FINAL REPORT

Estimating the Additional Hospital Inpatient Cost and Mortality Associated With Selected Hospital-Acquired Conditions

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PATIENT SAFETY

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Summary

Despite advancements in infection control and injury prevention, hospital-acquired conditions (HACs) continue to have a high financial burden on the health care system and contribute significantly to inpatient morbidity and mortality in the United States. Multiple Federal initiatives in patient safety highlight the need for better understanding of additional cost and excess mortality due to HACs, including the U.S. Department of Health and Human Services (HHS) National Quality Strategy,[1,2] the National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination,[3] and the National Action Plan for Adverse Drug Event Prevention.[4] Several efforts are underway at the Agency for Healthcare Research and Quality (AHRQ),Centers for Medicare & Medicaid Services (CMS), and the Centers for Disease Control and Prevention (CDC) to target and reduce the incidence of HACs through implementation of evidence-based strategies and better measurement and reporting. Federal agencies are leading significant efforts in these areas: for example, the public-private Partnership for Patients (PfP),[5] AHRQ's Comprehensive Unit-Based Safety Programs (CUSP), [6] National Scorecard for HACs,[7] Quality and Safety Review System (QSRS), [8] and CMS' HAC Reduction Program related to payment reform.[9]

The goal of this project, conducted by NORC at the University of Chicago (NORC) in partnership with Emory University, on behalf of AHRQ, is to estimate the excess cost and mortality associated with 10 HACs being targeted for improvement:

1. Adverse Drug Events (anticoagulants, opioids, and hypoglycemic agents)
2. Catheter-Associated Urinary Tract Infections
3. Central Line-Associated Bloodstream Infections
4. Falls
5. Obstetric Adverse Events
6. Pressure Ulcers
7. Surgical Site Infections
8. Ventilator Associated Pneumonia
9. Venous Thromboembolism
10. *Clostridium difficile* Infections

In this report, we present the findings of our literature review of empirical research on additional cost and excess mortality for the 10 HACs listed above. For this review, we used 69 studies in 20 individual meta-analyses to estimate the additional cost and excess mortality associated with each of the HACs on a per-HAC basis. Estimated added costs across all HACs ranged from $600 to $48,000 per case, while excess mortality estimates ranged from 5 deaths per 1,000 cases to 150 deaths per 1,000 cases. These values will assist Federal efforts to track progress on improving patient safety and eliminating HACs.

Introduction

The goal of this project is to generate updated, robust estimates of the excess costs and mortality associated with 10 hospital acquired conditions (HACs) being targeted by the the Department of Health and Human Services (HHS) part of the current Partnership for Patients program (PfP).[10] HACs are conditions that are not present upon hospital admission but rather are acquired during the period of hospitalization. They can stem from diagnostic or treatment errors (e.g., failure to follow antibiotic protocols); medical injuries or adverse events; or exposure to pathogens, such as *Clostridium difficile*. The consequences of HACs can be serious for patients, ranging from increased length of hospital stay to worsened health outcomes or unexpected mortality. Medical errors and HACs affect all age groups, from neonates and mothers during labor and delivery to surgical patients to elderly patients—all vulnerable during a hospital stay. Many HACs can be effectively addressed and prevented through training, adherence to evidence-based treatment guidelines, and hospital best practices, but only if the HACs are first properly measured and understood.[11] Of particular interest to AHRQ are 10 HACs:

- Adverse Drug Events (ADE)
- Catheter-Associated Urinary Tract Infections (CAUTI)
- Central Line-Associated Blood Stream Infections (CLABSI)
- Falls
- Obstetric Adverse Events (OBAE)
- Pressure Ulcers
- Surgical Site Infections (SSI)
- Venous Thromboembolism (VTE)
- Ventilator-Associated Pneumonia (VAP)
- *Clostridium difficile* Infections (CDI)

Since the Institute of Medicine's landmark publications *To Err Is Human* (1999) and *Crossing the Quality Chasm: A New Health System for the 21st Century* (2001) revealed the extent of preventable medical errors, significant effort has been directed at decreasing the incidence of these adverse events and improving patient safety.[12,13] Following passage of the Patient Protection and Affordable Care Act (ACA), HHS reestablished patient safety as a national health care priority area and sought to eliminate HACs through multipronged policy- and program-based approaches. These approaches are detailed in the AHRQ-led National Quality Strategy,[1,2] the National Action Plan to Prevent Health Care-Associated Infections: Road Map to Elimination,[3] and the National Action Plan for Adverse Drug Event Prevention.[4] These documents articulate the goals, priorities, and measures for improving quality and decreasing the

incidence of HACs, given their significant risks to patient health and safety. AHRQ and CMS, in particular, are leading this charge.

AHRQ and CMS are partnering with other HHS agencies to conduct a range of activities to address HACs, hospital-acquired-infections (HAIs), and medical errors specifically, as well as patient health and safety more generally. For example, both AHRQ and CMS encourage the practice of evidence-based quality and infection control—including through a national technical-assistance program implemented by CMS-funded Quality Innovation Network-Quality Improvement Organizations (QIN-QIOs), and through the Community-Based Care Transitions Program (CCTP), which aims to reduce hospital readmissions for high-risk Medicare beneficiaries by more effectively managing their care and transitions.[14] The goals of the PfP program are to improve safety in acute-care hospitals, and achieve a 20 percent reduction in HACs and a 12 percent reduction in 30-day readmissions as a population-based measure (readmissions per 1,000 people) from 2014 to 2019.[15,16]

CMS is also using payment model restructuring to encourage HAC reductions as part of payment reform efforts. Beginning in 2008, CMS identified the HACs (e.g., CAUTI, falls and trauma, surgical site infection) for which certain types of hospitals would be subject to mandatory reporting with payment penalties (i.e., they would not be paid for services related to treating those HACs).[17] In 2010, the ACA formally established the Hospital-Acquired Condition Reduction Program, offering incentives for HAC reduction; however, beginning in 2015, the ACA required CMS to reduce payments to hospitals performing in the bottom 25 percent on HAC-related quality measures.[18] The accuracy of these measures in capturing HACs has therefore become a key factor for both patient health and hospital payments.

AHRQ is pursuing a variety of measurement-related activities for improving patient safety and outcomes, including for specific HACs. For example, the AHRQ National Scorecard on Rates of Hospital-Acquired Conditions leverages data from the Medicare Patient Safety Monitoring System (MPSMS).[19] In its 2014 final report based on MPSMS and other data, AHRQ noted a decrease between 2010 and 2014 that corresponded to reductions of 17 percent, or 2.1 million HACs. Furthermore, the report finds significant improvements in additional cost and excess mortality: the reduction in HACs translated to a savings of 87,000 patient lives and $19.9 billion.[20]

Despite these achievements, HACs continue to have a significant financial and human cost, and efforts to quantify and reduce HACs are an important ongoing effort for HHS. There is broad consensus on the importance of accurately measuring the incidence and impact of HACs from the perspective of patient health and the role that such measures play in improving patient safety through performance-based payment reform. In particular, additional scrutiny is being applied to the measurement of HACs and their impact on inpatient hospital costs and mortality. For example, AHRQ is developing and implementing a successor system to MPSMS: the Quality and Safety Review System (QSRS), which will be described in

the section that follows. The QSRS will expand the number of HACs being targeted and include additional data types, sources, and capabilities to better measure HAC incidence and impact. [21,22]

Need for New Measurements

In addition to the patient safety implications, accurate measurement of HAC incidence and severity has direct consequences for hospital payments as part of the transition from fee-for-service to pay-for-performance reimbursement. Until recently, a combination of the MPSMS measures, ICD-9 codes (now ICD-10), and AHRQ Patient Safety Indicators (PSIs) were used to inform public health surveillance and reimbursement decisions. However, PSIs have been criticized for their reliance on claims rules instead of clinical criteria for defining HACs.[23] With greater availability of structured electronic health record data, it is now more feasible to incorporate clinical characteristics (e.g., laboratory test results) into patient safety event descriptions. Because of increased access to clinical data and questions about whether existing HAC definitions can fully capture the incidence of a given HAC, AHRQ has revised its definitions to incorporate clinical features into formerly claims-based definitions.

