnahme weder vorhanden noch in der Inkubationsphase war, wird sie als nosokomial bezeichnet (Geffers et al., 2002). Eine nosokomiale Infektion ist nach § 2 Infektionsschutzgesetz– IfSG wie folgt definiert:

„*eine Infektion mit lokalen oder systemischen Infektionszeichen als Reaktion auf das Vorhandensein von Erregern oder ihrer Toxine, die im zeitlichen Zusammenhang mit einer stationären oder einer ambulanten medizinischen Maßnahme steht, soweit die Infektion nicht bereits vorher bestand*" (Robert Koch Institut, 2011b).

Lokale oder systemische Anzeichen einer Infektion müssen nach Definition des Center for Disease Control and Prevention (CDC) bei der Diagnose einer nosokomialen Infektion nachgewiesen werden. Sie werden erst als nosokomial bezeichnet, wenn die Patienten mindestens 48 Stunden im Krankenhaus verbracht haben (Robert Koch Institut, 2011a). Es ist zu berücksichtigen, dass unterschiedliche Infektionen unterschiedliche Inkubationszeiten aufweisen, so dass jedes Ereignis einzeln ausgewertet werden muss, um die Beziehung zwischen seinem Auftreten und dem Krankenhausaufenthalt festzustellen (Gastmeier, 2016). Das Nationale Referenzzentrum für Surveillance von nosokomialen Infektionen (NRZ) hat in Zusammenarbeit mit dem Robert Koch

Institut (RKI) vergleichbare Definitionen für jede spezifische nosokomiale Infektion erarbeitet, um die unterschiedlichen nosokomialen Infektionen in den Krankenhäusern vergleichbar zu machen (Artz, 2008). Zahlreiche Faktoren fördern Infektionen bei Patienten im Krankenhaus. Dazu zählt z.B. eine verminderte Immunität. Eine zunehmende Vielfalt an medizinischen Verfahren und invasiven Techniken erhöhen das Risiko zusätzlich. Zahlreiche Studien haben versucht, das Risiko für die Entstehung nosokomialer Infektionen zu analysieren und immer wieder gezeigt, dass die Erreger bei chirurgischen Eingriffen oder bei der Anwendung invasiver Hilfsmittel in den Körper gelangen können (Iordanou et al., 2017, Weinstein und Darouiche, 2001). Die meisten Infektionsfälle bei schwerkranken Patienten im Krankenhaus sind mit invasiven medizinischen Maßnahmen verbunden (Weinstein und Darouiche, 2001). Die Studie von Richards et al. zeigte, dass 95% der Fälle von Harnwegsinfektionen Katheter-abhängig sind, 87% der Fälle der Blutbahninfektionen von einem vaskularen Gefäßkatheter stammen und 86% der Fälle von Lungenentzündungen mit einer medizinischen Beatmung verbunden sind (Richards et al., 1999).

1.2. Epidemiologie von nosokomialen Infektionen

Nach einer Studie von Gastmeier et al. treten pro Jahr circa 400.000 bis 600.000 nosokomiale Infektionen in Deutschland auf (Gastmeier und Geffers, 2008). Die zweite nationale Studie im Jahr 2011 zeigte eine Prävalenz von 5,1% für Patienten mit nosokomialen Infektionen (Behnke et al., 2013). Eine Schätzung des Europäischen Centre for Prevention and Disease Control (ECDC) weist darauf hin, dass jährlich circa 4 Millionen nosokomiale Infektionen in Europa auftreten, 37.000 davon führen zu nosokomial Infektions-assoziierten Todesfällen (Gastmeier et al., 2010). In einer nationalen Untersuchung waren postoperative Wundinfektionen (24%), Harnwegsinfektionen (23%) sowie Infektionen der unteren Atemwege (22%) die häufigsten nosokomialen Infektionen, gefolgt von *Clostridium difficile* Infektionen (6%) und der primären Sepsis (6%) (Behnke et al., 2013). Nach

dem deutschen Krankenhaus-Informationssystem sind die häufigsten Erreger auf Intensivstationen *Staphylococcus aureus* bei nosokomialen Pneumonien, *Koagulase-negative Staphylokokken* bei primärer Sepsis und *Escherichia coli* bei nosokomialen Harnwegsinfektionen (Geffers et al., 2002). Bei den Wundinfektionen können die Erreger nach Operationsgebiet bzw. Art der Operation unterschiedlich sein (Krämer und Reintjes, 2013). Nach Empfehlung der Kommission für Krankenhaushygiene und Infektionsprävention treten bestimmte fakultativ pathogene Erreger (z.B. *Koagulase-negative Staphylokokken*) nur in besonderen Konstellationen, zum Beispiel in Verbindung mit Implantaten auf (Mielke und Hansis, 2018). Die Daten von Krankenhaus-Infektions-Surveillance-Systemen (OP-KISS), welche auf der Basis von 10.601 Wundinfektions-Isolaten im Zeitraum Januar 2010 bis Dezember 2014 erhoben wurden, zeigten den Anteil der wichtigsten Erregerarten nach Operations-Gruppen (Tabelle 1).

Tabelle 1. Häufigste Erreger von Wundinfektionen bei ausgewählten Operationsarten in Prozent (Nationales Referenzzentrum für Surveillance von nosokomialen Infektionen (NRZ), 2015)

Erregerart	Allgemein-chirurgie	Abdominal-chirurgie	Gefäß-chirurgie	Herz-chirurgie	Neuro-chirurgie	Alle Operation
S. aureus	33,6	4,0	31,5	24,7	32,9	19,6
Enterococcus spp.	6,4	29,4	17,3	9,7	8,6	17,6
E. coli	6,4	30,4	14,6	5,4	7,9	15,2
Koagulase neg. Staph. *	7,2	1,0	6,9	20,9	13,2	10,3
P. aeruginosa	0,7	5,8	7,4	3,4	2,6	4,1
Enterobacter spp.	1,5	4,5	7,7	4,5	3,3	4,1
Klebsiella spp.	2,3	5,5	6,4	2,9	1,3	3,6

* als alleiniger Erreger

1.3. Entstehung von nosokomialen Infektionen

Nosokomiale Infektionen lassen sich nach der Herkunft der Erreger in endogene und exogene Infektionen unterteilen. Bei endogenen Infektionen sind Mikroorganismen der körpereigenen Flora

der Patienten die Ursache (Geffers et al., 2002). Solche Mikroorganismen können in Haut und Schleimhäute der Patienten kolonisieren und unter bestimmten Umständen sterile Körperbereiche erreichen (Gastmeier et al., 2010). Endogene nosokomiale Infektionen können in zwei Kategorien als primäre und sekundäre endogene nosokomiale Infektionen unterteilen werden (Gastmeier, 2008). Bei primär endogenen nosokomialen Infektionen gehören die Erreger zur normalen Flora der Patienten und sekundär endogenen nosokomialen Infektionen werden die Erreger im Laufe des Aufenthaltes in einem Krankenhaus Teil der patienteneigenen Flora (Gastmeier, 2016). Auf dieser Basis entwickelt sich eine endogene Infektion (Heberer et al., 2010). Hierbei können Operationen, Gefäßkatheter und viele andere Behandlungsfaktoren eine Rolle spielen (Gastmeier et al., 2010).

Exogene Infektionen entstehen durch Aufnahme von Infektionserregern aus der Umwelt oder von anderen Personen (Patienten oder Personal) (Häfner et al., 2015). Die Übertragung dieser Infektionserreger kann durch direkten Kontakt mit Personen (z. B. Hände des Personals), kontaminierte Objekte, die Luft oder durch Wasser geschehen (Gastmeier et al., 2010, Khan et al., 2017). Über den Anteil der durch exogene Erreger bedingten nosokomialen Infektionen gibt es unterschiedliche Angaben. In einer Studie von Grundmann et al. waren 14,5% der Krankenhaus-infektionen als exogene Infektionen durch Übertragung der Erreger über andere Personen verursacht (Grundmann et al., 2005). Laut einer Studie von Weist et al., die auf einer Intensivstation durchgeführt wurde, waren bei mindestens 37,5% aller identifizierten nosokomialen Infektionen exogene Übertragungen der Infektionserreger die Ursache (Weist et al., 2002). Im Gegensatz zu den durch endogene Erreger verursachten nosokomialen Infektionen, die nur teilweise zu verhindern sind, sollten exogen bedingte nosokomiale Infektionen generell verhindert werden (Gastmeier et al., 2010). Abbildung 1 zeigt die Routen der Akquisition nosokomialer Infektionen.

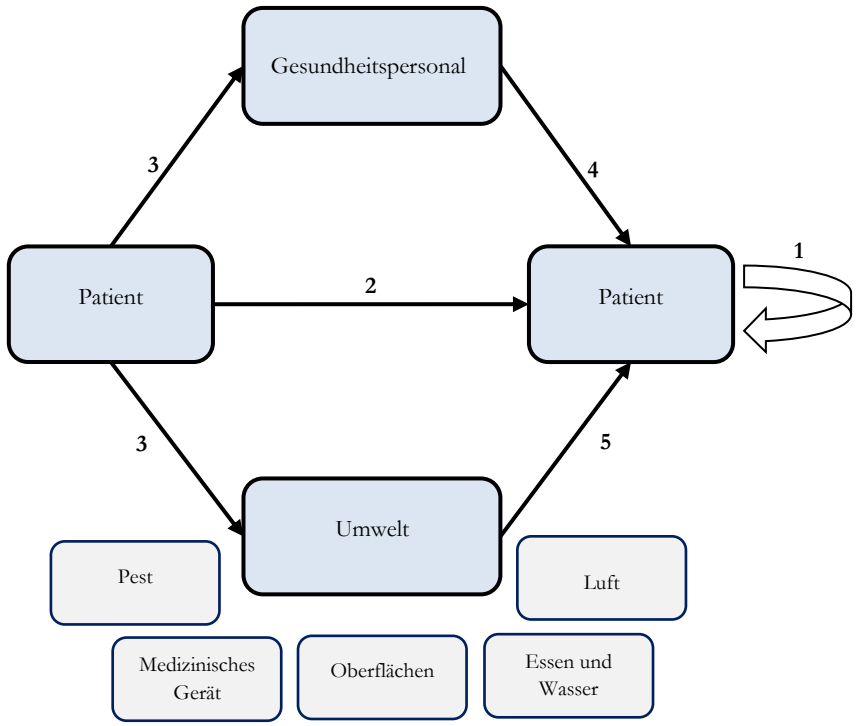

Abbildung 1. Routen der Akquisition nosokomialer Infektionen (Jenkins, 2017).

1. Infektion von Mikroorganismen der körpereigenen Flora der Patienten
2. Direkte Übertragung von Patient
3. Indirekte Übertragung von Patient zu Patient
4. Übertragung durch Gesundheitspersonal
5. Übertragung durch Umweltfaktoren

Im Rahmen des Krankenhaus-Infektions-Surveillance-Systems (KISS, 2018), das die Referenzdaten für das Auftreten nosokomialer Infektionen in Risikobereichen im deutschen Gesundheitssystem liefert und zusätzliche Präventionsmaßnahmen stimuliert, konnte gezeigt werden, dass es für verschiedene Risikogruppen und für verschiedene nosokomiale Infektionen möglich ist, die nosokomialen Infektionsraten durch wiederholte zusätzliche Präventionsmaßnahmen um 20-29% in einer großen Zahl von Krankenhäusern zu senken (Hagel et al., 2013). In einer kontrollierten Studie in Deutschland wurde auch aufgezeigt, dass Surveillance-Maßnahmen und Qualitätszirkel zu einer signifikanten Reduktion der nosokomialen Infektionen um bis 25% führen (Gastmeier et al., 2002). Aufgrund dieser Zahlen kann davon ausgegangen werden, dass in Deutschland 20-30% der nosokomialen Infektionen verhindert werden könnten (Gastmeier et al., 2010).

In den letzten Jahren wurden erhebliche Fortschritte bei der Verringerung der Inzidenz von nosokomialen Infektionen gemacht. Allerdings beschreibt CDC die aktuelle Situation immer noch als kritisch, weil die Verhinderung zahlreicher nosokomialer Infektionen noch immer eine Herausforderung darstellt (Centers for Disease Control and Prevention, 2017). Aufgrund mehrerer Studien zur Infektionspräventionen ist mittlerweile bekannt, dass nur ein Maßnahmenpaket gegen die Entstehung oder die Ausbreitung vorhandener nosokomialer Infektionen wirksam sein kann. Das heißt, einzelne Präventionsmaßnahmen aufgrund mehrerer Faktoren, einschließlich Patienten-variablen, Patientenversorgungsvariablen, administrativer Variablen und der Einsatz aseptischer Techniken durch medizinisches Personal, die die Entwicklung nosokomialer Infektionen beeinflussen, sind kaum wirksam (Collins, 2008).

1.4. Risikofaktoren

Für Krankenhauspatienten besteht ein hohes Infektionsrisiko (Geffers et al., 2002). Dazu kommt die größere Prävalenz von chronischen Krankheiten und der verstärkte Einsatz von diagnostischen und therapeutischen Verfahren, die das Immunsystem von Patienten (bzw. Host) beeinflussen (Ducel et al., 2002). Für jede Art von nosokomialen Infektionen existieren zahlreiche Risikofaktoren. Die folgenden vier sind die Wichtigsten und für die meisten Krankenhausinfektionen zutreffend:

- ***Patientenfaktoren:*** Das Risiko zur Entwicklung von nosokomialen Infektionen steigt durch krankheitsbedingte Vorschädigungen der Patienten. Dazu kommen Faktoren wie Alter, genetische Disposition, Ernährung und Immunabwehr, die im Laufe der Erkrankung eingeschränkt sein könnte (Ducel et al., 2002, Cruz et al., 2010). Eine Studie von Skeie et al. zeigte einen positiven Zusammenhang zwischen dem Ernährungsrisiko und der Inzidenz von Wundinfektion bei chirurgischen Patienten (Skeie et al., 2018). Es ist äußerst schwierig und kaum erfolgreich, diese Risikofaktoren zu beeinflussen.

- ***Umweltfaktoren:*** Patienten mit Infektionen oder Patienten als Träger der pathogenen Mikroorganismen sind potenzielle Infektionsquellen für andere Patienten. Darüber hinaus sind Patienten, die im Krankenhaus infiziert wurden, eine zukünftige Infektionsquelle (Ducel et al., 2002). Auch kann die Krankenhausumgebung die Übertragung nosokomialer Infektionen fördern. So zählen Luft, Wasser sowie die Hände des medizinischen Personals, die nicht desinfiziert wurden, zu den Umweltfaktoren (Jansen und Murphy, 2009, Anaissie et al., 2002).

- ***Mikrobiologische Faktoren:*** Erreger wie *S. aureus* und *P. aeruginosa* sind äußerst virulente Erreger und Verursacher vieler Infektionen. Ist die Immunabwehr bei Patienten eingeschränkt oder liegt eine Schädigung von Haut oder Schleimhaut vor, können schon Erreger mit geringer Virulenz eine Infektion auslösen (Geffers et al., 2002).

- ***Behandlungsfaktoren:*** Invasive Maßnahmen, Diagnostik, Therapie und die fortgeschrittene Gerätemedizin spielen eine immer wichtigere Rolle. Dadurch entstehen aber auch neue Eintrittswege der Erreger in den Körper (Al-Tawfiq und Tambyah, 2014).

1.5. Die wichtigsten nosokomialen Infektionen

Die folgenden vier nosokomialen Infektionen können als die wichtigsten nosokomialen Infektionen bezeichnet werden:

- ***Harnwegsinfektionen:*** Die Harnwegsinfektion ist eine der häufigsten nosokomialen Infektionen und verläuft häufig asymptomatisch (Behnke et al., 2013, Gastmeier und Geffers, 2008). Es gibt eine direkte Assoziation zwischen dem Einsatz von Harnwegskathetern und nosokomialen Harnwegsinfektionen (Saint und Chenoweth, 2003). 10% der Patienten mit Kurzzeit-Katheterisierung entwickeln eine Infektion (Stamm und Norrby, 2001), wobei das

Risiko einer Infektion mit der Länge der Katheterisierungsdauer steigt (Hooton et al., 2010, Al-Hazmi, 2015).

- ***Pneumonien:*** Untere Atemwegsinfektionen sind eine weitere häufige nosokomiale Infektion mit erhöhter Sterblichkeit. Eine Pneumonie kann frühestens 48–72 Stunden nach Aufnahme im Krankenhaus auftreten (Dalhoff et al., 2013). Ihre Inzidenz bei invasiv beatmeten Patienten beträgt 5,4/1000 Beatmungstage, d.h. in Deutschland treten jährlich etwa 15.500 Fälle auf Intensivstationen auf (Meyer et al., 2009).

- ***Postoperative Wundinfektionen:*** Wie andere nosokomiale Infektionen verlängern auch postoperative Wundinfektionen die Krankenhausaufenthaltsdauer und verursachen somit hohe Kosten (de Lissovoy et al., 2009). Die Wundkontaminationsklasse, die Operationsdauer und die Erkrankung des Patienten sind dabei Aspekte, die die Häufigkeit der postoperativen Wundinfektionen beeinflussen (Nagachinta et al., 1987, Leong et al., 2006).

- ***Sepsis (Blutvergiftung):*** In der Regel ist die Häufigkeit der nosokomialen Sepsis geringer als die anderer Krankenhausinfektionen, hat aber erhebliche Konsequenzen für Patienten und Krankenhäuser (Geffers et al., 2002). Die primäre Sepsis definiert sich durch einen kulturellen Nachweis von pathogenen Erregern im Blut, welche mit keiner Infektion an einer anderen Stelle verwandt sein dürfen **oder** durch den Nachweis von mindestens einem Symptom oder Zeichen wie Fieber >38 °C oder Schüttelfrost **und** einem gewöhnlichen Hautkeim (Robert Koch Institut, 2011a).

1.6. Prävention von nosokomialen Infektionen

1.6.1. Allgemeine Präventionsempfehlungen

Die Prävention nosokomialer Infektionen erfordert ein integriertes, überwachtes Programm auf

verschiedenen Ebenen. Ein wichtiger Faktor, um die Infektionsraten im Krankenhaus zu bestimmen, ist die Surveillance nosokomialer Infektionen. Kontrolle der Umweltrisikofaktoren, die Verhinderung der Übertragung der Organsimen zwischen Patienten durch Händedesinfektion, Einsatz von Handschuhen, aseptische Arbeitstechniken, Isolationsstrategien, Sterilisation und Desinfektion, Limitation der endogenen Infektionen bei Beschränkung invasiver Prozeduren und die Kontrolle der Antibiotikaanwendung sind weitere Komponenten der Prävention (Ducel et al., 2002, Geffers et al., 2002).

1.6.2. Überwachung der nosokomialen Infektionen und Risikostratifikation

Die Rate von nosokomialen Infektionen für Patienten in einer Einrichtung ist ein Indikator von Qualität und Sicherheit der Gesundheitsversorgung. Die Entwicklung des Beobachtungsprozesses dieser Rate ist ein erster wichtiger Schritt um das lokale Problem zu identifizieren, Prioritäten zu setzen und die Wirksamkeit von Programmen für eine Infektionskontrolle zu bewerten. Die Überwachung selbst ist ein wirksamer Prozess, um die Häufigkeit nosokomialer Infektionen zu reduzieren (Ducel et al., 2002). Eine Studie von Li et al. zeigte einen positiven Einfluss der Überwachung nosokomialer Infektionen auf die Rate der nosokomialen Infektionen (Li et al., 2017). Die Daten des Krankenhaus-Infektions-Surveillance-Systems zeigten eine Reduzierung der Harnwegsinfektionen um 14% oder der Blutvergiftungen um 17% von 1997 bis 2008 auf deutschen Intensivstationen (Gastmeier et al., 2011, Gastmeier et al., 2015). Darüber hinaus werden nosokomiale Infektionen durch Patientenfaktoren wie Immunstatus und durchgeführte medizinische Interventionen bestimmt. Eine Risikobewertung ist hilfreich, um Patienten zu kategorisieren und Interventionen zur Infektionsbekämpfung zu planen (Ducel et al., 2002, Loveday et al., 2014, Yokoe et al., 2016). Tabelle 2 beschreibt das Risiko für verschiedene Patientengruppen als ein Beispiel für den Ansatz, an den eine bestimmte Einrichtung angepasst werden könnte, welche die Weltgesundheitsorganisation (WHO) in dem praktischen Leitfaden für die Prävention von

nosokomialen Infektionen empfiehlt.

Tabelle 2. Differenzielles Risiko der nosokomialen Infektion nach Patienten und Interventionen (Ducel et al., 2002)

Risiko von Infektion	Art von Patienten	Art von Verfahren
Minimal	nicht immunsupprimiert, nicht signifikante Grunderkrankung	nicht invasive Methode keine Exposition gegenüber biologischen Flüssigkeiten*
Medium	infizierte Patienten oder Patienten mit manchen Risikofaktoren wie z.B. Alter oder Neoplasma	Exposition gegenüber biologischen Flüssigkeiten* oder invasive nicht operative Verfahren
High	schwer immunsupprimierte Patienten (<500 WBC per ml) , multiple Trauma, schwere Verbrennungen, Organtransplantation	Chirurgie oder hohes Risiko invasiver Verfahren

*Biologische Flüssigkeiten umfassen Blut, Urin, Kot, Cerebrospinalflüssigkeit, Flüssigkeit aus Körperhöhlen.

1.6.3. Reduzierung der Übertragung von Person zur Person

Die Desinfektion der Hände ist die wichtigste Einzelpräventionsmaßnahme bei nosokomialen Infektionen. Es ist allgemein akzeptiert, dass die Hände des Personals im Bereich der Patientenversorgung als Hauptursache für die Übertragung von Infektionserregern gelten (Gastmeier, 2008). Obwohl die Maßnahmen zur Prävention nosokomialer Infektionen und ihre Notwendigkeit zur Durchführung für jeden Mitarbeiter in diesem Bereich bekannt sein dürften, werden sie im klinischen Alltag allzu oft nicht durchgeführt. Ein Beleg kann die Compliance zur hygienischen Händedesinfektion des medizinischen Personals sein. Studien zeigten, dass lediglich 40% der erforderlichen Händedesinfektionen durchgeführt wurden (Safety und Organization, 2009) und bei 10% bis 78% des medizinischen Personals *Staphylokoccus aureus* nachgewiesen wurde (Kampf et al., 2009). Um die Rate der nosokomialen Infektionen zu reduzieren, hat die WHO die Verbesserung der Händehygiene als ein Ziel definiert und eine weltweite Kampagne „Clean care is safer care“ für effektive Maßnahmen zur Händehygiene gestartet (Pittet und Donaldson, 2005). Außerdem sind weitere Maßnahmen wie persönliche Hygiene, Schutzkleidung und beispielsweise sichere Injektionspraktiken für eine Reduzierung der Übertragung des Erregers von Person zu

Person entscheidend (Ducel et al., 2002).

1.6.4. Verhinderung der Übertragung aus der Umwelt

Um die Übertragung der Mikroorganismen von Instrumenten und Umwelt zu minimieren, müssen ausreichende Verfahren zum Reinigen, Desinfizieren und Sterilisieren vorhanden sein. Darüber hinaus müssen schriftliche Richtlinien und Verfahren, die regelmäßig aktualisiert werden sollten, für jede Einrichtung entwickelt werden (Bundesgesundheitsbl, 2012, Ducel et al., 2002). Gründliche Desinfektion, Verwendung von heißem Wasser und Sterilisation sind Maßnahmen, die durch die WHO für eine Prävention einer Übertragung aus der Umwelt empfohlen werden (Ducel et al., 2002).

1.7. Gesundheitsökonomische Grundbegriffe

1.7.1. Kosten

Die Komponenten der gesundheitsökonomischen Evaluation bestehen aus dem Ressourcen-verbrauch eines Gesundheitsprogramms einerseits und der Verbesserung des Gesundheitszustandes eines Individuums andererseits (Szucs et al., 2006). In der Gesundheitswirtschaft wird der Ressourcenverbrauch durch die Kosten determiniert und bewertet. Die Kosten werden in verschiedene Kategorien unterteilt. In einer der wichtigsten Kategorien werden die Kosten nach der Zurechenbarkeit nach direkten und indirekten Kosten klassifiziert (Schöffski und von der Schulenburg, 2011). Die direkten Kosten konzentrieren sich auf den Ressourcenkonsum von Gesundheitsleistungen, die sowohl aktuell als auch zukünftig erstellt werden (IQWIG, 2017). Sie sollten in zwei Unterkategorien differenziert werden. Einerseits die direkten nicht gesundheitsrelevanten Kosten, die außerhalb des medizinischen Bereichs als Folgen der Krankheitsbehandlung anfallen. Dazu zählen z.B. Fahrtkosten oder der ökonomisch bewertete Zeitaufwand der Patientenangehörigen, der durch die Erkrankung entsteht (Drummond et al., 2001). Andererseits die direkten gesundheitsrelevanten Kosten, welche in Finanz- oder Rechnungsanalysen

in variable und fixe Kosten klassifiziert werden. Die variablen Kosten variieren je nach Krankheiten und Behandlungen (Medikamente oder Arbeitszeit der Ärzte). Die fixen Kosten ändern sich bei Schwankungen der Fallzahl nicht und bleiben kurz- bis mittelfristig unverändert. Beispiele für die fixen Kosten sind Gebäudekosten oder medizinische Geräte (Roberts et al., 1999). Neben direkten Kosten gibt es indirekte Kosten, welche in ökonomischen Evaluationen ebenso berücksichtigt werden sollten. Bezüglich der indirekten Kosten sollte vor allem der volkswirtschaftliche Produktionsverlust aufgrund von Arbeitsunfähigkeit, Invalidität und vorzeitigem Tod beachtet werden. Hier können als Beispiel die Ergebnisse der Krankheitsartenstatistik der gesetzlichen Krankenversicherung zu Arbeitsunfähigkeit der Pflichtmitglieder - ohne Rentner – infolge Streptokokkensepsis (ICD 10: A40) angeführt werden, die zeigt, dass eine Streptokokkensepsis eines Mitarbeiters Ausfallzeiten in Höhe von 13 bis zu 26 Tagen verursachen kann oder eine sonstige Sepsis (ICD 10: A41) bei einer Mitarbeiterin bis zu 20 Arbeitsunfähigkeitstagen und bei einem Mitarbeiter bis zu 26 Tagen (GKV-Statistik KG8, 2016). In einer anderen Kategorie werden die Kosten nach der Tangibilität in tangible (z.B. Kosten des ärztlichen Dienstes) und intangible Kosten (z.B. Schmerzen bei der Behandlung) eingeteilt, die meist durch direkte Umfragen geschätzt werden können, obwohl indirekte Methoden für solche Schätzungen verfügbar sind (Schöffski und von der Schulenburg, 2011). Zu den intangiblen Kosten aufgrund nosokomialer Infektionen gehören psychologische Kosten (d. h. Angst, Trauer, Behinderung, Arbeitsplatzverlust), Schmerz und Leiden, Veränderungen in der sozialen Funktionsweise / täglichen Aktivitäten (Scott, 2009). Für sie sind allgemein akzeptierte Werte oft schwer zu finden.

1.7.2. Opportunitätskosten

Da die Ressourcen in einem Gesundheitssystem knapp sind, sollte berücksichtigt werden, dass der Entscheidungsträger aufgrund der Budgetbegrenzung in seinem Entscheidungshandeln eingeschränkt ist (Shiell et al., 2002). Das Grundkonzept der Opportunitäts- oder Alternativkosten

besteht darin, dass die Kosten einer Handlungsalternative der Nutzen einer oder mehrerer anderer Handlungsalternativen sind, welche aufgrund der Entscheidung nicht gewählt werden kann (Palmer und Raftery, 1999). Das Problem der Knappheit im Gesundheitswesen kann durch den Opportunitätskostenansatz sichtbar werden. Direkte Kosten beziehen sich hauptsächlich auf die Opportunitätskosten bzw. Alternativkosten von Gütern und Dienstleistungen im Gesundheitswesen (Schöffski und von der Schulenburg, 2011). Das Denken in alternativen Verwendungsmöglichkeiten ist typisch für das betriebswirtschaftliche Denken (Fleßa und Greiner, 2013).

1.7.3. Nutzen

Das Resultat des Produktionsprozesses ist nicht die Gesundheit, sondern eine Gesundheitsleistung, die quantitativ gemessen werden kann (Fleßa und Greiner, 2013). Demnach entsteht der Nutzen im Gesundheitswesen aus der Veränderung des Gesundheitszustandes. Wie die Kosten wird auch der Nutzen in die drei Kategorien direkt, indirekt sowie intangible klassifiziert. Beispielweise wäre ein indirekter Nutzen die Anzahl geretteter Leben bzw. gewonnener Lebensjahre, oder die Vermeidung künftiger Aufenthaltstage im Krankenhaus. Für den intangiblen Nutzen können die Effekte der Therapie genannt werden, z.B. die Verringerung von Angst und Schmerzen (Szucs et al., 2006). Mit indirekten Kosten und Nutzen können die positiven und negativen Effekte einer Gesundheitsleistung bewertet werden (Schöffski und von der Schulenburg, 2011).

1.7.4. Perspektive der Kosten und Nutzen

Die Auswahl der Perspektive hat einen wesentlichen Einfluss auf die Ergebnisse bei Zurechnung der Kosten und des Nutzens in gesundheitsökonomischen Evaluationen. Abhängig ist dies vom Ziel der Studien, und demzufolge der Sichtweise der gesundheitsökonomischen Analyse. Die Kosten und der Nutzen der medizinischen Leistungen können aus der Sicht der Gesellschaft, der Leistungserbringer, der Krankenkassen sowie anderer Kostenträger oder der Patienten betrachtet werden (Schöffski und von der Schulenburg, 2011). Es soll möglicherweise berücksichtigen werden in gesundheits-

ökonomischen Evaluationen Perspektive der Kosten und Nutzen bei jeder einzelner Komponenten zu synchronisieren (Graf von der Schulenburg et al., 2007).

1.7.5. Inflationsbereinigung und Diskontierung

Eine andere wichtige Voraussetzung der ökonomischen Evaluationen ist die zeitliche Anpassung der Kosten und des Nutzens. Die Kostendaten sollten aufgrund unterschiedlicher Zeitperioden des Datenstammes inflationsbereinigt werden. Die allgemeine Methode des IQWiG drückt aus, dass für die jährliche Inflation der harmonisierte Verbraucherpreisindex des Statistischen Bundesamts verwenden werden soll (IQWIG, 2017, Statistisches Bundesamt, 2018). Für die Inflationsbereinigung der Kostendaten aus anderen Ländern kann die Inflationsrate der World Bank (World Bank Group, o.D.) oder die jährliche Inflationsrate der OECD (Organisation for Economic Co-operation and Development, o.D.) verwendet werden. Aus ökonomischer Sicht ist die Berechnung von Gegenwartswerten notwendig, wenn die Kosten und/oder der Nutzen über mehr als ein Jahr anfallen. Künftige Kosten und Nutzen müssen deshalb mittels eines entsprechenden Zinssatzes diskontiert werden (Graf von der Schulenburg et al., 2007). Ein Diskussionsthema in der Gesundheitsökonomie ist die Höhe des zu verwendenden Diskontsatzes. Durch verschiedene Leitlinien wurden unterschiedliche Diskontierungsraten empfohlen, beispielweise ist die allgemeine Methode des IQWiG auf 3% festgeschrieben. Es wurde jedoch von deutsche Empfehlungen zur gesundheitsökonomischen Evaluation - dritte und aktualisierte Fassung des Hannoveraner Konsens - eine jährliche Referenz-Diskontierungsrate von 5% empfohlen (Graf von der Schulenburg et al., 2007). Es empfiehlt sich deshalb, die ökonomischen Evaluationen mehrmals mit verschiedenen Zinssätzen als Sensitivitätsanalyse zu berechnen, um deren Effekte auf das Ergebnis abschätzen und relativieren zu können (Attema et al., 2018).

1.8. Gesundheitsökonomische Evaluationsformen

In gesundheitsökonomischen Evaluation gibt es verschiedene Studienformen für Evaluationen, die die Kosten- und Nutzenkomponenten unterschiedlich betrachten. Die gesundheitsökonomischen Studien konnten in vergleichende Studien und nicht-vergleichende Studien unterschieden werden (Schöffski und von der Schulenburg, 2011). Abbildung 2 zeigt die Studienformen der gesundheitsökonomischen Evaluationen, die gemäß Fragestellung und Ziel für die Evaluationen ausgewählt werden können.

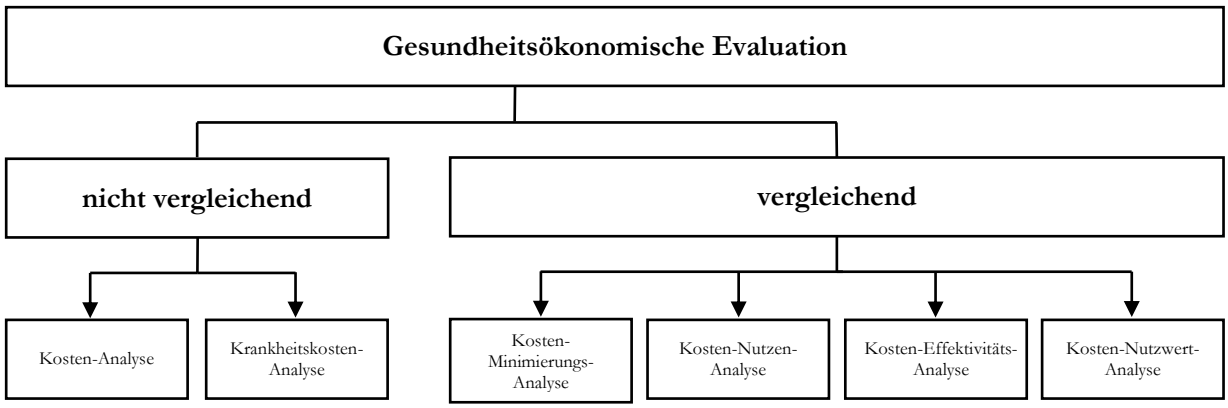

Abbildung 2. **Die Formen der gesundheitsökonomischen Evaluationen** (Schöffski und von der Schulenburg, 2011)

1.8.1. Kosten-Analyse

Ein andere Form der ökonomischen Studien ist die reine Kostenanalyse (englisch: cost analysis), die beispielweise für die Kostenberechnung der Behandlungsmethode oder einer bestimmten Maßnahme verwendet wird. In dieser Studienform sollten möglichst alle Kosten gemäß der gewählten Perspektive berücksichtigt werden. Mithilfe der Kostenanalyse können sowohl direkte als auch indirekte Kosten betrachtet werden. Es ist aber nicht möglich, allein mit den Ergebnissen derartiger Kostenanalysen Entscheidungen für oder gegen bestimmte Maßnahmen oder Behandlungsmethoden zu treffen (Schöffski und von der Schulenburg, 2011). Es ist jedoch ein Vergleich mit einer Alternative möglich, wenn auch eine Kostenanalyse für die alternative

Behandlungsmethode oder Maßnahme bewertet wird, dass in diesem Fall in Gesundheitsökonomie als Kosten-Kosten-Analyse bezeichnet wird (Drummond et al., 2015, Schöffski und von der Schulenburg, 2011).

1.8.2. Krankheitskostenanalyse

Die Krankheitskostenanalyse wird in ökonomischen Untersuchungen verwendet, wenn die wirtschaftliche Auswirkung einer Krankheit in Anbetracht aller Kosten sowie Konsequenzen ermittelt werden soll. Hier werden die direkten, indirekten und intangiblen Kosten, wenn möglich, für eine bestimmte Erkrankung bestimmt und erfasst (Byford et al., 2000). Zwar werden keine Therapieformen mit der Krankheitskostenanalyse verglichen, jedoch ist es von großer Bedeutung den Entscheidungsträgern im Gesundheitswesen eine Abschätzung der sozialen Belastung einer Krankheit zur Verfügung zu stellen. Auf diese Weise kann eine bessere Entscheidung bezüglich der Allokation der Ressourcen getroffen werden. Weiterhin könnten solche Studien die Grundlage weiterer sozioökonomischer Analysen bilden (Szucs et al., 2006, Jo, 2014). Die Methoden zur Krankheitskostenschätzung basieren in der Regel darauf, welche Daten verfügbar sind. Daher gibt es zahlreiche Variationen bei den Schätzverfahren. Diese Methoden können in *micro* und *macro costing* kategorisiert werden (Larg und Moss, 2011). Bei der *macro costing*-Methode werden für die Krankheitskostenanalyse hoch aggregierte volkswirtschaftlichen Daten, wie z.B. Anzahl der Sterbefälle, durchschnittliche Aufenthaltsdauer im Krankenhaus oder Arbeitsunfähigkeitstagen, die durch das Statistische Bundesamt oder die Verbände der Krankenkassen etc. zur Verfügung gestellt werden, verwendet (Schöffski und von der Schulenburg, 2011). Wenn die globale Zahl durch die Zahl der Betroffenen dividiert wird, werden die Krankheitskosten für den einzelnen Patienten bestimmt (Suaya et al., 2007). Bei der *micro costing*-Form sollte jeder einzelne Patient berücksichtigt werden. Es wird ein Durchschnittspatient mit einer bestimmten Erkrankung definiert. Die direkten Kosten können entweder gemäß ihres tatsächlichen Anfalls oder anhand der üblichen Behandlung

mit Hilfe von repräsentativen Entgelten, z.B. DRG bewertet werden (Schöffski und von der Schulenburg, 2011, Larg und Moss, 2011).

1.8.3. Kosten-Minimierungs-Analyse

Kosten-Minimierungs-Analyse (Kosten-Kosten-Analyse) ist eine wirtschaftliche Untersuchung, bzw. ein Vergleich zwischen separaten Kosten-Analysen von alternativen Maßnahmen (Schöffski und von der Schulenburg, 2011). Ziel der Kosten-Minimierungs-Analyse ist die Ermittlung der kostengünstigen Alternative. Typischerweise wird sie verwendet, um die Situation zu beschreiben, in der die Folgen von zwei oder mehr Behandlungen oder Programmen weitestgehend gleichwertig sind, so dass die Nettokosten verglichen werden, um die kostengünstigste Alternative zu ermitteln (Drummond et al., 2015).

1.8.4. Kosten-Nutzen-Analyse

Das Unterscheidungsmerkmal der Kosten-Nutzen-Analyse (englisch: cost-benefit analysis) ist der Einsatz der monetären Einheiten für gesundheitliche Nutzenkomponenten (Brent, 2004). In dieser gesundheitsökonomischen Untersuchungsform werden alle Kosten und Konsequenzen in Geldbeträgen ausgedrückt. Auf diese Weise können zwei oder mehr Behandlungsalternativen anhand der zusammenfassenden Metrik des Nettogeldnutzens verglichen werden. Hierbei handelt es sich um die Differenz zwischen dem Nutzen jeder Behandlung (ausgedrückt in Geldeinheiten) abzüglich der Kosten (Drummond et al., 2015, Szucs et al., 2006). Monetäre Bewertungen des gesundheitlichen Ergebnisses werden im Allgemeinen durch Erhebungen zur Zahlungsbereitschaft (WTP = Willingness To Pay) oder „*Discrete Choice Analysis*“ erhalten. „*Discrete Choice Analysis*“ ist eine quantitative Methode, die immer mehr zur Präferenzmessung im Gesundheitswesen eingesetzt wird, um Präferenzen von Teilnehmern (Patienten, Kostenträger, Beauftragten) zu entlocken, ohne sie direkt zu bitten, ihre bevorzugten Optionen anzugeben (York Health Economics Consortium,

2016b). Die Kosten-Nutzen-Analyse wird in der Gesundheitstechnologiebewertung selten eingesetzt, da es schwierig ist, monetäre Werte mit Gesundheitsergebnissen (wie erhöhte Überlebensrate) in Verbindung zu bringen (York Health Economics Consortium, 2016a).

1.8.5. Kosten-Effektivitäts-Analyse

Die Kosten-Effektivitäts-Analyse ist eine häufig verwendete gesundheitsökonomische Untersuchung, in welcher die medizinischen Ergebnisse einer Maßnahme oder eines Programms in nicht-monetären Einheiten und Kosten in monetären Einheiten berücksichtigt werden. Anhand der Kosten-Effektivitäts-Analyse werden die Differenzen der Kosten und Effekte einer Intervention und ein oder mehrerer Alternativen berechnet. Anschließend werden die berechneten Differenzen als Verhältnis (*ratio*) ausgedrückt (Gray et al., 2011). Die größte Einschränkung der Kosten-Effektivitäts-Analyse besteht darin, dass es aufgrund spezifischer Maßnahmen bei der Bewertung der Effekte einer bestimmten Behandlung bzw. eines Programms schwierig ist, die Opportunitätskosten anderer Programme zu bewerten, die in das gleiche Budget fallen (Drummond et al., 2015).