These changes take the form of AHRQ's new patient safety surveillance system—the QSRS that was mentioned above. It will replace the MPSMS and attempt to address some of the prior measurement limitations by 1) simplifying event descriptions, 2) expanding the scope of adverse events collected, and 3) creating consistency across other patient safety data collection initiatives (e.g., the AHRQ Common Formats for Surveillance definitions for hospital-acquired infections are based on the CDC's National Healthcare Safety Network definitions).[21,22] With these new definitions being used in QSRS and represented in the aforementioned PfP 2019 goals, it is important to update estimates of additional cost and excess mortality associated with HACs. These estimates can then inform patient safety and quality improvement efforts to measure success in reducing HACs and the burdens associated with them.

In spite of the new definitions used by QSRS—which will take time to be fully implemented and to be reflected in the literature—certain measurement challenges remain and must be taken into account when estimating and interpreting HAC prevalence. Exhibit 1 summarizes some of the often-highlighted threats to validity and consistency of current estimates.[24,25]

Exhibit 1. Threats to validity and consistency of current HAC estimates

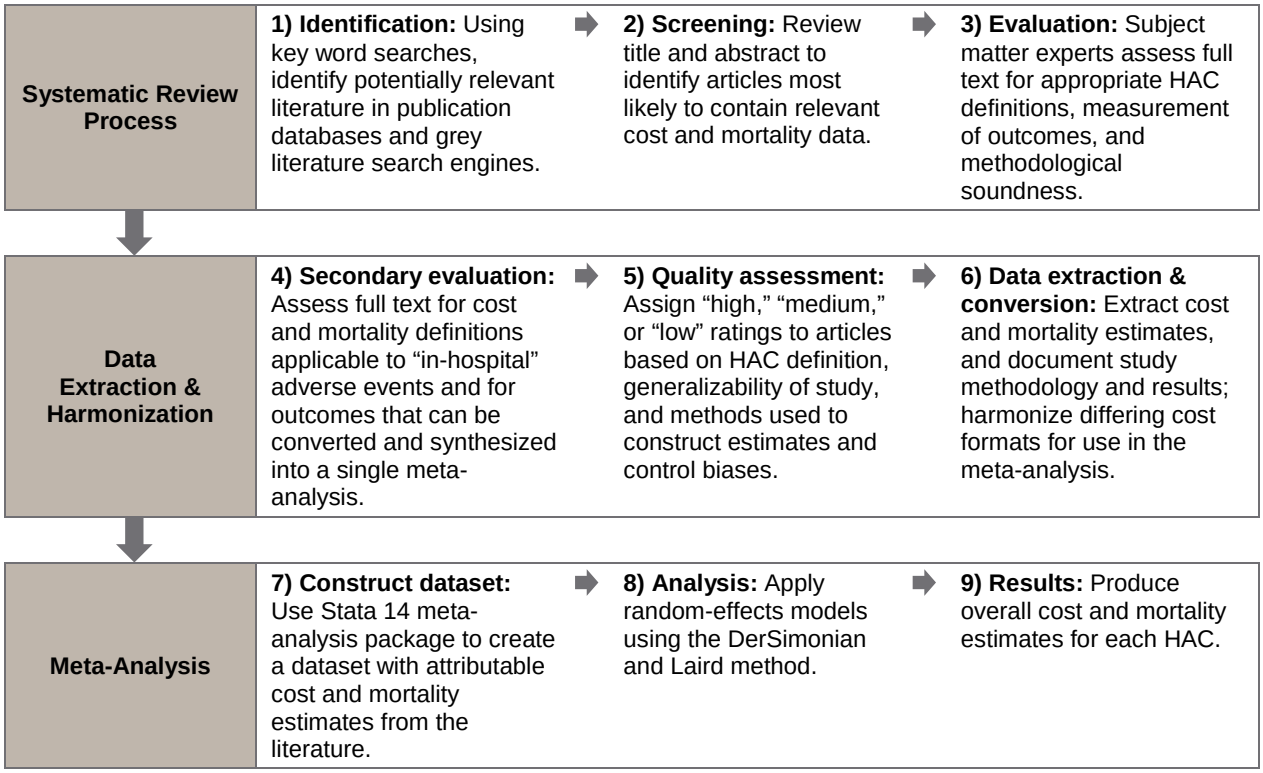
- Definitions of HACs vary by data source (clinical vs. claims-based)
- Estimates derived from a subpopulation of patients with specific conditions or insurance coverage
- Inconsistency in extent to which estimates of cost and mortality account for severity of HACs and interactions among different HACs
- Estimates not based on systematically combining pertinent quantitative data from studies
- Definitions of costs do not reflect actual additional incremental cost to the hospital attributable to the HAC
- Definitions of mortality do not reflect additional deaths associated with the HAC
- Estimates not based on recent literature

To address the need for updated estimates using the more recent QSRS-revised HAC definitions, AHRQ funded this study with the goal of producing valid, meaningful measures of additional cost and excess mortality. Below, we describe our systematic review of the literature, including our methods for identifying relevant literature on each HAC, and our search criteria for the clinical, cost, and mortality aspects of each HAC. We present our estimates of additional costs and excess mortality based on the meta-analysis and compare our estimates to prior estimates. Finally, we provide recommendations for additional research and describe challenges encountered and limitations to the findings.

Data and Methods

This section describes our approach (shown in Exhibit 2) of first reviewing the literature, then synthesizing the findings from the literature through meta-analysis, and finally producing estimates of additional costs and excess mortality for each HAC (Exhibit 2).

Exhibit 2. Methods overview for estimating HAC-associated cost and mortality



Systematic Review Process

The first stage of our work involved conducting a systematic review of published and grey literature for articles containing data on inpatient cost and/or mortality related to the HACs of interest. Our process is based on the PRISMA statement on systematic reviews and meta-analysis and includes three steps—identification, screening, and evaluation.[26] Throughout the review process, articles were assessed for relevance by applying increasingly rigorous criteria at each successive step. The remainder of this section describes each step in more detail.

Identification

The first step in the systematic review process was to define potentially relevant literature for each HAC. We developed HAC-specific search criteria to search publication databases, including PubMed, Scopus, and grey literature search engines. We then conducted forward and backward searches on relevant literature (e.g., references, articles that cited the original search results) and supplemented these searches with articles identified from the reference list of prior meta-analyses and systematic reviews. This multipronged search strategy better ensured that we captured the most relevant literature for each HAC.

Each search string contained three distinct groups of search terms, designed to target different aspects relevant to our review: HAC definition, outcomes (cost and/or mortality), and inclusion/exclusion criteria.

For each HAC, we used medical subject headings and included related terms drawn from AHRQ's recently developed Common Formats for Surveillance event description. AHRQ created the Common Formats for Surveillance as part of its effort to standardize HAC definitions and take into account both clinical and claims-based information in monitoring patient safety events. These definitions are intended to be applied by hospitals and patient safety officers in their surveillance for adverse events and form the basis for AHRQs transition from the MPSMS to QSRS. Exhibit 3 provides brief definitions for each HAC.

Exhibit 3. HAC definitions based on AHRQ Common Formats for Surveillance

HAC	Common Formats for Surveillance Definitions
Adverse Drug Events (ADE)	An event in which administration of a medication results in harm to a patient. Included are adverse reactions during or following administration without any apparent incorrect action.
Catheter-Associated Urinary Tract Infections (CAUTI)	Infection of the urinary tract that occurs subsequent to insertion of an indwelling urinary catheter during the hospital stay.
Central Line-Associated Bloodstream Infections (CLABSI)	Infection of the blood stream that occurs subsequent to insertion or access of a central line or umbilical catheter during the hospital stay.
Falls	Fall during an inpatient admission, with or without injury, whether or not fall was assisted.
Obstetric Adverse Events (OBAE)	An adverse maternal or fetal outcome that occurs during labor and/or birth. It includes eclampsia, infection not present on admission, injury to other body part, and fetal or maternal death, among others.
Pressure Ulcers	A new pressure ulcer developed during a stay, or Stage 1 or 2 pressure ulcer(s) present on admission advancing to Stage 3 or 4, unstageable, or the development of osteomyelitis, tunneling, or fissure contiguous to any pressure ulcer.
Surgical Site Infections (SSI)	Infection that occurs prior to discharge and within 30 days following an inpatient operative procedure that involves any part of the body that is opened or manipulated as part of the procedure.
Ventilator-Associated Pneumonia (VAP)	Acute pneumonia caused by bacteria, viruses, or fungi among inpatients mechanically ventilated for at least 2 days prior to pneumonia diagnosis.
Venous Thromboembolism (VTE)	A deep vein thrombosis (DVT) or pulmonary embolism (PE) developing among inpatients after admission.
Clostridium difficile Infections (CDI)	An infection of the gastrointestinal tract, in patients 2 years of age or older, that was not present on admission. Infection is indicated by clinical confirmation (i.e., notation of diarrhea or "pseudomembranous colitis" in medical records) or laboratory confirmation (i.e., positive test results for CDI toxin A and/or B or toxin producing CDI organism found in stool sample).

To develop search terms for cost and mortality outcomes, we focused search criteria on terms likely to produce articles on inpatient stays and methods that allow for calculating attributable or excess additional cost and excess mortality. Our initial inclusion/exclusion criteria limited results to original analyses of hospitalizations in the United States, articles published since 2000, and the English language. For some HACs where we found few studies of sufficient quality to include, we expanded the time frame to include pre-2000 data. A full list of search terms is provided in Appendix A. To be selected for review, articles needed to mention the HAC, include either inpatient cost or mortality, and meet the inclusion and exclusion criteria.

Screening

After article identification, a member of the NORC team assessed each article's relevance to the HAC, cost, and mortality through a multistep process of categorization and review. First, citations of articles in the search results were categorized by HAC and outcome (i.e., cost or mortality) and saved in Mendeley, a citation manager application. We then imported the citations into Covidence collaboration software, which was used to assign reviewers and track the review process. Once the citations were in Covidence,

at least one staff member screened the title and abstract of each article against the search and inclusion criteria to determine whether it would be included in the next stage of a full text review. As in the previous stage, articles had to involve primary or secondary analysis of data from U.S. hospitals and present cost and/or mortality related to one or more HACs. This screening was a necessary step to eliminate articles that were returned by the search but did not meet all the relevant criteria (e.g., non-U.S. data, community-acquired instead of hospital-acquired conditions).

Evaluation

The final step in the systematic review process was evaluation of the full text of remaining articles by a multidisciplinary team of experienced reviewers including epidemiologists, health economists, and clinicians. Two team members independently reviewed each article and provided an assessment on whether to include or exclude the paper from meta-analysis. In the event that the two reviewers provided differing assessments, a third reviewer made the final decision. Reviewers evaluated articles on three key dimensions for inclusions (Exhibit 4).

Exhibit 4. Dimensions and criteria for inclusion

Category	Specific Criteria
General	■ Reports on U.S. facilities ■ Contains HAC and cost or mortality information ■ Published in English
Methodology	■ Reports on recent data (after 1999) ■ Appropriate data for research objectives ■ Appropriate analytic methods for attributable cost or mortality estimation
Applicability	■ Reports data from inpatient settings ■ HAC case definitions can be applied using data presented ■ Incremental cost and/or mortality estimates provided

Since articles varied widely in the details they provided in the titles and abstracts, some articles passed the screening and were then excluded during full-text review for failing to meet general criteria (e.g., research conducted at a non-U.S. facility). However, the preponderance of full-text review focused on assessing the methodology and applicability of the studies to our research goals. Specifically, we excluded from the meta-analysis stage articles that met any of the following conditions:

- HAC definition did not approximate the Common Format for Surveillance definitions.
- Cost or mortality definitions did not approximate AHRQ's definition.
- Population studied was not in an inpatient setting.
- Study design or methods were deemed inappropriate for calculation of attributable cost or mortality.

Data Extraction and Harmonization

Once the full text reviews were completed, we moved the studies into the data extraction stage. Members of the data extraction team conducted a close reading of the remaining articles and evaluated them based on the appropriateness of HAC definitions used, outcomes measured, and methods applied for use in our analysis. We excluded articles from analysis if the definition used for the HAC did not approximate the Common Formats for Surveillance definitions closely enough to be appropriate for the final HAC estimates. We scrutinized cost and mortality definitions for their applicability to "in-hospital" adverse events. We also evaluated how the outcomes were reported (e.g., differences among groups, raw or adjusted, odds ratio versus relative risk) and whether these could be harmonized with other studies for the meta-analysis.

After providing a quality assessment for each article, team members progressed to extracting cost and mortality parameters and documenting pertinent details from each study's methodology and results. For mortality, we extracted the counts of HAC cases and controls, mortality rate or number of deaths for each group, and relative risk (RR) or odds ratio (OR) (if reported). If a study reported events for cases and controls, we calculated a relative risk from these values using the formula:

$$RR = \frac{\Pr(D|E)}{\Pr(D|E')}$$

Probability of death among the cases (Pr D|E) is divided by the probability of death for the controls (Pr D|E') to obtain the relative risk. When the RR was not reported or could not be calculated, we used the OR value to approximate RR, based on an assumption that the overall mortality rate was low.

Then, taking the relative risk—either as reported in the publication or as calculated based on case and control numbers or as approximated by the OR—we conducted meta-analysis with the log format of these values and the corresponding standard errors for mortality. In order to convert to excess mortality, we combined an underlying mortality rate of the at-risk population for the HAC with our pooled relative risk estimate from the meta-analysis, using the formula:

$$Excess\ Mortality = \Pr(D|E) - \Pr(D|E') = (RR - 1) * \Pr(D|E')$$

In the above formula, RR indicates the pooled relative risk estimate from our meta-analysis, and Pr(D|E') represents the underlying mortality in patients at risk for the HAC. Excess mortality is reported as the number of deaths per case of HAC. Appendix B provides more details on excess mortality calculations and underlying mortality rates used.

For cost parameters, we extracted available information to calculate additional cost estimates and standard error for each study. In Exhibit 5, we list examples of formats for cost outcomes found in various articles

and how we decided to convert those estimates into similar figures for use in meta-analysis. All the cost values were adjusted to 2015 U.S. dollars using Producer Price Index for general medical and surgical hospitals.[27] Final estimates of additional costs, similar to excess mortality, are presented as additional costs per case of HAC.

Exhibit 5. Format variations in cost reporting and conversion strategy

Cost Reporting Format	Conversion Strategy	Assumption/Reference
Hospital charges	Cost = charge * 0.5	Cost-to-charge ratio of 0.5[28]
Mean estimate for HAC and non-HAC group separately	Attributable cost estimate = Mean(HAC) – Mean(non-HAC)	Attributable cost is the adjusted mean difference between cases and non-cases
Standard deviation (SD)	Standard error (SE) = SD/SQRT(N)	
95% confidence interval	SE = (upper confidence limit – lower confidence limit)/2/1.96	
Median and interquartile range (presented as Q1 to Q3)	Mean = (Q1 + Median + Q3)/3 SD = (Q3 – Q1)/1.35	Higgins JPT and Green S (2011)[29]
Median and range (presented as Min to Max)	Mean = (Min + 2 * Median + Max)/4 SD = (Max – Min)/6	Hozo et al. (2005)[30]
SE for HAC and non-HAC group separately	SE of attributable cost estimate = SQRT{SE^2(HAC) + SE^2(non-HAC)}	Only if cases and non-cases are independent samples and the sample size is large

Meta-Analysis

After collecting and converting cost and mortality parameters for included studies, we conducted analysis using Stata 14 (StataCorp LP) meta-analysis packages. Specifically, we used the *metaan* command to generate attributable cost estimates and the relative risk for mortality estimates. We then calculated excess mortality based on the estimated relative risk and the underlying mortality of the at-risk population.[31]

We assumed that studies had enough in common to be incorporated in the meta-analysis for synthesis. Though studies are similar, they are not exactly the same; therefore, we allowed variation (heterogeneity) in effect estimates across studies due to factors such as study design type, analytic method, patient subpopulations, treatment standards, and geographic region in the United States. Thus, for analysis, we applied random-effects models using the DerSimonian and Laird method.[32,33] Random-effect models assume that studies included in the meta-analysis are a random sample of the distribution of effects and allow the true effect to vary from study to study. This method weights studies based on the inverse of the sum of the variance estimated between studies and the individual sampling variance. In the event that no substantial heterogeneity is observed from the random-effects model, we would then apply a fixed-effects model, which assumes that all the included studies share one true effect size. More details on the differences between random- and fixed-effect meta-analysis models are provided in Exhibit 6.