1.8.6. Kosten-Nutzwert-Analyse

Die Kosten-Nutzwert-Analyse (cost-utility analysis) ist eine weitere gesundheitsökonomische Untersuchungsform, die häufig als Unterform der Kosten-Effektivitäts-Analyse benannt wird (Liljas und Lindgren, 2001). Der einzige Unterschied zwischen den Formen ist die Nutzung eines generischen Maßes an gesundheitlichem Gewinn für die Konsequenzen jedoch als Nutzen (Drummond et al., 2015). Bei der ökonomischen Bewertung von Interventionen im Gesundheitswesen werden Nutzwerte verwendet, um die Präferenzen der betroffenen Zielgruppe für verschiedene Gesundheitszustände darzustellen. Wenn die Nutzwerte über eine Population von Respondern gemittelt werden, können sie als Bewertungen von Gesundheitszuständen betrachtet werden. Üblicherweise liegen die Werte zwischen 0 (Bewertung von Tod) und 1 (Zustand

vollkommener Gesundheit) (York Health Economics Consortium, 2016c). Die Nutzwerte können durch Schätzung oder durch Befragung von Beteiligten bestimmt werden. Darüber hinaus können sie durch Literaturrecherchen, bereits durchgeführte Erhebungen oder durch empirische Messungen berechnet werden (Szucs et al., 2006).

1.9. Belastung durch nosokomiale Infektionen

1.9.1. Letalität und Morbidität aufgrund nosokomialer Infektionen

Nosokomiale Infektionen stellen durch ihre hohe Letalität und Morbidität ein dringendes krankenhaushygienisches Problem in einem Gesundheitssystem dar. Schätzungen zur Letalität gehen davon aus, dass pro Jahr in Deutschland 10.000-15.000 Patienten bei 400.000–600.000 nosokomialen Infektionen versterben (Gastmeier und Geffers, 2008). Es wurde ebenfalls geschätzt, dass ca. 1.000 bis 4.000 Patienten pro Jahr in Deutschland an Infektionen durch multiresistente Erreger sterben (Gastmeier et al., 2016). 8,8% der Patienten mit nosokomialer Pneumonie versterben auf deutschen Intensivstationen. Die Letalität auf Intensivstationen bei Patienten mit primärer Sepsis beträgt 10,9% (Gastmeier et al., 2005). Nach den Daten der deutschen SepNet-Prävalenzstudie (SepNet Critical Care Trials Group, 2016) betrugen die Intensiv- und Krankenhaussterblichkeit 44,3% und 50,9% für den septischen Schock nach der neuen SEPSIS-3-Definition (Singer et al., 2016).

1.9.2. Ökonomische Konsequenzen der nosokomialen Infektionen

Nosokomiale Infektionen stellen einen erheblichen Kostenfaktor dar, da sie die Aufenthaltsdauer der Patienten im Krankenhaus verlängern. Darüber hinaus sind zusätzliche diagnostische Maßnahmen und medikamentöse Behandlungen notwendig (Graves et al., 2009). Insgesamt wird das US-Gesundheitssystem mit 28 bis 45 Milliarden US-Dollar jährlich durch direkte Kosten nosokomialer Infektionen belastet (Scott, 2009). Die europäische Kommission berichtete, dass das europäische Gesundheitssystem mit mindestens sieben Milliarden Euro durch Krankenhausinfektionen pro Jahr

belastet wird (Prevention und Control, 2008). Hinsichtlich der ökonomischen Belastung gilt insbesondere die Verweildauerverlängerung als Ursache für einen großen Anteil der Gesamtkosten (Graves et al., 2010).

Viele Publikationen konnten wiederholt zeigen, dass die Implementierung von Maßnahmen zur Infektionsprävention den größten Nutzen für die Patienten bringt. Aufgrund begrenzter einsetzbaren Mittels im Gesundheitswesen ist es nötig, dass die Ressourcen so eingesetzt werden, dass sie quantifizierbare gesundheitliche Vorteile liefern. Je mehr Nutzen pro ausgegebenem Euro erzielt werden kann, desto besser ist dies für eine optimale Ressourcenallokation (Graves et al., 2009). Hauptkostentreiber bei einer nosokomialen Infektion ist die dadurch verursachte längere Krankenhausverweildauer (Graves et al., 2010). Es ist bekannt, dass das Gesundheitssystem in Deutschland immer wieder versucht, die Verweildauer in Krankenhäusern zu verkürzen. Die durchschnittliche Verweildauer wurde in deutschen Krankenhäusern (Abbildung 3) von 13,3 Tagen im Jahr 1992 auf 7,3 Tage im Jahr 2017 verkürzt (Statistisches Bundesamt, o.D.). Problem hierbei ist die genaue Messung der durch die nosokomialen Infektionen verursachten zusätzlichen Verweildauer, da die nosokomialen Infektionen zu jeder Zeit des Krankenhausaufenthaltes auftreten können und durch andere Faktoren, wie Begleiterkrankungen beeinflusst werden können (Barnett et al., 2011). Darüber hinaus kann die durch die nosokomialen Infektionen verursachte Verweildauerverlängerung durch ein anderes medizinisches Ereignis, wie z.B. der Tod des Patienten, überlagert werden (Beyersmann et al., 2011). Daher wurden in verschiedenen Studien verschiedene Methoden zur Berechnung der Verweildauerveränderung durch nosokomiale Infektionen eingesetzt. Dabei hat jede dieser Methoden Vor- und Nachteile. Während z.B. ein „case review“ (deutsch: Fallstudie) sehr zeitaufwendig ist, besteht bei einer Fallkontrollstudie trotz Matching die Gefahr eines Selektionsbias bzw. bei vielen Matching-Variablen die Gefahr einer nicht ausreichenden Anzahl an Matching-Partnern. Matching im Rahmen der medizinischen Statistik ist der Prozess, bei dem die

Verteilung der Matchingfaktoren zwischen den Studiengruppen identisch ist. Einige häufig verwendete Matchingvariablen sind Alter, Geschlecht, Rasse und sozioökonomischer Status (Porta et al., 2014). Zudem ist bekannt, dass Fallkontrollstudien die ökonomische Belastung von nosokomialen Infektionen bis zum Faktor 2 überschätzen, da sie die Zeitabhängigkeit der nosokomialen Infektionen nicht berücksichtigen (Beyersmann et al., 2006). Um solche Verzerrungen bei der Berechnung der Verweildauerveränderung durch nosokomiale Infektionen zu vermeiden, sollte die Zeit des Auftretens der nosokomialen Infektionen berücksichtigt werden, welche in sog. Multistate-Modellen beachtet wird.

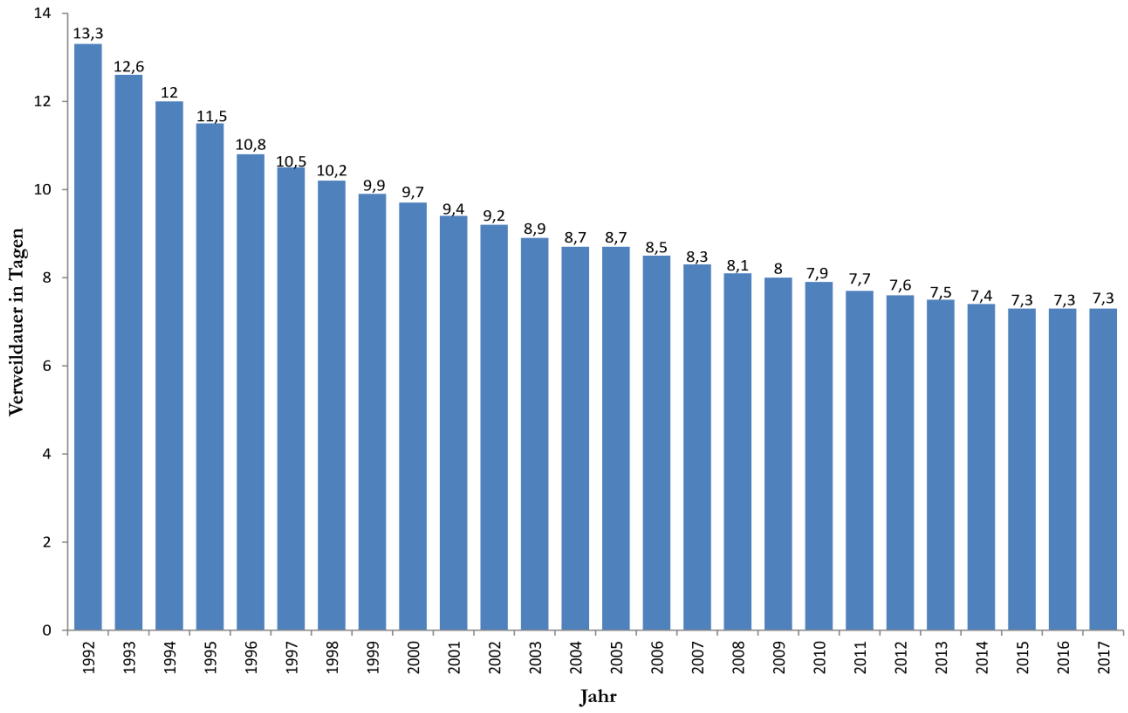

Abbildung 3. Durchschnittliche Verweildauer (in Tagen) in deutschen Krankenhäusern in den Jahren 1992 bis 2017 (Statistisches Bundesamt, o.D.)

1.10. Multistate-Modell

Als Bias (Verzerrung) ist die systematische Abweichung von Studienergebnissen oder Schlussfolgerungen von der Wahrheit definiert. Da ein Bias zu falschen Schlussfolgerungen führen

kann, ist dessen Minimierung ein wichtiges Ziel vieler guter Studien (Hennekens et al., 1987). In einer „Time-to-Event"- oder Überlebensanalyse können Probleme auftreten, wenn sich Variablen im Modell nach Beginn der Patientenbeobachtung ändern (Altman und Bland, 1998). Solche Variablen werden als „time-dependent" bezeichnet, da sich ihr Wert mit der Zeit ändern kann (van Walraven et al., 2004). Ein Beispiel für „time dependent"-Variablen sind nosokomiale Infektionen in Krankenhaus, die bei Aufnahme nicht vorhanden sind und erst nach 48 Stunden oder später nach Aufnahme in das Krankenhaus auftreten. „Time-dependent bias" können auftreten, wenn solche Variablen nicht angemessen analysiert werden (Beyersmann et al., 2008). Die Quantifizierung der zusätzlichen Verweildauer in Tagen aufgrund nosokomialer Infektionen ist entscheidend für gesundheitsökonomische und gesundheitspolitische Entscheidungsträger. Diese Analyse ist jedoch kompliziert, da die Patienten einige Zeit im Krankenhaus waren, bevor sie infiziert wurden. Diese Zeit erfordert eine spezifische Überlegung in der Analyse der Behandlung nosokomialer Infektionen als zeitabhängige Exposition (Barnett et al., 2011).

Mit Hilfe des Multistate-Modells kann die Änderung der Verweildauer durch nosokomiale Infektionen bestimmt werden. Multistate-Modelle haben im Gegensatz zu den anderen erwähnten Methoden den Vorteil, dass sie die Zeitabhängigkeit der nosokomialen Infektionen berücksichtigen können. Dabei sind Aufnahme, nosokomiale Infektion, Tod und Entlassung Zustände, in denen sich der Patient befinden kann, wobei Tod und Entlassung als Endpunkte betrachtet werden. Zwischen den Zuständen wird die Gefahr (Englisch: „Hazard") modelliert (Abbildung 4).

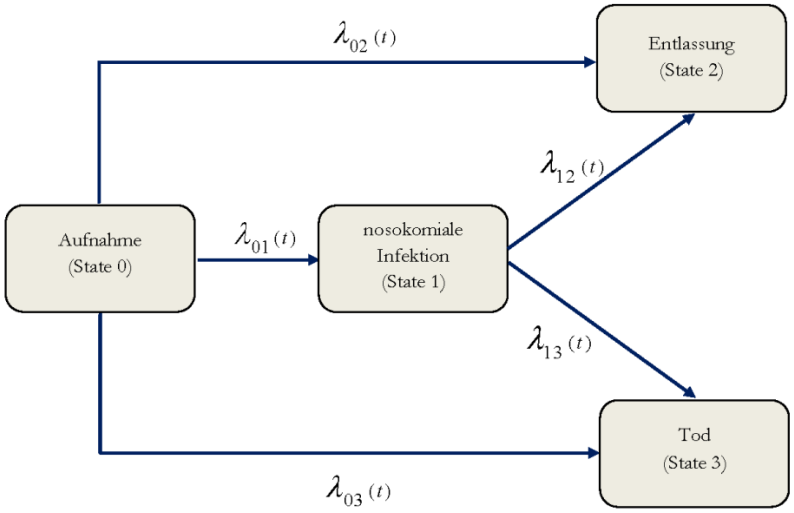

Abbildung 4. Multi State-Modell mit vier Zuständen

Die „Hazard" ist die Wahrscheinlichkeit, dass ein bestimmtes Ereignis innerhalb eines definierten Zeitraums stattfindet. In diesem Multistate-Modell ist „Hazard" ungefähr gleich der Wahrscheinlichkeit, Zustände im nächsten kurzen Zeitintervall zu ändern, geteilt durch die Länge des Intervalls, vorausgesetzt, die Patienten befanden sich bis zu diesem Zeitpunkt im aktuellen Zustand. Die Hazard kann so $\lambda_{ij}(t) = \lambda_{ij}$ als die Gefahr für den Übergang von Zustand i zum Zustand j bezeichnet werden (Allignol et al., 2011, Barnett et al., 2011). Die Verweildauerverlängerung aufgrund der nosokomialen Infektionen kann mit folgender Gleichung geschätzt werden:

$$\textbf{Zusätzliche Verweildauer} \text{ (in Tage)} = \left(\frac{\lambda_{02} + \lambda_{03}}{\lambda_{12} + \lambda_{13}} - 1\right) \times \frac{1}{\lambda_{01} + \lambda_{02} + \lambda_{03}}$$

Die Verweildauerverlängerung ist gleich null, wenn $\lambda_{02}+\lambda_{03} = \lambda_{12}+\lambda_{13}$, ist positiv, wenn $\lambda_{02}+\lambda_{03} > \lambda_{12}+\lambda_{13}$ und ist negativ, wenn $\lambda_{02}+\lambda_{03} < \lambda_{12}+\lambda_{13}$ (Barnett et al., 2011).

1.11. Antimikrobielle Therapie für nosokomialen Infektionen

Zwischen 2000 und 2010 stieg der weltweite Antibiotikakonsum um mehr als 30 Prozent, von rund 50 Milliarden auf 70 Milliarden Standardeinheiten an. Diese Zahlen basieren auf Daten aus 71 Ländern einschließlich der meisten bevölkerungsreichsten Länder (Van Boeckel et al., 2014). Der Verbrauch pro Kopf ist in Ländern mit hohem Einkommen höher, der größte Anstieg des Antibiotika-Konsums zwischen 2000 und 2010 war jedoch in den Ländern mit niedrigem und mittlerem Einkommen zu beobachten, in welchen der Verbrauch weiterhin steigt (Abbildung 5).

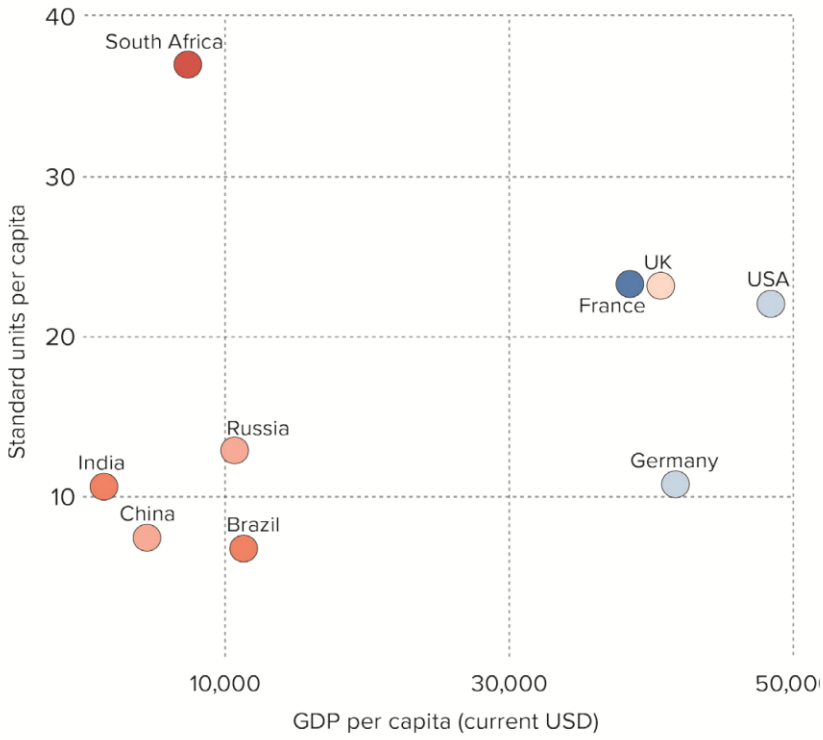

Abbildung 5. Antibiotikaeinsatz pro Kopf-Einkommen in ausgewählten Ländern in 2010 (Gelband et al., 2015)

Aktuelle Daten der European ESAC-Net (European Surveillance of Antimicrobial Consumption Network) zeigen, dass in Europa die höchsten Antibiotika-Konsumraten auf die südeuropäischen Staaten, die niedrigsten Verbrauchsraten auf Skandinavien und die Niederlande entfallen. Im europäischen Vergleich hat Deutschland einen mittleren bis niedrigen Antibiotika-Verbrauch im

ambulanten Sektor. Verglichen mit anderen europäischen Ländern jedoch werden Reserve- oder Breitspektrumantibiotika in Deutschland häufiger im ambulanten Bereich eingesetzt (Bundesministerium für Gesundheit, 2015). Abbildung 6 zeigt den Antibiotikaeinsatz in ausgewählten Ländern im Jahr 2015. Insgesamt erhielten etwa ein Viertel der hospitalisierten Patienten und die Hälfte der Patienten auf den Intensivstationen ein Antibiotikum. Etwa die Hälfte der Patienten erhielt ein Antibiotikum aufgrund einer erworbenen Infektion, etwa ein Drittel erhielt Antibiotika zur Prophylaxe und weniger als ein Fünftel erhielt Antibiotika aufgrund einer im Krankenhaus erworbenen Infektion (Hansen et al., 2013).

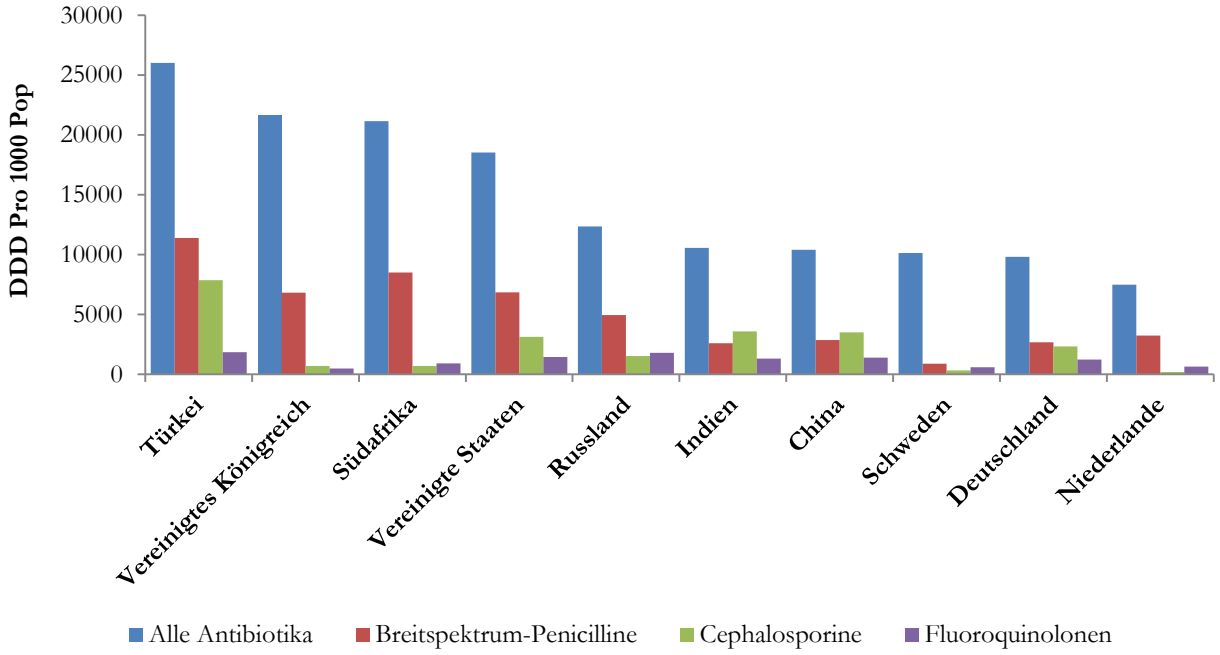

Abbildung 6. Antibiotikaeinsatz in ausgewählten Ländern im Jahr 2015 (Center for Disease Dynamics, 2018)

Nach einer Prävalenz-Studie im Jahr 2016 in deutschen Krankenhäusern, waren die am häufigsten eingesetzten Antibiotika-Klassen für die Behandlung der nosokomialen Infektionen Penicillin mit β-Lactamase, gefolgt von der Fluorchinolonen, Carbapenemen und Glycopeptiden. Cephalosporine der 2. Generation wurden am häufigsten für die präoperative Prophylaxe eingesetzt (Behnke et al.,

2017). Für die Therapie von nosokomialen Atemwegsinfektionen wurden am häufigsten Penicilline plus Beta-Lactamase-Inhibitoren, Fluorchinolone und Carbapeneme eingesetzt. Für die Therapie der nosokomialen Sepsis wurden Penicilline plus Beta-Lactamase-Inhibitoren, Glycopeptid-Antibiotika und Carbapeneme, und für die Therapie von nosokomialen Harnwegsinfektionen Fluorchinolone, Penicilline plus Beta-Lactamase-Inhibitoren und Cephalosporine der 2. Generation verwendet. Abbildung 7 zeigt die Anwendung der zehn häufigsten Antibiotika-Klassen für die Therapie von Atemwegsinfektion, Sepsis und Harnwegsinfektionen (Nationales Referenzzentrum für Surveillance von nosokomialen Infektionen (NRZ), 2016).

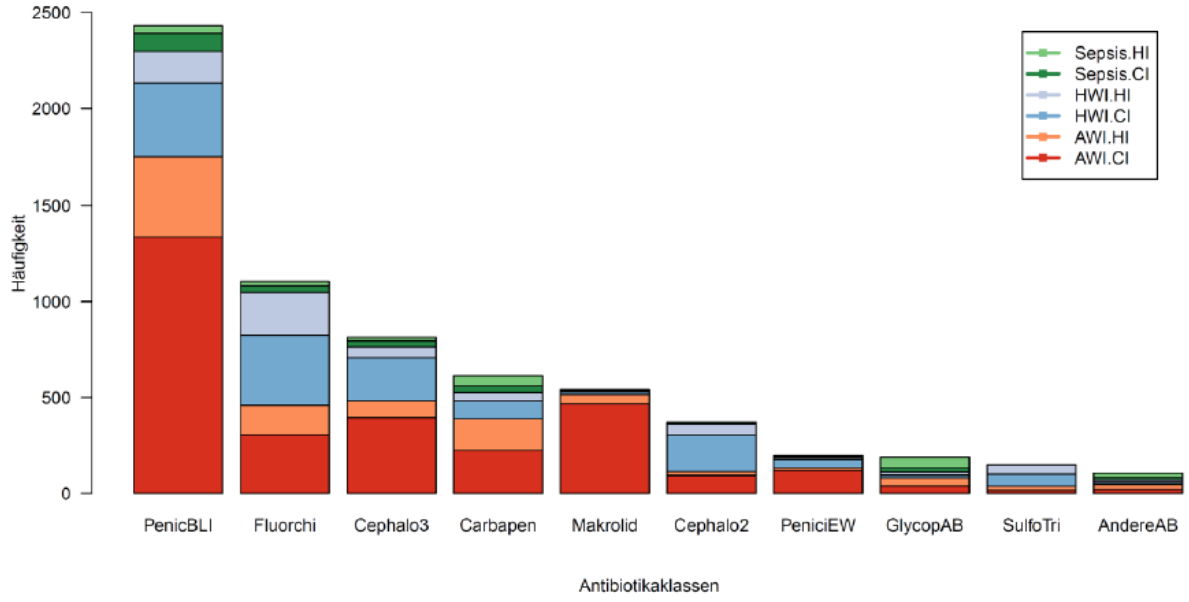

Abbildung 7. Anwendung der häufigsten Antibiotika-Klassen für die Therapie von Atemwegsinfektion, Sepsis und Harnwegsinfektionen (CI= mitgebrachte Infektion, HI= nosokomiale Infektion, PenicBLI= Penicilline plus Beta-Lactamase-Inhibitoren, Fluorchi= Fluorchinolone, Cephalo3= Cephalosporine der 3. Generation, Carbapen= Carbapeneme, Cephalo2= Cephalosporine der 2. Generation, PeniciEW= Penicilline mit erweitertem Wirkungsspektrum, GlycopAB=Glycopeptid-Antibiotika, SulfoTri=Kombinationen von Sulfonamiden und Trimethoprim inkl. Derivate, AB= Antibiotika) (Nationales Referenzzentrum für Surveillance von nosokomialen Infektionen (NRZ), 2016)

Obwohl ein längerer Krankenhausaufenthalt die wichtigste wirtschaftliche Konsequenz nosokomialer Infektionen ist, sind Daten zu den zusätzlichen Kosten der antimikrobiellen Behandlungen für gesundheitspolitische Entscheidungen sehr wichtig.

2. Ziele der Arbeit

Das Ziel der vorliegenden Arbeit bestand darin, eine gesundheitsökonomische Evaluation unter verschiedenen Aspekten bezüglich nosokomialer Infektionen durchzuführen. Im Fokus stand dabei, die Kosten der Sepsis aus verschiedenen Kostenperspektiven und durch verschiedene Methoden zu analysieren, Kosten-Nutzen Analysen der Präventionsmaßnahmen zur Verhinderung nosokomialer Infektionen durchzuführen, die Verweildauerveränderungen bei nosokomialen Patienten und die zusätzlichen Kosten zu berechnen. Darüber hinaus sollte die Verweildauerverlängerung und ökonomische Belastungen der postoperativen Wundinfektion nach Koronararterien-Bypass-Chirurgie (CABG) berechnet werden.

Als Ausgangspunkt für alle vorliegenden Arbeiten sollte zunächst relevante und wichtige Literatur zu den gesundheitsökonomischen Ergebnissen bei verschiedenen Interventionsmaßnahmen innerhalb von Präventionsprogrammen zur Verhinderung nosokomialer Infektionen identifiziert werden. Es sollte durch eine Kosten-Nutzen Analyse ermittelt werden, ob die verschiedenen Maßnahmen effizient sind bzw. ob aufgrund der vorliegenden Daten eine ökonomische Aussage möglich ist. Für dieses Ziel sollten die Interventionskosten und Kosteneinsparungen hinsichtlich der Interventionsmaßnahmen berechnet und durch ein „savings-to-cost ratio“ und „net-saving“ die Effizienz jeder Intervention bewertet werden. Einen weiteren Schwerpunkt der Arbeit bildeten krankenhausrelevante Kosten der Sepsis (Intensivstation bzw. gesamte Krankenhauskosten), die in relevanten Publikationen identifiziert werden sollten. Darüber hinaus sollten die eingeschlossenen gesundheitsökonomischen Studien hinsichtlich ihrer Qualität beurteilt und die Effekte jeder Charakterisierung der Studien wie Studientyp, Methoden der Kostenberechnungen oder Typ der Sepsis analysiert werden. In einem nächsten Schritt sollten die direkten krankenhausrelevanten Kosten von postoperativen Wundinfektionen bei CABG Patienten am Universitätsklinikum Jena anhand des Gesundheitsdienstleisters Perspektiv berechnet, die Effekte dieser Wundinfektionen auf

die Verweildauer bei CABG Patienten mit Hilfe eines Multistate-Modells analysiert und die vermutliche Verweildauerverlängerung aus der ökonomischen Sicht auf Basis der diagnosebezogenen Fallgruppenperspektive (German Diagnosis Related Groups, kurz G-DRG) bewertet werden. Im Schlussteil der Arbeit sollten die Änderung der Verweildauer und zusätzlichen Kosten bei nosokomialen Patienten am Universitätsklinikum Jena berechnet werden. Darüber hinaus sollte der Effekt eines krankenhausweiten Präventionsprogramms zur Verhinderung nosokomialer Infektionen auf Sterblichkeit, Verweildauer und Kosten beurteilt werden. Die Sterblichkeit sollte mithilfe einer „*Compating risk*"-Analyse, die Verweildauerverlängerung mithilfe eines Multi-State-Modells und die Kosten mithilfe der G-DRG berechnet werden.

3. Ergebnisse

Die vorliegende Dissertation wurde als kumulative Arbeit eingereicht. Grundlage dieser Arbeit sind fünf Publikationen. Im Folgenden wird die Eigenleistung dargelegt.

3.1. Manuskript I

Economic Evaluation of Interventions for Prevention of Hospital Acquired Infections

Habibollah Arefian, Monique Vogel, Anja Kwetkat, Michael Hartmann

Veröffentlicht in: PLoS One. 2016;11(1):e0146381

In dieser Studie wurde herausgefunden, dass die meisten Maßnahmen von Präventionsprogrammen zu nosokomialen Infektionen effizient sein können und sehr positive Kosten-Nutzen-Verhältnisse haben. Die meisten Interventionsmaßnahmen verhindern nosokomiale Infektionen signifikant durch ausreichende Händedesinfektion. Studien, die unterschiedliche nosokomiale Infektionen in ihrem Präventionsprogramm betrachteten, erzielten eine bessere „savings-to-cost ratio" als wenn nur eine Art der nosokomialen Infektion betrachtet wurde. Die Ergebnisse dieser Arbeit deuten darauf hin, dass die Qualität der gesundheitsökonomischen Studien im Bereich der Präventionsprogramme zu nosokomialen Infektionen niedrig ist. Sie sollten mithilfe relevanter Leitlinien verbessert werden, um bessere Informationen für die gesundheitspolitische Entscheidung bereitzustellen.

Habibollah Arefian	Konzeption und Planung des Projekts; Definition der Suchstrategie und Suche nach Publikationen in verschiedenen Datenbanken; Ermittlung der relevanten Publikationen; Beurteilung der Qualität der Studien; Daten-extraktion und Evaluierung der Daten; Analyse der Daten; Interpretationen der Ergebnisse; Erstellung des Entwurfs und Überarbeitung des

	Manuskripts; Konzeption und Erstellung aller Abbildungen; Erstellung aller Tabellen; Einarbeitung von Korrekturen während des Reviewprozesses
Monique Vogel	Ermittlung der relevanten Publikationen; Überarbeitung und Durchsicht des Manuskripts
Anja Kwetkat	Konzeptionelle Entwicklung der Studie, Überarbeitung des Entwurf des Manuskripts
Michael Hartmann	Konzeptionelle Entwicklung der Studie; Mitarbeit an der Erstellung und Überarbeitung des Entwurfs des Manuskripts; Durchsicht des Manuskripts; Erstellung von Korrekturen während des Reviewprozesses; Leitung

Manuskript I

PLOS | ONE

RESEARCH ARTICLE

Economic Evaluation of Interventions for Prevention of Hospital Acquired Infections: A Systematic Review

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Abstract

Objective

This systematic review sought to assess the costs and benefits of interventions preventing hospital-acquired infections and to evaluate methodological and reporting quality.

Methods

We systematically searched Medline via PubMed and the National Health Service Economic Evaluation Database from 2009 to 2014. We included quasi-experimental and randomized trails published in English or German evaluating the economic impact of interventions preventing the four most frequent hospital-acquired infections (urinary tract infections, surgical wound infections, pneumonia, and primary bloodstream infections). Characteristics and results of the included articles were extracted using a standardized data collection form. Study and reporting quality were evaluated using SIGN and CHEERS checklists. All costs were adjusted to 2013 US$. Savings-to-cost ratios and difference values with interquartile ranges (IQRs) per month were calculated, and the effects of study characteristics on the cost-benefit results were analyzed.

Results

Our search returned 2067 articles, of which 27 met the inclusion criteria. The median savings-to-cost ratio across all studies reporting both costs and savings values was US $7.0 (IQR 4.2–30.9), and the median net global saving was US $13,179 (IQR 5,106–65,850) per month. The studies' reporting quality was low. Only 14 articles reported more than half of CHEERS items appropriately. Similarly, an assessment of methodological quality found that only four studies (14.8%) were considered high quality.

Conclusions

Prevention programs for hospital acquired infections have very positive cost-benefit ratios. Improved reporting quality in health economics publications is required.

Introduction

Hospital acquired infections (HAIs), also called nosocomial infections, are a serious public health problem and a major cause of morbidity and mortality[1]. Moreover, HAIs can prolong the length of hospital stays and increase costs for healthcare systems [2]. The annual financial losses due to HAIs, including direct costs only, are estimated at approximately € 7 billion in Europe and US $6.5 billion in the USA [3,4]. In 2002, approximately 1.7 million infections (4.5 per 100 admissions) were acquired in US hospitals [5]. The most frequent HAIs are urinary tract infections, surgical wound infections, ventilator-associated pneumonia, and primary bloodstream infections [1]. A recent meta-analysis of HAIs showed that central line–associated bloodstream infections are tied up with the highest costs ($45,814), followed by ventilator-associated pneumonia ($40,144) and surgical wound infections ($20,785) [6]. Several systematic reviews have inspected the clinical effect of interventions for HAI prevention [7–9]. Most of the studies included in these reviews showed a reduction in the number of HAIs. However, the economic benefit of such interventions is not clear.

Therefore, we conducted this systematic review to provide a cost-benefit estimation for HAI prevention and to examine the quality of economic studies and their reporting.

Methods

Data Sources and Search Strategy

Our systematic review conforms to recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (S1 Table) [10] and guidance from the Campbell and Cochrane Economics Methods Group on incorporating economic evidence into systematic reviews [11].

Searches of eligible studies were conducted in Medline via PubMed and the National Health Service Economic Evaluation Database (NHS EED) to identify relevant articles in English and German published in a five year period between January 2009 and January 2014 with an abstract available for review.

We used several search terms, and keywords were matched to database-specific indexing terms (Mesh and ti). We used the operator AND to link keywords with different meanings and the operator OR for keywords with similar meanings. S2 Table shows our search strategy for eligible publications in PubMed.

Selection Criteria

All studies found were reviewed for eligibility by applying the PICO (patient problem or population, intervention, comparison, and outcomes) question format. Publications identified in the search of the two databases were combined and duplicates were removed.

Population. We included studies assessing interventions intended to prevent the four most common HAIs (urinary tract infections, surgical wound infections, hospital-acquired pneumonia, and primary bloodstream infections). There was no age or gender restriction in this systematic review.

Types of interventions. The interventions of interest were measures reducing person-to-person transmission (hand decontamination, personal hygiene, clothing, masks, gloves and safe injections); measures preventing transmission from the environment (cleaning of the hospital environment, use of hot/superheated water, discussion of patient equipment); and measures proven effective for the prevention of urinary tract infections, surgical site infections (SSI), pneumonia and vascular device infections that used the World Health Organization

(WHO) guidelines for HAI prevention [1]. Studies involving only an evaluation of any other preventive measures were excluded.

Control/Design. We included quasi-experimental and randomized trails, while articles without an explicitly formulated study design or method were excluded. We also excluded cross-sectional studies, reviews, guidelines, studies of pure mathematics, studies published as an abstract only and studies using a simulation or modeling published data.

Outcome measures. In this review, cost-effectiveness analyses (CEAs), cost-benefit analyses (CBAs), cost-minimization analyses (CMAs) and cost-utility analyses (CUAs) were included. Studies lacking quantitative economic parameters or reported outcomes were excluded.

Data Extraction

Two reviewers (H.A., M.V.) independently applied inclusion and exclusion criteria and extracted the data from eligible studies by screening titles, abstracts and full-text articles. Differences were resolved by discussion with a third review author. The reviewers documented the reasons for excluding articles from the review.

We extracted the characteristics and results of included health economics studies using a standardized data collection form [11]. We also consulted previous systematic reviews of health economics studies to improve our data collection form [12,13]. We extracted data on the intervention costs and the economic benefits following the intervention. When economic consequences of the intervention were described at several points in time, we used the longest follow up in the primary analysis. Base case costs were used if sensitivity analyses were performed. We extracted all direct and indirect costs of the intervention as well as savings to the extent that they were reported. As only some studies identified indirect costs, our analysis is limited to direct costs.

In cases of missing information concerning inflation adjustment, we assumed that the costs were adjusted to the last year of the study period. Moreover, if a low/high range of intervention costs or savings was reported, we used the average cost for our analysis.

Quality Assessment

The methodological quality of the economic evaluations was assessed based on the methodology checklist recommended by SIGN (Scottish Intercollegiate Guidelines Network). Additionally, for an overall assessment of studies we answered one question from selection 2 of the SIGN statement, "How well was the study conducted?", with the following coding: "++" denotes that all or most of the criteria have been fulfilled, "+"that some of the criteria have been fulfilled, and "−" that few or no criteria were fulfilled [14].

We used the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement to assess the reporting quality of studies [15], although one of the CHEERS criteria was not relevant for our systematic review because of the selection criteria. Each CHEERS criterion was assigned a weight ranging from one to three (representing studies that reported well, reported poorly or did not report).

Analysis of Results

Intervention costs and cost savings following the intervention were recalculated as costs per month during the intervention period and during the length of follow-up, respectively. We estimated the savings-to-cost ratio and the save–cost difference adjusted to 2013 US$. A savings-to-cost ratio larger than 1 indicated savings exceeding costs, and a positive save–cost difference value indicated net savings. Both intervention costs and cost savings were adjusted to 2013

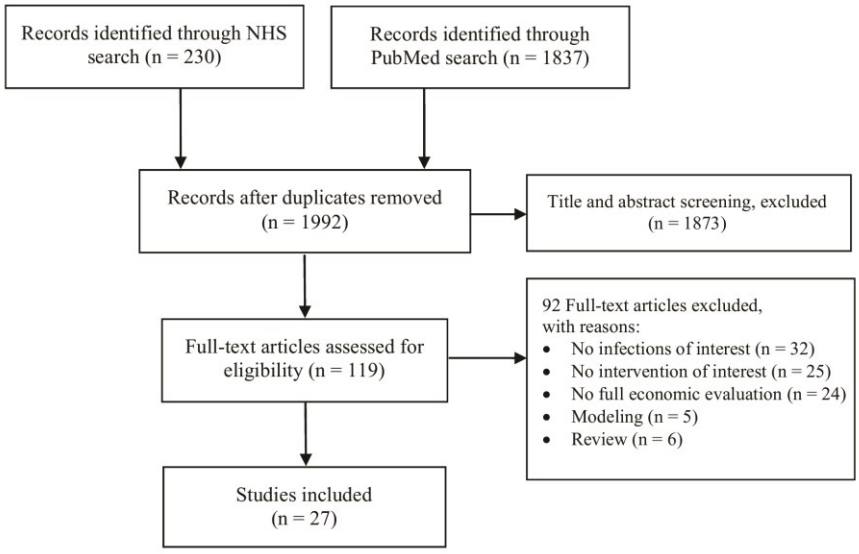

Fig 1. Flow diagram for the systematic review process to select studies.

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values using an annual country-specific consumer price index [16]. After adjustment, these values were converted to 2013 US$ using the purchasing power parity (PPP) conversion factor [17]. We computed the summary median cost, cost savings per month, savings-to-cost ratio and difference values per month with a minimum–maximum range. We analyzed the effects of study characteristics on the cost-benefit results. We assumed that heterogeneity could have been due to the types of HAIs studied, the intervention duration, the hospital sizes, the number of patients, the target populations and the varying levels of methodological quality among these economic evaluations. All analyses were performed in Microsoft Excel (2010 Microsoft Corporation).

Results

Literature Search

Through our searches, a total of 1992 potentially relevant citations were identified, of which twenty-seven articles fulfilled the inclusion criteria [18–44]. A flow diagram of the search and selection strategy is shown in Fig 1. Excluded studies are listed in S4 Table.

Study Descriptions

Most of the studies were performed in North America or Europe (n = 19, 70.4%). Approximately 63% of identified studies on the prevention of HAIs were performed in surgical departments (n = 10, 37.0%) or intensive care units (n = 7, 25.9%). The studies employed several methods to calculate effectiveness; 37.0% were randomized control studies (n = 10) and 63.0% were quasi-experimental (n = 17). More than half of the studies (n = 15, 55.6%) stated that they

used the definitions of HAIs provided by the Centers for Disease Control and Prevention (CDC). Five studies focused on more than one site of HAI (18.5%). Most interventions aimed to prevent HAIs by reducing person-to-person transmission (n = 7, 25.9%), primarily by hand decontamination (S3 Table). The most frequent method used to prevent SSIs was optimal antibiotic prophylaxis (n = 6, 75.0%). Education programs were included in 8 studies (29.6%). Most interventions lasted for more than one year (n = 16, 59.3%), and only 6 studies performed a sensitivity analysis (22.2%). CEAs and CBAs were the most common types of economic evaluations. Only two of the studies were not from the healthcare provider cost perspective (7.4%), although most of the studies did not report the cost perspective they adopted (n = 18, 66.7%). The majority of studies used data collection to obtain cost data (n = 15, 55.6%). Resource costs were calculated using micro-costing, charges and mixed models. Many of the studies were funded by government sources (n = 11, 40.7%), although several studies did not include a statement on funding (n = 10, 37.0%). Further characteristics of the included publications are listed in Table 1.