Exhibit 6. Comparison of random- and fixed-effect meta-analysis models

	Random-Effect Model	Fixed-Effect Model
Assumption	Studies were drawn from populations that differ from each other in ways that could impact on the treatment effect.	All studies shared a common true effect size.
Reason for effect size variation	Variation comes from random error within studies and true variation from one study to the next.	Variation comes from random error within studies.
Weight assignment	Large studies receive more weights than smaller studies.	Weights are balanced between large and small studies.

Due to the requirement of using consistent format of parameter inputs in meta-analysis, we had to exclude some studies even though they reported cost and/or mortality outcomes. For example, we excluded studies that only reported attributable cost and significance level because we cannot generate a standard error for the attributable cost based on that information.

Results

In total, we screened nearly 4,000 articles for possible inclusion in meta-analysis—the majority of which were screened out based on a title and abstract review (3,038 of 3,979, or 76.4 percent, were eliminated). Full text review eliminated 740 of the remaining 941 articles (78.6 percent). After further exclusions during data extraction based on the usability of study estimates in meta-analysis, we obtained our final list of articles included in meta-analysis for attributable cost and excess mortality associated with each HAC (Appendix C). In our final estimates, the number of studies included vary between HACs. CDI—the newest addition to the list of HAC—had the most robust body of literature with 9 studies for additional cost and 13 for excess mortality. In contrast, the literature contained far fewer usable studies for falls (3 for costs and 1 for mortality) and OBAE (2 for costs and none for mortality).

In Exhibit 7, we provide estimates for the additional costs associated with each HAC. The table shows the number of studies included, the range of costs estimates in those studies, and finally, the pooled meta-analysis based estimate of additional costs with a 95% confidence interval. The 95% CI arises from a two-sided test of the hypothesis that the estimate of additional costs does not differ from a value of zero dollars. When this CI does not include zero, we can assume the HAC does have additional costs associated with its treatment above and beyond the costs for a hospital stay for similar patients without the HAC.

We define additional cost as the incremental costs to the hospital for the inpatient stay attributable with the HAC of interest. The costs are limited to the hospital costs that would not have occurred had the HAC not occurred. These estimates do not include related costs (e.g., days of lost work) or costs of a readmission resulting from the HAC. Study results that report hospital charges have been transformed to costs using cost-to-charge ratios, a well-established method in the literature.[28] All costs are reported in 2015 dollar amounts and on a per-HAC-case basis. For example, the estimate of $5,746 for ADE means

that for each ADE, on average, the hospital incurs an additional $5,746 in costs caring for that patient above and beyond the costs associated with an inpatient stay for the same patient without an ADE.

Exhibit 7. Summary of meta-analysis additional cost estimates

	Studies (n)	Range of Estimates	Estimate (95% CI)
Adverse Drug Events (ADE)	2	$1,277–$9,062	$5,746 (-$3,950–$15,441)
Catheter-Associated Urinary Tract Infections (CAUTI)	6	$4,694–$29,743	$13,793 ($5,019–$22,568)
Central Line-Associated Bloodstream Infections (CLABSI)	7	$17,896–$94,879	$48,108 ($27,232–$68,983)
Falls	3	$2,680–$15,491	$6,694 (-$1,277–$14,665)
Obstetric Adverse Events (OBAE)	2	$13–$1,190	$602 (-$578–$1,782)
Pressure Ulcers	4	$8,573–$21,075	$14,506 (-$14,506–$41,326)
Surgical Site Infections (SSI)	5	$11,778–$42,177	$28,219 ($18,237–$38,202)
Ventilator-Associated Pneumonia (VAP)	5	$19,325–$80,013	$47,238 ($21,890–$72,587)
Venous Thromboembolism (VTE)	4	$11,011–$31,687	$17,367 ($11,837–$22,898)
***C. difficile* Infections (CDI)**	9	$4,157–$32,394	$17,260 ($9,341–$25,180)

More robust literature and higher overall additional costs were found for infectious HACs compared to non-infectious HACs. On average, 6.4 studies were included in estimates for infectious HACs, whereas only an average of three studies were available for non-infectious HACs. Of the infectious HACs (CAUTI, CLABSI, SSI, VAP, and CDI), we found the average cost attributable on a per-case basis to be approximately $31,000. The least expensive infectious HAC is CAUTI ($13,793), and the most expensive is CLABSI ($48,108), although both had wide ranges of estimates in the literature and wide confidence intervals in our results. The estimated attributable costs of non-infectious HACs are generally less than those of infectious HACs, with only VTE ($17,367) and pressure ulcers ($14,506) generating an estimated additional cost in the range of the infectious HACs.

To estimate excess mortality, we combined the results of meta-analysis with estimates of underlying mortality in the population as shown in Exhibit 8. For each HAC, we list the number of studies, the range of relative risk of death estimates from those studies, our pooled meta-analysis relative risk estimate, underlying mortality in the population, and finally, excess mortality and 95% CI for whether the estimated excess mortality is statistically different from zero. Underlying mortality values were taken from the literature and reflect our best estimate of the mortality rate for the population at risk for each of the HACs. More details on underlying mortality, including sources for each estimate, can be found in Appendix B.

Excess mortality is defined as the number of additional deaths due to a given HAC and shown as the number of deaths per HAC case. For example, we estimate for CLABSI that there are 0.15 excess deaths for each case. Stated another way, for every 1,000 CLABSI cases there are 150 excess deaths. Excess

mortality is calculated as the difference between the probability of death among those who have the HAC and the probability of death among those who do not have the HAC but are at risk. The formula used to estimate excess risk and sources for underlying mortality estimates are provided in Appendix B.

Exhibit 8. Summary of meta-analysis excess mortality estimates

	N	Range (RR)	Estimates of RR (95% CI)	Underlying Mortality	Estimates of Excess Mortality (95% CI)
Adverse Drug Events (ADE)	6	0.68–3.09	1.61 (1.14–2.27)	0.020	0.012 (0.003–0.025)
Cathether-Associated Urinary Tract Infections (CAUTI)	4	1.28–1.97	1.50 (1.06–2.11)	0.071	0.036 (0.004–0.079)
Central Line-Associated Bloodstream Infections (CLABSI)	5	1.86–4.88	2.72 (1.81–4.10)	0.086	0.150 (0.070–0.270)
Falls	1	3.50	3.50 (2.73–4.48)	0.020	0.050 (0.035–0.070)
Obstetric Adverse Events (OBAE)	—	—	—	—	0.005 (0.003–0.013)
Pressure Ulcers	3	2.42–5.06	3.26 (1.71–6.17)	0.018	0.041 (0.013–0.093)
Surgical Site Infections (SSI)	3	1.75–5.70	3.32 (1.79–6.18)	0.0114	0.026 (0.009–0.059)
Ventilator-Associated Pneumonia (VAP)	10	0.52–4.90	1.48 (0.64–3.42)	0.300	0.140 (-0.110–0.730)
Venous Thromboembolism (VTE)	9	1.01–13.63	3.15 (2.02–4.91)	0.020	0.043 (0.040–0.078)
***C. difficile* Infections (CDI)**	13	1.17–9.60	1.60 (1.38–1.87)	0.073	0.044 (0.028–0.064)

*No studies could be used in our relative risk-based meta-analysis methods, so estimates were produced from an alternative method described in more detail in the OBAE section below.

Our lowest estimates of excess mortality per case of HAC were for ADE, CAUTI, and SSI. It is possible that these HACs have been met with extensive in-hospital tracking and prevention efforts, compared to the other HACs in our study. The HACs with the highest excess mortality were CLABSI and VAP. These HACs tend to occur in sicker populations with an already increased risk for mortality. It is possible that the relatively higher risk of mortality from these HACs is due in part to the underlying morbidity in the types of populations vulnerable to such conditions. Estimates for VAP were extracted from a body of literature that was diverse in the types of specialty populations studied and thus may have limited generalizability. Of note, CLABSI has the highest estimate for both additional cost and excess mortality.

HAC Specific Considerations

The volume of literature, quality of studies, and relevance to our objectives varied for each of the HACs investigated. In this section, we briefly discuss these considerations for each HAC. Some of the factors we considered included:

- Recency of the data.
- Patient population studied related to the general population at risk for the HAC.
- Methods used to calculate cost and/or mortality.

- Analytic strategies used to assess additional cost and/or excess mortality.
- Generalizability of patient population studied to U.S. populations.
- Differences in HAC definitions used by each study.
- Variability in individual study estimates.

More details on each of the studies included in each estimate are provided in Appendix D. Forest plots for each additional cost and excess mortality meta-analysis for each HAC can be found in Appendix E.

Adverse Drug Events

Based on two studies reporting cost data, we estimated the additional cost for hospital-acquired ADE to be $5,746 (95% CI: -$3,950 to $15,441), whereas excess mortality, based on six studies, was estimated at 0.012 (95% CI: 0.003 to 0.025) per HAC case (meaning for every 1,000 in-hospital ADE cases, there are 12 excess deaths). The datasets used by our set of articles for these estimates are mixed. Two used hospital or administrative data; two used data from Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the ACC/AHA Guidelines (CRUSADE),[34] a registry of patients with unstable angina receiving antithrombotic agents; one used the HCUP-NIS; and the last used MPSMS data.[35,36,37,38] This mix of data resulted in a mix of patient populations studied—from all Medicare beneficiaries to adult surgical or cardiology patients—and methods used to identify HAC cases, from ICD-9 codes to reported dosing and surveillance.

The confidence interval for our additional cost estimate overlaps zero, indicating that the plausible range for the true estimate (with 95% confidence) includes no additional costs related to ADE. We believe this is due to the low number of articles we were able to include. Another caution: we were only able to include studies involving the administration of opioids and, thus, this estimate may not be generalizable to anticoagulants, hypoglycemic agents, or adverse drug events involving other drug classes.

For our mortality analysis, we were able to capture results from six studies collectively dealing with the three drug classes in the Common Formats for Surveillance definition of ADEs, including opioids, anticoagulants, and hypoglycemic agents. There was significant variability in reported mortality between studies, due mainly to variation in patient population and data source. For example, one study that focused on Medicare beneficiaries and multiple drug classes reported a relative risk more than double that of studies involving all adults and one drug class.[35]

Catheter-Associated Urinary Tract Infections

Based on six studies reporting cost data, we estimated the additional cost for hospital-acquired CAUTI to be $13,793 (95% CI: $5,019 to $22,568), whereas excess mortality, based on four studies, was estimated at 0.036 (95% CI: 0.004 to 0.079) per HAC case (meaning for every 1,000 in-hospital CAUTI cases, there

are 36 excess deaths). All patients in the considered studies were adult (ages >18) except for one, which studied pediatric patients exclusively (age 1–17 years).[39] Although all studies reported sample size either in terms of number of cases or number of patients with CAUTI, we found wide ranges of sample sizes from 18 in 6-year pooled data on colorectal resection patients[40] to 105,113 in 10-year pooled data on surgical oncology patients.[41] These discrepancies were largely due to the source of data and definition of populations used in each study. For instance, some studies involved all inpatient populations,[37,42] yet the majority of studies focused on specific medical and/or surgical conditions (e.g., surgical oncology in Sammon 2013; colorectal resection in Byrn 2015).[40,41] Additionally, the scope of the studies varied, from hospitals in a single network using data from EMRs[40,42] to nationally representative samples, with four studies using HCUP-NIS,[39,41,43,44] one using MedPAR claims,[45] and one using Cardinal Health MedMined data.[46] These factors potentially influenced our cost and mortality estimates, as exhibited in the large variations in individual estimates.

Central Line-Associated Bloodstream Infections

Based on seven studies reporting cost data, we estimated the additional cost for hospital-acquired CLABSI to be $48,108 (95% CI: $27,232 to $68,983), whereas excess mortality, based on five studies, was estimated at 0.15 (95% CI: 0.070 to 0.027) per HAC case (meaning for every 1,000 in-hospital CLABSI cases, there are 150 excess deaths). Individual studies produced a broad range of cost estimates for CLABSI, ranging from $18,000 to more than $90,000. The study with the lowest cost estimate was also the most recent study, using data from 2006 through 2012.[42] Overall, most of the studies included in meta-analysis focused on specific patient subpopulations including pediatric patients, intensive care unit patients, and those with specific conditions (e.g., epilepsy, cancer). Two of the cost studies and two mortality studies used national databases (HCUP-NIS); however, all four of these focused on specific patient subpopulations for analysis. Only studies of single hospitals or local hospital networks reported consequences of CLABSI for a general inpatient population.

Mortality studies used slightly different definitions of CLABSI. Two studies used lab results, and one used the CDC-NHSN to define cases.[42,47,48] CLABSI definitions used in cost studies also varied from clinical surveillance criteria to ICD-9-based definitions; however, these differences did not seem to influence the resulting attributable cost estimates.

Falls

Based on three studies reporting cost data, we estimated the additional cost for hospital-acquired falls to be $6,694 (95% CI: -$1,277 to $14,665), while excess mortality, based on one study, was estimated at 0.050 (95% CI: 0.035 to 0.070) per HAC case (meaning for every 1,000 falls cases, there are 50 excess deaths). Our search for recent literature on in-hospital falls in the United States returned very few results dealing with cost and/or mortality specifically for in-hospital events. Even fewer studies provided outcomes that could be incorporated into our meta-analysis. Much of the literature, which was screened

out of our meta-analysis, dealt with one of two topics: 1) studies reported on cost and/or mortality resulting from admissions due to a fall in the community and 2) articles studied the impact of fall-prevention programs and protocols on the incidence of in-hospital falls.

The three studies involved in our estimate of additional costs use either a national sample of orthopedic surgery patients or a small sample of adult inpatients specific to a hospital. This variation in sample size and type led to a wide range in initial cost estimates from the literature ($2,680 through $15,491). One study (by Bates, et.al) used for our cost estimate employed data from the late 1980s to the early 1990s.[49] In addition, many more recent studies that address additional cost due to in-hospital falls base their costs calculations on the Bates article.[49] Costs associated with prevention efforts, as well as direct and long-term costs of care after a fall that requires hospitalization, have been measured but are outside the scope of this analysis.[50,51,52]

The excess mortality estimate only represents the results of one study that used raw numbers found in the HCUP-NIS and should be treated with caution.[53] The dearth of literature on excess mortality may be due to the difficulty in finding reliable sources of data on injuries linked exclusively to in-hospital falls. Data on falls related to other health care settings, such as nursing homes, were not included in our analysis. While this may be a more relevant source of outcomes for falls specifically, based on articles found during screening, literature containing usable cost and mortality data is still limited for these other settings as well and may still face the same limitation of differentiating between falls leading to an admission and falls occurring in the institution.