Assessment of Reporting Quality

We assessed the reporting quality of 26 studies using the CHEERS statement. Of these, we were able to identify 13 studies as economic evaluations based on the title (50.0%). Most articles presented a clear study question and an explicit statement of the background for the study (n = 19, 73.1%). Studies generally reported the target population and subgroups well (n = 16, 61.5%). Statements regarding the perspective of the study and its relation to costs were missing in 17 studies (65.4%). The majority of studies did not include a statement on the choice of discount rates (n = 11, 42.3%) or included poor reporting on the choice (n = 6, 23.1%). Only 9 studies properly described what approaches were used to estimate resources and costs (34.6%). A price date, the method of price adjustment and the currency used were not noted in 10 studies (38.5%). Half of the selected studies did not report conflicts of interest (Table 2).

Assessment of Method Quality

Most of the 27 economic studies included in the method quality assessment defined an answerable study question (n = 14, 51.9%), but few papers included all costs relevant to the viewpoint of the study (Table 3). In the overall method quality assessment, 4 studies (14.8%) were evaluated as "++", 15 (55.5%) as "+" and 8 (29.6%) as "−". Since 2009, the quantity of publications regarding prevention programs for HAIs has increased, while the quality of these studies has not improved, as shown in Fig 2, which illustrates the method quality for different publication years.

Cost-Benefit Analysis

Common cost components included nurse/physician time, antimicrobials, administration costs and pharmaceuticals. Intervention costs were usually reported as the global costs of the intervention (n = 9, 33.3%). Extra costs of an HAI and costs of extra hospitalization days due to HAIs were the major cost components used for cost savings calculations.

The median savings-to-cost ratio across the 18 studies reporting both values was US $7.0 (IQR 4.2–30.9), and the median net global saving of the 19 studies was US $13,179 (IQR 5,106–65,850) per month. The median cost across the 20 studies reporting intervention costs was US $1,114 (IQR 174–6234) per month. The median saving across the 24 studies reporting this figure was US $12,519 (IQR 6,273–65,309) per month. Most of the 18 articles reporting both intervention and saved costs calculated a savings-to-cost ratio >1 and a positive save–cost difference, and only one study showed that infection control interventions were not economically justified because the savings-to-cost ratio was < 1 or the save–cost difference was negative (Table 4).

Table 1. Characteristics of the studies.

Descriptive characteristics		Number (%)	Descriptive characteristics		Number (%)
Geographical region of study	United States/Canada	10 (37.0)	**Type of intervention***	Hand hygiene	6 (22.2)
	Europe	9 (33.3)		Aseptic technique at insertion	4 (14.8)
	Asia	7 (25.9)		Optimal antibiotic prophylaxis	6 (22.2)
	Africa	1 (3.7)		Aseptic intubation and suctioning	2 (7.4)
Target population/setting	Intensive care unit	7 (25.9)		Limit duration of catheter	1(3.7)
	Surgery	11 (40.7)		Local skin preparation (catheters)	2 (7.4)
	Pediatric	1 (3.7)		Educational program	8 (29.6)
	Other patients or setting	5 (18.5)		Other interventions	20 (70.0)
	Hospital wide	3 (11.1)	**Type of economic evaluation**	CBA	9 (33.3)
Gender	Male	0 (0.0)		CEA	9 (33.3)
	Female	1 (3.7)		CMA	4 (14.8)
	Both	19 (70.4)		CEA+CBA	4 (14.8)
	Not stated	7 (25.9)		CEA+CUA	1 (3.7)
Age group	Children	1 (4)	**Cost perspective**	Healthcare provider	7 (25.9)
	Adult	4 (15)		Other perspective	2 (7.4)
	Mixed	13 (48)		Not stated	18 (66.7)
	Not stated	7 (26)	**Source of cost data**	Data collection	15 (55.6)
	Other (0–25, Patients ≥16)	2 (7)		Database	4 (14.8)
Type of HAIs	Surgical site infection	8 (29.7)		Mixed	8 (29.6)
	Urinary tract infection	4 (14.8)	**Source of effectiveness data**	Pre-post	8 (29.6)
	Bloodstream infection	5 (18.5)		Cohort	5 (18.5)
	Pneumonia	3 (11.1)		Randomized control trial	10 (37.0)
	More than one site of HAI	5 (18.5)		Case-control	1 (3.7)
	HAIs in general	2 (7.4)		Other quasi experimental design	3 (11.1)
HAI definition	CDC	15 (55.6)	**Method of cost calculation**	Accounting	2 (7.4)
	Other standard	5 (18.5)		Charges	7 (25.9)
	Not stated	7 (25.9)		Cost-to-charge-ratio	1 (3.7)
Duration of intervention	Six months or less	5 (18.5)		Micro-costing	6 (22.2)
	7–12 months	5 (18.5)		Mixed	7 (25.9)
	13–24 months	10 (37.0)		Other methods	4 (14.8)
	More than two years	6 (22.2)	**Discounting**	Yes	7 (25.9)
	Not stated	1 (3.7)		Not stated	14 (51.9)
Sensitivity analysis	Yes	6 (22.2)		Not necessary	6 (22.2)
	No	21 (77.8)			

HAI, hospital acquired infections; CDC, Centers for Disease Control and Prevention; CEA, Cost-effectiveness analysis; CBA, cost-benefit analysis; CMA, cost-minimization analysis; CUA, cost-utility analysis.

* Many of included studies used more than one type of intervention. Proportion based on total number of included studies.

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The effects of study characteristics on the savings-to-cost ratios and net savings were very diverse. Higher savings-to-cost ratios were observed in studies that focused on pneumonia prevention compared with prevention programs focusing on other infections. However, the

Table 2. Assessment of the reporting quality of included studies using CHEERS statement[a].

Section/item		Number of studies (%) reporting		
		well	poorly	not
Title and abstract Introduction Methods	Title	9 (34.6)	4 (15.4)	13 (50.0)
	Abstract	8 (30.8)	15 (57.7)	3 (11.5)
	Background and objectives	19 (73.1)	7 (26.9)	0 (0.0)
	Target population and subgroups	16 (61.5)	7 (26.9)	3 (11.5)
	Setting and location	18 (69.2)	5 (19.2)	3 (11.5)
	Study perspective	7 (26.9)	2 (7.7)	17 (65.4)
	Comparators	22 (84.6)	4 (15.4)	0 (0.0)
	Time horizon	20 (76.9)	5 (19.2)	1 (3.8)
	Discount rate	9 (34.6)	6 (23.1)	11 (42.3)
	Choice of health outcomes	18 (69.2)	7 (26.9)	1 (3.8)
	Measurement of effectiveness	17 (65.4)	8 (30.8)	1 (3.8)
	Measurement and valuation of preference based outcomes	16 (61.5)	6 (23.1)	4 (15.4)
	Estimating resources and costs	9 (34.6)	10 (38.5)	7 (26.9)
	Currency, price date, and conversion	13 (50.0)	3 (11.5)	10 (38.5)
	Assumptions	5 (19.2)	17 (65.4)	4 (15.4)
	Analytical methods	13 (50.0)	6 (23.1)	7 (26.9)
Results	Study parameters	18 (69.2)	4 (15.4)	4 (15.4)
	Incremental costs and outcomes	9 (34.6)	10 (38.5)	7 (26.9)
	Characterizing uncertainty	2 (7.7)	10 (38.5)	14 (53.8)
	Characterizing heterogeneity	10 (38.5)	10 (38.5)	6 (23.1)
Discussion	Study findings, limitations, generalizability, and current knowledge	13 (50.0)	10 (38.5)	3 (11.5)
Other	Source of funding	16 (61.5)	0 (0.0)	10 (38.5)
	Conflicts of interest	13 (50.0)	0 (0.0)	13 (50.0)

a. Pickard et al. excluded from the reporting quality section

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studies that considered several types of infections in their infection prevention program calculated a higher savings-to-cost ratio compared with studies dedicated to a single type of HAI. Savings-to-cost ratios were higher in studies with smaller number of patients. Larger hospitals (>500 beds compared with smaller hospitals) with shorter intervention durations (≤12 months compared with longer durations) exhibited higher savings-to-cost ratios. Nevertheless, savings-to-cost ratios were considerably lower in multi-center studies. Programs for prevention of HAIs in surgical units have higher savings-to-cost ratios compared with prevention programs for HAIs in intensive care units or in hospital-wide studies. Savings-to-cost ratios were much higher in studies that did not report or poorly addressed costs and had inappropriate measurement and evaluation, compared with studies addressing these factors adequately or well. This result shows that studies without complete identification and measurement of relevant costs overestimate the savings-to-cost ratios. We found similar savings-to-cost ratios among studies that were assigned an overall assessment of "-" (Table 5).

Discussion

We systematically reviewed and assessed the quality of the methods and reporting of selected economic evaluation studies regarding HAI prevention interventions and their economic benefits. Prevention interventions for HAIs were reported as statistically significantly efficacious in many studies, and our analysis shows that these interventions have significant economic

Table 3. Assessment of method quality of included studies using SIGN guideline.

In a well conducted economic study. . .	Well covered (%)	Adequately addressed (%)	Poorly addressed (%)	Not addressed (%)	Not reported (%)	Not applicable (%)
There is a defined and answerable study question	14 (51.9)	7 (25.9)	4 (14.8)	2 (7.4)	–	–
The economic importance of the question is clear	6 (22.2)	6 (22.2)	6 (22.2)	7 (25.9)	2 (7.4)	–
The choice of study design is justified	4 (14.8)	14 (51.9)	9 (33.3)	–	–	–
All costs that are relevant from the viewpoint of the study are included and are measured and valued appropriately	2 (7.4)	8 (29.6)	11 (40.7)	6 (22.2)	–	–
The outcome measures used to answer the study question are relevant to that purpose and are measured and valued appropriately	3 (11.1)	18 (66.7)	6 (22.2)	–	–	–
If discounting of future costs and outcomes is necessary, it has been performed correctly	4 (14.8)	2 (7.4)	1 (3.7)	6 (22.2)	8 (29.6)	6 (22.2)
Assumptions are made explicit, and a sensitivity analysis performed	4 (14.8)	3 (11.1)	3 (11.1)	16 (59.3)	1 (3.7)	–
The decision rule is made explicit, and comparisons are made on the basis of incremental costs and outcomes	1 (3.7)	8 (29.6)	9 (33.3)	7 (25.9)	2 (7.4)	–
If discounting of future costs and outcomes is necessary, it has been performed correctly	3 (11.1)	11 (40.7)	13 (48.1)	–	–	–

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benefits. On average, the savings of a prevention program were 11 times greater than the costs. The highest save–cost difference was identified in a study by Harris et al., which used improvement practices of hand hygiene, oral care and central-line catheter care in a single hospital [26]. Only Van den Broek et al. calculated a negative save–cost difference for a program intended to reduce the use of urethral catheters through an implementation strategy focused

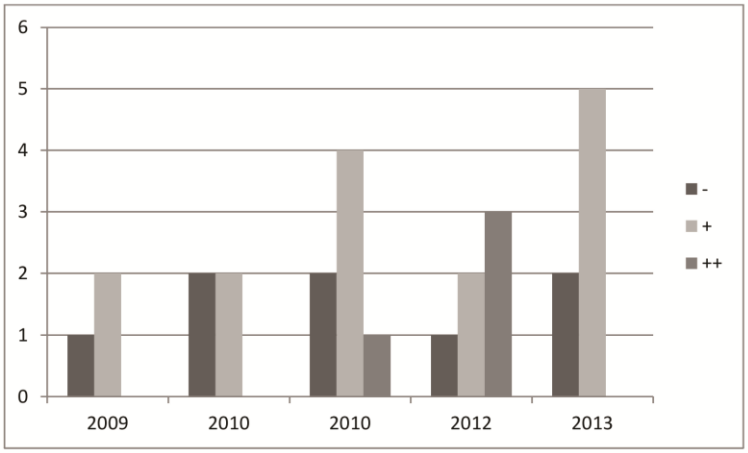

Fig 2. Methodological quality of studies and publication year.

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Table 4. Intervention costs and cost savings.

Study ID		Country	Intervention target	Duration ofintervention	Total number of patients	Total intervention cost[a]	Total cost savings[a]	savings-to-cost ratio	Save–cost difference[a]	Intervention efficacy[b]
Burden[18]		USA	ICU, 24 beds	24 months	6,059	5,567	23,306	4.2	17,739	Yes
Chen[19]		Taiwan	Hospital-wide, 2,200 beds	45 months	552,146	353	8,376	23.7	8,023	Yes
Clarke[20]		USA	Hospital-wide, 276 beds	19 months	2,228	2,130	6,742	3.2	4,612	Yes
Cohen[21]		USA	MICU, 20 beds	12 months	477	10,072	73,760	7.3	63,688	Yes
Dijksman[22]		Netherlands	Elective gastrointestinal surgery	12 months	289	2,318	45,892	19.8	43,573	Yes
Fraher[23]		Ireland	Hospital-wide, 535 beds	12 years	1,932	6,137	14,611	2.4	8,474	Yes
Harris[26]		USA	Pediatric ICU, 20 beds	9 months	2,379	702	889,697	1,267.4	888,995	Yes
Nakamura[30]		Japan	Surgical ward, 7,500 surgeries yearly	24 months	410	93	3,541	38.2	3,448	Yes
Perez[32]		Spain	Heart surgery, 500 heart surgery yearly	23 months	1,399	916	6,022	6.6	5,106	Yes
Pickard [33]	Nitrofurazone	UK	Catheterization patients, 24 hospitals	1,5 months	2,153	10,127	293,981	29.0	283,854	Yes
	Silver alloy	UK	Catheterization patients, 24 hospitals	1,5 months	2097	12,599	78,449	6.2	65,850	No
Piednoir[34]		France	ICU, 8 beds	24 months	919	133	7,195	53.9	7,062	Yes
Raschka[35]		Canada	Six acute care, 82,046 admissions yearly	48 months	NS	115,269	626,850	5.4	511,581	NS
Schwebel [36];	CHGIS dressing &3 days change	France	Seven ICUs	19 months	818	1,522	10,186	6.7	8,664	Yes
	CHGIS dressing &7 days change	France	Seven ICUs	19 months	818	1,114	4,536	4.1	3,422	Yes
Singh[37]		India	Cardiovascular surgical unit, 68 beds	4 months	2,838	589	21,468	36.5	20,879	Yes
Sona[38]		USA	ICU, 24 beds	12 months	1,648	215	68,775	320.5	68,560	Yes
Speroni[39]		USA	Ventilation Patients,155 beds	13 months	154	76	1,290	17.0	1,214	No
van den Broek[41]		Netherlands	10 hospitals	5 months	2,943	6,331	1,837	0.3	-4,494	No
Waters[42]		USA	103 ICU, 6 hospitals	4 months	NS	43,628	114,422	2.6	70,794	Yes
Gulluoglu[24]		Turkey	Surgical ward	6.5 years	369	NS	9	NA	NA	Yes
Halleberg Nyman[25]		Sweden	Orthopedic surgical ward	21 months	170	NA	1,130	NA	NA	No
Liau[27]		Singapore	Surgical ward	24 months	2,408	NS	12,057	NA	NA	Yes
Mathur[28]		India	Surgical ward	20 months	197	NA	616	NA	NA	No
Mian[29]		USA	Hematology-oncology unit	36 months	NS	NA	38,032	NA	NA	Yes
Nthumba[31]		Kenya	Surgical ward, 5000 procedures yearly	2 months	3,133	8	NS	NA	NA	No
Teshima[40]		Japan	Surgical ward	48 months	253	16–25	NS	NA	NA	Yes
Weight [43]		USA	Pediatric ward	NS	3600	NA	NS	NA	NA	No

(*Continued*)

Table 4. (*Continued*)

Study ID	Country	Intervention target	Duration ofintervention	Total number of patients	Total intervention cost[a]	Total cost savings[a]	savings-to-cost ratio	Save–cost difference[a]	Intervention efficacy[b]
Zhou[44]	China	Surgical ward	7 months	614	20,949–30,419	3,709	NA	13,179	No

NS, Not Stated; NA, Not Applicable; CHGIS, chlorhexidine gluconate-impregnated sponge; ICU, Intensive Care Unit; MICU, Medical Intensive Care Unit

a. Cost per month in 2013 US$.

b. Intervention reported to be statistically significantly efficacious.

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Table 5. Effects of study characteristics on results[a].

Characteristics		intervention cost	cost savings	savings-to-cost ratio	save–cost difference
Types of HAIs	Surgical site infection	50 (8–93), n = 2	3,541 (9–12057), n = 5	38.2, n = 1	8,313 (3448–13,179), n = 2
	Urinary tract infection	8,229 (2,130–12,599), n = 3	6,742 (1,130–293,981), n = 4	4.7 (0.3–29.0), n = 3	35,231 (-4,494–283,854), n = 3
	Bloodstream infection	5,567 (1,114–10,072), n = 4	12,399 (616–73,760), n = 5	4.2 (2.4–7.3), n = 4	8,664 (3,422–63,688), n = 4
	Pneumonia	215 (76–916), n = 3	6,022 (1,290–68,775), n = 3	17 (6.6–320.5), n = 3	5,106 (1,214–68,560), n = 3
	More than one site of HAI	702 (133–43,628), n = 5	45,892 (7,195–889,697), n = 5	36.5 (2.6–1,267.4), n = 5	43,573 (7,062–888,995), n = 5
	HAIs in general	57,811 (353–115,269), n = 2	317,613 (8,376–626,850), n = 2	14.6 (5.4–23.7), n = 2	259,802 (8,023–511,581), n = 2
Intervention duration	≤ 12 months	4,325 (8–43,628), n = 9	71,267 (1,837–889,697), n = 9	19.8 (0.3–1267.4), n = 8	64,769 (-4,494–888,995), n = 9
	> 12 months	1,114 (76–115,269), n = 10	6,969 (9–626,850), n = 15	6.6 (2.4–53.9), n = 10	7,062 (1,214–511,581), n = 10
Hospital size	≤500 beds	389 (8–2,130), n = 4	4,016 (1,130–889,697), n = 4	17.0 (3.2–1267.4), n = 3	4,612 (1,214–888,995), n = 3
	>500beds	752 (93–10,072), n = 10	11,494 (9–889,697), n = 14	21.7 (2.4–320.5), n = 10	13,179 (3,448–68,560), n = 11
	Several hospitals	10,127 (1,114–115,269), n = 5	78,449 (1,837–626,850), n = 5	5.4 (0.3–29.0), n = 5	65,850 (-4,494–511,581), n = 5
Number of Patients	≤1000	1,114 (76–10,072), n = 6	3,709 (9–73,760), n = 10	17.0 (4.1–53.9), n = 6	7,863 (1,214–63,688), n = 7
	1000–3000	2,130 (215–12,599), n = 8	18,039 (1,837–889,697), n = 9	6.6 (0.3–1267.4), n = 8	20,879 (-4,494–888,995), n = 8
	>3000	353 (8–5,567), n = 3	15,841(8,376–23,306), n = 2	13.9 (4.2–23.7), n = 2	12,881 (8,023–17,739), n = 2
Target population	Intensive care unit	1,318 (133–43,628), n = 7	46,040 (4,536–889,697), n = 7	7.0 (2.6–1,267.4), n = 7	40,714 (3,422–888,995), n = 7
	Surgery	589 (8–2,318), n = 5	3,709 (9–45,892), n = 9	28.1 (6.6–38.2), n = 4	13,179 (3,448–43,573), n = 5
	Hospital-wide	2,130 (353–6,137), n = 3	8,376 (6,742–14,611), n = 3	3.2 (2.4–23.7), n = 3	8,023 (4,612–8,474), n = 3
	Other patients or setting	8,229 (76–12,599), n = 3	38,032 (1,290–293,981), n = 4	11.6 (0.3–29.0), n = 3	33,532 (-4,494–283,854), n = 3
All costs are included andare measured and valued appropriately (SIGN)	Well covered	5,825 (1,114–12,599), n = 2	44,317 (4,536–293,981), n = 2	6.5 (4.1–29.0), n = 2	37,257 (3,422–283,854), n = 2
	Adequately addressed	2,318 (353–115,269), n = 7	14,922 (1,837–626,850), n = 8	5.4 (0.3–36.5), n = 7	17,029 (-4,494–511,581), n = 8
	Poorly or Not addressed	458 (8–10,072), n = 10	9,626 (9–889,697), n = 14	17.0 (2.4–1,267.4), n = 9	8,474 (1,214–888,995), n = 9
How well was the study conducted? (SIGN)	++	1,920 (353–12,599), n = 4	28,039 (4,536–293,981), n = 4	13.2 (4.1–29.0), n = 4	26,119 (3,422–283,854), n = 4
	+	2,130 (93–115,269), n = 11	16,762 (1,130–889,697), n = 14	6.6 (0.3–1,267.4), n = 11	19,309 (-4,494–888,995), n = 12
	-	105 (8–6,137), n = 4	4,243 (9–38,032), n = 6	17.0 (2.4–53.9), n = 3	7,062 (1,214–8,474), n = 3

HAI, Hospital acquired infections.

a. Median (Range) value, cost per month in 2013 US$. n, number of studies.

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on a limited number of recommendations from the Dutch Working Party on Infection Prevention (WIP) guideline [41]. Nevertheless, it should be noted here that the most important aspect of an infection prevention program is reduction of harm and loss of life. Although the hospital-wide hand decontamination had a high cost savings benefit, only one of four hand hygiene programs was hospital wide, while 3 were implemented in intensive care units.

Interventions targeting several types of HAIs or HAIs in general were associated with higher economic benefits than prevention interventions for a single type of infection. A strong association was identified between intervention duration and cost benefit. The median save–cost difference among studies with intervention periods of 12 months or less was 9 times greater than that among studies with longer intervention durations. Higher savings-to-cost ratios were found in larger hospitals. These ratios were very low in multi-center studies; however, the median save–cost difference in such studies was high. Multi-center trials are usually very expensive to implement and much more complex than single-center studies. Nevertheless, multi-center prevention programs exhibit a better net-savings than single-center programs.

The quality of reporting in the studies was low. Only fourteen articles reported more than half of the CHEERS items appropriately, and only seven studies reported 70% or more of these items well. We found similar results in our assessment of methodological quality. Various studies had low internal validity; for example, several studies did not include some of the relevant costs in the economic evaluation that could have a substantial impact on the results. Discounting future costs and outcomes was necessary in most of the selected studies; nevertheless, such discounting was often not performed. The quality of economic studies is directly related to the presence of a sensitivity analysis. Therefore, the Oxford Centre for Evidence-based Medicine (OCEBM) classified economic studies without a sensitivity analysis as level IV evidence [45]. Nevertheless, few studies in our review performed a sensitivity analysis of their economic evaluation.

Higher quality studies fulfilling all or most of the methodology criteria have higher savings-to-cost ratios compared with studies of intermediate quality, but the savings-to-cost ratios in low-quality studies fulfilling few or no criteria were extremely large. This may represent overestimation due to inappropriate designs for economic evaluations or the failure to consider some relevant costs. Low-quality clinical trials inflated the estimated treatment efficacy by 30–50%, according Moher et al. [46]. An overestimation of benefit-cost ratio may therefore exist in low-quality economic evaluations.

Only a small number of systematic reviews examined the economic impact of interventions for HAI prevention [9,12,13]. Farbman et al. [13] focused on economic evaluations of infection control interventions targeting methicillin-resistant *Staphylococcus aureus* (MRSA) in a study that was methodologically similar to our systematic review. They found that the median savings-to-cost ratio among 18 MRSA studies was US $7.16 (IQR 1.37–16), which is similar to the present findings. Their study observed that interventions with longer durations (>6 months) had higher savings-to-cost ratios compared with interventions of shorter duration. In contrast, the present study found higher savings-to-cost ratios for interventions with a duration of 12 months or shorter compared with interventions with longer durations.

Our study has some limitations, as is true of all systematic reviews of economic evaluations. Due to the wide variety of terminology in the fields of full economic evaluations, hospital acquired infections and prevention interventions, some relevant articles may have been missed in our review of the literature. However, we used two large literature databases, and a variety of keywords were matched to database-specific indexing terms. In this review, databases were searched based on the English and German languages. Therefore, publications in other languages were not detected using this search strategy. Because various types of interventions and various combinations of interventions were included and because some intervention cost

components were lacking, we could not classify the interventions' effects with respect to economic benefits. The distribution of cost values was not normal, and the homogeneity of costs was not high; therefore, we were unable to perform a formal meta-analysis. One further limitation of our study is a potential publication bias. Studies with a negative save to cost ratio are unlikely to get published compared to studies with a positive result and these studies are not included in our review.

In conclusion, the included studies indicate that HAI prevention interventions yield very positive cost-benefit estimations. The quality of economic evaluations should be improved to provide better information to healthcare policy makers and clinicians. International standardization of cost estimations for HAIs would enable economic evaluation studies to perform more precise assessments of economic benefits and cost changes associated with HAI prevention programs.

Supporting Information

S1 Table. PRISMA Checklist.
(PDF)

S2 Table. PubMed Search Strategy.
(PDF)

S3 Table. Hospital acquired infections interventions in individual studies.
(PDF)

S4 Table. Excluded studies with reason.
(PDF)

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Author Contributions

Conceived and designed the experiments: HA MH. Performed the experiments: HA MV. Analyzed the data: HA. Contributed reagents/materials/analysis tools: HA MH. Wrote the paper: HA MV AK MH.

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Supporting information

S1 Table. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3 & 25
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-9
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8-9
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

S2 Table. PubMed Search Strategy

(prevention) OR (health promotion) OR ("primary prevention"[Mesh]) OR (lifestyle) OR (intervention) OR (counseling) OR (multimodal) OR (multi-factor*) OR (multifactor*) OR (multi-component) OR (risk assessment) OR (risk factor*) OR (health education) OR ("health behavior"[Mesh]) OR ("risk reduction behavior"[Mesh]) OR ("risk factors"[Mesh]) AND ("Economics"[Mesh]) OR (Economics) OR (economic*) OR ("Costs and Cost Analysis"[Mesh]) OR (cost) OR (efficiency) OR (return on investment) OR (direct cost*) OR (indirect cost*) OR (economic evaluation*[ti]) OR (economic analy*[ti]) OR (cost analy*[ti]) OR (cost effectiveness[ti]) OR (cost benefit*[ti]) OR (cost utilit*[ti])) AND (nosocomial infection) OR (nosocomial) OR (hospital-acquired) OR (healthcare-associated) OR (hospital infection) OR ("Cross Infection"[Mesh])Filters: Publication date from 2009/01/01 to 2014/01/01; Humans; English; German

S3 Table. Hospital acquired infection interventions in individual studies

Study ID	Interventions
Burden[14]	A mandatory simulation-based program to teach central venous catheter insertion
Chen[15]	Hand hygiene promotion program; multidisciplinary approach involving cognition, equipment, and behavior
Clarke[16]	Exclusive use of silver alloy catheters, limit the movement of the catheter after insertion, repositioning of the catheter tubing, removal of the indwelling urinary catheter
Cohen[17]	Simulation-based education intervention in central venous catheter insertion
Dijksman[18]	Perioperative selective decontamination of the digestive tract
Fraher[19]	Total parenteral nutrition surveillance clinical nurse manager
Gulluoglu[20]	Prophylactic antibiotic administration
Halleberg Nyman[21]	Intermittent or indwelling urinary catheterisation
Harris[22]	Improving practices of hand hygiene, oral care and central-line catheter use
Liau[23]	Hair removal, antibiotic administration, glucose and temperature monitoring
Mathur[24]	Perioperative antibiotic prophylactic regimen
Mian[25]	Quality improvement: education, CVL maintenance care bundles, CVL insertion guideline
Nakamura[26]	Triclosan-coated polyglactin suture materials with antimicrobial activity
Nthumba[27]	Plain soap and water with alcohol-based handrub
Perez Granda[28]	Routine introduction of aspiration of subglottic secretions in patients after major heart surgery
Pickard[29]	Antimicrobial-impregnated silicone catheter (nitrofurazone) and antiseptic-coated hydrogel latex catheter (silver alloy) were compared to standard polytetrafluoroethylene-coated catheters
Piednoir[30]	Promotion of contact precautions and hand rubbing by additional training sessions, antibiotic policy and practices, systematic screening on admission by rectal swab
Raschka[31]	Reduction of bacteremias, control of MRSA, hand hygiene program, *Clostridium difficile* isolation and treatment guidelines, CAUTI prevention initiatives
Schwebel[32]	CHGIS versus no CHGIS (standard dressing), seven-day dressing change was compared with three-day dressing change
Singh[33]	Two-module training step-by-step teaching program
Sona[34]	A simple oral care protocol to assist in prevention of bacterial growth of plaque by cleaning the patients' teeth
Speroni[35]	Continuous subglottic suctioning endotracheal tubes versus standard endotracheal tubes among intubated patients
Teshima[36]	New hydrocolloid dressing (Karayahesive) or a polyurethane foam dressing (Tegaderm plus Pad) after sternal wound closure
Van den Broek[37]	Reduction of the use of urinary catheters
Waters[38]	Comprehensive Unit-Based Safety Program (improve safety culture, teamwork, and communication), evidence-based care to reduce CLABSIs and VAP
Weight[39]	Avagard (waterless, scrubless, and brushless hand antiseptic) was compared with traditional pre-surgical antiseptic-impregnated hand brush for hand scrubbing
Zhou[40]	A guideline for the appropriate use of antibiotics

CVL, central venous line; MRSA, methicillin-resistant Staphylococcus aureus; CAUTI, catheter-associated urinary tract infection; CHGIS, chlorhexidine gluconate-impregnated sponge; CLABSIs, central line–associated bloodstream infections; VAP, ventilator-associated pneumonia

S4 Table. Excluded studies with reason

	Study ID	Title	Reasons for exclusion
1	Adibi et al. (2013)	Reduction in hospital admission rates due to post-prostate biopsy infections after augmenting standard antibiotic prophylaxis	• No intervention of interest
2	Ahmed et al. (2012)	Catheter-associated bloodstream infection in the pediatric intensive care unit: a multidisciplinary approach	• No full economic evaluation
3	Al-Badriyeh et al. (2009)	Cost-effectiveness evaluation of voriconazole versus liposomal amphotericin B as empirical therapy for febrile neutropenia in Australia	• No intervention of interest
4	Ali et al. (2012)	Clostridium difficile infection in hospitalized liver transplant patients: a nationwide analysis	• No full economic evaluation • No infection of interest
5	Ali et al. (2012)	Effect of surface coating and finish upon the cleanability of bed rails and the spread of Staphylococcus aureus	• No full economic evaluation • No infection of interest
6	Al-Tawfiq et al. (2010)	Decreasing ventilator-associated pneumonia in adult intensive care units using the Institute for Healthcare Improvement bundle	• No intervention of interest • No full economic evaluation
7	Anderson et al. (2011)	The network approach for prevention of healthcare-associated infections: long-term effect of participation in the Duke Infection Control Outreach Network	• No intervention of interest
8	Apisarnthanarak et al. (2010)	Reduction of seasonal influenza transmission among healthcare workers in an intensive care unit: a 4-year intervention study in Thailand	• No infection of interest
9	Apisarnthanarak et al. (2010)	Impact of education and an antifungal stewardship program for candidiasis at a Thai tertiary care center	• No infection of interest
10	Attenello et al. (2010)	Hospital costs associated with shunt infections in patients receiving antibiotic-impregnated shunt catheters versus standard shunt catheters	• No intervention of interest
11	Bailey et al. (2011)	Economic value of dispensing home-based preoperative chlorhexidine bathing cloths to prevent surgical site infection	• Modeling
12	Balegar et al. (2013)	Extending total parenteral nutrition hang time in the neonatal intensive care unit: is it safe and cost effective?	• No full economic evaluation • No intervention of interest
13	Barbut et al. (2012)	New molecular methods for the diagnosis of Clostridium difficile infections	• Review
14	Barsanti et al. (2009)	Infection prevention in the intensive care unit	• Review
15	Bartsch et al. (2012)	The potential economic value of screening hospital admissions for Clostridium difficile	• No infection of interest
16	Baykasoglu et al. (2009)	Application of cost/benefit analysis for surgical gown and drape selection: a case study	• Modeling
17	Bilcke et al. (2009)	Cost-effectiveness of rotavirus vaccination: exploring caregiver(s) and "no medical care" disease impact in Belgium	• No infection of interest
18	Bird et al. (2010)	Adherence to ventilator-associated pneumonia bundle and incidence of ventilator-associated pneumonia in the surgical intensive care unit	• No full economic evaluation • No intervention of interest
19	Blumenstein et al. (2012)	A glycerin hydrogel-based wound dressing prevents peristomal infections after percutaneous endoscopic gastrostomy (PEG): a prospective, randomized study	• No full economic evaluation
20	Boccalini et al. (2011)	Economic and clinical evaluation of a catch-up dose of 13-valent pneumococcal conjugate vaccine in children already immunized with three doses of the 7-valent vaccine in Italy	• No intervention of interest

21	Boyce et al. (2013)	Obtaining blood cultures by venipuncture versus from central lines: impact on blood culture contamination rates and potential effect on central line-associated bloodstream infection reporting	• No intervention of interest
22	Bukhari et al. (2012)	Application of ventilator care bundle and its impact on ventilator associated pneumonia incidence rate in the adult intensive care unit.	• No full economic evaluation
23	Byington et al. (2012)	Costs and infant outcomes after implementation of a care process model for febrile infants	• No infection of interest
24	Catanzaro et al. (2012)	Real-time polymerase chain reaction testing for Clostridium difficile reduces isolation time and improves patient management in a small community hospital	• No full economic evaluation • No infection of interest
25	Ceppa et al. (2013)	Reducing surgical site infections in hepatopancreatobiliary surgery.	• No intervention of interest
26	Chenoweth et al. (2013)	Preventing catheter-associated urinary tract infections in the intensive care unit	• Review
27	Chow et al. (2012)	Effect of continuous oral suctioning on the development of ventilator-associated pneumonia: a pilot randomized controlled trial	• No full economic evaluation
28	Christopher et al. (2011)	Transmission dynamics of methicillin-resistant Staphylococcus aureus in a medical intensive care unit in India	• No intervention of interest • No infection of interest • No full economic evaluation
29	Courville et al. (2012)	Cost-effectiveness of preoperative nasal mupirocin treatment in preventing surgical site infection in patients undergoing total hip and knee arthroplasty: a cost-effectiveness analysis	• No intervention of interest
30	Cummings et al. (2010)	Hand hygiene noncompliance and the cost of hospital-acquired methicillin-resistant Staphylococcus aureus infection	• No infection of interest
31	Dancer et al. (2009)	Measuring the effect of enhanced cleaning in a UK hospital: a prospective cross-over study	• No infection of interest
32	Dendle et al. (2009)	Staphylococcus aureus bacteraemia as a quality indicator for hospital infection control	• No infection of interest
33	Doan et al. (2012)	Clinical and cost effectiveness of eight disinfection methods for terminal disinfection of hospital isolation rooms contaminated with Clostridium difficile 027	• No infection of interest
34	Dranitsaris et al. (2011)	Posaconazole versus fluconazole or itraconazole for prevention of invasive fungal infections in patients undergoing intensive cytotoxic therapy for acute myeloid leukemia or myelodysplasia: a cost effectiveness analysis	• No infection of interest
35	Eagye et al. (2009)	Surgical site infections: does inadequate antibiotic therapy affect patient outcomes?	• No intervention of interest
36	Forte et al. (2011)	Comparative cost-efficiency of the EVOTECH endoscope cleaner and reprocessor versus manual cleaning plus automated endoscope reprocessing in a real-world Canadian hospital endoscopy setting	• No intervention of interest
37	Gagne et al. (2010)	Systematic patients' hand disinfection: impact on meticillin-resistant Staphylococcus aureus infection rates in a community hospital	• No infection of interest
38	Gerber et al. (2013)	Identifying targets for antimicrobial stewardship in children's hospitals	• No full economic evaluation
39	Giglio et al. (2010)	Cost-effectiveness of the CRM-based 7-valent pneumococcal conjugated vaccine (PCV7) in Argentina	• No intervention of interest
40	Gray, M. (2010)	Reducing catheter-associated urinary tract infection in the critical care unit	• Review
41	Greer et al. (2009)	Keeping vulnerable children safe from pertussis: preventing nosocomial pertussis transmission in the neonatal intensive care unit	• No intervention of interest

42	Halton et al. (2010)	Cost-effectiveness of a central venous catheter care bundle	• Modeling
43	Hanmore et al. (2013)	Economic benefits of safety-engineered sharp devices in Belgium - a budget impact model	• No intervention of interest • No infection of interest
44	Heimes et al. (2011)	Implementation and enforcement of ventilator-associated pneumonia prevention strategies in trauma patients	• No full economic evaluation
45	Hollenbeak et al. (2011)	Electronic measures of surgical site infection: implications for estimating risks and costs	• No full economic evaluation
46	Holmen Moller et al. (2012)	A cost-effectiveness analysis of reducing ventilator-associated pneumonia at a Danish ICU with ventilator bundle	• No intervention of interest
47	Holzmann-Pazgal et al. (2011)	Active surveillance culturing impacts methicillin-resistant Staphylococcus aureus acquisition in a pediatric intensive care unit	• No full economic evaluation • No infection of interest
48	Huynh et al. (2013)	Plastic freezer bags: a cost-effective method to protect extraction sites in laparoscopic colorectal procedures?	• No intervention of interest
49	Illingworth et al. (2011)	Is closure of entire wards necessary to control norovirus outbreaks in hospital? Comparing the effectiveness of two infection control strategies	• No full economic evaluation • No infection of interest
50	Johnson et al. (2010)	Preoperative chlorhexidine preparation and the incidence of surgical site infections after hip arthroplasty	• No full economic evaluation
51	Kaambwa et al. (2010)	Cost-effectiveness of rapid tests and other existing strategies for screening and management of early-onset group B streptococcus during labour	• No infection of interest
52	Kennedy et al. (2013)	Estimating hospital costs of catheter-associated urinary tract infection	• No intervention of interest
53	Landre-Peigne et al. (2011)	Efficacy of an infection control programme in reducing nosocomial bloodstream infections in a Senegalese neonatal unit	• No full economic evaluation
54	Lee at al. (2011)	The economic value of screening haemodialysis patients for methicillin-resistant Staphylococcus aureus in the USA	• No infection of interest
55	Lee at al. (2009)	Should vascular surgery patients be screened preoperatively for methicillin-resistant Staphylococcus aureus?	• No infection of interest
56	Lee at al. (2010)	The economic effect of screening orthopedic surgery patients preoperatively for methicillin-resistant Staphylococcus aureus	• No infection of interest
57	Lee at al. (2011)	Routine pre-cesarean Staphylococcus aureus screening and decolonization: a cost-effectiveness analysis	• No infection of interest
58	Leonhardt at al. (2011)	Clinical effectiveness and cost benefit of universal versus targeted methicillin-resistant Staphylococcus aureus screening upon admission in hospitals	• No infection of interest
59	Li et al. (2012)	Cost-effectiveness of supplementing a broth-enriched culture test with the Xpert meticillin-resistant Staphylococcus aureus (MRSA) assay for screening inpatients at high risk of MRSA	• No infection of interest
60	Lin et al. (2010)	Cost-effectiveness of influenza immunization in adult cancer patients in Taiwan	• Modeling • No infection of interest
61	Lin et al. (2013)	Impact of an antimicrobial stewardship program with multidisciplinary cooperation in a community public teaching hospital in Taiwan	• No infection of interest
62	Lorente et al. (2011)	Lower associated costs using rifampicin-miconazoleimpregnated catheters compared with standard catheters	• No intervention of interest
63	Luan et al. (2011)	Universal prophylaxis is cost effective in cytomegalovirus serology-positive kidney transplant patients	• No infection of interest

64	Lusardi et al. (2013)	Antibiotic prophylaxis for short-term catheter bladder drainage in adults	• Review
65	Magalini et al. (2013)	Observational study on preoperative surgical field disinfection: povidone-iodine and chlorhexidine-alcohol	• No full economic evaluation
66	Matsushima et al. (2011)	Pre-emptive contact precautions for intubated patients reduced healthcare-associated meticillin-resistant Staphylococcus aureus transmission and infection in an intensive care unit	• No full economic evaluation • No infection of interest
67	McLaws et al. (2012)	Zero risk for central line-associated bloodstream infection: are we there yet?	• No full economic evaluation
68	Meddings et al. (2012)	Effect of nonpayment for hospital-acquired, catheter-associated urinary tract infection: a statewide analysis	• No full economic evaluation
69	Minhas et al. (2011)	Risk factors for positive admission surveillance cultures for methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci in a neurocritical care unit	• No full economic evaluation • No infection of interest
70	Murthy et al. (2010)	Cost-effectiveness of universal MRSA screening on admission to surgery	• No infection of interest • Modeling
71	Nelson et al. (2010)	Cost-effectiveness of adding decolonization to a surveillance strategy of screening and isolation for methicillin-resistant Staphylococcus aureus carriers	• No infection of interest
72	Nyman et al. (2011)	Cost of screening intensive care unit patients for methicillin-resistant Staphylococcus aureus in hospitals	• No infection of interest
73	Oncel et al. (2012)	Respiratory syncytial virus prophylaxis in preterm infants: a cost-effectiveness study from Turkey	• No infection of interest
74	O'Sullivan et al. (2009)	Cost-effectiveness of posaconazole versus fluconazole or itraconazole in the prevention of invasive fungal infections among neutropenic patients in the United States	• No infection of interest • No intervention of interest
75	O'Sullivan et al. (2012)	Cost-effectiveness of posaconazole versus fluconazole for prevention of invasive fungal infections in US patients with graft-versus-host disease	• No infection of interest • No intervention of interest
76	Ozgun et al. (2010)	Peri-operative antibiotic prophylaxis: adherence to guidelines and effects of educational intervention	• No full economic evaluation
77	Perez et al. (2013)	Integrating rapid pathogen identification and antimicrobial stewardship significantly decreases hospital costs	• No intervention of interest
78	Platt et al. (2010)	Cluster randomized trials in comparative effectiveness research: randomizing hospitals to test methods for prevention of healthcare-associated infections	• No full economic evaluation
79	Rijen et al. (2009)	Costs and benefits of the MRSA Search and Destroy policy in a Dutch hospital	• No infection of interest
80	Robotham et al. (2011)	Screening, isolation, and decolonisation strategies in the control of meticillin resistant Staphylococcus aureus in intensive care units: cost effectiveness evaluation	• No infection of interest
81	Samransamruajkit et al. (2010)	Effect of frequency of ventilator circuit changes (3 vs 7 days) on the rate of ventilator-associated pneumonia in PICU	• No intervention of interest
82	Scheetz et al. (2009)	Cost-effectiveness analysis of an antimicrobial stewardship team on bloodstream infections: a probabilistic analysis	• Modeling
83	Shorr et al. (2009)	Cost-effectiveness analysis of a silver-coated endotracheal tube to reduce the incidence of ventilator-associated pneumonia	• No intervention of interest
84	Simoens et al. (2009)	Search and destroy policy for methicillin-resistant Staphylococcus aureus: cost-benefit analysis	• No infection of interest
85	Slover et al. (2011)	Cost-effectiveness of a Staphylococcus aureus screening and decolonization program for high-risk orthopedic patients	• No infection of interest

86	Smith et al. (2010)	Cost-effectiveness of pneumococcal polysaccharide vaccine among healthcare workers during an influenza pandemic	• No infection of interest • No intervention of interest • Modeling
87	Stocker et al. (2012)	Antibiotic surveillance on a paediatric intensive care unit: easy attainable strategy at low costs and resources	• No intervention of interest
88	Stone et al. (2010)	Healthcare savings associated with reduced infection rates using antimicrobial suture wound closure for cerebrospinal fluid shunt procedures	• No infection of interest
89	Tubbicke et al. (2012)	Cost comparison of MRSA screening and management - a decision tree analysis	• Review
90	Vos et al. (2011)	Cost-effectiveness of routine (18)F-FDG PET/CT in high-risk patients with gram-positive bacteremia	• No intervention of interest • No infection of interest
91	Wassenberg et al. (2011)	Cost-effectiveness of preoperative screening and eradication of Staphylococcus aureus carriage	• No intervention of interest
92	Yam et al. (2011)	Rethinking hospital general ward ventilation design using computational fluid dynamics	• No full economic evaluation

3.2. Manuskript II

Hospital-related cost of sepsis

Habibollah Arefian, Steffen Heublein, André Scherag, Frank M. Brunkhorst, Mustafa Z. Younis, Onnen Moerer, Dagmar Fischer, Michael Hartmann

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In dieser Studie wurde untersucht, welche Kosten der Sepsis bisher publiziert wurden und wie die Qualität der ökonomischen Evaluationen einzuschätzen ist. Darüber hinaus wurden umfassende Kostenvergleiche nach Methoden, Schweregrad der Sepsis, Perspektive der Kosten usw. durchgeführt. Es wurde herausgefunden, dass die Krankenhauskosten der Sepsis pro Patient von 13.299 $ bis 75.015 $ variieren können. Die schwere Sepsis auf der Intensivstation kostet 1.737 $ pro Tag in Frankreich und 4.651 $ in den USA. Die Qualität der Publikationen ist teilweise sehr niedrig. Die CHEERS Guideline (Husereau et al., 2013) könnte als ein Standard die Qualität erhöhen.