Obstetric Adverse Events

Based on two studies reporting cost data, we estimated the additional cost for hospital-acquired OBAE to be $602 (95% CI: -$578 to $1,782). Our estimate of additional costs associated with OBAE is based on two studies reporting on a subset of conditions included in the maternal adverse event definition. One study used national representative data (HCUP-NIS) for obstetrical trauma (defined based on AHRQ PSI).[54] The other study used 2010 all deliveries in a single State, and adverse events included postpartum hemorrhage, preeclampsia/eclampsia, and anesthesia-related adverse events.[55] With only two costs estimates that spanned a wide range ($13 to $1,190), the confidence interval for overall meta-analysis overlapped with zero increased costs. This additional cost estimate should be used with caution because it does not include a comprehensive set of maternal adverse events. For example, no data on costs associated with infections were found, and such infections could be costly.

Our systematic literature review found that there is a gap in current literature to examine the impact of maternal adverse events on hospital mortality in the United States. Instead of reporting on mortality associated with maternal adverse events, most studies analyzed maternal adverse events as the end point. This left us with only one study examining the risk of maternal mortality for adverse events acquired in

hospitals, and the adverse event was obstetrical trauma only.[54] Further, this study found no increase in mortality for obstetrical trauma.

In addition, given the low incidence rate of maternal adverse events (1 percent) and low maternal mortality rate (0.02 percent), data analysis would require a national or a combination of multi-state databases across multiple years in order to achieve a large enough sample size to detect any increased risk. Furthermore, databases such as HCUP-NIS may have limitations to clearly identify cases (e.g., some researchers stated that they cannot distinguish a condition acquired prior to or during hospitalization). A surveillance system for maternal adverse events (not only for maternal mortality) would be helpful to understand the relationship between the adverse events and the associated outcome, including mortality and resource utilization.

Since we were not able to identify studies providing estimates of mortality due to OBAE, we used an alternative method to directly estimate the excess mortality using data on incidence of maternal adverse events and the risk of death among women experiencing maternal adverse events.

First, we estimated the total number of deaths due to maternal adverse events based on National Vital Statistics Data and CDC Pregnancy Mortality Surveillance Systems. From these sources and published literature, we estimated:

- Total number of live-births: 3,978,497 (2015 data).[56]
- Overall maternal mortality rate: 23.8 per 100,000 live births (2014 data).[57]
- Proportion of overall maternal deaths related to pregnancy: 38.2 percent (2011-2013 data).[58]
- Percentage of pregnancy-related deaths due to adverse events: 37.1 percent (2011-2013 data).[58]

We included the following conditions as the adverse events: infection (12.7 percent), hemorrhage (11.4 percent), hypertensive disorders of pregnancy (7.4 percent), amniotic fluid embolisms (5.5 percent), and anesthesia complications (0.1 percent). From the product of combining the number of live births, the maternal mortality rate, the maternal mortality rate related to pregnancy, and the percent of pregnancy-related deaths due to adverse events, we estimated the annual number of inpatient deaths due to maternal adverse events in the United States was 134, based on the assumption that all of the OBAE-related deaths happen in the inpatient setting.

Second, we estimated the incidence of maternal adverse events during delivery hospitalizations from four nationwide studies.[59,60,61,62] The incidence rate ranged from 220 to 1,148 per 100,000 deliveries. The studies varied by sample size (116,000 to 49 million), study period (1991 through 2011), study duration (3 years to 11 years), and data sources (one used National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network, one used National Hospital Discharge Survey, and two used HCUP data). They also differed in the conditions that were counted as maternal adverse events

(all four studies included infection/sepsis, hemorrhage/blood transfusion, and eclampsia/hypertensive complications; three studies included amniotic fluid embolisms and anesthesia complications; two studies included intracranial injuries and internal injuries of thorax, abdomen, and pelvis; one study included iatrogenic events. Among those conditions, hemorrhage/blood transfusion is the most commonly acquired condition (137 to 1,044 per 100,000 deliveries), followed by eclampsia/hypertensive complications (48 to 63 per 100,000 deliveries), and infection/sepsis (17 to 33 per 100,000 deliveries). We used meta-analysis to estimate the overall incidence rate for maternal adverse event as 688 (95% CI: 257 to1,118) per 100,000 deliveries. Using a total of 3,978,497 live-births in the U.S. in 2015, the total number of cases with maternal adverse events were estimated as: 27,372 (95% CI: 10,225 to 44,480).

Dividing the number of pregnancy-related maternal deaths due to adverse events calculated in step one, by the total number of maternal adverse events calculated in step two, we arrive at an estimate of 0.005 (95% CI: 0.003 to 0.013) for excess mortality due to OBAE (meaning for every 1,000 OBAE cases, there are 5 excess deaths).

From these numbers it is also possible to calculate the percentage of maternal inpatient deaths due to OBAE. For this calculation, we took the number of inpatient deaths due to maternal adverse events (i.e., 134 as calculated earlier) and divided by the total number of inpatient maternal deaths in the United States. Total inpatient maternal deaths is calculated from the total number of live births, overall mortality rate, and percentage of maternal mortality occurring in the inpatient setting (based on the literature, estimated to be 62 percent).[63] Thus, we estimated 23 percent of maternal inpatient deaths are due to OBAE. Of note, this calculation assumes all OBAE-related deaths happen in the hospital setting, which, if not true, would mean excess mortality and percentage of inpatient maternal deaths due to OBAE are overestimates.

Pressure Ulcers

Based on three studies reporting cost data, we estimated the additional cost for hospital-acquired pressure ulcers to be $14,506 (95% CI: -$12,313 to $41,326), whereas excess mortality, based on three studies, was estimated at 0.041 (95% CI: 0.013 to 0.093) per HAC case (meaning for every 1,000 pressure ulcer cases, there are 41 excess deaths).

We identified six studies providing estimates of costs and/or mortality for hospital-acquired pressure ulcers. Patients in the included studies were mostly adult (ages >18), except for one that studied pediatric patients exclusively (ages 1–17 years),[39] and another that studied patients of all ages, including patients younger than 18 years of age.[54] All studies used nationwide data with five relying on HCUP-NIS.

The sample size and standard error of individual study estimates ranged widely from 148 patients across 4 years[39] to 670,767 patients across a 5-year study period.[64] These differences were largely due to the source of data and the definition of population applied in each study and likely are the cause of the large

confidence interval for our additional cost estimate (-$12,313 to $41,326). For instance, some studies involved all inpatient populations, whereas others focused on specific medical and/or surgical conditions (e.g., epilepsy in Mendizabal 2016, and surgical patients in Spector 2016).[65,66] Given the evidence that the incidence of pressure ulcers increases with age,[64] we performed a sensitivity analysis that excluded the pediatric study (Goudie 2015) and estimated the additional cost for hospital-acquired pressure ulcers among adult inpatients to be $12,712 ($278 to $25,145).

Surgical Site Infections

Based on five studies reporting cost data, we estimated the additional cost for hospital-acquired SSI to be $28,219 (95% CI: $18,237 to $38,202), whereas excess mortality, based on three studies, was estimated at 0.026 (95% CI: 0.009 to 0.059) per HAC case (meaning for every 1,000 SSI cases, there are 26 excess deaths).

Only two studies were explicit about the types of infection included in their definition of SSI. One study counted all superficial, deep, and organ-space SSIs, whereas the other included only deep and organ-space infections.[67,68] The data sources used and cost estimates found in both of these studies did not vary from those in the other included studies. Three studies were regionally specific and involved single hospitals, one of which included all surgical patients that met the HAC definition.[42,67,68] The three remaining studies used national claims databases but focused on specialized surgical populations.[41,69,70]

Studies for both cost and mortality estimation had a wide range of individual estimates. Studies varied in their source of cost data, from national claims databases (i.e., HCUP-NIS) to hospital administrative data systems. For example, the study with the lowest cost estimate ($11,778) involved chart review at a single medical center and had one of the lowest number of cases (N=186) among all included studies.[67] For mortality, studies with the largest and smallest estimates (relative risk of 6.18 and 1.79, respectively) both used close to 10 years of data from the HCUP-NIS database, but the study with the smallest estimate included a much larger population of surgical patients.[41,69]

Ventilator Associated Pneumonia

Based on five studies reporting cost data, we estimated the additional cost for hospital-acquired VAP to be $47,238 (95% CI: $21,890 to $72,587), whereas excess mortality, based on 10 studies, was estimated at 0.14 (95% CI: -0.11 to 0.73) per HAC case (meaning for every 1,000 VAP cases, there are 140 excess deaths).