Habibollah Arefian	Konzeptionelle Entwicklung der Studie; Definition der Suchstrategie und Suche nach Publikationen in verschiedenen Datenbanken; Ermittlung der relevanten Publikationen; Beurteilung der Qualität der Studien; Datenextraktion und Evaluierung der Daten; Analyse der Daten; Interpretationen der Ergebnisse; Erstellung des Entwurfs und Überarbeitung des Manuskripts; Konzeption und Erstellung aller Abbildungen; Erstellung aller Tabellen; Einarbeitung von Korrekturen während des Reviewprozesses

Steffen Heublein	Konzeption und Planung des Projekts; Definition der Suchstrategie und Suche nach Publikationen in verschiedenen Datenbanken; Ermittlung der relevanten Publikationen; Mitarbeit an der Beurteilung der Qualität der Studien; Mitarbeit an der Datenextraktion und Analyse der Daten; Bearbeitung und Diskussion des Manuskripts
André Scherag	Interpretationen der Ergebnisse; Überarbeitung und Durchsicht des Manuskripts; Mitarbeit an der Erstellung von Korrekturen während des Reviewprozesses
Frank M. Brunkhorst	Konzeption und Planung des Projekts; Überarbeitung und Durchsicht des Manuskripts
Mustafa Z. Younis	Interpretationen der Ergebnisse, Überarbeitung des Entwurf des Manuskripts
Onnen Moerer	Ermittlung der relevanten Publikationen; Interpretationen der Ergebnisse; Überarbeitung und Durchsicht des Manuskripts
Dagmar Fischer	Interpretationen der Ergebnisse; Überarbeitung und Durchsicht des Manuskripts; Mitarbeit an der Erstellung von Korrekturen während des Reviewprozesses
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REVIEW

Hospital-related cost of sepsis: A systematic review

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Summary *Objectives:* This article systematically reviews research on the costs of sepsis and, as a secondary aim, evaluates the quality of economic evaluations reported in peer-reviewed journals.
Methods: We systematically searched the MEDLINE, National Health Service (Abstracts of Reviews of Effects, Economic Evaluation and Health Technology Assessment), Cost-effectiveness Analysis Registry and Web of Knowledge databases for studies published between January 2005 and June 2015. We selected original articles that provided cost and cost-effectiveness analyses, defined sepsis and described their cost calculation method. Only studies that considered index admissions and re-admissions in the first 30 days were published in peer-reviewed journals and used standard treatments were considered. All costs were adjusted to 2014 US dollars. Medians and interquartile ranges (IQRs) for various costs of sepsis were calculated. The quality of economic studies was assessed using the Drummond 10-item checklist.

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Results: Overall, 37 studies met our eligibility criteria. The median of the mean hospital-wide cost of sepsis per patient was $32,421 (IQR $20,745–$40,835), and the median of the mean ICU cost of sepsis per patient was $27,461 (IQR $16,007–$31,251). Overall, the quality of economic studies was low.
Conclusions: Estimates of the hospital-related costs of sepsis varied considerably across the included studies depending on the method used for cost calculation, the type of sepsis and the population that was examined. A standard model for conducting cost improve the quality of studies on the costs of sepsis.

Introduction

Sepsis, regardless of its precise definition, is a severe syndrome with a high mortality rate that affects over one million people in the US each year.[1] Worldwide, there are 35 million sepsis cases and 19.4 million severe sepsis cases annually.[2] Treatment of sepsis is listed as the most expensive condition in US hospitals, costing more than $20 billion annually.[3] However, precise costs are not available due to both controversy regarding the definition of sepsis[4] and the nature of sepsis, which is typically accompanied by comorbidities, such as diabetes or pneumonia. Each disease entails individual treatment costs, which increases the difficulty of calculating the costs attributable to specific treatments. Because there is no widely accepted approach available to circumvent this challenge, it can be assumed that to an extent, this issue negatively impacts many studies on sepsis costs.

In the present study, we conducted a systematic review that examined previous publications on the costs of sepsis. The primary aim of this systematic review was to provide an overview of hospital-related costs of sepsis reported in previous publications. The secondary aim was to examine the quality of each study's estimated costs of sepsis because determining the quality of published economic studies is essential for appropriately interpreting the results of these studies and allocating resources rationally.[5]

Methods

Data sources and search strategy

We conducted our review according to accepted guidelines[6] and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement while preparing our manuscript.[7] We searched MEDLINE, three National Health Service databases (Database of Abstracts of Reviews of Effects, Economic Evaluation Database and Health Technology Assessment Database), the Cost-effectiveness Analysis (CEA) registry and Web of Knowledge (WOK) for articles from January 2005 to June 2015 with the aim of comparing the costs of sepsis over this long period. Only studies published in English were included. The search strategy for eligible publications in MEDLINE is shown in Appendix 1. To identify other possibly relevant studies, we searched the references of publications obtained from the search.

Selection criteria

Two independent reviewers applied the inclusion and exclusion criteria and extracted the data from eligible studies by screening titles, abstracts and full-text articles. Inclusion in the analysis required the publication to 1) describe the definition of sepsis applied, 2) describe the method used to calculate the stated costs and 3) calculate the costs for either index admissions or re-admissions within the first 30 days.

A publication was excluded if 1) it was not a peer-reviewed article in a journal listed in the Journal Citation Reports,[8] 2) it was an abstract, editorial, letter or review or 3) the study only provided costs for non-standard therapies (e.g., recombinant human activated protein C (rhAPC)). There were no age or gender restrictions in our systematic review.

Data extraction

The extracted data included the title, authors, study type, country of origin, publication year, severity of sepsis (type of sepsis), cost method, cost perspective, calculated costs of sepsis, sepsis definition, number of participants, age group and source of funding. Any disagreements between the reviewers were resolved by discussion.

Definition

The ***study type*** was categorized into *cost-effectiveness* or *cost-analysis* studies and into *retrospective*, *prospective* or *mixed model* studies. ***Severity of sepsis*** indicated the stated degree of severity of sepsis, i.e., *sepsis*, *severe sepsis*, *septic shock* or *septicemia*. If in doubt, the category used was sepsis. The ***sepsis definition*** categorized studies according to how they identified septic patients. The possible categories were 1) *ACCP/SCCM*, the sepsis definition proposed by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM)[9]; 2) *ICD-9*, if patients were identified using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes[10]; and 3) *other*, if other definitions were used.

Statement of discounting identified whether a study considered discounting. This categorization could be accomplished by naming a currency year to which costs were discounted or by discounting health measurements (QALYs) or future long-term costs. The ***stated cost perspective*** was

that of the healthcare provider (i.e., the hospital) or of the healthcare payer (i.e., the patient or the insurance company). A lack of a clear statement on perspective was also recorded. The ***calculation method of unit costs*** was examined and extracted. If several different calculation cases were published (e.g., as part of a sensitivity analysis), only the baseline calculation was included. We focused on the calculation of the costs of sepsis.

Any ***funding*** was categorized according to the given funding statements. If applicable, funding could be categorized as *industry* with an *unrestricted industry* grant or without industry (*no industry*). Similarly, ***conflicts of interest/affiliation*** was categorized based on conflict of interest and affiliation statements. If all study authors were employees of either hospitals or non-profit organizations and declared no conflict of interest, the *hospital/non-profit* category was used. If all were industry employees, the *industry* category was used. Combinations of employment status (e.g., one industry author or one author with conflicts of interest) were categorized as *mixed*.

Analysis of costs

To ensure comparability among studies conducted in different years and countries, we adjusted costs to 2014 US dollars.

Costs were converted to US dollars from the provided currency year using purchasing power parities for gross domestic product provided by the Organisation for Economic Co-operation and Development (OECD).[11] After this conversion, costs were adjusted to 2014 dollars using the country-specific harmonized index of consumer prices (HICP).[12] If the HICP was not available, we used data from the World Bank[13] or the relevant national bureau of statistics.[14]

If the currency base year was not stated, it was assumed to have been two years before publication. Studies that performed their own currency conversions were examined, and their costs recalculated using our methodology when possible. We extracted the median and interquartile ranges (IQRs provided as the 1st and 3rd quartile) of the reported mean and median hospital and ICU costs of sepsis per stay and per day in 2014 US dollars.

Effects of study characteristics on the mean hospital cost per stay

We analyzed the effects of study characteristics on the means of total hospital cost results. We assumed that heterogeneity could have been due to systematic differences in the geographical region of the study, the investigated age groups, the number of patients, the method of cost calculation, the severity of sepsis, the cost perspective or the type of the study. The medians of total hospital cost per stay with the maximum–minimum ranges are reported. Descriptive analyses were performed using Microsoft Excel (© 2010, Microsoft Corporation).

Quality assessment

The quality of economic studies was analyzed using the Drummond checklist for assessing economic evaluations.[15] This 10-item checklist provides a global assessment of quality of evidence. For each selected study, an answer of *"Yes"* or *"No"* was determined for each checklist item based on the information provided in the examined publication. If an article did not provide sufficient information to determine the answer for an item, the answer used for the item was *"Can't tell"*.

Results

A total of 2382 potentially relevant publications were identified, 37 of which were articles/studies that fulfilled the inclusion criteria.[16–52] A flow diagram of search and selection is shown in Fig. 1.

Study descriptions

The majority of studies were performed in the US (n = 21, 56.8%). Many of the studies were retrospective cost analyses (n = 17, 54.5%). Compared to other severity degrees, severe sepsis was assessed more frequently (n = 13, 35.1%). Eighteen studies used the definitions of sepsis provided by the ACCP/SCCM (48.6%), and fourteen studies identified septic patients based on ICD-9-CM codes (37.8%). Seven studies had fewer than 100 patients (18.9%), but 15 studies included over 5000 patients (40.5%). The included studies used several different methods to calculate their unit costs. Seven studies based their calculations on cost-to-charge ratios (18.9%). The 2 French studies[16,22] used the Omega score for their calculations (5.4%). Eleven studies used more than one cost approach to estimate the costs of sepsis (29.7%). Three studies took the perspective of the healthcare payer (8.1%), while eight (21.6%) took that of the healthcare provider (i.e., the hospital). Four studies did not include statements on funding (10.8%). Twenty-three studies were not industry funded (62.2%). Three studies[19,25,48] were supported by an unrestricted industry grant (8.1%), and 7 studies (18.9%) received funding independently from industry. Ten studies declared that at least one of their authors was affiliated with industry or had a conflict of interest (27%). The most commonly declared industry affiliations and conflicts of interest mentioned Eli Lilly or one of its national branches (n = 9).[16,21,24,35,41,43,47–49] Further characteristics of the included publications are listed in Appendix 2.

Calculated costs of sepsis

Three types of costs were calculated in the included studies. Twenty-eight studies calculated hospital costs only. Six studies calculated ICU costs only; 3 studies published both cost types (Tables 1 and 2). The included studies did not calculate indirect costs of sepsis.

Costs of sepsis per stay

The published costs across types varied considerably and differed between survivors and non-survivors.

Total hospital costs per stay

The mean total hospital cost per patient varied between $13,292[19] and $75,015.[28] The median (IQR) of the mean

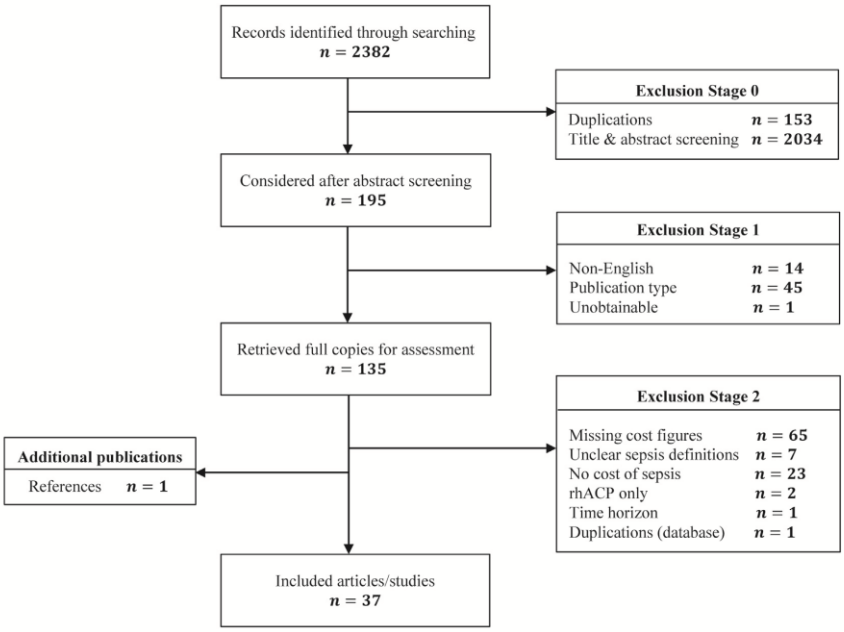

Figure 1 Flow diagram for the systematic review process to select studies. rhAPC = recombinant human activated protein C.

reported total hospital costs was $32,421 ($20,745–$40,835). The medians of the mean reported hospital-wide costs (IQR) of survivors and non-survivors were $34,855 ($26,075–$40,427) and $20,537 ($16,747–$34,564), respectively.

Thirteen studies calculated the median hospital cost per stay, which varied between $5,051[25] and $64,788.[51] Medians (IQRs) were $27,567 ($22,801–$38,849) for the reported medians of hospital-wide cost and $24,216 ($16,388–$24,216) for survivors. The median hospital costs per stay for non-survivors were not calculated in the selected studies (Table 1 and Appendix 3).

Total ICU costs per stay

The median (IQR) of calculated means of the ICU cost per stay was $27,461 (16,007–31,251), with non-survivors being more expensive ($35,774) than survivors ($29,195).

Median ICU costs per stay (evaluated in five studies) ranged from $10,942[47] to $79,769.[42] The median (IQR) of all reported median ICU costs was $16,056 (13,603–21,656), with higher costs for non-survivors (median $27,413; IQR 19,060–87,095) than for survivors (median $24,093; IQR 17,689–40,118; Table 2 and Appendix 3).

Costs of sepsis per day

Fewer studies calculated daily costs of sepsis.

Total hospital costs per day

Only one study[20] estimated the mean total hospital cost of sepsis per day, which was $586. The mean total hospital daily cost of survivors was $351, while that of non-survivors was $948.

Total ICU costs per day

Adrie et al.[16] calculated the daily mean ICU costs of severe sepsis in France, and Ruth et al.[42] estimated the daily median ICU costs (IQR) of severe sepsis in the US, which were $1737 and $4651 (3349–6635), respectively (Appendix 3).

Effects of study characteristics on the costs of sepsis

The effects of study characteristics on the mean total hospital costs of sepsis differed considerably. The median cost of sepsis was lower in the US ($32,421) than in Europe ($37,424). The costs were considerably higher for children ($75,015) than for other participant types. The median cost reported in studies with large numbers of patients (>5000) was $35,861 (range 20,728–75,015). Studies that used the Omega score to calculate costs reported particularly high costs ($46,834), as did studies that focused on severe sepsis and septic shock ($42,268). The costs were considerably lower for septicemia ($20,740) than for other degrees of sepsis severity. Higher costs were observed in studies focused on the healthcare provider perspective ($33,266) than in studies focused on the healthcare payer ($30,842). The median cost was higher in retrospective studies ($37,374) than in prospective studies ($20,547). Studies that were considered high quality produced higher cost

Table 1 Total hospital costs per stay in 2014 US dollars.

Study ID	Country	Patients[b]	Severity of sepsis	Method	Perspective [Healthcare]	Parameter	Overall cost (± SD or IQR) [$]	Survivor cost (± SD or IQR) [$]	Non-survivor cost (± SD or IQR) [$]
Alvarez 2012[17]	Spain	54	SS + SSH	Accounting	Provider	Mean	62,652	–	–
Balamuth 2014[18]	USA	136,382	SS + SSH	Charges	Payer[a]	Median	54,475 (19,328–148,754)	–	–
Berto 2011[19]	Italy	64	SS + SSH	Mixed	Provider	Median	34,374	–	–
						Mean	58,537 (±79,022)	–	–
Cheng 2007[20]	China	318	SS	Accounting	Provider[a]	Mean	13,292 (±13,368)	11,509 (±12,513)	12,956 (±13,895)
Davies 2005[21]	UK	7234	SS	Mixed	Payer	Mean	35,861	–	–
Dhainaut 2007[22]	France	587	SS	Omega score	Provider	Mean	46,834	45,377	48,591
Eber 2010[23]	USA	493,250	S	CCR	Provider[a]	Median	18,290	–	–
						Mean	37,374	–	–
Giamarellos-Bourboulis 2014[25]	Greece	298	S + SS + SSH	Micro-costing	Provider[a]	Median	–	5051	–
Goodwin 2015[26]	USA	84,575	SS + SSH	Charges	Payer[a]	Mean	–	25,888 (±39,346)	–
Green 2006[27]	UK	NA	SS	Mixed	Payer	Mean	–	30,932	20,537
Hartman 2013[28]	USA	17,542	SS	Charges	Payer[a]	Median	38,849	–	–
						Mean	75,015	–	–
Huang 2007[29]	USA	133	S + SS + SSH	CCR	Provider	Mean	44,139 (±37,289)	–	–
Jones 2011[31]	USA	79	SSH	Charges	Provider[a]	Mean	15,064 (±15,782)	–	–
Judd 2014[32]	USA	181	SS + septicemia	Mixed	Provider[a]	Mean	14,809 (±12,331)	–	–
Karlsson 2009[33]	Finland	470	SS + SSH	Accounting	Provider[a]	Mean	–	38,777	–
Lagu 2012[35]	USA	1,115,112	Septicemia	Mixed	Payer[a]	Mean	20,728 (±368)	–	–
Micek 2012[36]	USA	754	SS + SSH	Accounting	Provider[a]	Median	22,801 (12,190–44,322)	22,843 (12,808–42,503)	–
Mouncey 2015[37]	UK	348	SS	Mixed	Provider[a]	Mean	16,810 (±23,141)	–	–
Nissenson 2005[38]	USA	11,572	Septicemia	Costs-paid	Payer[a]	Mean	20,751 (±26,492)	–	–
Noritomi 2014[39]	Brazil	1882	SS + SSH	Accounting	Provider	Mean	24,284	–	–
Page 2015[40]	USA	34,829	SS	Charges	Payer[a]	Median	39,520 (20,605–75,366)	–	–
Riou-Franca 2006[41]	France	9948	SS	Mixed	Provider[a]	Mean	38,986	–	–
Sadique 2011[43]	UK	1650	SS	Mixed	Provider[a]	Mean	22,610 (±25,133)	–	–
Shah 2009[44]	USA	192	SSH	CCR	Provider[a]	Median	17,212 (9655–38,620)	–	–
Shorr 2007[45]	USA	60	SSH	CCR	Provider[a]	Median	25,656 (4213–116,461)	25,588 (4213–116,461)	–
Silverman 2011[46]	USA	19	S + SS + SSH	Accounting	Provider[a]	Median	38,290	–	–
						Mean	39,733 (±25,925)	–	–
Suarez 2011[48]	Spain	854	SS + SSH	Mixed	Payer	Mean	25,998 (±28,438)	–	–
Talmor 2008[49]	USA	51	SSH	Accounting	Payer	Mean	35,685 (±1807)	–	–
Vaughan-Sarrazin 2011[50]	USA	13,878	S + SS + SSH	Other	Provider	Mean	29,157 (±74,955)	–	–
Vogel 2010[51]	USA	6,512,921	S	CCR	Provider[a]	Median	64,788	–	–
Walkey 2014[52]	USA	56,997	SS	CCR	Provider[a]	Median	27,567 (22,951–33,630)	–	–

S = sepsis; SS = severe sepsis; SSH = septic shock; ICU = intensive care unit; CCR = cost-to-charge ratio.

[a] Assumed cost perspective.

[b] Participants on which cost calculations are based.

Table 2 Total ICU costs per stay in 2014 US dollars.

Study ID	Country	Patients[b]	Severity of sepsis	Method	Perspective [Healthcare]	Parameter	Overall cost (± SD or IQR) [$]	Survivor cost (± SD or IQR) [$]	Non-survivor cost (± SD or IQR) [$]
Adrie 2005[16]	France	713	SS	Omega score	Provider	Median	21,656 (12,199–39,612)	19,737 (10,006–36,871)	27,413 (16,996–42,901)
						Mean	31,251 (±29,332)	29,195 (±29,058)	35,774 (±29,606)
Davies 2005[21]	UK	7234	SS	Mixed	Payer	Mean	27,461	–	–
Ernst 2006[24]	USA	516,157	SS	CCR	Provider	Mean	41,289	–	–
Jiang 2013[30]	China	71	SS + SSH	Micro-costing	Provider[a]	Median	13,603	–	–
						Mean	14,109 (±12,623)	–	–
Karlsson 2009[33]	Finland	470	SS + SSH	Accounting	Provider[a]	Mean	–	28,449	–
Lagu 2013[34]	USA	40,265	S	Mixed	Provider and payer	Median	16, 056 (9409–27,624)	–	–
Ruth 2014[42]	USA	49,153	SS	Charges	Payer[a]	Median	79,769 (33,521–188,962)	75,124	146,776
Sadique 2011[43]	UK	1650	SS	Mixed	Provider[a]	Mean	16,007 (±20,261)	–	–
Sogayar 2008[47]	Brazil	524	S + SS + SSH	Micro-costing	Provider[a]	Median	10,942 (5206–20,888)	11,543 (4324–20,674)	10,707 (5716–22,249)

S = sepsis; SS = severe sepsis; SSH = septic shock; ICU = intensive care unit; CCR = cost-to-charge ratio; SD = standard deviation; IQR = interquartile range.

[a] Assumed cost perspective.

[b] Participants on which cost calculations are based.

Table 3 Effects of study characteristics on the mean hospital costs per stay in 2014 US dollars.

	Overall costs (range) [$]	Survivor costs (range) [$]	Non-survivor costs (range) [$]
Geographical region of study			
United States	32,421 (14,809–75,015), n = 10	–	–
Europe	37,424 (16,810–62,652), n = 8	38,777 (30,932–45,377), n = 3	34,564 (20,537–48,591), n = 2
Asia	13,292, n = 1	11,509, n = 1	12,956, n = 1
South America	24,284, n = 1	–	–
Age group			
Children	75,015, n = 1	–	–
Adult	25,998 (13,292–58,537), n = 15	34,855 (11,509–45,377), n = 4	20,537 (12,956–48,591), n = 3
Not stated	33,266 (24,284–62,652), n = 4	–	–
Number of patients			
≤100	39,733 (15,064–62,652), n = 5	30,932, n = 1	20,537, n = 1
101–500	15,810 (13,292–44,139), n = 4	25,143 (11,509–38,777), n = 2	12,956, n = 1
501–1000	36,416 (25,998–46,834), n = 2	45,377, n = 1	48,591, n = 1
1001–5000	23,447 (22,610–24,284), n = 2	–	–
>5000	35,861 (20,728–75,015), n = 7	–	–
Method of cost calculation			
Accounting	35,685 (13,292–62,652), n = 5	25,143 (11,509–38,777), n = 2	12,956, n = 1
Charges	45,040 (15,064–75,015), n = 2	–	–
Cost-to-charge-ratio	40,757 (37,374–44,139), n = 2	–	–
Omega score	46,834, n = 1	45,377, n = 1	48,591, n = 1
Cost-paid to hospital	20,751, n = 1	–	–
Mixed methods	25,998 (14,809–58,537), n = 9	30,932, n = 1	20,537, n = 1
Severity of sepsis			
Sepsis	37,374, n = 1	–	–
Severe sepsis	35,861 (13,292–75,015), n = 7	30,932 (11,509–45,377), n = 3	20,537 (12,956–48,591), n = 3
Septic shock	25,375 (15,064–35,685), n = 2	–	–
Septicemia	20,740 (20,728–20,751), n = 2	–	–
Severe sepsis & septic shock	42,268 (24,284–62,652), n = 4	38,777, n = 1	–
Sepsis & severe sepsis & septic shock	39,733 (29,157–44,139), n = 3	–	–
Severe sepsis & septicemia	14,809, n = 1	–	–
Assumed cost perspective			
Healthcare payer	30,842 (20,728–75,015), n = 6	30,932, n = 1	20,537, n = 1
Healthcare provider	33,266 (13,292–62,652), n = 14	38,777 (11,509–45,377), n = 3	30,774 (12,956–48,591), n = 2

(*continued on next page*)

Table 3 (*continued*)

	Overall costs (range) [$]	Survivor costs (range) [$]	Non-survivor costs (range) [$]
Study type			
Retrospective	37,374 (14,809–75,015), n = 11	–	–
Prospective	20,547 (13,292–46,834), n = 6	38,777 (11,509–45,377), n = 3	30,774 (12,956–48,591), n = 2
Mixed model	35,685 (22,610–44,139), n = 3	30,932, n = 1	20,537, n = 1

n = number of studies.

estimates ($45,487) than those of middle ($27,578) or low ($29,236) quality (Table 3).

Assessment of study quality

Most of the selected studies posed a well-defined question in an answerable form (n = 25, 67.6%); however, a comprehensive description of the competing alternatives was missing in 20 studies (54.1%). Twenty-one studies (56.8%) identified and evaluated all costs relevant to sepsis, but only 7 studies accurately measured costs and consequences. Most of the selected studies included a statement on the currency year (n = 23, 62.2%), and a statement on discounting was provided or unnecessary for 26 studies (70.3%). Only 6 studies calculated incremental costs (16.2%), and most of the studies were not planned (n = 30, 81.1%). Future quality assessments based on the Drummond checklist are provided in Table 4.

Discussion

We systematically reviewed and assessed the quality of 37 studies estimating hospital- and ICU-related costs of sepsis. Our systematic review showed that the estimated cost of treating a septic patient varied considerably among these studies. One obvious reason is that the quality of cost studies on sepsis is relatively low. Several of the excluded studies were missing basic information, such as an unambiguous definition of sepsis or statements about the study population. Nevertheless, even studies that were included were highly variable with respect to methods and results, suggesting ambiguity regarding problems with study quality. Many studies did not include basic statements on discounting or perspective and thus created doubts about the economic rigor of their analyses. Some studies could be considered of high economic quality, as they included not only these statements but also used precise micro-costing calculation or equivalent methods.

Several studies published costs that we could not reproduce. For example, Ernst et al.[24] claimed that they calculated ICU-related costs, but this claim is dubious because their costs were based on diagnosis-related groups (DRGs). These examples demonstrate the importance of publishing detailed cost calculations, as the economic rigor of these analyses must otherwise be doubted.

Appraising study quality proved to be rather difficult. A stated method for calculating unit costs appears to be a

Table 4 Quality assessment against Drummond checklist.

Checklist	Yes *n* (%)	No *n* (%)	Can't tell *n* (%)
1. Was a well-defined question posed in answerable form?	25 (67.6)	12 (32.4)	0 (0.0)
2. Was a comprehensive description of the competing alternatives given?	17 (45.9)	20 (54.1)	0 (0.0)
3. Was the effectiveness of the programmes or services established?	22 (59.5)	15 (40.5)	0 (0.0)
4. Were all the important and relevant costs and consequences for each alternative identified?	21 (56.8)	8 (21.6)	8 (21.6)
5. Were costs and consequences measured accurately in appropriate physical units prior to valuation?	7 (18.9)	27 (73.0)	3 (8.1)
6. Were costs and consequences valued credibly?	21 (56.8)	5 (13.5)	11 (29.7)
7. Were costs and consequences adjusted for differential timing?	26 (70.3)	5 (13.5)	6 (16.2)
8. Was an incremental analysis of costs and consequences of alternatives performed?	6 (16.2)	31 (83.8)	0 (0.0)
9. Was uncertainty in the estimates of costs and consequences adequately characterized?	14 (37.8)	23 (62.2)	0 (0.0)
10. Did the presentation and discussion of study results include all issues of concern to users?	31 (83.8)	6 (16.2)	0 (0.0)

major quality indicator for cost studies, as precise calculation methods promise more reliable results. In our appraisal of cost calculation methods, we followed the order proposed by Drummond et al.[15] in which micro-costing is the most precise cost measurement method.

Some calculations could not be categorized easily. In particular, modeling studies that used more than one calculation method were difficult to appraise, as they often used precise approaches for high-cost intensive care units but less precise approaches for general wards. Nevertheless, we required that all cost data be precisely acquired for a study to be considered high quality. Other studies used approaches that did not easily fit into the framework offered by Drummond et al.,[15] such as the Omega score used by the French studies. This method was shown to be precise, but it is less precise than micro-costing and is not methodologically comparable to DRG-based approaches.

Certain prior publications have indicated that non-survivors tended to be more expensive patients than survivors with respect to direct cost per day; this pattern is often explained by physicians' efforts to save patients' lives by utilizing expensive medications.[53,54] Our findings support this cost relationship between survivors and non-survivors. However, several articles in this systematic review indicated that compared with non-survivors, survivors have higher or comparable total hospital-related costs.

Beyond the above-mentioned limitations that primarily refer to the original studies, our systematic review itself has several limitations. We searched several databases and used a variety of keywords matched to database-specific indexing terms; thus, certain publications on costs of sepsis may have been overlooked. Many studies on costs of sepsis may have been published in non-scientific journals, such as reports and books, or in languages other than English. Such publications are not included in our review, but we would expect a similar or more pronounced variability.

Conclusions

The included studies of hospital- and ICU-related costs of sepsis involve a wide range of costs; however, despite all of the limitations of these original reports, sepsis treatment is consistently extremely expensive. The overall quality of studies on sepsis cost is poor based on accepted quality criteria for economic evaluations. To provide the research community and decision makers in healthcare systems with more reliable and comparable costs, we must 1) standardize the estimation of sepsis-related costs; 2) utilize consensus sepsis definitions to reduce the heterogeneity of sepsis diagnoses, with the "Third International Consensus Definitions for Sepsis and Septic Shock" representing an important step in the correct direction[55]; 3) standardize economic methods; and 4) use publication guidelines such as the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement[5] to improve reporting.

Conflicts of interest

No author or immediate family member has a potential conflict of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jinf.2016.11.006.

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Supporting information

Appendix 1: Medline Search Strategy

Search Strategy:

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1. sepsis.mp. or exp Sepsis/
2. septic shock.mp. or Shock, Septic/
3. Systemic Inflammatory Response Syndrome/
4. septic?emia.mp.
5. "severe sepsis".mp.
6. critical care.mp. or exp Critical Care/
7. or/1-6
8. Economics/
9. "costs and cost analysis"/
10. Cost allocation/
11. Cost-benefit analysis/
12. Cost control/
13. Cost savings/
14. Cost of illness/
15. Cost sharing/
16. "deductibles and coinsurance"/
17. Medical savings accounts/
18. Health care costs/
19. Direct service costs/
20. Drug costs/
21. Employer health costs/
22. Hospital costs/
23. Health expenditures/
24. Capital expenditures/
25. Value of life/
26. exp economics, hospital/
27. exp economics, medical/
28. Economics, nursing/
29. Economics, pharmaceutical/
30. exp "fees and charges"/
31. exp budgets/
32. (low adj cost).mp.
33. (high adj cost).mp.
34. (health?care adj cost$).mp.
35. (fiscal or funding or financial or finance).tw.

36. (cost adj estimate$).mp.

37. (cost adj variable).mp.

38. (unit adj cost$).mp.

39. (economic$ or pharmacoeconomic$ or price$ or pricing).tw.

40. or/8-39

41. 7 and 40

42. letter.pt.

43. editorial.pt.

44. or/42-43

45. 41 not 44

46. limit 45 to (english language and yr="2005 -2015")

Appendix 2. Study characteristics of the 37 included studies of the systematic review.

Descriptive characteristics	Number (%)		Descriptive characteristics	Number (%)	
Geographical region of study			*Severity of sepsis*		
United States	21	(56.8)	Sepsis	3	(8.1)
Europe	12	(32.4)	Severe sepsis	13	(35.1)
Asia	2	(5.4)	Septic shock	4	(10.8)
South America	2	(5.4)	Septicemia	2	(5.4)
Age group			Severe sepsis, Septic shock	9	(24.3)
Children	4	(10.9)	Sepsis, Severe sepsis, Septic shock	5	(13.5)
Adult	27	(63.6)	Severe sepsis, Septicemia	1	(2.7)
Mixed	1	(7.3)	*Sepsis definition*		
Not stated	5	(13.5)	ACCP/SCCM	18	(48.6)
Numbers of patients			ICD-9-CM	14	(37.8)
≥100	7	(18.9)	Other	5	(13.5)
101-500	7	(18.9)	*Reported cost perspective*		
501-1000	5	(13.5)	Healthcare provider	8	(21.6)
1001-5000	2	(5.4)	Healthcare payer	3	(8.1)
>5000	15	(40.5)	Healthcare provider and payer	1	(2.7)
Not stated	1	(2.7)	Not stated	25	(67.6)
Study type			*Assumed cost perspective*		
Cost-analysis, Retrospective	17	(45.9)	Healthcare provider	27	(73.0)
Cost-effectiveness, Retrospective	5	(13.5)	Healthcare payer	9	(24.3)
Cost-analysis, Prospective	3	(8.1)	Healthcare provider and payer	1	(2.7)
Cost-effectiveness, Prospective	7	(18.9)	*Discounted/adjusted*		
Cost-analysis, Mixed model	1	(2.7)	Explicitly stated or not necessary	26	(70.3)
Cost-effectiveness, Mixed model	4	(10.8)	Not stated	11	(29.7)
Method of cost calculation			*Cost increment calculated*		
Accounting	7	(18.9)	Yes	6	(16.2)
Charges	6	(16.2)	No	31	(83.8)
Cost-to-charge-ratio	7	(18.9)	*Source of funding*		
Micro-costing	3	(8.1)	Unrestricted industry grant	3	(8.1)
Omega score	2	(5.4)	No industry	23	(62.2)
Cost-paid to hospital	1	(2.7)	Industry	7	(18.9)
Mixed	11	(29.7)	Not stated	4	(10.8)

Appendix 3. Median costs of sepsis in 2014 US dollars.

Parameter Median of …	**Overall cost** (IQR) [$]	**Survivor cost** (IQR) [$]	**Non-survivor cost** (IQR) [$]
mean hospital costs per stay	32,421 (20,745-40,835), n=20	34,855 (26,076-40,427), n=4	20,537 (16,747-34,564), n=3
mean ICU costs per stay	27,461 (16,007-31,251), n=5	29,195, n=1	35,774, n=1
mean hospital costs per day	586 , n=1	351, n=1	948, n=1
mean ICU costs per day	1,737, n=1	–	–
median hospital costs per stay	27,567 (22,801-38,849), n=13	24,216 (23,529-24,902), n=2	–
median ICU costs per stay	16,056 (13,603-21,656), n=5	24,093 (17,689-40,118), n=4	27,413 (19,060-87,095), n=3
median hospital costs per day	–	–	–
median ICU costs per day	4,651, n=1	–	–

n= number of studies; IQR= interquartile rang

3.3. Manuskript III

Extra length of stay and costs because of health care-associated infections at a German university hospital

Habibollah Arefian, Stefan Hagel, Steffen Heublein, Florian Rissner, André Scherag, Frank Martin Brunkhorst, Ross J. Baldessarini, Michael Hartmann

Veröffentlicht in: Am J Infect Control 2016;44(2):160-6.

In dieser Studie wurden die Daten der Vorinterventionsphase (01.09.2011–31.08.2012) einer prospektiven Kohortenstudie aus gesundheitsökonomischer Sicht bewertet. Die Auswertungen der Daten mit Hilfe eines Multi-State Modells zeigten eine abteilungsabhängige Verweildauer-verlängerung von 5,26 ± 1,82 Tagen in der Geriatrie und bis zu 21,3 ± 8,9 Tagen in der Neurologie durch nosokomiale Infektionen nach der CDC Definition. Die Verweildauerverlängerung für Patienten auf den Normalstationen betrug 8,45 ± 0,80 Tage und 8,09 ± 0,91 Tage für die Patienten, die sowohl auf einer Normal- als auch einer Intensivstation behandelt wurden. Die zusätzlichen Kosten durch nosokomiale Infektionen für die Patienten, die sowohl auf einer Normal- als auch einer Intensivstation behandelt wurden, waren 3,0- bis 7,5-mal größer als für Patienten auf der Normalstation. Zusätzliche Kosten durch eine nosokomiale Infektion betrugen zwischen 5.823 € und 10.572 € pro Patient.

Habibollah Arefian	Konzeption und Planung des Projekts; Präparation und Bearbeitung der Daten; Evaluierung der Daten; Entwicklung der Methoden; Analyse der Verweildauerverlängerung und gesundheitsökonomische Evaluationen; Interpretationen der Ergebnisse; Erstellung des Entwurfs und

	Überarbeitung des Manuskripts; Konzeption und Erstellung aller Abbildungen; Erstellung aller Tabellen; Einarbeitung von Korrekturen während des Reviewprozesses
Stefan Hagel	Konzeption und Planung des Alerts-Projekts; Interpretationen der Ergebnisse; Überarbeitung des Manuskripts; Mitarbeit an der Erstellung von Korrekturen während des Reviewprozesses;
Steffen Heublein	Konzeption und Planung des Projekts; Präparation der Daten; Durchsicht des Manuskripts
Florian Rissner	Präparation der Daten; Durchsicht des Manuskripts
André Scherag	Interpretationen der Ergebnisse; Überarbeitung des Manuskripts; Mitarbeit an der Erstellung von Korrekturen während des Reviewprozesses
Frank M. Brunkhorst	Konzeption und Planung des Alerts-Projekts; Durchsicht des Manuskripts
Ross J. Baldessarini	Interpretationen der Ergebnisse; Überarbeitung des Manuskripts
Michael Hartmann	Konzeption und Planung des Projekts; Interpretationen der Ergebnisse; Überarbeitung des Manuskripts; Mitarbeit an der Erstellung von Korrekturen während des Reviewprozesses; Leitung

Manuskript III

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Major article

Extra length of stay and costs because of health care–associated infections at a German university hospital

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Key Words:
Cost
Health care–associated infection
Hospital
Inpatients
Length of stay

Background: Health care–associated infections (HAIs) can be associated with increased health care costs. We examined extra length of hospital stay (LOS) and associated per diem costs attributable to HAIs in a large academic medical center.