Compared to the other HACs studied, the cost literature for VAP is older. The most recent estimate comes from 2009, and two others date from prior to 2000.[71,72,73] The two studies prior to 2000 reported the lowest attributable costs at $19,000 and $33,000. All of the later studies' estimates fall between $40,000 and $80,000.

The majority of VAP studies included in both cost and mortality estimates were conducted among ICU patients with only three studying patients outside of these units, one looking at cancer patients, and another examining all hospitalized patients.[41,74,75] Two of the studies included in the mortality estimate reported on pediatric populations, one from a PICU and the other a NICU.[76,77] Most VAP studies drew data from hospital medical records or databases that combined records from several hospitals. This enabled them to use VAP definitions that incorporated clinical information such as laboratory testing that closely mirror the QSRS definitions. Because many of these studies were conducted in single institutions or small groups of hospitals, the number of cases was small in each study. The preponderance of studies reporting on local data may limit the generalizability of estimates to the entire United States.

More than half of the studies included in the mortality estimate used regression modeling techniques to estimate mortality due to VAP; however, there were a large minority (four studies) reporting only deaths for VAP patients and a matched comparison group. Estimates of relative risk for mortality varied and included two studies showing protective effects for ventilated patients with pneumonia compared to those without pneumonia.[71,74] When these studies are excluded, the estimate for excess mortality increases to 26 percent of cases (meaning that for every 1,000 cases there are 260 excess deaths).

In 2013, the CDC introduced the concept of ventilator–associated events (VAEs).[78] This represents a fundamental shift in the focus of HACs related to mechanical ventilation from a single adverse event (i.e., pneumonia) to a broader concept that includes additional potential pathophysiologic etiologies (e.g., VTE, volume overload, non-pulmonary infections).[79] While VAEs have a significant impact on patient outcomes (e.g., mortality and hospital length of stay), much work remains to further characterize the effect of VAEs on cost and mortality in isolation and in relation to other HACs.[80]

Venous Thromboembolism

Based on four studies reporting cost data, we estimated the additional cost for hospital-acquired VTE to be $17,367 (95% CI: $11,837 to $22,898), whereas excess mortality, based on nine studies, was estimated at 0.043 (95% CI: 0.040 to 0.078) per HAC case (meaning for every 1,000 VTE cases, there are 43 excess deaths).

Eleven studies were included in our review for VTE. Four addressed costs related to VTE leading to a pooled estimate of $17,367 additional costs for each VTE event. Most of the studies included in our estimates reported on adult inpatient populations,[65,69,81,82,83,84,85] with two studies considering patients of all ages[86,87] and one study focused on pediatric patients exclusively.[39] Sample size varied greatly in terms of total population, number of cases identified, and incidence rate of events. These variations were largely due to the definition of population applied in individual studies. For instance, some studies evaluated all inpatient populations, yet others focused on specific medical and/or surgical conditions (e.g., epilepsy in Mendizabal 2016; cirrhosis as denominator condition for Ali 2011; patients who underwent an ablative

procedure for a malignant oral cavity, laryngeal, hypopharyngeal, or oropharyngeal neoplasm for Hennesey 2012).[65,82,83]

Clostridium difficile Infections

Based on nine studies reporting cost data, we estimated the additional cost for hospital acquired CDI to be $17,260 (95% CI: $9,341 to $25,180), whereas excess mortality, based on 13 studies, was estimated at 0.044 (95% CI: 0.028 to 0.064) per HAC case (meaning for every 1,000 in-hospital CDI cases, there are 44 excess deaths). Methods of the included studies ranged from analysis of national hospital discharge data to reviews of a single hospital's CDI rates. The majority of studies in our analysis focused on specific patient subpopulations (e.g., trauma patients, cancer patients, those admitted for organ transplant). Analytic methods also varied considerably, as studies using a matched control group tended to be more comparable to cases on observed covariates and may be a better approximation of attributable cost and/or mortality than those studies using a pooled control sample. Finally, few studies used clinical definitions of *C. difficile* infection and instead relied on ICD-9-based definitions, which may miss cases and may misclassify community-acquired cases as hospital-acquired.

Discussion

In 2010, AHRQ estimated the attributable inpatient cost and excess inpatient mortality for HACs. Since then, these numbers have been used to quantify progress on the PfP goals of reducing hospital-acquired conditions, most recently in the *National Scorecard on Rates of Hospital-Acquired Conditions, 2010 to 2015*.[88] This report is an update to those estimates, primarily relying on the most current literature, which included more than 4,000 studies across 10 HACs. There are some categorical departures from the 2010 report. First, the definition of *venous thromboembolism* events has been expanded beyond post-operative events to include any deep vein thrombosis or pulmonary embolism occurring in hospital. Second, *C. difficile* infections were not in the 2010 list, but are included here.

The approach to study selection in this report favored studies using high-quality design and robust statistical techniques to control for confounding and, therefore, possibly better estimate excess or attributable mortality and costs. We focused on studies from 2000s and later, which were deemed timely, but we did not employ strict restrictions on time frame for data included, especially in cases where there were few published studies. Exhibit 9 presents the comparison between the 2010 report results, recalibrated to 2015 dollars, and the current report results are in Exhibit 9.

Exhibit 9. Comparison to 2010 AHRQ estimates

	Additional Cost		Excess Mortality	
	Current Study Estimate (95% CI)	2010 AHRQ Estimate*	Current Study Estimate (95% CI)	2010 AHRQ Estimate
ADE	$5,746 (-$3,950–$15,441)	$5,452	0.012 (0.003–0.025)	0.020
CAUTI	$13,793 ($5,019–$22,568)	$1,090	0.036 (0.004–0.079)	0.023
CLABSI	$48,108 ($27,232–$68,983)	$18,537	0.150 (0.070–0.270)	0.185
Falls	$6,694 (-$1,277–$14,665)	$7,888	0.050 (0.035–0.070)	0.055
OBAE	$602 (-$578–$1,782)	$3,271	0.005 (0.003–0.013)	0.0015
Pressure Ulcers	$14,506 (-$12,313–$41,326)	$18,537	0.041 (0.013–0.093)	0.072
SSI	$28,219 ($18,237–$38,202)	$22,898	0.026 (0.009–0.059)	0.028
VAP	$47,238 ($21,890–$72,587)	$22,898	0.140 (-0.110–0.730)	0.144
VTE	$17,367 ($11,837–$22,898)	$8,723	0.043 (0.040–0.078)	0.104
CDI	$17,260 ($9,341–$25,180)	N/A	0.044 (0.028–0.064)	N/A

*Note: 2010 AHRQ estimates have been converted to 2015 dollars for comparison to the meta-analysis-based estimates.

While the estimation of additional cost per HAC remained stable for ADE, falls, and SSI, we did observe differences in estimated additional cost for other HACs: some increases (CAUTI, CLABSI, VTE, VAP) and some reduction (OBAE). The most notable increase was for CAUTI, where the prior estimate was based on a single study using cost data from two small studies conducted outside the United States and prior to 1995.[89] When compared to AHRQ estimates of excess mortality, only VTE decreased when compared to 2010 AHRQ estimates. This difference in excess mortality for VTE may be related to the change in definition to include all hospital-acquired VTE—not just postoperative VTE events. In all other HACs, while we observed some increase (CAUTI) and some decrease (ADE, pressure ulcers) compared to the 2010 estimated excess mortality rates, the differences were not statistically significant at the 0.05 significance level.

When looking at these differences by HACs, we observe some interesting variations. For instance, since AHRQ last estimated cost and mortality associated with CLABSI, the mortality has decreased from more than 18 percent of cases to 15 percent. While mortality has tended to decrease (although in statistically insignificant ways), cost associated with each CLABSI case has increased substantially from $18,537 to more than $48,000. Similarly, the mortality associated with VAP remained at approximately 14 percent in both 2010 and 2017 estimates, but the additional cost associated with VAP doubled from $22,898 in 2010 to $47,238 in 2017. CAUTI also shows a similar pattern of higher costs alongside comparable excess mortality.