Methods: Data for analysis were acquired in a preinterventional phase of a prospective cohort study (ALERTS) conducted over 12 months in 27 general and 4 intensive care units at Jena University Hospital. HAIs were identified among patients hospitalized for ≥48 hours with at least 1 risk factor for HAI and new antimicrobial therapy; the diagnosis was confirmed by U.S. Centers for Disease Control and Prevention criteria. Extra LOS was estimated by multistate modeling, and associated extra costs were based on average per diem costs for clinical units sampled.

Results: Of a total of 22,613 patients hospitalized for ≥48 hours, 893 (3.95%) experienced 1,212 episodes of HAI during 12 months. The associated mean extra LOS ± SEM in general units was 8.45 ± 0.80 days per case and 8.09 ± 0.91 days for patients treated in both general and intensive care units. Additional costs attributable to HAIs were €5,823-€11,840 ($7,453-$15,155) per infected patient.

Conclusion: HAIs generated substantial extra costs by prolonging hospitalization. Potential clinical and financial savings may be realized by implementing effective infection prevention programs.

The prevalence of all nosocomial or health care–associated infections (HAIs) in Germany was 5.1% in 2011, involving approximately 800,000 patients annually.[1,2] In addition to extra morbidity and mortality, HAIs are associated with increased health care costs, owing primarily to increased hospital length of stay (LOS).[3,4] Most health economic evaluations of the effects of such infections in hospitals have used a matched case-control study design to compare patients with and without HAI, without considering when HAIs occurs or where they are treated. Not considering the time of occurrence typically overestimates of extra LOS caused by HAIs and exaggerates the extra costs involved.[4-6] To eliminate such time-dependent bias, multistate models that take into account times of hospitalization, occurrence of an HAI, and hospital discharge have been recommended.[7]

In this study, we applied multistate modeling to limit bias in estimating extra LOS associated with HAI so as to improve accuracy of estimated HAI-attributable costs. In contrast with previous evaluations focusing on intensive care units (ICUs) only, we compared extra LOS and costs associated with HAIs among patients

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Conflicts of interest: The authors declare that neither they nor their immediate family members have potential conflicts of interest relevant to this report.

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treated solely in general inpatient units with those who also required ICU care. We also contrasted HAI-associated costs by clinical department. Data were collected hospital-wide over 12 months in the Effectiveness of a hospital-wide educational program for infection control to reduce the rate of healthcare-associated infections and related sepsis (ALERTS) study at a large German university hospital.

METHODS

Data collection

The ALERTS study is based at the Jena University Hospital, a tertiary care medical center affiliated with Friedrich-Schiller University, with 1,500 beds and approximately 52,000 admissions per year. The ALERTS study uses a prospective, quasi-experimental cohort design and is registered with the German Clinical Trials Register (Trial DRKS-00003166). The protocol was approved by the hospital's ethics committee. The ALERTS study is comprised of 3 study periods: (1) a 12-month preinterventional surveillance period (September 2011-August 2012) involving 31 clinical units, including 27 general wards (737 beds) and 4 ICUs (72 beds); (2) an intervention; and (3) a second ongoing, surveillance period.[8]

Data for cost analyses were derived from the initial 12-month surveillance period of the ALERTS study. Daily surveillance was based on a computerized antimicrobial drug reporting program involving all patients hospitalized for at least 48 hours, with at least 1 risk factor for HAI (presence of intravenous or urinary tract catheter or a surgical procedure during the index hospitalization). Two study physicians, including 1 infectious disease specialist and 3 research nurses, performed structured retrospective chart reviews to gather clinical, laboratory, microbiologic, and imaging findings relevant to this study. Data capture was performed using commercial software (OpenClinica; OpenClinica, Waltham, MA) that meets regulatory requirements for patient confidentiality (GCP[9] 21CFR Part11[10]). Diagnosis of HAI met definitions of the U.S. Centers for Disease Control and Prevention.[11] To avoid misclassification (eg, infections with an onset preceding index hospitalization), we excluded patients hospitalized for <48 hours continuously in 1 of the 31 clinical units under surveillance and those with evidence of infections before or at hospital admission. Times of HAI occurrence, hospital admission, and discharge or death represented the basic dataset for multistate modeling. To compare prolongation of LOS associated with HAIs in various types of clinical units and departments, dates of admission, discharge or death, timing of event, length of stay on ICU and general wards, hospitalization within the previous 30 days, and sociodemographic data also were collected. To organize the findings, we used the Consolidated Health Economic Evaluation Reporting Standards guidelines, which recommend 24 items for optimal reporting of health economic evaluations. Rather than reporting only consequences of an intervention, economic evaluations require consideration of items such as resource use and costs.[12]

Statistical methods

In addition to standard summary statistics for measures, including frequencies, we report cumulative incidence (number of patients with at least 1 new HAI among all patients at risk) and incidence rates (number of new HAIs per person days under surveillance) with their 95% confidence intervals. Data considered included the entire 12-month preinterventional surveillance phase of the ALERTS study.

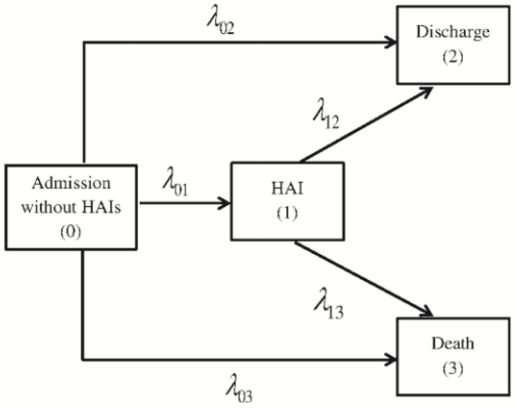

Fig 1. Multistate model with 4 states: 0, admission without an HAI; 1, HAI (exposed); 2, discharge; and 3, death. All patients entered into the initial state 0 (alive and hospitalized). Then the patient may acquire an HAI, moving to intermediate state 1, be discharged without an HAI, moving to state 2, or die without an HAI. Once infected with an HAI, the patient can move from state 1 to 2 or from 1 to 3; patients in state 2 cannot enter state 3. Hazard rates are denoted by λij, with indices i and j indicating the states which they connect. *HAI*, health care–associated infection.

To estimate extra LOS specifically associated with HAIs, we used a multistate approach regarding HAI as a possible intermediate state between admission and discharge or death. In the 4-state model used, admission (patients without HAIs) is state 0, HAI is state 1, and discharge (state 2) or death (state 3) indicates the end of hospital LOS. Patients in state 2 cannot enter state 3 (Fig 1).

We assumed that the distribution of time to event followed a recommended exponential distribution.[11] For cases in a given state up to a specified time, the hazard (λ) approximates the probability of moving from one state to another in a short interval, divided by the length of the interval. These hazards are provided in the subsequent equation, with subscripts denoting the respective state switch.[7] The extra LOS for a patient with HAI compared with a patient without HAI is given by the following equation[13]:

$$\text{Extra LOS(days)} = \left(\frac{\lambda_{02}+\lambda_{03}}{\lambda_{12}+\lambda_{13}} - 1\right) \times \frac{1}{\lambda_{01}+\lambda_{02}+\lambda_{03}}$$

All analyses were performed using R 3.0.3 statistical software (R-Packages etm 0.6-1 and changeLOS 2.1; R Development Core Team, Vienna, Austria).[14,15] SEMs for extra LOSs were calculated by bootstrap sampling using 1,000 replicates.

Economic evaluation

Cost analysis is based on the perspective of the hospital. Costs per bed day include total direct costs of each hospital day, based on the legally required German G-DRG system of billing (German-Diagnosis Related Groups-System, Germany), which includes costs of accommodation, medical treatment, laboratory procedures, materials and services, and physician and nursing care.[16] Indirect costs, such as loss of productivity, absenteeism, or mortality, are not included. Results are reported in 2012 euro and in U.S. dollars at the average exchange rate of €1 = $1.28 during the study period, standardized to 2012 values using Consumer Price Index calculator (http://data.bls.gov/cgi-bin/cpicalc.pl). Costs per ICU bed day are the averages calculated from the 4 ICUs studied. Multiplying the number of HAI cases by the derived extra LOS and the estimated

Table 1
Number and incidence rates of HAIs in specific hospital departments

Where treated	Surgery*	Gynecology	Geriatrics	Internal medicine	Neurology	Total
HAI, cases/total patients						
General units	59/5,188	19/1,518	41/480	150/10,383	4/1,609	273/19,178
General units plus ICUs†	448/2,260	19/80	19/57	105/693	29/345	620/3,435
Total	507/7,448	38/1,598	60/537	255/11,076	33/1,954	893/22,613
HAIs in general units and ICUs, n (%)						
General units	63 (18.86)	21 (6.29)	52 (15.57)	194 (58.08)	4 (1.20)	334
General units plus ICUs	650 (74.03)	21 (2.39)	28 (3.19)	142 (16.17)	37 (4.22)	878
Total	713 (58.83)	42 (3.47)	80 (6.60)	336 (27.72)	41 (3.38)	1,212
Cumulative incidence, % (95% CI)						
General units	1.13 (0.88-1.46)	1.25 (0.80-1.95)	8.54 (6.36-11.38)	1.44 (1.23-1.69)	0.25 (0.10-0.64)	1.42 (1.27-1.60)
General units plus ICUs	19.82 (18.23-21.52)	23.75 (15.76-34.14)	33.33 (22.49-46.28)	15.15 (12.67-18.01)	8.41 (5.92-11.81)	18.05 (16.80-19.37)
Total	6.81 (6.26-7.40)	2.38 (1.74-3.25)	11.17 (8.78-14.12)	2.30 (2.04-2.60)	1.69 (1.21-2.36)	3.95 (3.70-4.21)
General units	1.58 (1.23-2.02)	2.50 (1.65-3.83)	4.80 (3.66-6.29)	2.75 (2.39-3.16)	0.37 (0.15-0.94)	2.37 (2.13-2.64)
General units plus ICUs	14.86 (13.77-16.05)	10.93 (7.19-16.65)	10.93 (7.59-15.76)	11.83 (10.05-13.93)	8.84 (6.43-12.16)	13.63 (12.77-14.56)
Total	8.53 (7.93-9.18)	4.08 (3.02-5.51)	5.97 (4.80-7.42)	4.06 (3.65-4.52)	2.73 (2.01-3.70)	5.91 (5.59-6.25)

CI, confidence interval; *HAI*, health care–associated infection; *ICU*, intensive care unit.
*General; visceral; and vascular, cardiothoracic, and neurologic surgery.
†Surgical ICUs (n = 2), medical ICU (n = 1), and neurologic ICU (n = 1).

costs per bed day reflect the extra economic burden associated with HAIs. We estimated additional HAI-related costs in general wards as follows:

$$\text{Extra costs}(€) = \text{HAI patients}(\text{general wards}) \times \text{extra LOS} \times \text{costs/bed day}$$

Sensitivity analyses

Sensitivity analyses estimated extra costs for patients treated in both general units and ICUs, based on modifying the aforementioned equation by assuming a best- and a worst-case scenario. For the worst case, we assumed that patients with HAIs treated in both general and ICUs stayed only 1 day in a general unit and the remaining days of in an ICU; for the best case, we assumed the opposite (only 1 of the extra days in an ICU).

In addition, to enable comparisons with other tertiary care hospitals, the economic impact of HAI-associated extra LOS was recalculated based on average unit costs per bed day in German tertiary care-teaching hospitals derived from the World Health Organization's Choosing Intervention (WHO-CHOICE) project.[17] Median costs of hospitalization were estimated from unit costs for the years 2007 and 2008 for relevant hospitals in Germany.[18] In addition, we used the base lending rate of every year from 2008-2012 published by the German Central Bank[19] and estimated the costs of hospitalization for German tertiary care hospitals for 2012 using the future value of money[20]:

$$P_n = P_0(1 + r)^n$$

where P_n is the future value, P_0 is the original amount, n is the number of periods, and r is the interest rate for that period. We estimated additional HAI-related costs by multiplying the number of HAI cases by the derived extra LOS from the ALERTS study and the estimated costs per bed day from the WHO-CHOICE project.

RESULTS

Subjects and HAIs

Between September 1, 2011, and August 31, 2012, 22,637 patients were hospitalized for at least 48 hours in 1 of the 31 clinical units under surveillance; 24 were excluded because of evidence that infections started before hospitalization. Of the remaining 22,613 persons at risk, 893 cases of HAI (3.95%) experienced 1,212 separate episodes of infection (1.36 per person). By descending incidence, HAIs included the following: surgical site infections (352/1,212; 29.0%), lower respiratory tract infections (286/1,212; 23.6%), all other infections (172/1,212; 14.2%), primary bloodstream infection (158/1,212; 13.0%), gastroenteritis (123/1,212; 10.2%), and urinary tract infections (121/1,212; 10.0%).

Of the 22,613 patients at risk, 3,435 (15.2%) were admitted at least once to an ICU, and 19,178 (84.8%) were treated exclusively on general wards. The cumulative incidence of HAIs was highest in geriatric units (11.17%) and lowest in neurologic units (1.69%), with intermediate risks on surgical (6.81%), gynecologic (2.38%), and general medical units (2.30%). There were 273 (1.42%) HAI episodes in general ward patients and 620 (18.0%) episodes in patients who required some ICU care. The overall incidence of HAIs was 5.91 per 1,000 patient days, ranging from 8.53 on surgical units to 2.73 on neurologic units (Table 1).

Table 2
Costs per bed day

Department	Total costs	Person days	Costs per bed day
Internal medicine	€62,209,277 ($79,627,875)	102,744	€605 ($775)
Surgical	€53,021,822 ($67,867,932)	83,709	€633 ($811)
ICUs*	€48,857,795 ($62,537,978)	24,346	€2,007 ($2,569)
Neurology	€8,989,185 ($11,506,157)	16,756	€536 ($687)
Gynecology	€7,045,853 ($9,018,692)	11,554	€610 ($781)
Geriatric	€3,678,299 ($4,708,223)	13,179	€279 ($357)

ICU, intensive care unit.
*Costs per bed day of ICUs are the average costs per bed day in 4 ICUs, based on financial data for Jena University Hospital; other costs are for general wards.

Economic evaluation

Costs per bed day ranged from an average high of €2,007 ($2,569) in ICUs to €279 ($357) for geriatrics units, with intermediate cost of €605 ($775) for internal medicine units (Table 2).

These per diem costs were used to estimate total additional costs associated with HAIs. Using the multistate model, the expected LOS on each day is illustrated for patients with HAIs versus those without, considering those treated only on general versus both general units and ICUs (Fig 2).

For HAI patients exclusively treated in general wards, the extra LOS ± SEM associated with HAIs ranged from 5.26 ± 1.82 days in geriatrics units to 21.28 ± 8.09 days in neurologic units. Overall, HAIs prolonged hospital LOS by 8.45 ± 0.80 days in general wards,

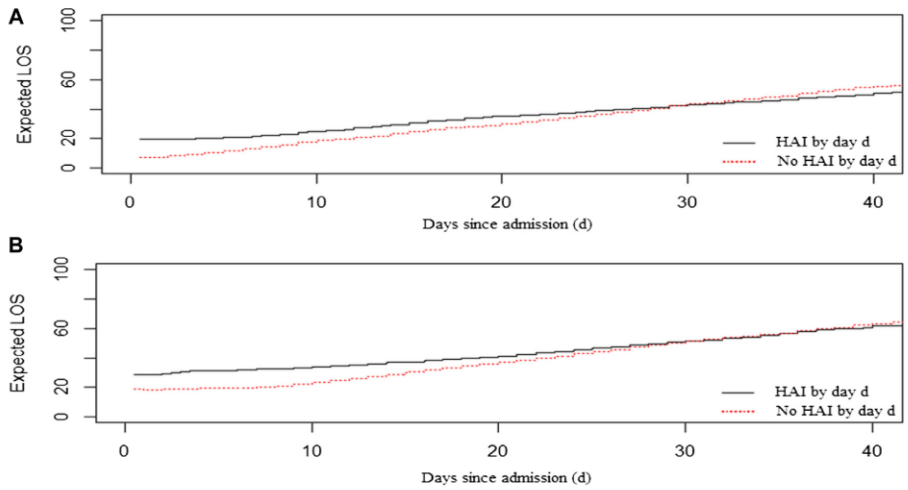

Fig 2. Plot of the expected LOS in hospital. The solid line shows that an HAI has occurred, and the dashed line indicates a lack of HAI up to 40 days after hospitalization. (A) Patients treated only in general wards, and (B) patients treated in both general wards and in intensive care units. *HAI*, health care–associated infection; *LOS*, length of stay.

based on days required for treatment of HAIs, and resulted in total extra costs of €1,228,782 ($1,572,841) per year (€4,501 [$5,761] per non-ICU case) over the study observational period (Table 3, Appendix 1).

For patients with HAI treated in both ICUs and general units, the extra LOS required to treat HAIs ranged from 6.91 ± 1.79 days for neurologic patients to 11.3 ± 3.76 days for gynecology patients, and it averaged 8.09 ± 0.91 days overall. Total extra costs for those with HAIs treated in both general and ICUs were €3,971,412 ($5,083,407) per year (€6,405 [$8,198] per case) under the best-case scenario and €9,343,598 ($11,959,805) per year (€15,070 [$19,290] per patient) under the worst-case scenario (Table 3). The average arising from these scenarios is €10,738 ($13,745) per case or 2.4 times more than for general unit alone cases (€10,738/€4,501 [$13,745/$5,761]).

Considering patients with HAIs treated exclusively in general units or in both general and ICUs, additional costs per case attributable to HAIs were highest for gynecology units (€6,181 [$7,912] to €12,691 [$16,244] under best- vs worst-case assumptions, respectively). The least extra cost per case involving ICU care was in geriatric units (€2,313 [$2,961] to €5,946 [$7,611]). Overall, estimated extra costs attributable to HAIs ranged from €5,200,194 ($6,656,248) per year (€5,823 [$7,453] per patient) to €10,572,380 ($13,532,646) per year (€11,840 [$15,155] per patient) under best- versus worst-case scenarios, respectively (Table 3).

To estimate HAI-related costs more generally, and not specifically at the study site, we also considered information on median costs of hospitalization throughout Germany, as provided by the World Health Organization. Estimates for 2007 and 2008 were €518.60 per bed day in German tertiary care teaching hospitals. Using German Central Bank information, estimates for similar settings for 2012 were an average per diem costs of €544.75 ($697.28). The total HAI-associated extra costs for 12 months, based on the estimates for comparable German medical centers, were €3,935,023 ($5,036,829) or €4,407 ($5,641) per patient (Table 3).

DISCUSSION

We evaluated extra LOS and per diem costs associated with HAIs for various types of inpatient units and departments in a large tertiary care, German teaching hospital using multistate modeling. As expected, treatment involving ICUs and general units was more costly than for cases involving only general wards. Consequently, the estimated total additional costs caused by extra LOS caused by HAIs among patients treated in both general units and in ICUs were 3.0-7.5 times greater than for patients treated only in general wards. Moreover, extra LOS and costs associated with clinical management of HAIs varied by >4-fold among clinical departments, from 5.25 in geriatrics to 21.3 days per case in neurology. Prolongation of LOS was relatively low compared with other similar studies,[21-23] largely because of the differences in methods and because of a high proportion of elderly patients (median age of infected patients was 70 years). Many studies that considered prolongation of LOS as a result of HAIs did not use multistate modeling[21,22] and may have overestimated extra days in hospital specifically associated with HAI.[7] Other studies using multistate models found prolongation of LOS with HAIs ranging from 0.9-11.5 days[5,6,23,24] compared with 8.09-8.45 days in this study. This wide range of previous estimates even with multistate modeling may reflect differences in mixes of infection types, patient characteristics, and clinical settings. For example, Mitchell et al[24] found 0.9 that extra LOS associated with *Clostridium difficile* infections at a tertiary care hospital in Australia, whereas Macedo-Vinas et al[23] found that extra LOS averaged 11.5 days for infections with methicillin-resistant *Staphylococcus aureus* in acute care wards at a Swiss hospital. Other studies, including a report by Beyersmann et al[5] focusing on HAIs treated in ICUs in Germany, estimated an average of 5.3 days of extra ICU treatment in association with broadly defined HAIs. In contrast, the present study found an additional LOS of 8.1 days for patients with HAI who were treated in both ICUs and general wards.

Our estimates of extra costs associated with HAIs are consistent with findings in other studies. A systematic review of costs associated with HAIs in 24 reports in 2001-2004 found an average cost of 4 common type of HAIs of $18,240 based on 2002 currency values or approximately €18,186 ($23,278) based on 2012 currency values.[25] In a U.S. study, added costs associated with HAI averaged $20,549-$25,903 based on 2007 dollar values or approximately €17,777-€22,409 ($22,754-$28,683) based on 2012 currency values.[26] Although these several studies were conducted in various

Table 3
Extra days of hospitalization and additional costs associated with health care–associated infections

Model	Surgical	Gynecologic	Geriatric	Internal medicine	Neurology	Total
Additional LOS ± SEM, d						
General units	6.50 ± 1.64	6.66 ± 2.95	5.26 ± 1.82	8.84 ± 1.06	21.28 ± 8.09	8.45 ± 0.80
General units plus ICUs	7.48 ± 1.13	11.32 ± 3.76	8.64 ± 3.56	11.01 ± 2.08	6.91 ± 1.79	8.09 ± 0.91
Additional cost per case (range), €						
General units	4,117 (3,078-5,156)	4,061 (2,262-5,860)	1,468 (960-1,976)	5,352 (4,711-5,994)	11,416 (6,641-16,191)	4,501 (3,652-5,350)
General units plus ICUs; best case	6,111 (5,395-6,827)	8,300 (6,007-10,593)	4,139 (3,146-5,133)	8,067 (6,808-9,327)	5,177 (4,217-6,138)	6,405 (5,529-7,282)
General units plus ICUs; worst case	13,637 (11,370-15,905)	21,320 (13,774-28,866)	15,611 (8,467-22,755)	20,693 (16,519-24,868)	12,397 (8,804-15,989)	15,070 (12,107-18,034)
Total additional cost per case (range), €						
Best case*	5,879 (5,126-6,633)	6,181 (4,135-8,227)	2,313 (1,652-2,976)	6,470 (5,574-7,366)	5,933 (4,511-7,356)	5,823 (4,956-6,691)
Worst case†	12,529 (10,405-14,654)	12,691 (8,018-17,363)	5,946 (3,337-8,556)	11,669 (9,573-13,766)	12,277 (8,542-16,013)	11,840 (9,522-14,156)
Additional cost based on WHO-CHOICE per case (range), €‡						
General units	3,541 (2,647-4,434)	3,628 (2,021-5,235)	2,865 (1,874-3,857)	4,816 (4,238-5,393)	11,592 (7,185-15,999)	4,264 (3,428-5,100)
General units plus ICUs	4,075 (3,459-4,690)	6,167 (4,118-8,215)	4,707 (2,767-6,646)	5,998 (4,865-7,131)	3,764 (2,789-4,739)	4,469 (3,665-5,274)

HAI, health care–associated infection; *ICU*, intensive care unit; *WHO-CHOICE*, World Health Organization's Choosing Intervention.
*Additional costs (general units) + additional costs (best case for general + ICU patients)/HAI cases.
†Additional costs (general units) + additional costs (worst case for general + ICU patients)/HAI cases.
‡Data are based on WHO-CHOICE database information on per diem costs in German, tertiary care teaching hospitals and represent extra costs encountered with HAIs owing to extra length of stay. Total extra cost calculated for each department by multiplying the extra length of stay (general and both general plus ICUs) by estimated costs per bed day from the WHO-CHOICE database information.

countries at different times using different methods, their results are quite similar to the present findings.

There are several limitations to the present study. Based on sampling over 1 year in a single center in Eastern Germany, its findings may not generalize to other settings. In addition, the numbers of new infections in some units and specialties (notably, neurology) were sometimes relatively small, potentially making estimates of extra time and costs involved less stable and possibly less accurate; therefore, estimates for specific specialties and sites should be considered as tentative. Almost all ICU patients in our sample were treated some of the time in general units, and many experienced several episodes of infection involving both general units and ICUs. We could not specify days of hospitalization during treatment of infections that were associated with general wards versus ICUs, but we did compare cases with only general unit care with those involving treatment in both settings. Finally, we may not have included all added costs involved in treating hospital-acquired infections, including extra diagnostic testing, consultations, and extra medications, because the cost basis was per diem costs associated with added days of hospitalization, which is the largest factor contributing to extra costs.[4] Moreover, in German hospitals, basic per diem costs include most costs, including basic medical and nursing care, medicines, and laboratory tests.[16]

In conclusion, this study found expected, large increases in hospital LOS and increased costs of care associated with hospital-based infections and preliminary indications of marked differences in extra LOS and costs among specialties. Gastmeier et al estimated in 2010[27] that 20%-30% of HAIs may be preventable by effective preventive programs, with potential cost savings of at least €2 million ($2.5 million) per year for a major tertiary care medical center, in addition to providing major clinical benefits for hospitalized patients.

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Supporting information

Appendix 1
Extra days of hospitalization and additional costs associated with health care–associated infections

Model	Surgical	Gynecologic	Geriatric	Internal medicine	Neurology	Total
Additional LOS ± SEM, d						
General units	6.50 ± 1.64	6.66 ± 2.95	5.26 ± 1.82	8.84 ± 1.06	21.28 ± 8.09	8.45 ± 0.80
General units plus ICUs	7.48 ± 1.13	11.32 ± 3.76	8.64 ± 3.56	11.01 ± 2.08	6.91 ± 1.79	8.09 ± 0.91
Additional cost per case (range), $						
General units	5,270 (3,940-6,600)	5,198 (2,895-7,501)	1,879 (1,229-2,529)	6,851 (6,030-7,672)	14,642 (8,500-20,724)	5,761 (4,675-6,848)
General units plus ICUs; best case	7,822 (6,906-8,739)	10,624 (7,689-13,559)	5,298 (4,027-6,570)	10,326 (8,714-11,939)	6,627 (5,398-7,857)	8,198 (7,077-9,321)
General units plus ICUs; worst case	17,455 (14,554-20,358)	27,290 (17,631-36,948)	19,982 (10,838-29,126)	26,487 (21,144-31,831)	15,868 (11,269-20,466)	19,290 (15,497-23,084)
Total additional cost per case (range), $						
Best case	7,525 (6,561-8,490)	7,912 (5,293-10,531)	2,961 (2,115-3,809)	8,282 (7,135-9,428)	7,594 (5,774-9,416)	7,453 (6,344-8,564)
Worst case	16,037 (13,318-18,757)	16,244 (10,263-22,225)	7,611 (4,271-10,952)	14,936 (12,253-17,620)	15,715 (10,934-20,497)	15,155 (12,188-18,120)
Additional cost based on WHO-CHOICE per case (range), $						
General units	4,532 (3,388-5,676)	4,644 (2,587-6,701)	3,667 (2,399-4,937)	6,164 (5,425-6,903)	14,838 (9,197-20,479)	5,458 (4,388-6,528)
General units plus ICUs	5,216 (4,428-6,003)	7,894 (5,271-10,515)	6,025 (3,542-8,507)	7,677 (6,227-9,128)	4,818 (3,570-6,066)	5,720 (4,691-6,751)

HAI, health care–associated infection; *ICU*, intensive care unit; *WHO-CHOICE*, World Health Organization's Choosing Intervention.

3.4. Manuskript IV

Economic burden of surgical site infections in patients undergoing cardiac surgery

Axel Findeisen, Habibollah Arefian, Torsten Doenst, Stefan Hagel, Mathias W Pletz, Michael Hartmann, Jens Maschmann
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In dieser ökonomischen Evaluationsstudie wurden zusätzliche Kosten und Verweildauer-verlängerungen durch Wundinfektionen nach Koronararterien-Bypass Chirurgie (CABG) am Universitätsklinikum Jena untersucht. Die Ergebnisse zeigen, dass die Krankenhauskosten für Patienten mit Wundinfektionen nach CABG um etwa 7.000 Euro aus der Perspektive der Krankenversicherung und um etwa 8.300 Euro aus der Perspektive des Krankenhauses anstiegen. Wundinfektionen nach CABG sind somit mit einer signifikanten Verlängerung der Verweildauer und höheren Ausgaben verbunden.

Axel Findeisen	Konzeptionelle Entwicklung der Studie; Präparation und Bearbeitung der Daten; Durchsicht des Manuskripts
Habibollah Arefian	Konzeption und Planung des Projekts; Präparation und Bearbeitung der Daten; Evaluierung der Daten; Entwicklung der Methoden; Auswertung der Verweildauerverlängerung durch Wundinfektionen und die Krankheitskosten-Analyse; Interpretationen der Ergebnisse; Erstellung des Entwurfs und Überarbeitung des Manuskripts; Konzeption und Erstellung aller Abbildungen; Erstellung aller Tabellen; Einarbeitung von Korrekturen während des Reviewprozesses
Torsten Doenst	Konzeptionelle Entwicklung der Studie; Überarbeitung des Manuskripts;

	Mitarbeit an der Erstellung von Korrekturen während des Reviewprozesses
Stefan Hagel	Konzeption und Planung des Projekts; Überarbeitung des Manuskripts; Mitarbeit an der Erstellung von Korrekturen während des Reviewprozesses
Mathias W Pletz	Konzeptionelle Entwicklung der Studie; Durchsicht des Manuskripts
Michael Hartmann	Konzeption und Planung des Projekts; Überarbeitung des Manuskripts; Interpretationen der Ergebnisse; Mitarbeit an der Erstellung von Korrekturen während des Reviewprozesses
Jens Maschmann	Konzeptionelle Entwicklung der Studie; Überarbeitung des Manuskripts; Leitung

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Economic burden of surgical site infections in patients undergoing cardiac surgery†

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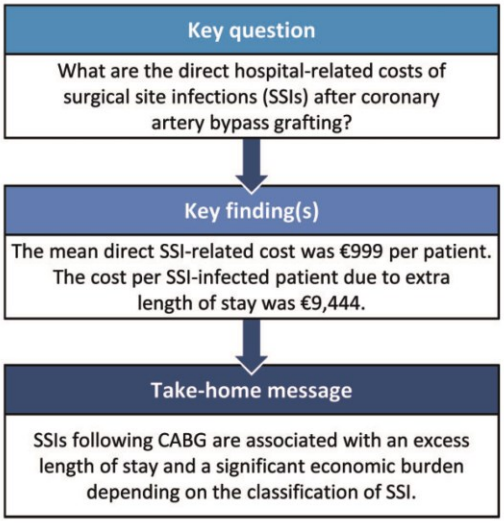

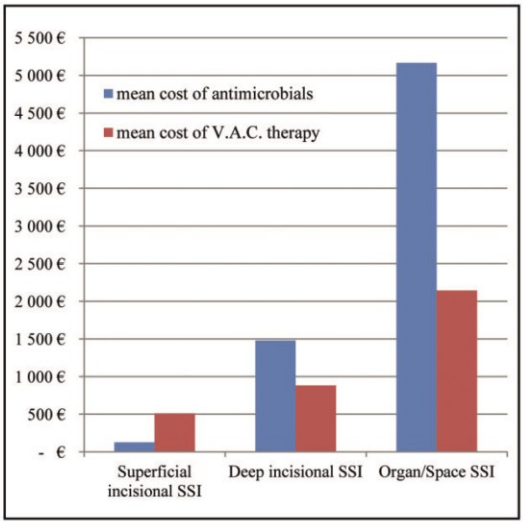

Abstract

OBJECTIVES: This study aimed to determine the additional costs and length of stay (LOS) due to surgical site infections (SSIs) after coronary artery bypass grafting (CABG) at Jena University Hospital.

METHODS: The data of 999 consecutive patients who underwent CABG from January 2013 to December 2014 were collected. We extracted the number, type and duration of antimicrobial therapy and V.A.C.® therapy (negative pressure wound therapy) treatments and calculated the additional SSI-related costs based on the hospital's perspective. We also evaluated the prolongation of LOS using a multi-state model and calculated the costs due to the additional LOS.

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RESULTS: In total, 983 patients were included in our analysis, and 126 patients with SSIs following CABG were identified during the study period; 124 patients with SSIs (98.4%) were discharged alive. The mean cost of antimicrobial therapy to treat the SSIs was €818 [95% confidence interval (CI) 392–1245], and the mean cost of V.A.C. therapy was €1179 (95% CI 748–1610) per infected patient. The mean additional LOS due to SSIs (±standard error) was estimated to be 9.3 ± 2.6 days. The cost per SSI-infected patient attributable to the additional LOS was €9444 (95% CI 4242–14 645).

CONCLUSIONS: SSIs following CABG are associated with an additional LOS and a significant economic burden depending on the classification of SSI. A very important component of the additional cost is the prolongation of LOS. Therefore, it is essential to shorten the hospital stay due to SSIs as far as possible.

Keywords: Cost • Surgical site infection • Cardiac surgery • Length of stay

INTRODUCTION

Coronary artery bypass grafting (CABG) is still the most common type of open heart surgery in Germany, with approximately 50 000 CABG procedures performed annually [1]. Surgical site infections (SSIs) following CABG procedures are one of the most serious complications in cardiac surgery and are associated with significant morbidity and mortality [2]. Previous studies have reported rates of CABG-linked complex (deep and organ/space) SSIs ranging from 0.25% to 4% [3]. The rate of all SSIs is often in a low 2-digit range and is directly dependent on patients' comorbidities [2]. Importantly, SSIs are associated with increased postsurgical costs [4]. Because current and increasing economic pressures will continue to limit expenditures for healthcare provision in many countries, a better understanding of the economic cost of infections as well as the specific determinants and drivers of expenditures is required [4, 5]. Health policymakers and hospital managers must estimate the additional financial costs related to SSIs to highlight the intensity of the problem. Moreover, updated information on how costs will change with the adoption of infection control programmes is required and would thereby provide some positive economic insight for allocating resources to prevent infections [6].

In this study, we aimed to estimate the economic burden of SSIs in cardiac surgical patients. We primarily aimed to calculate the direct hospital-related costs of SSIs from the perspective of a healthcare provider (a German university hospital). Furthermore, we determined the additional length of stay (LOS) using a multistate model and estimated costs attributable to the additional LOS due to SSIs from the healthcare payer's perspective.

MATERIALS AND METHODS

The underlying data were collected from the Department of Cardiothoracic Surgery at Jena University Hospital from patients who underwent isolated elective CABG between January 2013 and December 2014 [7]. For the surveillance of healthcare-associated infections, a retrospective medical chart review was performed for all the patients. Healthcare-associated infections were classified according to the Centers for Disease Control and Prevention (CDC) definition [8]. SSIs were classified as 'superficial incisional SSIs', 'deep incisional SSIs' and 'organ/space SSIs'. Post-discharge surveillance was not performed; however, patients readmitted to the hospital due to SSIs were recorded. All suspected SSI cases were reviewed by infectious disease physicians. Decisions on treatment were the responsibility of the attending physician. The decision on specific treatment modalities, e.g. initiation of antimicrobial therapy or V.A.C.® therapy (negative pressure wound therapy), was at the discretion of the attending physician. The decision on the initiation of antibiotics was based on clinical aspects, such as fever, leukocytosis, microbiological results and purulent wound discharge. The decision to start or continue V.A.C. therapy was based on wound discharge, depth of wound and granulation. Both decisions—V.A.C. therapy and antimicrobial therapy—were made at the individual patient level.

An SSI was recorded, according to the CDC definition, as soon as a new antibiotic therapy was started postoperatively. The time of SSI occurrences, hospital admissions and discharges or deaths represented the basic dataset for the multistate model. The number of days spent in our hospital was recorded during the index hospitalization for all the patients. For patients who were readmitted due to SSI, the number of days of hospitalization from readmission to discharge or death was added to the initially calculated LOS. The study was approved by the institutional review board and was conducted in accordance with the Declaration of Helsinki.

ECONOMIC EVALUATION

Costs from a healthcare provider's perspective

This analysis was based on the perspective of the cost to the hospital because the healthcare provider is responsible for the cost of treatment for patients with SSIs. According to the study perspective, the direct hospital-related costs of SSIs for each patient included the number of antimicrobials used for the treatment of SSIs and the number and length of treatments with V.A.C. therapy.

The economic costs of antimicrobials and V.A.C. therapy were evaluated by applying the unit costs in 2014 from the hospital pharmacy data. We multiplied the number of each antimicrobial substance by the unit cost, which resulted in the total costs of antimicrobials used to treat the SSIs. We also extracted the number and length of treatments with V.A.C. therapy and multiplied it by the unit cost. All costs are reported in Euros (value in 2014: 1€ = 1.36 US$). We applied a 3% annual discount rate to the costs, if it was necessary. In addition, for all patients with and without SSIs who were included in this study, the hospital costs were provided by the financial department of the Jena University hospital.

Costs from a healthcare payer's perspective

To estimate the SSI-related costs more generally, we considered the costs per bed-day in the Department of Cardiothoracic Surgery at Jena University Hospital based on the German-

Table 1: Selected baseline characteristics of the study cohort

Characteristics	Values
Male sex, *n* (%)	761 (77.4)
Age (years), mean (±SD)	67.48 (±10.0)
BMI (kg/m^2), mean (±SD)	28.45 (±4.5)
EuroSCORE (25th/median/75th)	3/5/7
Diabetes mellitus, *n* (%)	570 (58.0)
Surgical incision, *n* (%)	
Median sternotomy	883 (89.8)
MIDCAB	100 (10.2)
Number of bypass grafts, *n* (%)	
1	151 (15.4)
2	428 (43.5)
3	357 (36.3)
≥4	47 (4.8)
Duration of operative procedure (min), mean (±SD)	165 (±54.2)
Type of bypass graft, *n* (%)	
Arterial and venous	554 (56.4)
Arterial	394 (40.1)
Venous	35 (3.6)
Concomitant postoperative HAI, *n* (%)	
Lower respiratory tract infection	67 (6.8)
Urinary tract infection	20 (2.0)
Central-line-associated bloodstream infection	25 (2.5)
Clostridium difficile infection	12 (1.2)
In-hospital death, *n* (%)	32 (3.3)

BMI: body mass index; HAI: healthcare-associated infection; MIDCAB: minimally invasive direct coronary artery bypass; SD: standard division.

Diagnosis-Related Groups (G-DRG) system. The cost per bed-day referred to the total direct costs for each hospital day, including the costs of accommodation, medical treatment, laboratory procedures, materials and services, and physician and nursing care. Multiplying the derived additional LOS due to SSIs by the estimated costs per bed-day reflected the additional economic burden associated with SSIs. In addition, the hospital costs of illness were calculated for all the patients with and without SSIs from a healthcare payer's perspective.

Statistical analysis

Non-parametric tests (the Mann–Whitney *U*-test) were used for the continuous variables. All the statistical tests were 2-sided, and *P*-values of ≤0.05 were considered statistically significant. No correction for multiple testing was performed. The qualitative variables are presented as frequencies and percentages. The quantitative variables, including the costs, were expressed as the mean ± standard division or standard error (SE), mean of the 95% confidence interval (CI) or median (25th–75th percentile).

Estimation of the prolongation of hospital stay

We applied a multistate method to model the additional LOS due to SSIs. One advantage of this model is the ability to integrate time-dependent exposures [9]. The time of the occurrence of the SSI, which is the time-dependent exposure in this study, is important to evaluate the additional LOS related to SSIs because SSIs can prolong the length of the hospitalization after their occurrence. An extensive description of the methods used to determine the additional LOS is provided in a previous study [10]. We described the SSIs using a multistate model as a possible intermediate event between admission and discharge or death (Supplementary Material, Data S1). In this model, State 0 is admission, which includes all the patients without SSIs. The patients enter into State 1 (intermediate event) if they acquire an SSI. The end of the hospital LOS occurs at discharge (State 2) or death (State 3). All the included patients were observed as control subjects in this model as long as they remained free of SSIs and were classified as case patients, if an SSI occurred. The hospital LOS was determined by moving into the absorbing state (day of discharge or death) [9–11]. We also evaluated the extra LOS based on the classification of the SSIs.

Additionally, we estimated the effects of the causative microorganism on the initial length of hospital stay and total LOS with hospital duration after readmission. Furthermore, we calculated the effect of the causative pathogen of hospitalization costs for patients with SSI following CABG.

All the cost analyses were performed using SPSS (IBM Corp, released 2015, version 23.0, Armonk, NY, USA). Additional LOS analyses were performed using the R 3.0.3 statistical software (R-Packages etm 0.6–1 2.1; R Development Core Team, Vienna, Austria) [12]. The standard error for the additional LOS was calculated using bootstrap sampling with 1000 replicates. We used the Consolidated Health Economic Evaluation Reporting Standards guidelines for optimal reporting of health economic evaluations [13].

RESULTS

In total, 999 patients underwent isolated CABG procedure during the study period, of whom 16 were excluded because of infections at the donor site. In total, 983 patients were included in our analysis, amounting to an observation period of 14 152 patient-days. In total, 126 patients with SSIs were recorded. This rate corresponded to an incidence density of 8.90 (95% CI 7.42–10.60) SSIs per 1000 patient-days of all patients. Ninety-six patients had a superficial incisional SSI, 20 patients had a deep incisional SSI and 10 patients had an organ/space SSI; 124 patients with SSIs survived the observation period. The difference between mortality rates of patients with and without SSIs was not statistically significant ($P = 0.259$). The selected baseline characteristics of the study cohort are shown in Table 1.

Additional length of stay

The mean duration of hospital stay (±SE) was 14.4 ± 0.3 days, and the median LOS was 12 days. The expected LOS of each day is shown in Fig. 1 for the patients with and without SSIs. In total, the mean additional LOS due to SSIs (±SE) was estimated to be 9.3 ± 2.6 days. However, the additional LOS according to the type of SSI was different. There was no additional LOS for patients with superficial incisional SSI, but the mean additional LOS (±SE) for the patients with deep incisional SSIs and organ/space SSIs was 26.07 ± 5.16 days and 59.31 ± 16.57 days, respectively. The estimated probability of acquiring an SSI is illustrated in Fig. 2.

Economic evaluation

Cost of antimicrobial therapy. The mean (95% CI) per-patient cost of antimicrobials to treat SSIs was €818 (392–1245) during the study period. The mean cost of antimicrobial therapy was significantly higher in patients with organ/space SSIs (€5167;

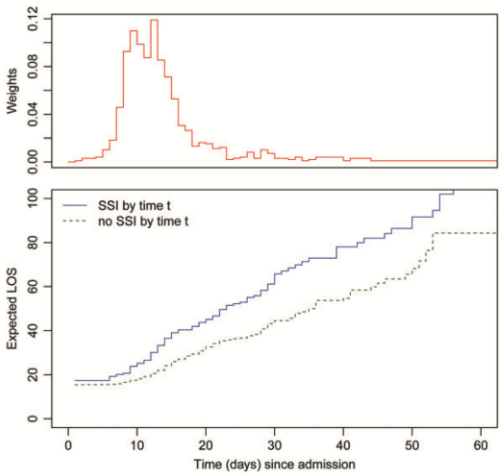

Figure 1: Weights and expected LOS for patients with and without SSI within the first 60 days. A plot of the expected LOS showing that the SSI has occurred (solid line) and not yet occurred (dashed line) based on the time on the *x*-axis up to 60 days after admission. The weights (distribution of the time to SSI) are illustrated in the upper plot. The weights are given by the distribution of the time until group membership (infected with SSI and not infected with SSI) becomes definite, i.e. when a patient leaves the initial state. LOS: length of stay; SSI: surgical site infection.

95% CI 1422–8913) compared with patients with the superficial incisional SSIs (€127; 95% CI 45–209; $P \leq 0.001$) or deep incisional SSI (€1479; 95% CI 514–2444; $P = 0.039$). The total cost of antimicrobials to treat SSIs during the observation period was €91 671. Superficial incisional SSIs accounted for 11.4% (€10 415/€91 671), deep incisional SSIs for 32.3% (€29 583/€91 671) and organ/space SSIs accounted for 56.4% (€51 673/€91 671). The total amount of each antimicrobial substances used to treat the SSIs and the related costs are shown in Supplementary Material, Data S2.

V.A.C. therapy costs. In total, 29 patients with SSIs received V.A.C. therapy, with overall costs of €34 203. The mean per-patient cost of V.A.C. therapy was €1179 (95% CI 748–1610). Only 4 patients (4%) in the superficial incisional SSI group received V.A.C. therapy. In contrast, 17 patients (85%) in the deep incisional SSI group and 8 patients (80%) in the organ/space SSI group received V.A.C. therapy. The mean cost of V.A.C. therapy was significantly higher in the organ/space SSI group (€2144, 95% CI 1043–3244) than in the deep incisional SSI group (€883, 95% CI 422–1344; $P = 0.002$) and the superficial incisional SSI group (€511, 95% CI 72–949; $P = 0.006$).

Total costs. The mean total direct SSI-related costs (antimicrobials and V.A.C. therapy) per patient was €999 (95% CI 522–1476). The mean total cost in the organ/space SSI group was €6882 (95% CI 2352–11 412) per patient, which was higher than the total cost in the deep incisional SSI group (€2230; 95% CI 1193–3266; $P = 0.053$) and the superficial incisional SSI group (€130; 95% CI 55–205; $P \leq 0.001$). The total cost of SSI for all the cardiac surgery patients over the 24 months was €125 874. The future economic assessments are provided in Table 2.

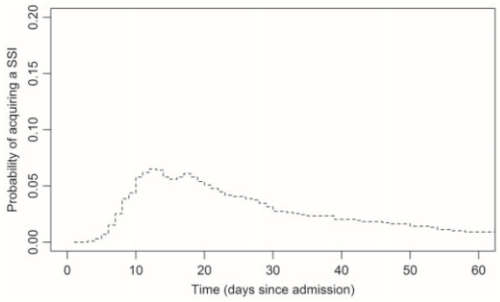

Figure 2: Estimated probability of acquiring an SSI in patients undergoing cardiac surgery. SSI: surgical site infection.

The hospital costs from the healthcare provider's perspective for patients with SSIs (mean €22 933; CI 17 229–28 636 per patient) were significantly higher than for patients without SSIs (mean €14 591; CI 13 487–15 695; $P \leq 0.001$). The mean total direct SSI-related cost was approximately 4.4% (€999/€22 933) of the total hospital costs for patients with SSIs undergoing cardiac surgery.

Costs from a healthcare payer's perspective according to the German-Diagnosis-Related Groups

The cost per bed-day in the Department of Cardiothoracic Surgery was €1010 during the study period. The per diem costs and extra LOS were used to estimate the total costs associated with the SSIs. For the 126 patients in our study, total costs attributable to the additional LOS due to SSIs in the patients undergoing cardiac surgery was €1 189 881 (95% CI 534 492–1 845 270). The cost per SSI-infected patient at Jena University Hospital amounted to €9444 (95% CI 4242–14 645) based on the G-DRG. The additional cost attributable to organ/space SSIs was considerably higher (€59 903; 95% CI 27 098–92 708) than that for deep incisional SSIs (€26 331; 95% CI 16 120–36 542).

The hospital costs from the healthcare payer's perspective for patients with SSI (mean €23 748 CI 17 862–29 633 per patient) was significantly higher than for patients without SSIs (mean €16 697; CI 15 595–17 799; $P \leq 0.001$).

Impacts of causative pathogen on costs and length of stay

The most commonly isolated pathogen in our study was coagulase-negative staphylococci, which caused the infection in 74 of 126 (59%) patients. The highest initial LOS was 37.91 ± 11.06 for SSI-infected patients with *Enterococcus faecalis*. However, total LOS (with readmission) was the highest in patients with SSI related to *Escherichia coli* (62.83 ± 23.25). The cost of antimicrobial therapy and total hospitalization cost were the highest for patients with SSI caused by *Enterococcus faecium* (Table 3).

DISCUSSION

Our results demonstrate that SSIs following CABG are associated with an excess LOS and a significant economic burden

Table 2: Prolongation of LOS and costs of SSIs

	Superficial incisional SSI (*n* = 96)	Deep incisional SSI (*n* = 20)	Organ/space SSI (*n* = 10)	Total SSI (*n* = 126)
Extra LOS				
Mean days ± SE	-1.41 ± 0.81	26.07 ± 5.16	59.31 ± 16.57	9.35 ± 2.64
Cost of antimicrobials (€)				
Number of cases	82	20	10	112
Mean ± SE	127 ± 41	1479 ± 461	5167 ± 1658	818 ± 215
95% CI	45–209	514–2444	1422–8913	392–1245
Total	10 415	29 583	51 673	91 671
Cost of V.A.C. therapy (€)				
Number of cases	4	17	8	29
Mean ± SE	511 ± 138	883 ± 217	2144 ± 465	1179 ± 210
95% CI	72–949	422–1344	1043–3244	748–1610
Total	2043	15 010	17 150	34 203
Total costs (€)				
Number of cases	96	20	10	126
Mean ± SE	130 ± 38	2230 ± 495	6882 ± 2002	999 ± 241
95% CI	55–205	1193–3266	2352–11 412	522–1476
Total	12 458	44 593	68 823	125 874

CI: confidence interval; LOS: length of stay; SE: standard error; SSI: surgical site infections; V.A.C. therapy: negative pressure wound therapy.

Table 3: Micro-organisms causing surgical site infections among 983 patients, LOS and related costs

	n	LOS[a], mean days ± SE	LOS with readmission, mean days ± SE	Cost of antimicrobials[b] (€), mean (95% CI)	Cost of V.A.C. therapy[b] (€), mean (95% CI)	Hospitalization cost[c] (€), mean (95% CI)
Coagulase-negative staphylococci	74	21.16 ± 2.04	27.26 ± 2.86	596 (251 to 942)	1169 (640 to 1698)	21 330 (17 012 to 25 648)
Staphylococcus aureus	14	19.43 ± 4.69	43.71 ± 8.03	1117 (-747 to 2981)	1239 (58 to 2420)	21 017 (9982 to 32 053)
Enterococcus faecalis	11	37.91 ± 11.06	53.82 ± 15.44	1299 (-668 to 3266)	2745 (-9 to 5499)	29 748 (6203 to 53 293)
Enterococcus faecium	4	23.25 ± 2.75	27.25 ± 5.79	4497 (-6453 to 15 447)	1718[d]	47 395 (-49 128 to 143 918)
Proteus mirabilis	2	11.50 ± 2.50	22.00 ± 8.00	10 (-21 to 42)	713[d]	12 782 (5961 to 19603)
Escherichia coli	6	32.33 ± 13.87	62.83 ± 23.25	1650 (-2016 to 5315)	2367 (-1555 to 6288)	35 831 (-9845 to 81 507)
Other bacteria	19	25.68 ± 5.33	36.68 ± 7.53	1357 (2 to 2711)	940 (416 to 1464)	26 014 (13 381–38 647)

[a]LOS from the initial hospitalization without readmission.
[b]Costs from a healthcare provider's perspective.
[c]Mean hospitalization costs from a healthcare payer's perspective.
[d]Only 1 SSI-infected patient with this micro-organism received V.A.C. therapy.
CI: confidence interval; LOS: length of stay; SE: standard error; V.A.C. therapy: negative pressure wound therapy.

depending on the classification of the SSI. A very important component of the additional cost is the prolongation of LOS. Therefore, it is essential to shorten the hospital stay due to SSIs as much as possible. We found that the hospital cost increased by approximately €7000 based on the healthcare payer's perspective and by approximately €8300 based on healthcare provider's perspective for patients with SSIs after CABG. The additional costs attributable to the extra LOS due to deep incisional SSIs and organ/space SSIs were approximately €26 300 and €59 900, respectively.

Because deep incisional SSIs and organ/space SSIs significantly prolonged hospital stay, and costs are strongly dependent on the LOS, there was a significant increase in the hospitalization costs. However, patients with superficial incisional SSIs did not have a longer LOS in the hospital than patients without SSIs. We found that the cost attributable to the additional LOS due to SSIs was more than one-third of the total hospital costs for patients with SSIs undergoing cardiac surgery. Moreover, the estimated additional cost of SSIs caused by the prolonged LOS based on the G-DRG shows that the total costs of the antimicrobials and V.A.C. therapy were only one-tenth of the total cost of the SSIs.

The rate of deep sternal SSIs (deep incisional and organ/space SSIs) was similar to that in previous studies [3]. However, the rate of superficial incisional SSI of 9.8% was higher than what has been reported previously. Published rates of superficial incisional SSIs ranged from 2.2% to 6.4% [14–17]. One reason for this difference could be that the study was performed from a retrospective chart review. Antibiotic therapy may have been started as a precautionary measure in some cases, but according to the CDC definition, superficial incisional SSI occurred when the surgeon started antibiotic therapy. The diagnosis of SSI could not be verified prospectively in this study, which led to substantial overestimation of the rate of superficial incisional SSIs. The finding that there was no additional LOS for patients with superficial incisional SSI in our analysis supports the argument of an overestimation of the true rate of wound infections.

A large proportion of the costs can be reliably estimated using bed-days lost due to SSIs [18]. Therefore, a precise estimation of

the additional LOS is required to generate reliable cost data. In this analysis, we evaluated the prolongation of the LOS associated with SSIs using multistate modelling to eliminate the time-dependent bias [19]. The additional LOS due to SSIs was relatively low compared with other studies that ignored the time of infection [20, 21]. However, the additional LOS due to deep incisional and organ/space SSIs were longer than those in previous studies [22]. The reason for this difference could be due to the fact that we added the number of days of hospitalization from readmission to discharge or death to the initially calculated LOS.

Comparing the cost of CABG-related SSIs between different studies is difficult because of the various cost calculation methods, types of cost perspectives, study methods, different geographical regions of the studies and various populations. Only a small number of publications have focused specifically on the economic impact of SSIs in patients undergoing cardiac surgery. Hollenbeak *et al.* [23] estimated that the additional costs of deep SSIs following CABG surgery were US $20 012 in 1999 (= €23 072 in 2014 value) using the cost-to-charge ratio for cost calculation, whereas Jenney *et al.* [24] estimated the cost to be $31 597 in Australian dollars in 1999 (= €33 967 in 2014 value) using cost accounting based on the monetary value of increased postoperative LOS. Jenney *et al.* [24] also estimated the antimicrobial costs associated with SSIs after CABG to be $391 Australian dollars (= €420 in 2014 value) per case with 6.1 additional LOS days, compared with €818 antimicrobial costs per case and 9.35 extra days in this study. SSIs after CABG increased the postoperative healthcare expenditures by US $27 631 (= €25 902 in 2014 value) in Japan [21]. In contrast to our study, the study by Coskun *et al.* [20] showed a mean additional hospital cost of US $6850 (= €7227 in 2014 value) for deep sternal SSIs and US $3740 (= €3946 in 2014 value) for superficial incisional SSIs in Turkey. Differences between results achieved in these studies and ours can be explained by the perspective of cost and country-specific differences in unit cost and resource use. A study by Graf *et al.* [25] assessed the lost costs for every case of deep sternal SSI in patients undergoing CABG to be €22 905 (= €27 350 in 2014 value) at the Hannover Medical School in Germany, compared with €26 300 in the present study.

Limitations

The main strength of our study was the precise cost analysis for each case and the estimation of the prolongation of the LOS using a multistate model. However, this study has several limitations. In this study, we did not actively perform and monitor the post-discharge surveillance, which may be influenced by the number of SSIs. However, the potential resulting information bias due to the routine readmission of all patients with deep sternal SSIs to the Department of Cardiothoracic Surgery, at least for deep sternal SSIs, should be negligible.

Our results may not be generalized to other settings because it was conducted at a single centre with a relatively low number of procedures. We included the costs of antimicrobials and V.A.C. therapy related to SSIs after CABG, which may have exempted some costs involved in treating SSIs; however, we provided an additional total cost analysis based on the G-DRG. We also did not evaluate the indirect costs of CABG-related SSIs, such as those that occur as a consequence of productivity loss caused by the absence of a person from their workplace.

CONCLUSION

In conclusion, the present study provides up-to-date information about the costs of antimicrobials and VAC therapy, additional LOS and associated costs related to SSIs after CABG. This study shows that SSIs following CABG are accompanied by an additional burden of costs, which is most pronounced in patients with deep incisional and organ/space SSIs.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Funding

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Conflict of interest: none declared.

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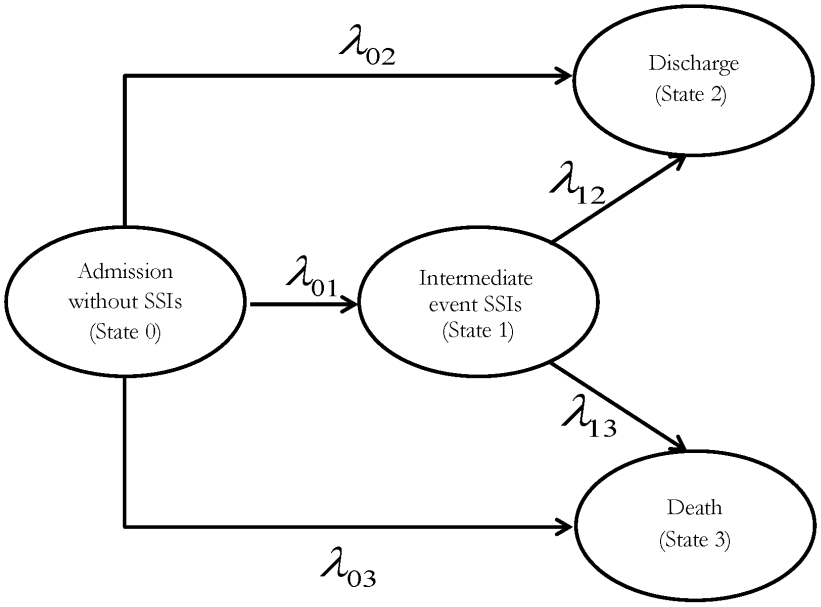
Supporting information



Supplementary data 1. Multistate model with four states: 0, admission without surgical site infections (SSIs); 1, SSIs (exposed) after coronary artery bypass grafting (CABG) as intermediate event; 2, discharge; 3, death. All of the included patients entered into initial state 0 (alive and hospitalized). Then the patient may acquire a SSI after CABG, moving to intermediate state 1, be discharged without SSI and moving to state 2, or die without SSI. Once infected with SSI, the patient can move from state 1 to 2 or from 1 to 3; patients in state 2 cannot enter state 3. Hazard rates are denoted by λ_{ij} with indices i and j indicating the states which they connect [9-11]. The additional length of Stay for a patient with SSI compared to a patient without SSI is given by the following equation:

$$\text{Additional length of Stay [days]} = \left(\frac{\lambda_{02}+\lambda_{03}}{\lambda_{12}+\lambda_{13}} - 1\right) \times \frac{1}{\lambda_{01}+\lambda_{02}+\lambda_{03}}$$

Supplementary data 2. Total antibiotic use for SSI treatment and related costs

Antibiotic [Dose]	**Type**	**Quantity**	**Total cost [€]**
Amoxicillin/clavulanic acid [1 g]	p.o.	70	11
Amphotericin B [500 mg]	i.v.	3	1,519
Ampicillin/sulbactam [3 g]	i.v.	348	186
Anidulafungin [100 mg]	i.v.	19	7,337
Caspofungin [50 mg]	i.v.	27.5	12,612
Cefazolin [2 g]	i.v.	206	100
Ceftazidime [2 g]	i.v.	316	300
Ceftriaxone [2 g]	i.v.	108	52
Cefuroxime [1.5 g]	i.v.	40	32
Ciprofloxacin [500 mg]	p.o.	315	19
Ciprofloxacin [400 mg]	i.v.	401	577
Clarithromycin [500 mg]	p.o.	10	2
Clarithromycin [500 mg]	i.v.	6	17
Clindamycin [600 mg]	p.o.	1,084	217
Clindamycin [600 mg]	i.v.	342	222
Colistin [90 mg]	i.v.	10	105
Daptomycin [500 mg]	i.v.	175	22,759
Doxycycline [200 mg]	p.o.	7	1
Erythromycin [250 mg]	i.v.	60	43
Flucloxacillin [2 g]	i.v.	299.5	592
Fluconazole [400 mg]	i.v.	53	97
Fosfomycin [3 g]	i.v.	3	74
Gentamicin [320 mg]	i.v.	4	7
Levofloxacin [500 mg]	p.o.	92	29
Levofloxacin [500 mg]	i.v.	24	61
Linezolid [600 mg]	p.o.	183	5,067
Linezolid [600 mg]	i.v.	176	1,369
Meropenem [1 g]	i.v.	822	3,218
Metronidazole [500 mg]	p.o.	47	9
Metronidazole [500 mg]	i.v.	4	2
Moxifloxacin [400 mg]	p.o.	120	110
Moxifloxacin [400 mg]	i.v.	12	46
Piperacillin+Tazobactam [4.5 g]	i.v.	909	15,826
Rifampicin [450 mg]	p.o.	471	1,044
Rifampicin [600 mg]	i.v.	74	866
Tigecycline [100 mg]	i.v.	126	15,240
Tobramycin [400 mg]	i.v.	18	196
Trimethoprim/sulfamethoxazole [960 mg]	p.o.	152	12
Trimethoprim/sulfamethoxazole [960 mg]	i.v.	105	319
Vancomycin [250 mg]	p.o.	369	237
Vancomycin [1 g]	i.v.	468.5	1,140

p.o. = orally; i.v. = intravenously

3.5. Manuskript V

Estimating extra length of stay due to healthcare-associated infections before and after implementation of a hospital-wide infection control program

Habibollah Arefian, Stefan Hagel, Dagmar Fischer, André Scherag, Frank Martin Brunkhorst, Jens Maschmann, Michael Hartmann

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Die Auswertungen haben gezeigt, dass sich die Verweildauer durch nosokomiale Infektionen nach Interventionsmaßnahmen am Universitätsklinikum Jena weiterhin verlängert. Eine signifikante Reduzierung an Verweildauerverlängerung konnten lediglich in der Klinik für Innere Medizin beobachtet werden. Die Verweildauerverlängerung wurde bei Patienten mit Harnwegsinfektionen signifikant verändert. Die Ergebnisse zeigen, dass für Patienten mit nosokomialer Infektion ein höheres Risiko besteht, zu versterben. Die Studie hat weiterhin gezeigt, dass die Auswertung der Verweildauerverlängerung aufgrund von nosokomialen Infektionen mit Hilfe eines Multistate-Modells von mehreren Faktoren wie z.B. Infektionsart oder Krankenhausabteilungen, abhängig sind.

Habibollah Arefian	Konzeptionelle Entwicklung der Studie; Präparation und Bearbeitung der Daten; Evaluierung der Daten; Entwicklung der Methoden; Auswertung der Verweildauerverlängerung durch nosokomiale Infektionen; Interpretationen der Ergebnisse; Erstellung des Entwurfs und Überarbeitung des Manuskripts; Konzeption und Erstellung aller Abbildungen; Erstellung aller Tabellen; Einarbeitung von Korrekturen während des Reviewprozesses

Stefan Hagel	Konzeption und Planung des Alerts-Projekts; Präparation der Daten; Durchsicht des Manuskripts; Mitarbeit an der Erstellung von Korrekturen während des Reviewprozesses
Dagmar Fischer	Interpretationen der Ergebnisse; Durchsicht des Manuskripts; Mitarbeit an der Erstellung von Korrekturen während des Reviewprozesses
André Scherag	Interpretationen der Ergebnisse; Überarbeitung des Manuskripts; Mitarbeit an der Erstellung von Korrekturen während des Reviewprozesses
Frank M. Brunkhorst	Konzeption und Planung des Alerts-Projekts; Durchsicht des Manuskripts
Jens Maschmann	Interpretationen der Ergebnisse; Überarbeitung des Manuskripts
Michael Hartmann	Konzeptionelle Entwicklung der Studie; Interpretationen der Ergebnisse; Überarbeitung des Manuskripts; Mitarbeit an der Erstellung von Korrekturen während des Reviewprozesses; Leitung

PLOS ONE

RESEARCH ARTICLE

Estimating extra length of stay due to healthcare-associated infections before and after implementation of a hospital-wide infection control program

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Competing interests: The authors have declared that no competing interests exist.

Abstract

Introduction

Healthcare-associated infections (HAIs) are a major health concern and have substantial effects on morbidity and mortality and increase healthcare costs. We investigated the effect of a hospital-wide program for the prevention of HAIs on additional length of stay (LOS).

Methods

We analyzed data from a prospective, single-center, quasi-experimental study with two surveillance periods before and after implementation of an infection prevention intervention program. HAI diagnosis was made according to surveillance definition criteria established by the US Centers for Disease Control and Prevention. A multistate model was used to estimate additional LOS for patients with HAI in both surveillance periods.

Results

During the first and second periods, 1,568 and 2,336 HAIs were identified among 26,943 and 35,211 patients, respectively. For HAI patients exclusively treated in a general ward, additional LOS was 8.4 (95% confidence interval, CI: 6.8–10.0) days in the first period and 9.6 (95% CI: 8.3–11.0) days in the second period ($p = 0.26$). For HAI patients treated in both an intensive care unit (ICU) and a general ward, additional LOS was 8.1 (95% CI: 6.3–9.9) days in the first period to 7.3 (95% CI: 6.1–8.5) days in the second period ($p = 0.47$).

Conclusions

Healthcare-associated infections prolong LOS. A hospital-wide infection control program did not alter the prolongation of LOS.

Introduction

Healthcare-associated infections (HAIs) are a major health concern and have substantial effects on morbidity and mortality[1]. HAIs prolong patients' length of stay (LOS) and increase the costs of treatment [2]. Minimizing HAIs, particularly within hospitals, is a key aspect of patient safety initiatives in many countries, including Germany. The World Health Organization reported an estimated number of 5 million HAIs in acute care hospitals in Europe, resulting in 50,000 deaths and €13–24 billion in extra costs per year[3].

Because the cost of HAIs is strongly dependent on patients' LOS, many studies have estimated additional LOS due to HAIs. Additional hospital stay must be calculated to assess how many bed-days might be gained from prevention measures[4]. Generally, most health economic studies have not considered the time of occurrence of HAIs and temporal dynamics of the individual patient (from hospital admission to discharge alive or death) in the estimation of additional LOS. Thus, the additional LOS and extra costs resulting from HAIs may be overestimated [5, 6]. Multistate models have been recommended to eliminate this time-dependent bias and estimate the extra time spent in the hospital due to HAIs using transition probabilities[7]. Such models define events over the course of time as transitions between various states, and the transition hazards are the main statistical quantities[8]. An intervention prevention program is an effective process to decrease the number of HAIs. Previous studies have shown that the implementation of an infection prevention program has benefits for patients and can reduce the numbers of HAI [9, 10]. Furthermore, we know that the severity of HAI is influenced by an infection control program and HAI management [11]. However, it remains unclear whether a reduction of severe HAIs can also influence extra LOS due to HAIs.

Therefore, we hypothesised that the extra length of stay associated with HAIs can be changed with the help of an infection prevention intervention program. We aimed to assess the impact of HAIs on LOS using multistate models in the surveillance period 1 and the surveillance periods 2 of a hospital-wide infection control program at Jena University Hospital.

Materials and methods

Study design

We analyzed data on HAIs from the ALERTS study [11], a prospective, quasi-experimental study at Jena University Hospital, a tertiary care medical center in Germany. The data protection commissioner and institutional review board approved the study with a waiver of informed consent for individual patients (ID: 3139-05/11). The trial has been registered at the German Clinical Trials Register (DRKS00003166) and the protocol was approved by the ethics committee of the Medical Faculty of the Friedrich-Schiller-University Jena. The need for consent was waived by the ethics committee. The TREND statement checklist was used for the reporting of non-randomized trials (S1 Table). The design of the ALERTS study included 1) a 12-month first surveillance period that was performed between September 2011 and August 2012; 2) a multifaceted hospital-wide program for infection control starting in October 2012; and 3) a second surveillance period to evaluate the effectiveness of the intervention, which was

implemented from May 2013 to August 2014. Note that we previously published data on additional LOS and economic costs for the first surveillance period [2].

The multifaceted intervention program for infection control in the ALERTS study involved the hospital-wide promotion of hand hygiene and the implementation of prevention bundles for specific HAIs (S1 Fig). This intervention started in October 2012 and was conducted throughout the remainder of the study period. HAI were identified among patients hospitalized for ≥48 hours with at least 1 risk factor for HAI and new antimicrobial therapy. HAI diagnosis was made according to surveillance definition criteria established by the US Centers for Disease Control and Prevention[12]. All inpatients with a hospital stay ≥ 48 hours admitted to one of the wards under surveillance were eligible for inclusion. Wards under surveillance included 11 internal medicine wards (336 beds), 9 surgical wards (250 beds), 2 geriatric wards (39 beds), 2 neurological wards (50 beds), 3 gynecological wards (51 beds) and 5 intensive care units (ICUs)/intermediate critical care units (91 beds). Further details of the ALERTS study have been described elsewhere[11].

Length of stay

A multistate model was used to estimate additional LOS due to HAIs considering HAIs as a potential intermediate state between admission and discharge or death to address the time-dependent bias.

In this model, all patients were regarded as "non-exposed patient" as long as they did not acquire an HAI during their stay in the hospital. If a patient acquired more than one HAI, the time of the occurrence of the first HAI was used in the multistate model. The prolongation of LOS was derived as a function of the hazard of transition in the next short time between the health states[2, 5, 13]. Using the general multistate model displayed in Fig 1, we estimated the

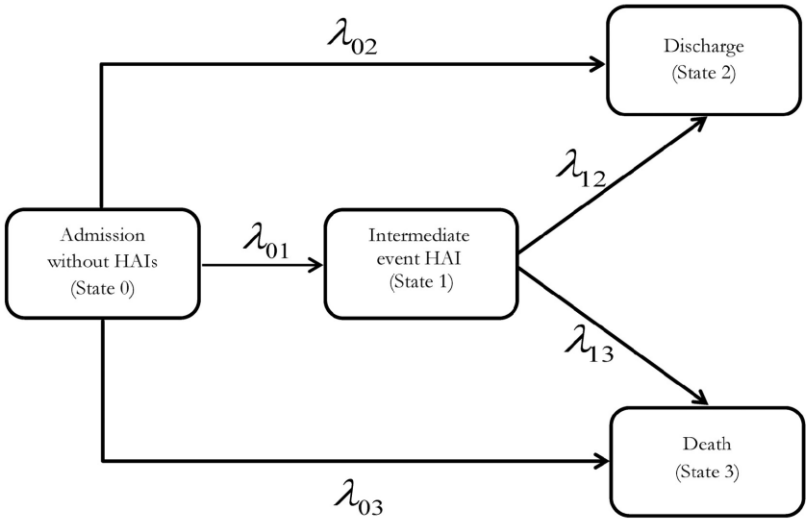

Fig 1. Multistate model with four states. Admission (state 0) is the first state, and all patients entered into the initial state without HAIs. The patient may acquire an HAI and move to intermediate state 1. Discharge (state 2) or death (state 3) indicates the end of hospitalization.

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prolongation of LOS using two approaches. Model approach 1 estimated additional LOS due for the following HAIs (jointly and stratified) separately for the first and second surveillance periods: surgical site infection (SSI), lower respiratory tract infection (LRTI), urinary tract infection (UTI), primary blood stream infection (BSI), *Clostridioides difficile*-associated infection (CDI), other infections, and multiple infections (grouped under the category "Multiple"). Model approach 2 estimated the prolongation of LOS associated with HAIs stratified by department because the costs of bed-days largely differ across departments. Moreover, from the health economic perspective is important to know the extra LOS explicitly for patients stayed in ICU, because the daily costs of intensive care are higher than the treatment costs in general wards. Therefore, we estimated additional LOS separately for patients treated in general wards (surgical, internal medicine, geriatric, gynecology and neurology) and for patients treated in both a general ward and an ICU. The department or unit that discharged the patient from the hospital was considered as the main ward.

Statistical analyses

In this study, we used multistate models that describe the daily risk of transition between multiple health states. The expected LOS associated with HAI (in days) was computed by a function of these transition probabilities[8]. The Aalen-Johnson estimator was used as a nonparametric estimator for the matrix of transition probabilities for all observed transition times[14]. We calculated the standard error (SE) and confidence intervals (CIs) for extra LOS by bootstrap sampling using 1,000 replicates. Additional LOS due to HAIs in the two surveillance periods were compared by using the z-test. The statistical tests were 2-sided and p-values of ≤ 0.05 were considered statistically significant.

In addition, we used the landmark method[15] to evaluate whether HAIs prolonging effect. We selected a range of landmark time points (s) for the analysis, $s > 2$. Given HAI status at time s, we then compared the probabilities of having reached the absorbing states 2 (discharge alive) and 3 (death) by time t, $s \leq t$. We computed probability estimates within HAI groups defined at time s, taking s as the new time origin. In our multistate setting, we utilized the Aalen-Johansen estimator for patients discharged alive [$P_{02}(s, t)$ and $P_{12}(s, t)$] and for death [$P_{03}(s, t)$ and $P_{13}(s, t)$] for different landmark time points (s)[16].

All statistical analyses were performed using R version 3.2.3 (R Foundation for Statistical Computing), including the etm 0.6–2, mvna 2.0, and kmi packages[16].

Results

During the ALERTS study, 26,943 patients in the first and 35,211 patients in the second surveillance period were admitted to the Jena University Hospital (Fig 2). In total, 1,170 patients in the first and 1,711 patients in the second surveillance period experienced 1,568 and 2,336 separate episodes of HAIs, respectively. The percentage of patients with HAI was 4.3% in the first surveillance period and 4.9% in the second surveillance period. The incidence of HAIs did not significantly differ between the first and second surveillance periods in general wards (Incidence rate ratio: 1.296; 95% CI, 0.784–2.145, p = 0.312) and in ICU (Incidence rate ratio: 0.592; 95% CI, 0.267–1.310, p = 0.196). A detailed comparison of the HAIs in the two periods has been reported elsewhere[11].

The median LOS of patients included in our analysis was six days (interquartile range (IQR): 3–11) in the first surveillance period and seven days (IQR: 4–11) in the second surveillance period. The median LOS of patients with HAI was 28 days (IQR: 18–42) in both periods. In total, 893 (3.3%) and 1,191 (3.4%) of the included patients died in the hospital during the first and second surveillance periods, respectively (Table 1).

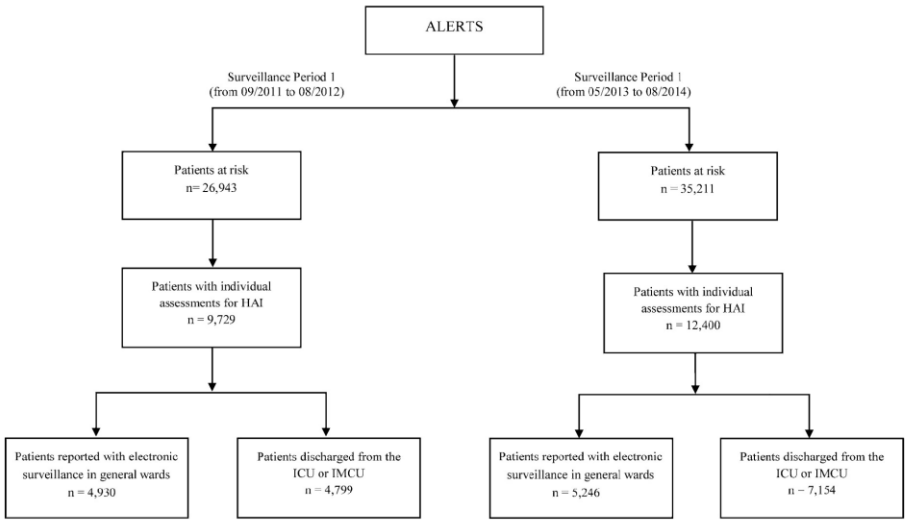

Fig 2. Flow chart of surveillance of healthcare-associated infections (HAIs) in ALERTS study.

https://doi.org/10.1371/journal.pone.0217159.g002

Prolongation of length of stay using a multistate model

Overall, the additional LOS due to HAIs (regardless of the unit in which the patients stayed; Model approach 1) was 12.0 (95% CI: 10.9–13.2; SE: ± 0.6) days in the first surveillance period

Table 1. Selected characteristics of patients in the ALERTS study (for details, see Hagel et al. publication[11]).

Characteristic	Value	
	Surveillance Period 1 (09/2011 to 08/2012)	Surveillance Period 2 (05/2013 to 08/2014)
Number of patients with HAI—no. (%)	1,170	1,711
- Patients with one HAI	899 (77%)	1,268 (74%)
- Patients with more than one HAI	271 (23%)	443 (26%)
Male sex—no. (%)	643 (55%)	983 (57%)
Age, median years (IQR)	69 (56–76)	69 (57–76)
Hospitalization in the previous 3 months—no. (%)	329 (28%)	447 (26%)
Patients with severe sepsis/septic shock—no. (%)	351 (30%)	434 (25%)
In-hospital deaths due to HAIs–no. (%)	113 (10%)	164 (10%)
Site of infection—no. (%)[a]	1,568	2,336
- Surgical site infection	448 (29%)	625 (27%)
- Respiratory tract infection	385 (25%)	682 (29%)
- Primary bloodstream infection	202 (13%)	278 (12%)
- Urinary tract infection	162 (10%)	309 (13%)
- *Clostridioides difficile*-associated infection	163 (10%)	176 (8%)
- Other	208 (13%)	266 (11%)

HAI, healthcare-associated infection; IQR, interquartile range.

[a] The percentages are about site of infection

https://doi.org/10.1371/journal.pone.0217159.t001

Table 2. Model approach I: Results of additional length of stay estimates from the multistate model stratified by infection site/type and surveillance period.

Comparison	Surveillance period 1[a] *Additional LOS in days (95% CI)*	Surveillance period 2[a] *Additional LOS in days (95% CI)*	p-value[b]
Urinary tract infection	3.3 (3.1–3.5)	5.3 (3.5–7.1)	0.03
Clostridioides difficile-associated infection	6.1 (3.2–9.1)	6.8 (4.3–9.4)	0.73
Lower respiratory tract infection	8.8 (7.1–10.6)	9.0 (7.5–10.4)	0.92
Primary blood stream infection	12.5 (8.0–17.0)	9.3 (6.7–11.9)	0.22
Surgical site infection	12. 9 (10.6–15.1)	13.2 (11.1–15.3)	0.84
Other infections	6.0 (3.1–8.9)	7.1 (4.1–10.1)	0.59
Multiple infections	25.6 (22.6–28.5)	25.4 (23.0–27.8)	0.93
Total	12.0 (10.9–13.2)	12.3 (11.4–13.2)	0.71

CI, confidence interval; LOS, length of stay.

[a] Surveillance period 1 was from 09/2011 to 08/2012 and period 2 was from 05/2013 to 08/2014

[b] P-Value relate to surveillance period 1 versus surveillance period 2

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and varied by type of HAI from 3.3 (95% CI: 3.1–3.5; SE: ± 0.1) days for UTI to 12.9 (95% CI: 10.6–15.1; SE: ± 1.1) days for SSI. In the second surveillance period, the additional LOS was similar, with 12.3 (95% CI: 11.4–13.2; SE: ± 0.4) days, and varied by type of HAI from 5.3 (95% CI: 3.5–7.1; SE: ± 0.8) days for UTI to 13.2 (95% CI: 11.1–15.3; SE: ± 1.1) days for SSI. The additional LOS for patients with multiple HAIs was 25.6 ± 1.5 days and 25.4 (95% CI: 23.0–27.8; SE: ± 1.2) days during the first and second surveillance periods, respectively (Table 2).

The estimates of prolongation of LOS due to HAIs according to the multistate model examined by department (Model approach 2) showed that additional LOS among patients exclusively treated in a general ward was increased from 8.4 (95% CI: 6.8–10.0; SE: ± 0.8) days in the first period to 9.6 (95% CI: 8.3–11.0; SE: ± 0.7) days in the second period. By contrast, the additional LOS decreased from 8.1 (95% CI: 6.3–9.9; SE: ± 0.9) days in the first period to 7.3 (95% CI: 6.1–8.5; SE: ± 0.6) days in the second surveillance period for patients with HAIs treated in both a general ward and an ICU (Table 3). However, the prolongation of LOS due to HAIs did not significantly change between the first and second surveillance periods among patients exclusively treated in a general ward ($p = 0.23$) or in both a general ward and an ICU ($p = 0.47$).

The additional LOS due to HAIs was reduced in internal medicine departments from 11.0 (95% CI: 6.8–15.2; SE: ± 2.1) days in the first period to 6.4 (95% CI: 4.0–8.7; SE: ± 1.2) in the

Table 3. Model approach 2: Extra days of hospitalization due to healthcare-associated infections stratified by department (rows), clinical unit stay of the patient and surveillance period (columns).

Model	Extra days (95% CI); patients treated exclusively in a general ward			Extra days (95% CI); patients treated in a general ward and an ICU		
	Surveillance period 1[a]	*Surveillance period 2*[a]	p-Value[b]	*Surveillance period 1*[a]	*Surveillance period 2*[a]	p-Value[b]
Surgical	6.5 (3.2–9.8)	10.9 (7.3–14.5)	0.07	7.5 (5.2–9.7)	7.4 (5.8–9.1)	0.97
Geriatric	5.3 (1.6–8.9)	6.9 (4.2–9.5)	0.47	8.6 (1.5–15.8)	4.7 (-1.5–11.0)	0.41
Gynecology	6.7 (0.8–12.6)	9.2 (2.7–15.6)	0.57	11.3 (3.8–18.8)	4.8 (0.6–9.1)	0.13
Internal medicine	8.8 (6.7–11.0)	8.0 (6.3–9.6)	0.51	11.0 (6.8–15.2)	6.4 (4.0–8.7)	0.05
Neurology	21.3 (3.5–39.1)	8.2 (4.7–11.7)	0.15	6.9 (3.3–10.5)	7.3 (4.8–9.9)	0.84
Total	8.4 (6.8–10.0)	9.6 (8.3–11.0)	0.26	8.1 (6.3–9.9)	7.3 (6.1–8.5)	0.47

CI, confidence interval.

[a] Surveillance period 1 was from 09/2011 to 08/2012 and period 2 was from 05/2013 to 08/2014

[b] P-Value relate to surveillance period 1 versus surveillance period 2

https://doi.org/10.1371/journal.pone.0217159.t003

second period (P = 0.05) for patients who were treated temporary in ICU. Fig 3 illustrates the expected LOS on each day up to 60 days after admission using the multistate model for HAI patients versus non-HAI patients considering the patients treated only in a general ward versus those treated in both a general ward and an ICU in the first and second periods.

Our analysis for patients discharged alive [$P_{02}(s, t)$ and $P_{12}(s, t)$] based on a range of landmarks s in the first surveillance period (Fig 4) showed that the prolonging effect of HAI is illustrated by the fact that, overall, $P_{02}(s, t) \geq P_{12}(s, t)$, meaning that the probabilities of discharged alive for patients without HAI are in different range of landmarks higher than for patients with HAI. The effect was most pronounced for early landmarks. Conversely, this analysis for death [$P_{03}(s, t)$ and $P_{13}(s, t)$] for the same range of landmarks in the first period (Fig 4) showed that $P_{13}(s, t) \geq P_{03}(s, t)$, meaning that the probabilities of death for patient with HAI are higher than for patient without HAI in the same range of landmarks. The results were very similar in the second surveillance period (S2 Fig).

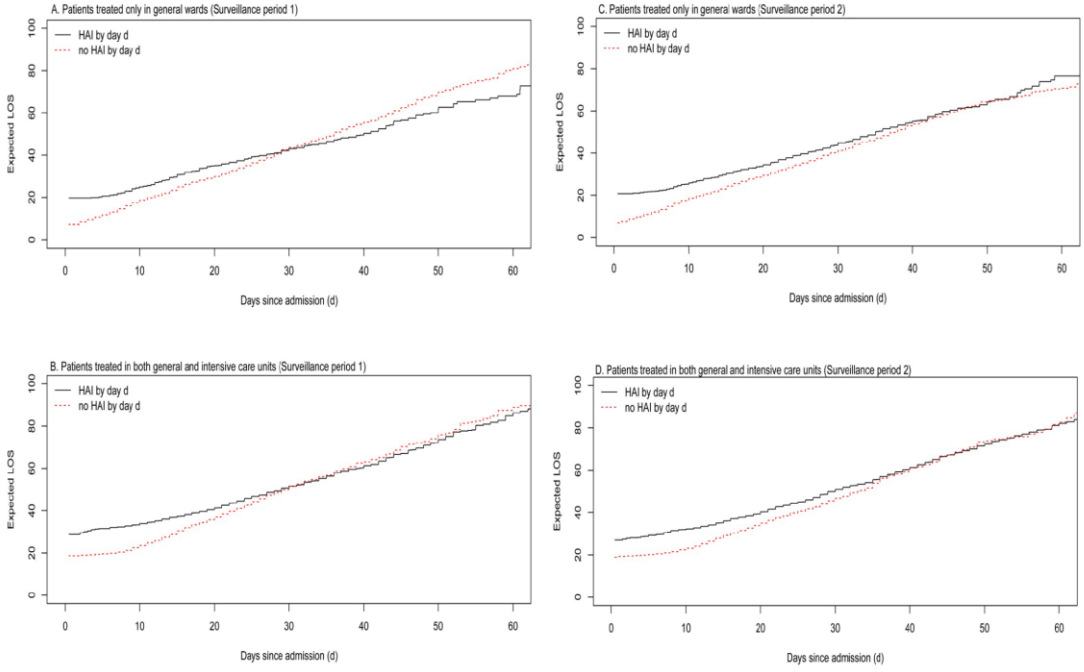

Fig 3. Results of multistate models to determine expected length of stay for patients with and without HAIs up to 60 days after admission.

https://doi.org/10.1371/journal.pone.0217159.g003

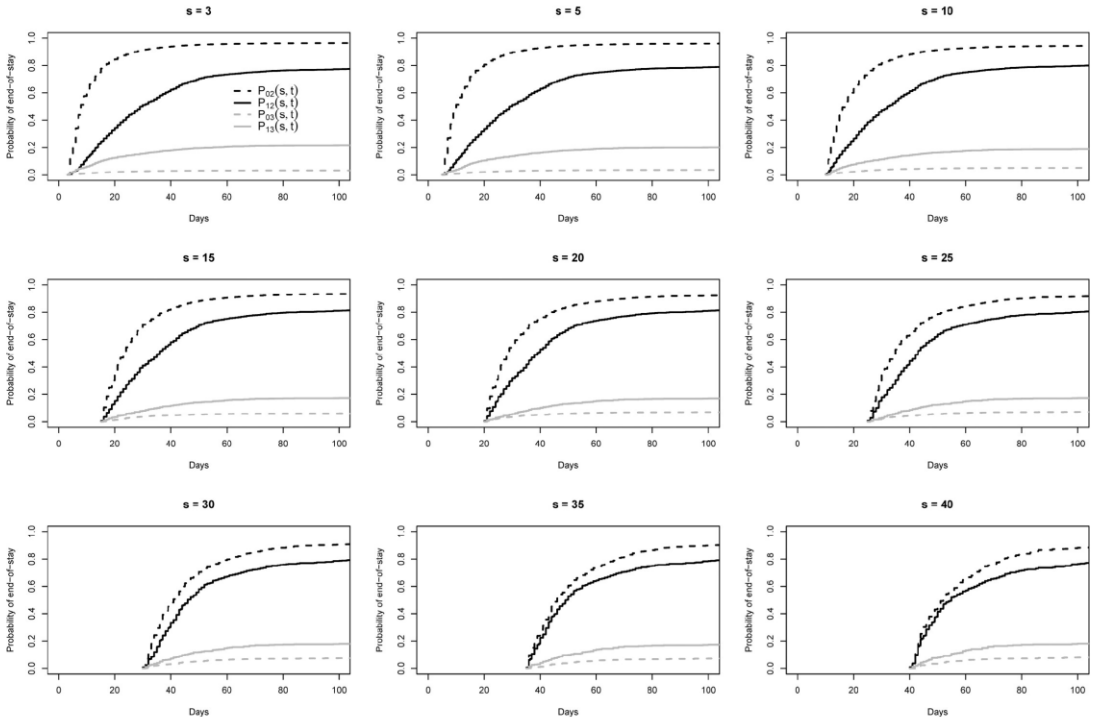

Fig 4. Results of the Aalen-Johansen estimator for patients discharged alive [P02(s, t) (black dashed lines) and P12(s, t) (black solid lines)] and for death [P03(s, t) (dark grey dashed lines) and P13(s, t) (dark grey solid lines)] for different landmark times s in surveillance period 1.

https://doi.org/10.1371/journal.pone.0217159.g004

Discussion

We estimated the impact of HAIs on prolongation of LOS during the first and second surveillance periods of the ALERTS study. Our analyses showed that the estimation of additional LOS due to HAIs based on the multistate model was sensitive to several factors, including the inpatient units and type of infection. For example, when patients were included in the multistate model based on ICU or non-ICU stay (model approach 2), the additional LOS due to HAIs was clearly lower than the estimated additional LOS associated with HAIs in model approach 1 when the inpatient units were ignored in analyses. The results also showed that prolongation of LOS due to multiple HAIs was 2 times greater than that due to SSI and 7 times greater than that due to UTI during the first surveillance period, and similar results were found in the second surveillance period.

However, the incidence of HAIs in the second surveillance period did not differ significantly after the intervention prevention program. Only a reduction in severe HAIs were observed in the second surveillance period in the ICUs[11]. Furthermore, our result shows that the additional LOS due to HAIs was reduced in internal medicine wards during in second surveillance period for patients who were treated some time in ICU. Infection prevention program for HAI cannot reduce additional length of stay due to HAI, but can change the ICU

length of stay in some type of HAI. This is important to know because a reduction of LOS in intensive care unit can lead to substantial reduction in total inpatient cost[17].

A landmark method was applied to illustrate the prolonging effect of HAI for exposed patients in comparison with non-exposed patients. The results showed that the probabilities of discharged alive for patients with HAI were lower than patients without HAI at the same landmark. Furthermore, the probability of death for exposed patients is higher compared to non-exposed patients. Differences were higher at earlier landmark, meaning that the impact of occurrence of HAI in early days after admission on competing events (discharge alive, death) is much higher.

A systematic review of published literature concluded that additional LOS due to HAIs in studies using time-fixed methods was 9.4 days on average longer than that in studies using multistate models[18]. Therefore, our results are similar to those of other recent studies using a multistate model. For example, Stewardson et al. estimated that prolongation of LOS averaged 12.22 and 10.35 days for primary BSI with methicillin-resistant staphylococcus aureus and methicillin-susceptible staphylococcus aureus of acute care admissions at 10 European hospitals[19]. Macedo-Vinas et al. estimated a similar impact of HAIs at a tertiary care hospital in Switzerland[20].

This study has several limitations. We were unable to conduct an economic analysis because the infection control program did not reduce the incidence rate of HAIs. Our study analyzed data from a single-center study in Germany; thus, the results may not be generalizable to other settings. In addition, our data does not allow for an adjustment according to sex, age or comorbidities because of low number of patients with HAI in some categories.

The role of hand hygiene as the most important factor in the prevention of HAIs is accepted, and several studies have reported that the rate of adherence to hand hygiene can increase significantly with a multifaceted intervention, which can reduce the risk of HAIs[21]; however, the incidence of HAIs and extra LOS due to HAIs was not significantly reduced in the ALERTS study. One potential reason is that hand hygiene compliance is usually lower in some units, including ICUs, because of high activity level, lack of time and high workload[22, 23]. Moreover, hand hygiene compliance could have been affected by the Hawthorne bias in this study. Hagel et al. reported that hand hygiene events by healthcare workers can be increased from 8 to 21 events per hour because of the presence of a direct observer[24].

In conclusion, healthcare-associated infections prolong LOS and can therefore increase the hazard of hospital mortality and costs of care. Our analyses demonstrated that additional LOS varied across HAI sites. This information can help health policy makers determine which hospital infection prevention measures to invest in to improve health and save costs.

Supporting information

S1 Fig. Characterization of interventions for infection control in the ALERTS.
(PDF)

S2 Fig. Results of the Aalen-Johansen estimator for patients discharged alive [P02(s, t) (black dashed lines) and P12(s, t) (black solid lines)] and for death [P03(s, t) (dark grey dashed lines) and P13(s, t) (dark grey solid lines)] for different landmark times s in surveillance period 2.
(PDF)

S1 Table. TREND statement checklist.
(PDF)

S1 Dataset. Copy of dataset.
(XLSX)

Acknowledgments

The results were presented as an abstract at the annual meeting of the German Pharmaceutical Society-DphG 2017 (https://www.dphg.de/fileadmin/downloads/DPhG2017_ConferenceBook_final.pdf).

Limited data about the first surveillance period were previously published in the American Journal of Infection Control (http://dx.doi.org/10.1016/j.ajic.2015.09.005).

Author Contributions

Conceptualization: Habibollah Arefian, Stefan Hagel, Dagmar Fischer, André Scherag, Frank Martin Brunkhorst, Michael Hartmann.

Data curation: Habibollah Arefian, Stefan Hagel.

Formal analysis: Habibollah Arefian.

Funding acquisition: Frank Martin Brunkhorst.

Investigation: Stefan Hagel.

Methodology: Habibollah Arefian, Michael Hartmann.

Project administration: Frank Martin Brunkhorst, Michael Hartmann.

Resources: Stefan Hagel.

Software: Habibollah Arefian.

Supervision: Dagmar Fischer.

Validation: Habibollah Arefian, André Scherag, Michael Hartmann.

Writing – original draft: Habibollah Arefian.

Writing – review & editing: Habibollah Arefian, Stefan Hagel, Dagmar Fischer, André Scherag, Frank Martin Brunkhorst, Jens Maschmann, Michael Hartmann.

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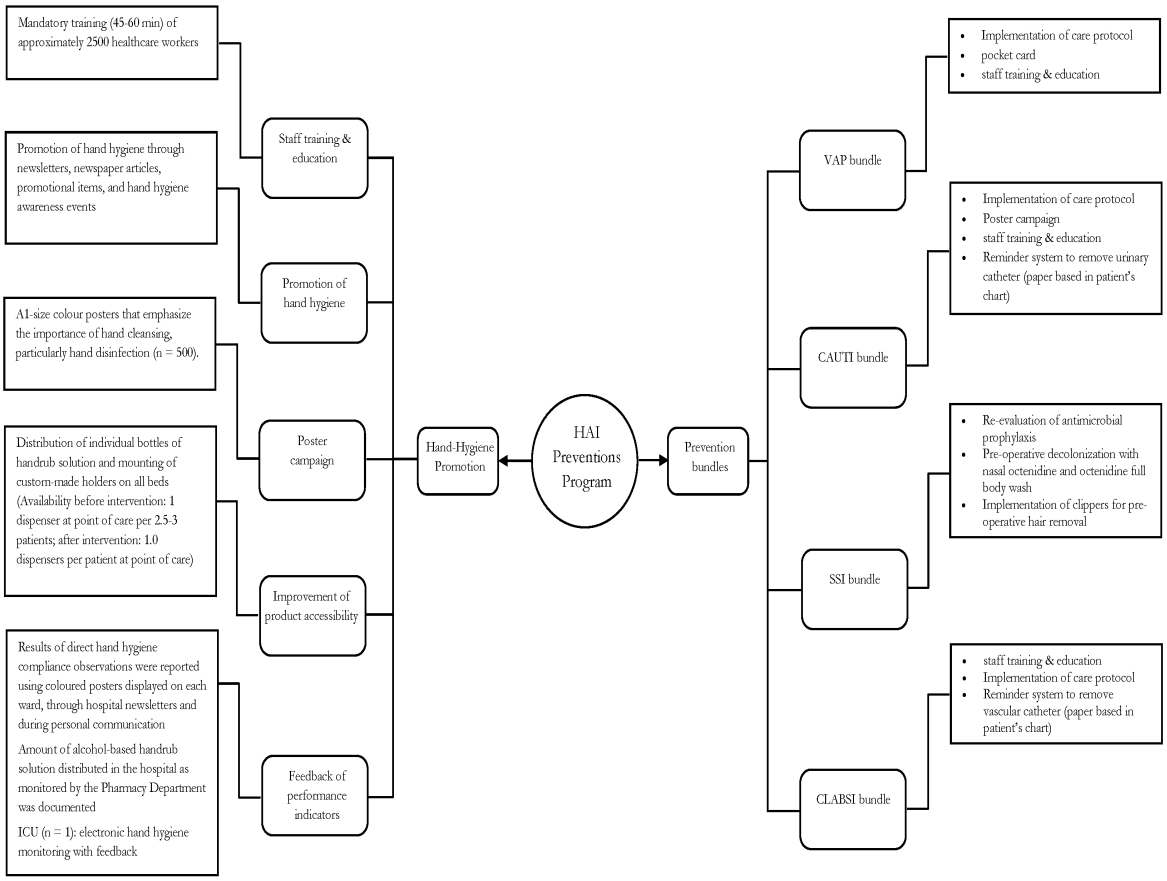
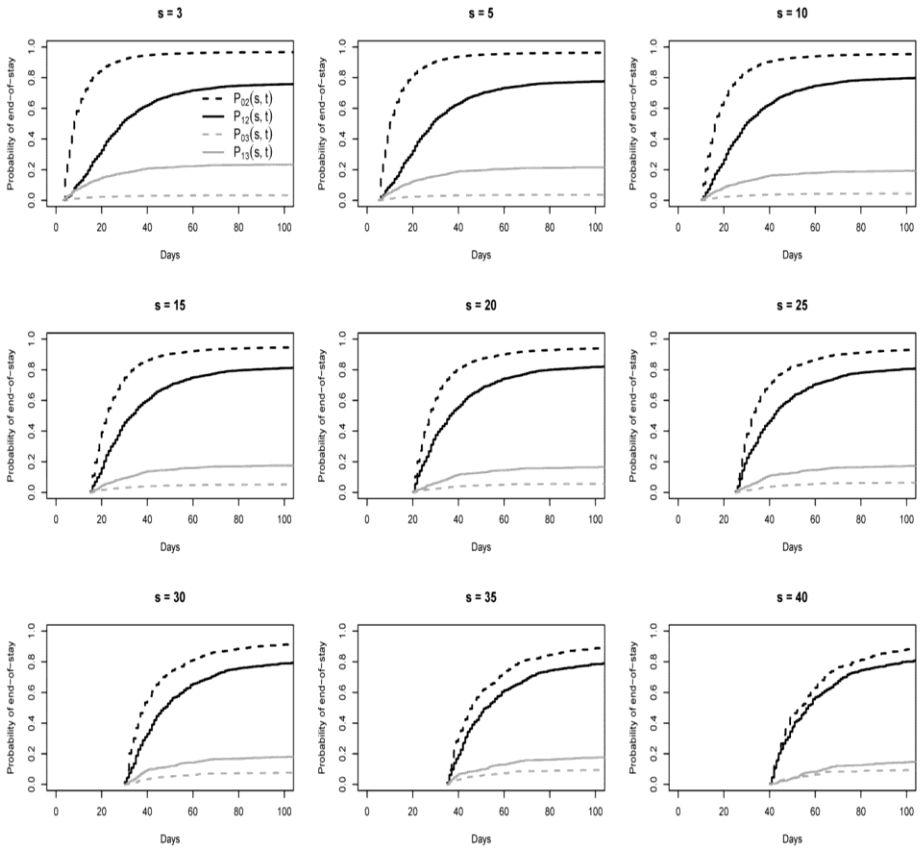
Supporting information



S1 Fig. Characterization of interventions for infection control in the ALERTS.

VAP, ventilator associated pneumonia; CAUTI, catheter-related urinary tract infection; SSI, surgical site infection; CLABSI, central line-associated bloodstream infections; ICU, intensive care unit.



S2 Fig. Results of the Aalen-Johansen estimator for patients discharged alive [P02(s, t) (black dashed lines) and P12(s, t) (black solid lines)] and for death [P03(s, t) (dark grey dashed lines) and P13(s, t) (dark grey solid lines)] for different landmark times s in surveillance period 2.

TREND Statement Checklist

Paper Section/ Topic	Item No	Descriptor	Reported? ✓	Reported? Pg #
Title and Abstract				
Title and Abstract	1	• Information on how unit were allocated to interventions	✓	1&2
		• Structured abstract recommended	✓	2
		• Information on target population or study sample	✓	2
Introduction				
Background	2	• Scientific background and explanation of rationale	✓	3
		• Theories used in designing behavioral interventions		n/a
Methods				
Participants	3	• Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	✓	4
		• Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	✓	3&4
		• Recruitment setting	✓	3&4
		• Settings and locations where the data were collected	✓	4
Interventions	4	• Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:	✓	4
		○ Content: what was given?	✓	S1 Fig
		○ Delivery method: how was the content given?	✓	S1 Fig
		○ Unit of delivery: how were the subjects grouped during delivery?	✓	S1 Fig
		○ Deliverer: who delivered the intervention?	✓	S1 Fig
		○ Setting: where was the intervention delivered?	✓	S1 Fig
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?	✓	4
		○ Time span: how long was it intended to take to deliver the intervention to each unit?	✓	S1 Fig
		○ Activities to increase compliance or adherence (e.g., incentives)		n/a
Objectives	5	• Specific objectives and hypotheses	✓	3
Outcomes	6	• Clearly defined primary and secondary outcome measures	✓	4&5
		• Methods used to collect data and any methods used to enhance the quality of measurements	✓	4&5
		• Information on validated instruments such as psychometric and biometric properties	✓	4&5
Sample Size	7	• How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules		n/a
Assignment Method	8	• Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)		n/a
		• Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)		n/a
		• Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)	✓	4-5

TREND Statement Checklist

Blinding (masking)	9	• Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed.	✗	
Unit of Analysis	10	• Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community)	✓	4-5
		• If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)	✓	4-5
Statistical Methods	11	• Statistical methods used to compare study groups for primary methods outcome(s), including complex methods of correlated data	✓	5
		• Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis	✓	5
		• Methods for imputing missing data, if used		n/a
		• Statistical software or programs used	✓	5
Results				
Participant flow	12	• Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (a diagram is strongly recommended)	✓	6&Fig 2
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study	✓	6&Fig 2
		○ Assignment: the numbers of participants assigned to a study condition	✓	6&Fig 2
		○ Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention	✓	6&Fig 2
		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition		n/a
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition	✓	
		• Description of protocol deviations from study as planned, along with reasons		n/a
Recruitment	13	• Dates defining the periods of recruitment and follow-up		n/a
Baseline Data	14	• Baseline demographic and clinical characteristics of participants in each study condition	✓	6-7
		• Baseline characteristics for each study condition relevant to specific disease prevention research	✓	7
		• Baseline comparisons of those lost to follow-up and those retained, overall and by study condition		n/a
		• Comparison between study population at baseline and target population of interest	✓	6-7
Baseline equivalence	15	• Data on study group equivalence at baseline and statistical methods used to control for baseline differences	✓	6-7

TREND Statement Checklist

Numbers analyzed	16	• Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible		n/a
		• Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses		n/a
Outcomes and estimation	17	• For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	✔	7-9
		• Inclusion of null and negative findings	✔	6-8
		• Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any		n/a
Ancillary analyses	18	• Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	✔	9
Adverse events	19	• Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)		n/a
DISCUSSION				
Interpretation	20	• Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	✔	10
		• Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	✔	10-11
		• Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	✔	10-11
		• Discussion of research, programmatic, or policy implications	✔	11
Generalizability	21	• Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues	✔	10
Overall Evidence	22	• General interpretation of the results in the context of current evidence and current theory	✔	11

n/a= not applicable

From: Des Jarlais, D. C., Lyles, C., Crepaz, N., & the Trend Group (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. *American Journal of Public Health*, 94, 361-366. For more information, visit: http://www.cdc.gov/trendstatement/

4. Diskussion

4.1. Ökonomische Evaluation von nosokomialen Infektionen

Gesundheitsökonomische Evaluationen werden neben der medizinischen Wirksamkeit aufgrund der knappen Ressourcen im öffentlichen Gesundheitswesen in zunehmendem Maß verwendet. In der vorliegenden Dissertation wurden zunächst veröffentlichte gesundheitsökonomische Studien über Präventionsmaßnahmen zu nosokomialen Infektionen untersucht. Unsere Untersuchungen zeigen, dass Präventionsmaßnahmen zur Verhinderung von Krankenhausinfektionen sehr effizient sind. Die Anwendung ausreichender Hand-Hygiene kann nicht nur die Krankenhausinfektionsrate senken, sondern auch gesundheitsökonomisch überaus sinnvoll sein. Das hängt jedoch von vielen Voraussetzungen ab, die im Präventionsprogramm beachtet werden müssen. In der vorliegenden Arbeit wurden die meisten eingeschlossenen Studien zur Händedesinfektion auf Intensivstationen durchgeführt. Die Ergebnisse dieser Arbeit zeigen, dass Präventionsprogramme für alle nosokomialen Infektionen sehr gute Effekte ergeben. Das heißt, die multiplen Interventionen für nosokomiale Infektionen können in den meisten Fällen Anzahl der nosokomialen Infektionen signifikant reduzieren und positive Nutzen-Kosten-Verhältnis ausweisen. Darüber hinaus sind Interventionen mit kurzer Dauer kosteneffektiver. Die Qualität der gesundheitsökonomischen Studien ist gering und muss verbessert werden. Um dieses Ziel zu erreichen, sollte auch eine einheitliche Definition für nosokomiale Infektionen verwendet werden. Außerdem ist es wichtig, Leitlinien, die für die Standardisierung der gesundheitsökonomischen Evaluation definiert wurden, richtig anzuwenden.

Die Behandlung der Sepsis wird als eine der teuersten Erkrankungen in Krankenhäusern bezeichnet (Torio und Moore, 2016). Allerdings ist eine präzise Krankheitskosten-Analyse für Sepsis aufgrund der Kontroverse bezüglich Sepsisdefinition und Natur der Sepsis, welche typischerweise von Komorbiditäten wie Diabetes oder Pneumonie begleitet wird, sehr schwierig. Andererseits

berücksichtigen zahlreiche Studien zur Kostenbewertung der Sepsis nicht die richtigen gesundheitsökonomischen Prinzipien. Die Ergebnisse der vorliegenden Arbeit zeigen, dass bei der Kostenermittlung der nosokomialen Sepsis in vielen Studien nicht alle für die gewählte Perspektive relevanten Kosten, die nach den Empfehlungen der Leitlinien für gesundheitsökonomische Evaluationen berücksichtigen werden müssen, ermittelt werden. In der Kostenbewertung der nosokomialen Infektionen können verschiedene Perspektiven sinnvoll sein. Je nach Ziel der Studie kann Krankenkasse, Krankenhaus, Sozialversicherung oder eine andere Perspektive gewählt werden. Jedoch muss die Perspektivwahl immer begründet sein. Grundsätzlich sind die Kosten der nosokomialen Sepsis aufgrund aufwändiger Therapien und langer Krankenhausaufenthalte außerordentlich hoch. In der vorliegenden Arbeit wurde auch festgestellt, dass zwischen den Kosten der Sepsis und dem Studientyp, den verschiedenen Kostenperspektiven, den Methoden zur Kostenkalkulation, dem Schweregrad der Sepsis (Anzahl des Organversagens), der geographischen Region und der Altersklasse der Patienten eine Korrelation besteht. Außerdem wurde durch eine multiple lineare Regressions-Analyse das Verhältnis zwischen durchschnittlichen Krankenhauskosten der nosokomialen Sepsis pro Aufenthalt (als abhängige variable) und Charakteristika der Studien (als unabhängige Variabel) untersucht. Bei diesem multiplen linearen Regressionsmodell wurde die Kategorie Kinder (relativ zur Kategorie Erwachsene) als ein unabhängiger Faktor ($p<0,05$) nach Bereinigung um andere unabhängige Variablen identifiziert, die Einfluss auf die durchschnittlichen Krankenhauskosten der nosokomialen Sepsis pro Aufenthalt haben (Tabelle A1). Das heißt, die durchschnittlichen Krankenhauskosten der nosokomialen Sepsis für Kinder sind deutlich höher als die anderer Altersgruppen.

Aufgrund der Berücksichtigung der Zeitschrift und Gutachten wurden die Studien von 2005 bis 2015 in Publikation bewertet, aber tatsächlich wurden ebenfalls die Studien von Januar 1997 bis Dezember 2004 in der Recherche berücksichtigt. Diese Daten wurden extra analysiert. In diesem Zeitraum

wurden achtzehn Studien bezüglich nosokomialer Sepsis eingeschlossen. Nach Adjustierung der Kosten in 2014 US-Dollar wurden die Krankheitskosten der eingeschlossenen Studien hinsichtlich Perspektive der Kosten, verwendete Methoden für die Kostenkalkulation sowie der Schweregrad der Sepsis analysiert. Die Ergebnisse zeigen, dass der Median der durchschnittlichen Kosten der Sepsis pro Krankenhausaufenthalt (in Zeitraum 1997-2004) im Bereich 27.081$ (IQR: 12.632-39.884) liegt. Verglichen mit den Sepsis-Kosten im Zeitraum 2005 bis 2015 ist dieser deutlich niedriger (Tabelle A2). Die meisten Patienten mit Sepsis werden auf der Intensivstation (ITS) behandelt. Da die Behandlung auf der ITS aufgrund des höheren Ressourcenverbrauches, wie z.B. künstliche Beatmung sehr teuer ist, wurden die Kosten der nosokomialen Sepsis auf einer ITS in zahlreichen Studien untersucht. In der Periode von 1997-2004 haben vier Studien die durchschnittlichen ITS-Kosten pro Aufenthalt berechnet und haben gezeigt dass der Median dieser Kosten bei 23.590$ liegt. Dieser Wert ist deutlich niedriger als die Kosten im Zeitraum 2005-2015 (27.461$). Das heißt, die Behandlungskosten der nosokomialen Sepsis sind sowohl im gesamten Krankenhaus als auch auf den Intensivstationen angestiegen(Tabelle A3). Die ITS-Kosten pro Aufenthalt wurde in einer Studie (Edbrooke et al., 1999) als Median und in anderen Studien als durchschnittliche Kosten ausgegeben. Die Kosten für die Behandlung der nosokomialen Sepsis auf Intensivstationen pro Tag liegen zwischen 1.229$ und 4.160$ im Zeitraum 1997-2004. Hingegen im Vergleichszeitraum (2005-2015) pro Tag 1.737$ in Frankreich bis 4.651$ in den USA. Es scheint, dass die Behandlung der Sepsis weiterhin zu den kostenintensivsten Therapien der Intensivstationen gehört. Die Ergebnisse dieser Arbeit zeigen, dass die ITS-Kosten für Behandlung der nosokomialen Sepsis für Überlebende und nichtüberlebende Patienten in verschiedenen Ländern unterschiedlich sind (Tabelle A4). Durchschnittliche direkte Behandlungskosten für Patienten, welche die Sepsis nicht überleben, sind deutlich mehr als Überlebende. Hex et al. schätzten, dass 90% der Kosten von Sepsis indirekte Kosten sind (Hex et al., 2017). Aber nur eine Studie berechnete die indirekten Kosten der schweren

Sepsis in der Schweiz, mit jährlich zwischen 3.500 und 8.500 Fällen. Die gesamten indirekten Kosten betragen in der Schweiz zwischen 230,8 und 560,7 Millionen US-Dollar pro Jahr (Schmid et al., 2004). Die nosokomiale Infektionen können durch Erwerbsunfähigkeit sowie vorzeitigen Tod beim Humankapitalansatz zu hohen indirekten Kosten führen, welche aus gesellschaftlicher Sicht sehr wichtig sind und mehr in ökonomische Evaluationen beachtet werden muss.

Die Bedeutung der Händehygiene als wichtigster Faktor zur Prävention von nosokomialen Infektionen ist allgemein bekannt. In mehreren Studien wurde berichtet, dass die Einhaltung der Handhygiene durch verschiedene Interventionen erhöht und das Risiko einer nosokomialen Infektion reduziert werden kann (Allegranzi und Pittet, 2009). Jedoch wurde die Inzidenz von nosokomialen Infektionen in der Alerts-Studie nicht signifikant reduziert. Eine mögliche Ursache dafür kann sein, dass die Einhaltung der Händehygiene aufgrund hoher Arbeitsbelastung und Zeitmangels vernachlässigt wird (Erasmus et al., 2010, McGuckin et al., 2009). Hagel et al. berichteten, dass sich die Rate pro Mitarbeiter durch Monitoring von 8 auf 21 Händedesinfektionen pro Stunde erhöhen lässt (Hagel et al., 2015). Da in der Alerts-Studie die Händehygiene nicht permanent durch Dritte überprüft wurde, könnte dieser Hawthorne Bias die Durchführung der Händehygiene und damit die Ergebnisse beeinflusst haben. Ein weiterer möglicher Grund könnte auch in der Krankenhausumgebung liegen, die den Ausbruch nosokomialer Infektionen sowie die Übertragung von Krankheitserregern zur Entwicklung nosokomialer Infektionen beeinflussen kann. Zum Beispiel kann Barrierepflege die Übertragung von Krankheitserregern durch räumliche Trennung verringern oder eine gute Händehygieneinfrastruktur, wie die sichtbare Platzierung von Händehygienespendern, die Einhaltung der Händehygiene erhöhen (Steinberg et al., 2013). Jedoch wurde eine signifikante Reduzierung der Anzahl von Patienten mit schwerer Sepsis/septischem Schock in der zweiten Überwachungsperiode der Alerts-Studie beobachtet. Da ein hoher Anteil von Patienten mit nosokomialen Infektionen eine schwere Sepsis/septischen Schock entwickelt hat und

diese Patienten auf der Intensivstation behandelt werden, ist dieses als Erfolg zu werten. Durch ein Interventionsprogramm zur Verhinderung von nosokomialen Infektionen kann die Inzidenz von schwerer Sepsis/septischem Schock vermindert und damit auch die Mortalität und die Kosten der intensivmedizinischen Versorgung reduziert werden.

Eine wichtige Konsequenz der nosokomialen Infektionen ist längere Krankenhausverweildauer, welche nicht nur die Behandlungskosten sondern die Mortalitätsrate beeinflussen kann. In der vorliegenden Arbeit wurde den möglichen Zusammenhang zwischen Verweildauer und Sterblichkeit im Krankenhaus berechnet. Um das tägliche Risiko („Hazard") beim Erreichen des Endpunkts zu vergleichen, wurden sowohl in der ersten als auch in der zweiten Überwachungsperiode der Alerts-Studie „Cox-Proportional-Hazard-Modelle" (Beyersmann et al., 2014, Beyersmann et al., 2011) zwischen den beiden Patientengruppen (infizierte Patienten und nicht infizierte Patienten) verwendet. Die Endpunkte in der Analyse waren der Tod oder die Entlassung aus dem Krankenhaus. In diesem Cox-Modell wurden zeitabhängige Kovariaten eingegeben und der Infektionsstatus als zeitabhängige Variable eingeschlossen. Die Ergebnisse von Cox-Proportional-Hazard-Analysen für Tod und Entlassung in der ersten und zweiten Überwachungsperiode der Alerts-Studie zeigten ein signifikant erhöhtes Risiko für Tod im Krankenhaus bei Patienten mit nosokomialen Infektionen im Vergleich zu nicht-infizierten Patienten. Darüber hinaus reduzierten nosokomiale Infektionen aller Art sowohl in der ersten als auch in der zweiten Überwachungsperiode das Risiko der Entlassung des lebendigen Patienten aus dem Krankenhaus. Die Risikoquotienten („hazard Ratio") für die Entlassung waren unter 1, was darauf hindeutet, dass Patienten mit nosokomialen Infektionen eine längere Krankenhausaufenthaltsdauer haben und dass die zusätzliche Verweildauer das tägliche Sterblichkeitsrisiko erhöhte und Risikoquotienten für Mortalität von mehr als 1 zur Folge hatte. Der Risikoquotient für die Entlassung war am höchsten bei Patienten mit mehreren nosokomialen Infektionen-Episoden (Multiple) und war bei Patienten

mit Harnwegsinfektionen am niedrigsten (Tabelle A5). Abbildung A1 und Abbildung A2 zeigen die Ergebnisse des Nelson-Aalen-Schätzers der kumulativen Übergangswahrscheinlichkeits-Risikoquotient (Englisch: cumulative transition hazards) in absorbierende Zustände (Tod oder Entlassung) für die erste bzw. zweite Überwachungsperiode. Nosokomiale Infektionen erhöhen die Mortalität, weil sie die Gefahr einer Entlassung des lebendigen Patienten verringern und die Sterblichkeitsgefahr im Krankenhaus erhöhen.

In der vorliegenden Arbeit wurde die zusätzliche Verweildauer aufgrund jeder Art von nosokomialen Infektionen berechnet, wenn die Aufnahmen am Tag 45 künstlich rechtszensiert wurden, basierend auf der Annahme, dass ein Krankenhausaufenthalt von mehr als 45 Tagen nicht durch nosokomiale Infektionen verursacht werden konnte. Das Ziel dieser Analyse bestand darin, die Effekte von Rechtszensur in der Einschätzung der Verweildauerverlängerung von nosokomialen Infektionen mit Hilfe von Multistate-Modellen zu berechnen. Die Ergebnisse zeigen dass die Rechtszensur an Tag 45 im Multistate-Modell die Einschätzung der Verweildauerverlängerung weitgehend beeinflusste. Insgesamt verlängerten die nosokomialen Infektionen den Krankenhausaufenthalt um 7,71 (95%-CI: 7,03 - 8,39; SE: ± 0,34) zusätzliche Tage in der ersten Überwachungsperiode und 7,66 (95%-CI: 7,10 - 8,22; SE: ± 0,28) zusätzliche Tage in der zweiten Überwachungsperiode, in dem die Aufnahmen am Tag 45 rechtszensiert wurden (Tabelle 6).

Es gibt viele Untersuchungen über den Einfluss nosokomialer Infektionen auf die Verlängerung der Krankenhausverweildauer. Die Verweildauerverlängerung hängt dabei von der verwendeten Methode und den untersuchten Patienten ab und unterscheidet sich daher in den verschieden Studien. Um das Ausmaß der zusätzlichen Verweildauer bei nosokomialen Infektionen abzuschätzen, werden verschiedene Methoden in den Untersuchungen angewandt. Die zusätzliche Verweildauer bei nosokomialen Infektionen wird in den Studien oft durch den Vergleich der gesamten Verweildauer aller infizierten Patienten und der Verweildauer der nicht infizierten

Patienten gemessen. Dadurch wird aber die zusätzliche Verweildauer in der Regel überschätzt. Dieses Verfahren kann als einfacher Vergleich der Mittelwerte, als ein Multivariate Regression Model verwendet werden. Dabei kann ein sogenannter Time-dependent Bias auftreten, da der Zeitpunkt des Auftretens der Infektion nicht berücksichtigt wird (Barnett et al., 2011, Beyersmann et al., 2011). Eine andere Methode ist das sogenannte Matching-Verfahren. In der Literatur gibt es mehrere Studien mit Matching-Verfahren zur Ermittlung der zusätzlichen Verweildauer bei nosokomialen Infektionen. Die Matching-Kriterien sind jedoch sehr unterschiedlich. Meistens berücksichtigten sie die Entlassungsdiagnose, das Alter und Geschlecht der Patienten und/oder die Art der Erkrankungen (Kappstein et al., 1991). In manchen Studien mit Matching-Verfahren war zusätzlich gefordert, dass die Aufenthaltsdauer der Kontrollen (Patienten ohne nosokomiale Infektion) und der Fälle mit nosokomialer Infektion bis zum Auftreten der Infektion gleich lang zu sein hat. Dabei werden zu jedem Patienten, bei dem eine nosokomiale Infektion auftrat, ein oder mehrere Kontrollpatienten mit ähnlichen Faktoren gesucht. Ein wesentlicher Kritikpunkt an einem Matching-Verfahren ist die mögliche Verzerrung der Ergebnisse durch Selektions-Bias. Es gibt auch weitere Faktoren, die die Krankenhausverweildauer beeinflussen. Diese Faktoren können vermutlich selbst das Infektionsrisiko erhöhen und im Laufe der Zeit verschiedene Effektgrößen haben.

Ein weiterer potentieller Bias ergibt sich aus der Beziehung zwischen den Variablen nosokomiale Infektion und Verweildauer. Obwohl bekannt ist, dass die nosokomiale Infektion die Verweildauer erhöht, gibt es Hinweise, dass die Dauer des Aufenthalts auch das Risiko einer nosokomialen Infektion erhöht. Diese umgekehrte Kausalität induziert eine Korrelation zwischen den Fehlerbegriffen und den unabhängigen Variablen, was zu „verzerrten"-Schätzungen führt. Dieses Problem heißt „endogenen Variablen Bias". Die Kontrolle von Bias aus endogenen Variablen und die Interpretation der Ergebnisse eines unverzerrten Modells ist eine Herausforderung für die Forschung (Graves et al., 2005, Graves et al., 2007).

Zahlreiche Studien haben die Verweildauerverlängerung bei nosokomialen Infektionen mit verschiedenen Methoden berechnet, um die Unterschiede der Ergebnisse bzw. den vermutlichen Bias zu untersuchen. In der von Schulgen et al. veröffentlichten Studie (Schulgen et al., 2000) wurde die Verweildauerverlängerung aufgrund der postoperativen Wundinfektion am Universitätsklinikum Freiburg geschätzt. Die Ergebnisse zeigten, dass Patienten mit Wundinfektion 20,7 zusätzliche Tage im Krankenhaus verbrachten, wenn die Verweildauern infizierter und nicht infizierter Patienten mit konventioneller Methode verglichen wurde. Die Verweildauerverlängerung betrug 16,9 Tage mit einfachem Matching Verfahren, 11,4 Tage mit Zeit-Matching Methode und 9,8 Tage mit Multi-State Methode. In ihrer Studie wurde auch der Einfluss von Pneumonie auf die Verweildauer mit allen möglichen Verfahren geprüft. Mit Hilfe eines konventionellen Verfahrens war sie bei ITS-Patienten um 14,4 Tage verlängert, mit Hilfe eines einfachen Matching-Verfahrens um 12,3 Tage, mit Zeit-Matching um 8,2 und mit Multi-State Model um 3,4 Tage. Bei Roberts et al. (Roberts et al., 2010) wurde auch der Einfluss auf die Verweildauer von nosokomialen Infektionen mit Hilfe des Multi-State Modells und Matching-Verfahrens untersucht. Die extra Verweildauer betrug beim Multi-State Model 5,9 Tage und beim Matching-Verfahren 8,1 Tage. Bei Barnett et al. (Barnett et al., 2011) wurden die prospektiv gesammelten Daten aus einer Beobachtungstudie in Argentinien analysiert, um den time-dependent Bias zu zeigen. Die Verweildauerverlängerung aufgrund der nosokomialen Infektionen betrug 11,23 Tage beim Matching-Verfahren und nur 1,35 Tage im Multi-State Model. Schumacher et al. (Schumacher et al., 2013) untersuchten ITS-Patienten in Deutschland, um den Einfluss der nosokomialen Pneumonie auf die Krankenhausverweildauer abzuschätzen. Die Verlängerung der Verweildauer durch nosokomiale Pneumonie betrug in dieser Untersuchung 21,9 Tage nach konventionellem Verfahren, 11,3 Tage nach Matching Verfahren und 6,2 Tage nach Multi State Model. Das Ignorieren des Zeitpunktes des Auftretens der nosokomialen Infektion kann zu einer starken Überschätzung der zusätzlichen Verweildauer des Krankenhausaufenthaltes führen.

Unsere Studien zeigten, dass die Verweildauerverlängerung aufgrund multipler nosokomialer Infektionen im Vergleich zu einzelnen nosokomialen Infektionen sehr hoch ist. Verweildauerverlängerung aufgrund multipler nosokomialer Infektionen war im Vergleich zu postoperativen Wundinfektionen um das Zweifache höher und siebenfach höher als bei Harnwegsinfektionen. Das Ergebnis der vorliegenden Arbeit zeigt weiterhin, dass bei Abschätzung der Verweildauerverlängerung mit einem Multi-State Model auch die Fachabteilung der nosokomial infizierten und nicht infizierten Patienten berücksichtigt werden muss. Weiterhin sollte das sogenannte right-censoring (Rechtszensierung) beim Abschätzen der zusätzlichen Verweildauer durch ein Multi-State Model beachtet werden.

Durch die vorliegende Arbeit wurden die nosokomiale Infektionen ökonomisch bewertet. Nach Abschätzung der zusätzlichen Krankenhausverweildauer wurden die extra Aufenthaltstage aufgrund nosokomialer Infektionen mit ihrem wirtschaftlichen Wert bzw. den Kosten pro Bett-Tag multipliziert. Die Kosten pro Bett-Tag wurden anhand der Finanzdaten des Universitätsklinikums Jena berechnet und beruhten auf dem deutschen Diagnosis Related Groups-System (G-DRG). Die auf G-DRG basierenden Kosten pro Tag beinhalten die Kosten für Unterkunft, medizinische Behandlung, Laborverfahren, Material und Dienstleistungen sowie Arzt- und Krankenpflege. Die Kosten pro Bett-Tag wurden auf Abteilungsebene kalkuliert. Es wurden die Relativgewichte (RG) durch die Gesamtzahl der Krankenhausbett-Tage geteilt und dann mit dem Landesbasisfallwert (LBFW) für 2015 multipliziert.

$$BC_s = \frac{RG_s}{BT_s}.LBFW_t$$

BC_S bezeichnet die Bett-Tag-Kosten der Station s, RG_S bezeichnet die Relativgewichte der Station s, BT_S sind die gesamten Aufenthaltstage der Station s, und $LBFW_t$ ist der Landesbasisfallwert im Zeitraum t. Der Landesbasisfallwert ist ein monetärer Wert auf Landesebene, der jedes Jahr von den Landesverbänden der Krankenkassen und den Landeskrankenhausgesellschaften verhandelt wird

und als Basispreis für die Höhe der Erlöse einzelner DRG-Leistungen genutzt wird (Reimbursement Institute, o.D.-b). Der LBFW für Thüringen betrug 3.190,91€ im Jahr 2015 (AOK-Bundesverband, 2015). Das Institut für das Entgeltsystem im Krankenhaus (InEK) berechnet die Relativgewichte durch Division der Kosten einer DRG durch die InEK-Bezugsgröße. Das Institut berechnet die Werte für jede einzelne DRG durch Kostendaten, die von Kalkulationskrankenhäusern geliefert werden, jährlich. Die Kalkulationskrankenhäuser sind Krankenhäuser aus Deutschland, die die tatsächlich angefallenen Kosten für die einzelnen Fallpauschalen liefern (Reimbursement Institute, o.D.-a). Da die Bett-Tag-Kosten auf Intensivstationen im Vergleich zu Normalstationen wesentlich höher sind, wurden in dieser Arbeit die Bett-Tag-Kosten der Intensivstationen als einzelne Abteilung berechnet. Außerdem wurde angenommen, dass die Hälfte der Verweildauerverlängerung aufgrund nosokomialer Infektionen für Patienten, die sowohl auf der Normalstation als auch auf der Intensivstation behandelt wurden, der ITS zuzuordnen ist und die andere Hälfte der Normalstation. Die Kostenkalkulation erfolgte aus der Krankenkassen-Perspektive. Die durchschnittlichen Kosten für einen Aufenthaltstag am Universitätsklinikum Jena betrugen 724 € für eine Normalstation und 2.158 € für eine Intensivstation (Tabelle A7).

Für Patienten, deren nosokomiale Infektion in einer allgemeinen Abteilung behandelt wurde, beliefen sich die zusätzlichen Kosten (95% CI) in der ersten Überwachungsperiode auf 6.118 € (4.959 € - 7.276 €) und in der zweiten Überwachungsperiode auf 6.972 € (6.002 € - 7.942 €). Die zusätzlichen Kosten (95% CI) für die Patienten mit nosokomialer Infektion, die sowohl auf einer Normalstation als auch auf einer Intensivstation behandelt wurden, betrugen im ersten Überwachungszeitraum 11.658 € (9.035 € - 14.280 €) und im zweiten Überwachungszeitraum 10.534 € (8805 € - 12.263 €). Die höchsten Zusatzkosten (95% CI) pro Fall in Verbindung mit der Intensivstation betrugen im zweiten Überwachungszeitraum in der chirurgischen Abteilung 10.665 € (8.314 € - 13.016 €), die geringsten zusätzlichen Kosten 5.749 € (-1.851 € - 13.349 €) in der

geriatrischen Abteilung (Tabelle A8).

Es wurde weiterhin eine Robustheit der Analyse mit Hilfe der Sensitivitätsanalyse überprüft. In der Sensitivitätsanalyse werden die Opportunitätskosten von Bett-Tag auf Basis der publizierten Daten über die Zahlungsbereitschaft (willingness-to-pay; WTP) pro Bett auf Normalstation und für ein ITS-Bett neu berechnet (Stewardson et al., 2016). Die zusätzlichen Kosten für Patienten, die sowohl auf einer Normalstation als auch auf einer Intensivstation behandelt wurden, wurden auf Basis der *best-* und *worst-case*-Szenarien kalkuliert. In dem *Worst-Case*-Szenario wurde angenommen, dass die Patienten mit nosokomialen Infektionen nur einen Tag zusätzliche Verweildauer auf einer Normalstation hatten und die Resttage auf der ITS angefallen sind. Für *best-Case*-Szenario wurde das Gegenteil angenommen (nur ein Tag auf ITS). Die Ergebnisse der Sensitivitätsanalyse der zusätzlichen Kosten aufgrund nosokomialer Infektionen sind in Tabelle A9 für die erste und in Tabelle A10 für zweite Überwachungsperiode aufgeführt.

Die kalkulierten zusätzlichen Kosten gemäß der WTP waren deutlich weniger in Vergleich zu den zusätzlichen Kosten auf Basis der DRG. Es sollte hier berücksichtigt werden, dass die WTP berechneten Bett-Kosten niedriger sind als DRG, da WTP entweder durch eine Umfrage über den Betrag (für z.B. Bett-Tag), den die Befragten zu zahlen bereit sind (direkte Umfragen) oder durch verschiedene Optionen priorisieren (indirekte Umfragen) kalkuliert wird (Breidert et al., 2006). Die Ergebnisse der Sensitivitätsanalyse zeigen, dass die Kosten bezüglich der Verweildauerverlängerung im Worst-Case Szenario zweimal höher sind als die Kosten des Best-Case Szenario bzw. die Kosten für Normalstationen.

Das Schätzen der durch Krankenhausinfektionen verursachten Kosten ist schwierig. Obwohl viele Studien bezüglich der Kosten nosokomialen Infektionen durchgeführt wurden und direkte medizinische und nicht medizinische Kosten ermittelt wurden, ist die Übertragbarkeit dieser, meistens nordamerikanischer, Daten aufgrund der unterschiedlichen Gesundheitssysteme nicht ohne

weiteres auf europäische Verhältnisse möglich (Frank, 2006). In der Literatur liegen nur wenige Studien für Deutschland vor. Diese Studien haben unterschiedliche Methoden und Perspektiven in ihrer Analyse verwendet. Kappstein et al. (Kappstein et al., 1992) haben die ökonomischen Konsequenzen von nosokomialen Pneumonien bei beatmeten Patienten von Juli 1988 bis September 1989 auf den Intensivstationen des Universitätsklinikums Freiburg untersucht. In dieser Studie wurde eine mittlere zusätzliche Verweildauer von 10,13 Tagen und ein Mehraufwand von 8.800 US$ pro Patient ermittelt (Kappstein et al., 1992). Es wurde ein Matching-Verfahren in ihrer Verweildaueranalyse verwendet. Die zusätzlichen Kosten wurden durch Multiplizieren der durchschnittlichen Anzahl der zusätzlichen Tage mit den ITS Bettkosten pro Tag berechnet. In einer Fall-Kontrolle Studie (2005-2007) an der medizinischen Hochschule Hannover wurden für die MRSA- Pneumonie zurechenbare Kosten von 17.281€ pro Patient errechnet und es wurde von einer Unterdeckung ihrer durch DRG-System erzielten Erlöse um 11.701€ pro Patient berichtet (Ott et al., 2010). Die ökonomischen Aspekte der Sepsis sind auch in Deutschland untersucht worden. Greiner et al. (Greiner et al., 2007) haben in ihrer multizentrischen Studie die Kosten der nosokomialen Staphylococcus aureus-Sepsis bei Hämodialyse- Patienten von 1999 bis 2005 betrachtet. Es wurden Behandlungskosten in Höhe von 17.157€ nach DRG-Erlösen errechnet (Greiner et al., 2007). In der Leistner et al. Studie wurden die direkten Kosten der durch zentralvenöse Katheter (ZVK)-assoziierten Sepsis von Januar bis Dezember 2010 am Universitätsklinikum Charité Berlin abgeschätzt. Die zusätzlichen Kosten betrugen 29.909 € pro infizierten Fall und sieben zusätzliche Behandlungstage (Leistner et al., 2014). In einer anderen Studie von Leistner et al. wurde geschätzt, dass ITS-Patienten mit einer beatmungsassoziierten tiefen Atemwegsinfektion einen um 9 Tage längeren Krankenhausaufenthalt aufweisen und zusätzliche Kosten von insgesamt circa 17.000 € entstehen (Leistner et al., 2013). Ehlken et al. haben in ihrer multizentrischen Studie (1999-2001) die direkten Kosten von nosokomialen Harnwegsinfektion bei Kindern in Deutschland mit 2.814 €

geschätzt (Ehlken et al., 2005). Vonberg et al. konnte zeigen, dass Patienten mit Harnwegsinfekten eine durchschnittlich vier Tage längere Verweildauer haben und zusätzliche Kosten von etwa 1.000 € produzieren (Vonberg et al., 2008a). Eine weitere Studie aus Hannover kam zu dem Ergebnis, dass Patienten aufgrund einer nosokomialen *Clostridium difficile* Infektion 7 Tage länger im Krankenhaus verweilen (Vonberg et al., 2008b). Die ökonomischen Kosten der nosokomialen Infektionen unterschieden sich von Studie zu Studie aufgrund der verwendeten Methoden zur Kostenabschätzung, unterschiedlicher Kostenperspektiven, Art der Infektionen und unterschiedlicher Patientenkollektive. Unsere Studien zeigten, dass die zusätzlichen Kosten pro nosokomial infizierten Patienten auf Intensivstationen circa zweimal höher sind als auf einer Normalstation. Allein das Universitätsklinikum Jena hat geschätzt bis zu 10 Mio. € zusätzliche Kosten pro Jahr aufgrund der durch die nosokomialen Infektionen verursachten Verweildauerverlängerung.

Zusammenfassend kann festgestellt werden, dass nosokomiale Infektionen weiterhin ein großes Problem im Gesundheitswesen darstellen, einen erheblichen Einfluss auf die Mortalität der betroffenen Patienten haben und die Verweildauer des Krankenhausaufenthaltes verlängern. Sie erhöhen das Risiko der Krankenhaussterblichkeit und die Kosten der Behandlungen. Aufgrund des ansteigenden Durchschnittsalters der Bevölkerung in Deutschland und die notwendige steigende medizinische Versorgung benötigen immer mehr Menschen Kontakt zu medizinischen Einrichtungen. Damit könnte die Häufigkeit der nosokomialen Infektionen noch zunehmen. Deshalb sollten Maßnahmen zur Reduktion der nosokomialen Infektionen weiterhin eine hohe Priorität haben. Die starke ökonomische und gesundheitliche Belastung durch nosokomiale Infektionen muss dazu führen, national die Aufmerksamkeit auf Präventionsprogramme zu lenken und die Eindämmung der nosokomialen Infektionen zu verstärken. Aus gesundheitsökonomischen Gründen muss die Aus- und Weiterbildung in der modernen Krankenhaushygiene unbedingt

verbessert werden.

Fazit ist, dass die meisten Maßnahmen von Präventionsprogrammen zur Verhinderung von nosokomialen Infektionen effizient sind. Insbesondere die Übertragung von Person zur Person kann durch ein passendes Präventionsprogramm reduziert werden. Die Durchführung der regelmäßigen und sorgfältigen hygienischen Händedesinfektionen ist auch heute eine der wichtigsten Maßnahmen zur Prävention nosokomialer Infektionen und kann darüber hinaus die Verweildauerverlängerung aufgrund nosokomialer Infektionen verkürzen. Da die Versorgungen in den Intensivstationen sehr kostenintensiv sind, können die Behandlungskosten so reduziert werden. Weiterhin wurde gezeigt, dass Mortalität, zusätzliche Verweildauer und die damit verbundenen Kosten aufgrund nosokomialer Infektionen von der Fachabteilung des Krankenhauses abhängig sind.

5. Zusammenfassung

In der vorliegenden Arbeit wurden gesundheitsökonomische Evaluationen nosokomialer Infektionen durchgeführt. Nosokomiale Infektionen sind ein großes Problem im Gesundheitswesen aufgrund ihrer hohen Morbidität und Mortalität sowie den hohen Folgekosten. Präventionsprogramme der nosokomialen Infektionen sind daher wichtige Aspekte für die Patientensicherheit im Krankenhaus und sollten aufgrund der Begrenztheit der Ressourcen im Gesundheitssystem effizient sein. Gesundheitsökonomische Evaluationen können in diesem Zusammenhang den Gesundheits-managern und Entscheidungsträgern wichtige Informationen geben, die als Grundlage für eine rationale Ressourcenallokation verwendet werden können. Ziel dieser Arbeit war es daher, die Effizienz von Präventionsmaßnahmen zur Vermeidung nosokomialer Infektionen zu beurteilen und ökonomische Aspekte der Sepsis hinsichtlich verschiedener Kostenperspektiven zu analysieren. Weitere Fragestellungen waren die Qualität der gesundheitsökonomischen Evaluationen bei nosokomialer Infektionen sowie die Verweildauerverlängerung und die damit verbundenen Kosten bei nosokomialen Patienten am Universitätsklinikum Jena. Darüber hinaus wurde auch die Verlängerung der Verweildauer im Krankenhaus und die ökonomische Belastungen der postoperativen Wundinfektion nach Koronararterien-Bypass-Chirurgie (CABG) ermittelt und der Effekt eines krankenhausweiten Präventionsprogramms mit u.a. Förderung der hygienischen Händedesinfektion zur Verhinderung nosokomialer Infektionen auf Sterblichkeit, Verweildauer und Kosten beurteilt. Dabei wurde die Sterblichkeit mit einer „Compating risk"-Analyse, die Verweildauerverlängerung mit einem Multistate-Modells und die Kosten mit Hilfe des deutschen DRG-Systems berechnet.

Die meisten Präventionsprogramme zur Verhinderung von nosokomialen Infektionen erwiesen sich in den verschiedenen Studien als effizient. Jeder für ein Präventionsprogramm eingesetzte Dollar ergab eine Ersparnis von sieben Dollar. Die Studien, die verschiedene nosokomiale Infektionsarten

in ihrem Infektionspräventionsprogramm berücksichtigten, errechneten ein höheres „Saving to cost"-Verhältnis im Vergleich zur Studien, die sich auf einen einzigen Typ beziehen. Anzumerken ist auch, dass insbesondere bei Krankheitskosten-Analyse verschiedene Aspekte wie z.B. Perspektive der Kosten, Kostenkomponenten, etc. beachtet werden müssen, da sie wesentliche Einflüsse auf die Ergebnisse haben. Folglich zeigten die Auswertungen, dass Schätzungen der krankenhausrelevanten Kosten der Sepsis zwischen den Studien je nach der Methode zur Kostenberechnung, Art der Sepsis und der untersuchten Population erheblich variierten. Dabei waren die durchschnittlichen Krankenhauskosten der Sepsis für Kinder erheblich höher als für andere Altersgruppen. Ergebnisse von Cox-Proportional-Hazard-Analysen für Tod und Entlassung zeigten ein signifikant erhöhtes Risiko („Hazard ratio") zu sterben bei Patienten mit nosokomialen Infektionen. Die Verweildauerverlängerung multipler nosokomialer Infektionen war im Vergleich zur Verweildauerverlängerung aufgrund von nur einer Wundinfektionen zweimal höher und sogar siebenmal höher als die Verweildauerverlängerung, die durch eine Harnwegsinfektion verursacht wurde. Postoperative Wundinfektionen nach Koronararterien-Bypass-Chirurgie verlängern die Aufenthaltsdauer im Krankenhaus um insgesamt neun Tage, postoperative tiefe Wundinfektionen und Infektionen von Organen und Körperhöhlen im Operationsgebiet nach CABG verzeichnen einen wesentlich höheren Antibiotikaverbrauch, vermehrte V. A. C. Therapie sowie erhöhte Verweildauer und Behandlungskosten im Vergleich zu den oberflächlichen Wundinfektionen. Die Inzidenz von nosokomialen Infektionen konnte durch Präventionsprogramme im Universitäts-klinikum Jena leider nicht reduziert werden, aber es gelang die Verweildauerverlängerung durch Harnwegsinfektionen signifikant zu vermindern. Darüber hinaus wurden die Kosten aufgrund nosokomialer Infektionen auf Intensivstationen um ca. 1.100 € pro infiziertem Patienten reduziert.

Allgemein ist kritisch anzumerken, dass die Qualität der bisher publizierten gesundheitsökomischen Studien oft mangelhaft ist und dringend verbessert werden muss. Nur dann können sie den

Entscheidungsträgern in der Gesundheitsversorgung sowie den Ärzten bessere Informationen zur optimalen Ressourcenallokation zur Verfügung stellen.

6. Abstract

In the present thesis, health economic evaluations of Healthcare-associated infections (HAIs) were performed from different aspects. HAIs are a serious public health problem and have substantial effects on morbidity and mortality with a huge economic burden for every healthcare system. Prevention programs of HAIs are a key aspect for patient safety in hospital. Because of the limitation of resources in health care, prevention interventions should be efficient. Health economic evaluation can help healthcare managers and decision maker to allocate resources in an efficient way. This thesis examined the efficiency of prevention programs for HAIs and analyzed the economic burden of sepsis based on various cost perspectives. Further questions were the quality of health economic evaluation of HAIs as well as the prolongation of length of stay (LOS) and associated costs attributable to HAIs in Jena University Hospital. In addition, the extra costs and LOS due to surgical site infections after coronary artery bypass grafting (CABG) were determined and the effect of a hospital-wide prevention program regarding hand-hygiene promotion etc. for specific HAIs on mortality, additional LOS and economic costs were calculated. A multistate model was used to estimate additional LOS, additional costs were calculated using average per diem costs based on German-DRG reimbursement scheme and a "Competing risk" analysis were used for the estimation of the effect of HAI on mortality.

Most prevention programs for HAIs were reported as statistically efficacious in many studies. Our analysis shows that these interventions have a significant economic benefit. The median saving-to-cost ratio was about seven US dollar. Interventions targeting several types of HAIs were associated with higher economic benefits than prevention interventions for a single type of infection. It should be noted that in health economic evaluation, in particular cost-of-illness analysis, must be taken into account the various aspects, such as the perspective of costs, cost components, etc., which have significant effects on results. The results showed that estimates of the hospital-related costs of sepsis

varied considerably across the included studies depending on the method used for cost calculation, the type of sepsis and the population that was examined. The costs of sepsis were considerably higher for children than for other participants. The results of cox proportional hazards analyses for death and discharge alive showed a significantly increased hazard of hospital death for patients with HAIs as compared with non-infected patients. Prolongation of LOS due to multiple HAIs was two times greater than that due to SSI and seven times greater than that the LOS due to urinary tract infection (UTI). Surgical site infections (SSIs) after coronary artery bypass grafting (CABG) extend the length of stay of nine days. Deep incisional SSI and organ/space SSI after CABG showed significantly higher antibiotic consumption, V.A.C. therapy, LOS and treatment costs compared to superficial wound infection. Although, the incidence of HAIs did not differ significantly after the intervention prevention program in Jena University Hospital, the length of stay due to UTI was significantly reduced. In addition, extra costs due to HAIs in intensive care units were reduced by approximately 1100 Euro per infected patient.

It should be noted that the overall quality of published studies on health economic evaluation and cost analysis of HAIs is poor based on published quality criteria for economic evaluations. Therefore, the quality of economic studies has to be improved to provide better information to healthcare policy makers and clinicians.

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8. Anhang

Tabelle A1. Multiple lineare Regressionsanalyse für durchschnittliche Krankenhauskosten der nosokomialen Sepsis pro Aufenthalt in 2014 US-Dollar.

unabhängige Variablen	durchschnittliche Krankenhaus Kosten pro Aufenthalt	
	Koeffizient (95 % CI) [US $]	**p-Wert**
Geographische Region der Studien		
Vereinigte Staaten/Kanada	Ref.	
Asien	-19.954 (-58.740 — 18.833)	0,292
Europa	5.290 (-12.251 — 22.832)	0,532
Südamerika	-8.962 (-47.748 — 29.825)	0,631
Altersklasse der Patienten		
Erwachsene	Ref.	
Kinder	45.026 (13.481 — 76.571)	0,007
Nicht festgelegt	8.378 (-8.810 — 25.565)	0,318
Anzahl der Patienten		
>5000	Ref.	
≤100	5.495 (-1.5815 — 26.806)	0,591
101-500	-14.576 (-37.388 — 8.235)	0,193
501-1000	-422 (-29.604 — 28.758)	0,976
1001-5000	-13.391(-42.573 — 15.789)	0,344
Schweregrad der Sepsis		
Schwere Sepsis	Ref.	
Sepsis	1.744 (-40.302 — 43.791)	0,929
Septischer Shock	-10.255 (-41.790 — 21.280)	0,495
Septikämie	-14.890 (-46.425 — 16.645)	0,326
Schwere Sepsis & Septischer Shock	7.238 (-17.414 — 31.890)	0,536
Sepsis & schwere Sepsis & septischer Shock	2.047 (-25.094 — 29.187)	0,873
Schwere Sepsis & Septikämie	-20.821 (-62.867 — 21.225)	0,304
Kostenperspektiven		
Gesundheitsdienstleister	Ref.	
Zahlungspflichtige	2.510 (-15.468 — 20.488)	0,773
Studientyp		
Retrospektive	Ref.	
Prospektive	-15.705 (-33.328 — 1.918)	0,077
Mix Model	-5.274 (-27.890 — 17.343)	0,629

CI= Konfidenz Intervall

Tabelle A2. Durchschnittliche gesamte Krankenhauskosten der nosokomialen Sepsis pro Aufenthalt in 2014 US-Dollar (Periode Jan.1997 - Dez.2004).

Studien	Länder	schwergrad der Sepsis	Perspektiven	Gesamte Kosten (± SD) [$]	Überlebende (± SD) [$]	nicht-Überlebende (± SD) [$]
(Angus et al., 2001)	USA	Schwere Sepsis	Leistungserbringer *	30.233	28.181	35.431
(Angus et al., 2003)	USA	Schwere Sepsis	Gesellschaft	48.172	54.168	35.576
(Baine et al., 2001)	USA	Septikämie	Leistungserbringer *	11.363 (±11.749)	—	—
(Bates et al., 2003)	USA	Sepsis	Leistungserbringer *	77.476 (± 1.058)	73.670 (±1.095)	110.363 (±5.630)
(Braun et al., 2004)	USA	Schwere Sepsis	Zahlungspflichtige	34.437 (±71.776)	31.185	46.997
(Brun-Buisson et al., 2003)	Frankreich	mix Θ	Leistungserbringer	37.121 (±35.053)	43.000 (±31.040)	33.762 (±37.164)
(Letarte et al., 2002)	Kanada	Schwere Sepsis	Gesellschaft	14.733	20.837	9.738
(Neilson et al., 2003)	Deutschland	Schwere Sepsis	Zahlungspflichtige	23.929	—	—
(Watson et al., 2003)	USA	Schwere Sepsis	Leistungserbringer *	59.330	56.985	80.364
(Weycker et al., 2003)	USA	Schwere Sepsis	Leistungserbringer *	57.266 (±770)	—	—
(Williams et al., 2004)	USA	Schwere Sepsis	Leistungserbringer *	34.140 (±44.233)	—	—
(Yu et al., 2003)	USA	Schwere Sepsis	Leistungserbringer *	130.550 (±193.806)	—	—

SD= Standardabweichung; * Vermutliche Perspektiven von Kosten; Θ Sepsis + Schwere Sepsis + septischer schock

Tabelle A3. ITS-kosten der nosokomialen Sepsis pro Aufenthalt in 2014 US-Dollar (Periode Jan.1997 - Dez.2004).

Studien	Länder	schwergrad der Sepsis	Perspektiven	Gesamte Kosten (± SD oder IQR) [$]	Überlebende (± SD) [$]	nicht-Überlebende (± SD) [$]
(Edbrooke et al., 1999)	UK	Schwere Sepsis & septischer schock	Leistungserbringer	13.884# (4.750-26.850)	—	—
(Jacobson et al., 2004)	Sweden	mix Θ	Leistungserbringer *	38.427	51.025	—
(Moerer et al., 2002)	Deutschland	Schwere Sepsis	Leistungserbringer	31.110 (±24.879)	29.356	33.979
(Neilson et al., 2003)	Deutschland	Schwere Sepsis	Zahlungspflichtige	18.546	—	—
(Schmid et al., 2004)	Switzerland	Schwere Sepsis	Gesellschaft	28.636 (±22.765)	25.873 (±18.679)	31.491 (±26.357)

ITS= Intensiv Station; SD= Standardabweichung;
# median kosten; * Vermutliche Perspektiven von Kosten; Θ Sepsis + Schwere Sepsis + septischer schock

Tabelle A4. ITS-kosten der nosokomialen Sepsis pro Tag in 2014 US-Dollar (Periode Jan.1997 - Dez.2004).

Studien	Länder	schwergrad der Sepsis	Perspektiven	Gesamte Kosten (± SD) [$]	Überlebende [$]	nicht-Überlebende[$]
(Edbrooke et al., 1999)	UK	Schwere Sepsis & septischer schock	Leistungserbringer	1.229#	—	—
(Jacobson et al., 2004)	Sweden	mix Θ	Leistungserbringer *	4.161	—	—
(Moerer et al., 2002)	Deutschland	Schwere Sepsis	Leistungserbringer	—	1.552	2.202
(Schmid et al., 2004)	Switzerland	Schwere Sepsis	Gesellschaft	2.223 (±519)	2.057	2.385

ITS= Intensiv Station; SD= Standardabweichung;
# median kosten; * Vermutliche Perspektiven von Kosten; Θ Sepsis + Schwere Sepsis + septischer schock

Tabelle A5. Die Ergebnisse der Proportional-Hazards-Modelle für die Krankenhaussterblichkeit und Entlassung am Leben

Comparison	Überwachungsperiode 1		Überwachungsperiode 2	
	Mortalität HR (95% CI)	Entlassung am Leben HR (95% CI)	Mortalität HR (95% CI)	Entlassung am Leben HR (95% CI)
WI gg. nicht-infizierte	1,32 (0,93 – 1,87)	0,41 (0,36 – 0,46)	1,32 (0,76 – 1,68)	0,42 (0,37 – 0,47)
LRTI gg. nicht-infizierte	3,87 (2,98 – 5,04)	0,37 (0,32 – 0,43)	3,88 (3,02 – 4,98)	0,37 (0,33 – 0,42)
HWI gg. nicht-infizierte	1,33 (0,63 – 2,82)	0,69 (0,56 – 0,85)	1,44 (0,80 – 2,56)	0,63 (0,54 – 0,74)
CDI gg. nicht-infizierte	2,17 (1,24 – 3,81)	0,61 (0,49 – 0,77)	2,40 (1,34 – 4,30)	0,56 (0,45 – 0,71)
Primäre Sepsis gg. nicht-infizierte	1,58 (0,91 – 2,73)	0,45 (0,36 – 0,56)	2,75 (1,82 – 4,13)	0,45 (0,37 – 0,54)
Andere gg. nicht-infizierte	2,65 (1,57 – 4,47)	0,58 (0,45 – 0,73)	3,21 (2,02 – 5,09)	0,48 (0,38 – 0,59)
Multiple gg. nicht-infizierte	1,67 (1,27 – 2,19)	0,24 (0,21 – 0,28)	2,18 (1,72 – 2,77)	0,20 (0,18 – 0,23)
Total gg. nicht-infizierte	2,23 (1,87 – 2,68)	0,39 (0,37 – 0,42)	2,78 (2,35 – 3,29)	0,36 (0,34 – 0,39)

CI, Konfidenz Interval; HR, hazard ratio; WI, Wundinfektion; LRTI, Infektion der unteren Atemwege; HWI, Harnweginfektion; CDI, *Clostridium diffizile* infektion.

Tabelle A6. Ergebnisse der Einschätzung der zusätzlichen Verweildauer mit Multistate-Modell (Rechtszensur an Tag 45)

	Überwachungsperiode 1	**Überwachungsperiode 2**	**p-Value**
	Verweildauerverlängerung in Tage (95% CI)	*Verweildauerverlängerung in Tage (95% CI)*	
Wundinfektion	7,45 (6,03 – 8,87)	6,91 (5,63 – 8,19)	0,5721
Infektion der unteren Atemwege	7,40 (6,04 – 8,76)	7,98 (6,94 – 9,02)	0,4981
Harnwegsinfektionen	3,63 (1,79 – 5,47)	4,60 (3,28 – 5,92)	0,3916
Clostridium diffizile Infektion	4,90 (2,66 – 7,14)	7,04 (4,62 – 9,46)	0,1943
Primäre Sepsis	7,77 (5,45 -10,09)	6,77 (4,87 – 8,67)	0,5048
Andere Infektionen	5,34 (2,92 – 7,76)	3,39 (1,33 – 5,45)	0,2197
Multiple Infektionen	14,70 (12,96 – 16,44)	13,53 (12,29 – 14,77)	0,2734
Total	7,71 (7,03 – 8,39)	7,66 (7,10 – 8,22)	0,9096

CI, Konfidenz Interval

Tabelle A7. Kosten des Krankenhausaufenthaltes pro Bett-Tag am Universitätsklinikum Jena.

Department	Relativgewicht [€]	Bett-tage	RG/BT	Kosten pro Bett-Tag [€]
Chirurgie	17.621	79.322	0,222	709
Geriatrie	1.133	12.983	0,087	278
Gynäkologie	2.135	10.655	0,200	639
Innere Medizin	20.622	112.464	0,183	585
Neurologie	4.096	22.282	0,184	587
Intensivstationen	12.587	18.612	0,676	2.158
Total normal-stationen	58.194	256.318	0,227	724

Tabelle A8. Zusätzliche Kosten aufgrund nosokomialer Infektionen nach Abteilungen (Zeilen) und Überwachungszeitraum (Spalten).

Model	**Extra costs (95% CI)[€];**		**Extra costs (95% CI)[€];**	
	Aufenthalt ausschließlich in einer allgemeinen Station		**Aufenthalt sowohl in einer allgemeinen Station als auch einer Intensivstation**	
	Überwachungsperiode 1	*Überwachungsperiode 2*	*Überwachungsperiode 1*	*Überwachungsperiode 2*
Chirurgie	4.609 (2.283 – 6.934)	7.714 (5.162 – 10.266)	10,723 (7,483 – 13,962)	10,665 (8,314 – 13,016)
Geriatrie	1.462 (450 – 2.474)	1.913 (1.173 – 2.652)	10,524 (1,851 – 19,196)	5,749 (-1,851 – 13,349)
Gynäkologie	4.256 (486– 8.026)	5.860 (1.719 – 10.000)	15,831 (5,314 – 26,348)	6,769 (867 – 12,670)
Innere Medizin	5.171 (3.931 – 6.412)	4.657 (3.697 – 5.616)	15,100 (9,395 – 20,806)	8,736 (5,527 – 11,946)
Neurologie	12.491 (2.043 – 22.940)	4.819 (2.777 – 6.862)	9,484 (4,570 – 14,398)	10,088 (6,574 – 13,601)
Total	6.118 (4.959 – 7.276)	6.972 (6.002 – 7.942)	11,658 (9,035 – 14,280)	10,534 (8,805 – 12,263)

CI, Konfidenz Intervall.

Tabelle A9. Sensitivitätsanalyse der zusätzlichen Kosten aufgrund nosokomialer Infektionen in der ersten Überwachungsperiode

Model	**allgemein Station**	**Allgemein- und Intensivstation**	
		best case	*worst case*
Chirurgie	475 (235 – 714)	665 (500 – 830)	1.317 (883 – 1.751)
Geriatrie	384 (118 – 650)	750 (230 – 1.269)	1.540 (173 – 2.907)
Gynäkologie	486 (55 – 917)	945 (396 – 1.494)	2.054 (611 – 3.498)
Innere Medizin	645 (491 – 800)	923 (619 – 1.226)	1.995 (1.196 – 2.794)
Neurologie	1.553 (254 – 2.853)	623 (362 – 885)	1.208 (520 – 1.895)
Total	617 (500 – 734)	710 (577 – 842)	1.434 (1.085 – 1.784)

Tabelle A10. Sensitivitätsanalyse der zusätzlichen Kosten aufgrund nosokomialer Infektionen in der zweiten Überwachungsperiode

Model	**allgemein Station**	**Allgemein- und Intensivstation**	
		best case	*worst case*
Chirurgie	794 (531 – 1.057)	662 (542 – 782)	1.309 (995 – 1.624)
Geriatrie	502 (308 – 696)	464 (-230 – 919)	787 (-173 – 1.985)
Gynäkologie	669 (196 – 1.142)	472 (45 – 780)	810 (119 – 1.621)
Innere Medizin	581 (461 – 701)	584 (413 – 755)	1.104 (655 – 1.553)
Neurologie	599 (345 – 853)	656 (469 – 842)	1.292 (801 – 1.784)
Total	703 (605 – 801)	653 (565 –740)	1.285 (1.054 – 1.515)

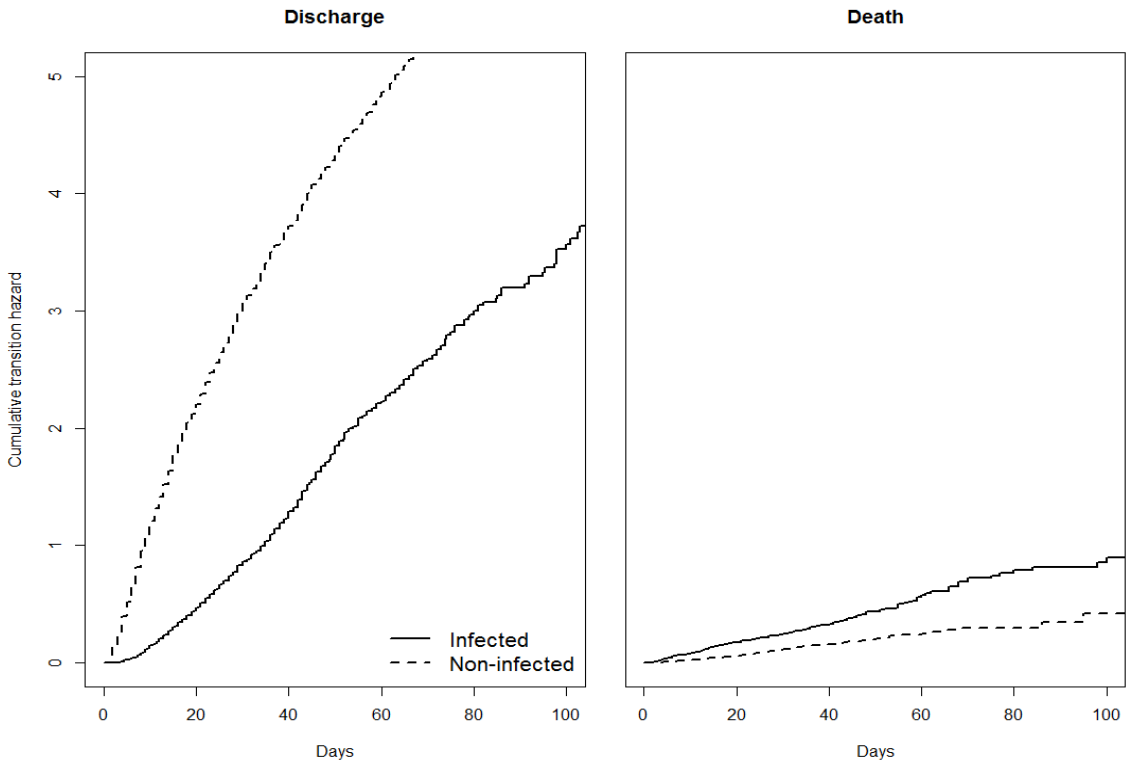

Abbildung A1. Die Ergebnisse der Nelson-Aalen Schätzer für kumulative Übergangswahrscheinlichkeit Risikoquotient von Entlassung (links) und Tod (rechts) für Patienten in Überwachungsperiode 1.

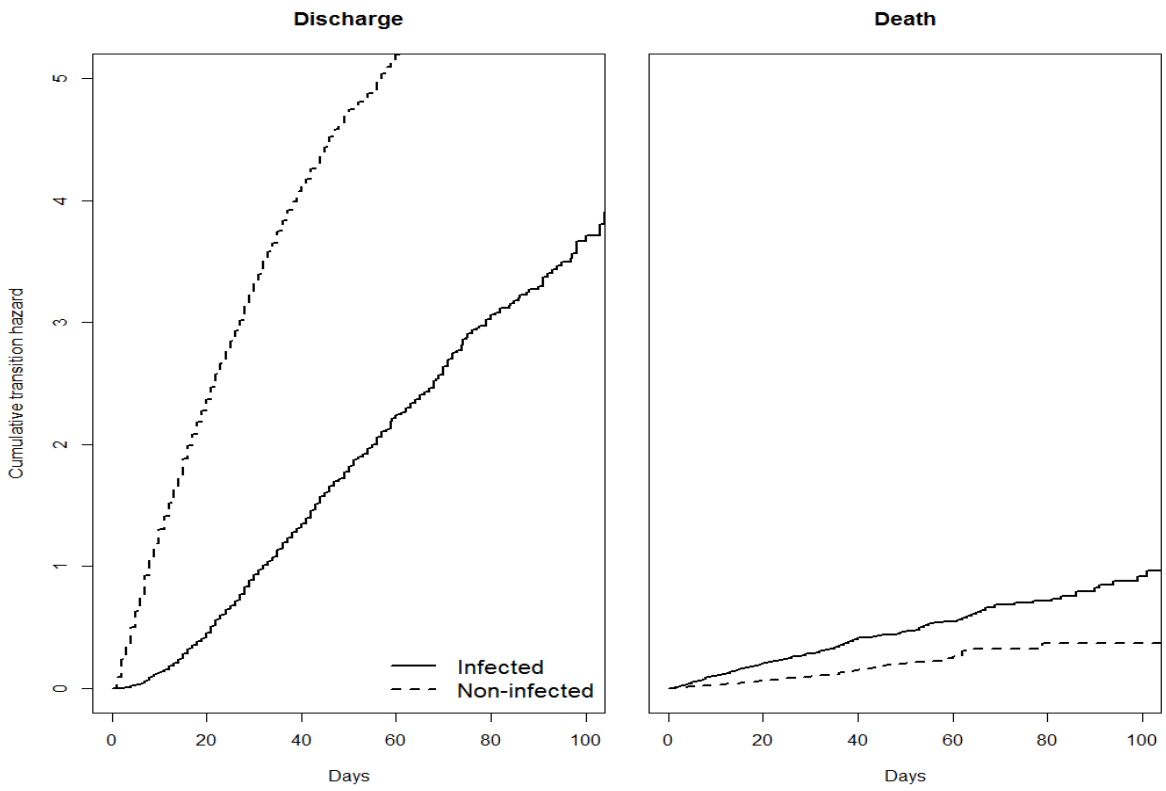

Abbildung A2. Die Ergebnisse der Nelson-Aalen Schätzer für kumulative Übergangswahrscheinlichkeit Risikoquotient von Entlassung (links) und Tod (rechts) für Patienten in Überwachungsperiode 2.

Eigenständigkeitserklärung

Hiermit erkläre ich, Habibollah Arefian, geboren am 31.05.1982 in Noshahr, dass mir die geltende Promotionsordnung der Fakultät für Biowissenschaft der Friedrich-Schiller-Universität Jena bekannt ist. Ich habe die vorliegende Arbeit selbständig angefertigt, keine Textabschnitte eines Dritten oder eigener Prüfungsarbeiten ohne Kennzeichnung übernommen und alle benutzen Hilfsmittel, persönliche Mitteilungen und Quellen in der Arbeit angegeben. Die in den Manuskripten angegebenen Personen haben mich lediglich bei der Auswahl und der Auswertung des Materials sowie bei der Erstellung der Manuskripte unterstützt. Ich habe weder die Hilfe eines Promotionsberaters in Anspruch genommen, noch unmittelbar oder mittelbar geldwerte Leistungen in Zusammenhang mit dem Inhalt meiner Dissertation an Dritte erbracht. Ich habe diese Dissertation noch nicht als Prüfungsarbeit für eine staatliche oder andere wissenschaftliche Prüfung eingereicht. Ich habe weder die gleiche oder eine in wesentlichen Teilen ähnliche, noch eine andere Abhandlung bei einer anderen Hochschule als Dissertation eingereicht.

Habibollah Arefian

Jena, den .....

Curriculum vitae

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Publikationen und Kongress Beiträge

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