Several potential etiologies may account for this pattern of similar to improved mortality and increased cost. First, prevention efforts may have disproportionately eliminated the least severe and least costly infections. For example, CAUTI has been the focus of several national prevention initiatives, including the AHRQ-sponsored CUSP Stop CAUTI program.[90] One strategy used by these programs has been to reduce exposure to urinary catheters by focusing on the medical need for initial placement and

maintenance of a catheter throughout a hospital stay. At the same time that prevention efforts were ramping up, the CDC National Healthcare Safety Network updated their CAUTI definition, clarifying the criteria for defining a CAUTI event.[91] Together these factors likely lead the remaining HAC cases to be among patients with more severe infections and, thus, likely more costly.

Second, prevention efforts may have been more effective at reducing the risk of developing these HACs early in the exposure to the related devices (e.g., central lines, urinary catheters, invasive mechanical ventilation).[92,93,94] This disproportionate reduction would thus shift the overall makeup of patients with these infections toward those requiring longer lengths of stay and higher costs. Third, HAC-prevention efforts may have been particularly effective at reducing these complications in severely ill patients at a high risk for early mortality but who still died. Thus, the remaining patients are those requiring longer-term devices (e.g., central venous access for dialysis, Foley catheters, or invasive mechanical ventilation) with a lower baseline risk of mortality but longer average hospital stays and associated costs.

Limitations

Since the estimate of additional cost and excess mortality are obtained from combining, via meta-analysis, individual estimates for the published literature, the quality of the estimates depends on the quality of the underlying studies. In conducting this review of the literature, several concerns about the underlying studies arose. These are detailed in subsections below.

Competing Risk and Double Counting Issues

Hospitalized patients are often suffering multimorbidity, and in many cases are also physically frail. This poses problems when estimating additional cost and mortality for a specific HAC; the issue also permeates the research literature on HACs.

Conceptually, any number of specific clinical conditions or events might result in death, with each condition considered a competing risk in comparison to the others. Essentially, death from one cause precludes death from another cause. In studies of attributable mortality for patient populations who develop a HAC, there is often not a readily available and reasonably similar comparison group of patients to assess the counterfactual of what would have happened to a similarly ill patient population in the absence of the HAC under study.

The competing risk issue is further compounded by the fact that the probability of these events is often higher among those with more clinical conditions, or more severe manifestation of any given condition. However, most studies focus on the outcomes of patients where a particular HAC is documented and compare it to those without the specific HAC, with less-than-adequate accounting for differences in latent health. Similarly, some patients with a HAC may have been more likely to die (even absent the HAC)

than those in the comparison population. As such, much of the current literature tends to overstate attributable costs and mortality associated with HACs.

Relatedly, many patients with a given HAC may have other HACs. This means that the sum of deaths from studies that focus on the effects of a single HAC, and do not exclude patients with other HACs from each study, will inevitably double-count some death as being attributable to HACs more generally. In fact, the majority of underlying studies we found focus on one HAC without considering the presence of other HACs—at best, studies focus on those with only one particular HAC documented. Because of this, the sum of deaths for each individual HAC exceeds the sum of deaths from any HAC. In the extreme, summing across excess deaths from a list of HACs could lead to implied death rates exceeding the actual overall in-hospital death rate.

Conversely, the few studies that estimate "any HAC"-related cost and mortality circumvent the competing risk concern by studying the effect of the presence of any HAC. While these types of studies garner headlines because of the magnitude of the overall concern, the tradeoff is that they provide little insight into potential points of intervention. This is because HACs have different underlying causes both in the healthcare system and from a biological standpoint.

The competing-risk and double-counting concerns may be addressed through better study designs that decompose (statistically) causes of death within a patient population. They also may benefit if studies assign weights to numerous potential causes of death. Well-constructed studies using approaches that account for numerous potential causes of death are not readily available in the literature. A lack of these studies represents a large knowledge gap that should be addressed.

Underlying Data Concerns

Many of the studies used for this meta-analysis conducted their analysis using AHRQ's Healthcare Cost and Utilization Project National Inpatient Sample (HCUP-NIS). These administrative data have appeal in that they are well validated, centrally collected and curated, and collected using sampling frames that can generate national estimates.

However, these data are administrative billing data. They are not collected with the express purpose of studying HACs. As such, they are less reliable than clinical record data in distinguishing between present-on-admission and hospital-acquired conditions. They also lack clinical information used to define some HACs and may under-report HACs.

Additional research using electronic health record databases would substantially add to the literature on HAC incidence and consequences. The challenge with current studies that use these types of electronic health record data sources is questions about generalizability and scaling to national estimates. Emerging

data sources that link clinical record data to billing data may facilitate substantially improved estimates of additional cost and excess mortality arising from HACs.

Another concern is that, although the QSRS Common Formats for Surveillance definitions use clinical information in addition to ICD codes for defining HACs, much of the literature still relies on definitions of HACs consisting primarily of ICD codes. Definitions relying on ICD codes can miss cases resulting in lower estimates of incidence and prevalence of HACs. Since the cases captured are true cases, additional cost and excess mortality estimates made using ICD-code-based definitions can likely be relied upon. In light of the changing definitions used in QSRS, future research should study HACs using these new definitions to better understand the incidence and consequences of HACs.

A final data concern is that many of the studies included in the meta-analysis did not directly report costs. Since a large proportion of the literature relies on national claims databases, they report on charges instead of costs. These charges are converted to costs using cost-to-charge ratios. To the extent that this methodology is used consistently over time, this would not drive observed differences in attributable cost from previous reports. Of course, a more accurate method would be to estimate costs directly using hospital records; however, the localized nature of such data opens the door to idiosyncratic center-specific and system-specific costing approaches, which is more difficult to address across studies than the issue of adjusting charges to arrive at an approximate measure of cost.

Opportunities for Future Research

There are a few distinct opportunities to improve the research on the attributable mortality and cost from HACs. First, some effort should focus on estimating the incidence of multiple HACs to address the concerns arising from double-counting and competing risks from other HACs. Second, there is room for improvement in understanding of the patient-level factors that raise the risk for HACs and using this understanding to construct more valid comparison populations. Both of these improvements combined with methods to weight likely causes of deaths would generate more valid estimates of the attributable mortality and costs from HACs than currently exist in the research literature.

Third, there are emerging sources of data that combine some form of administrative claims data with at least partial electronic medical record information across broader patient populations than have been studied using single-system data. Use of such data has the potential to leverage the strengths of the studies using the HCUP-NIS data (including standardization and wider generalizability) and those employing data from a single hospital or system (better identification of conditions and potentially the genesis of their onset). Estimates from such studies might provide a more rigorous estimate of the extent to which HACs increase mortality and costs.

Finally, the study undertaken here focused only on inpatient mortality and costs during the index hospitalization. Future work needs to account for the full effect of HACs on mortality and costs beyond the inpatient setting. Such research would provide insight into the extent to which HACs compress mortality and the full direct and indirect costs to the system. The challenge here would, of course, be access to data sources that facilitate these types of analyses.

Appendix A. PubMed Search Criteria

Common Search Criteria for Cost
("Costs and Cost Analysis"[mh] OR "Cost of Illness"[mh] OR "Economics"[mh] OR "Health Care Costs"[mh] OR "Direct Service Costs"[mh] OR "Hospital Costs"[mh] OR “Health Expenditures”[mh] OR cost[tiab] OR costs[tiab] OR expenditure*[tiab] OR expense[tiab] OR spend*[tiab] OR “financial outcome”[tiab] OR “financial outcomes”[tiab] OR “financial impact”[tiab] OR “financial impacts”[tiab] OR “economic impact”[tiab] OR “economic impacts”[tiab] OR “economic outcome”[tiab] OR “economic outcomes”[tiab]) AND (incremental[tiab] OR additional[tiab] OR extra[tiab] OR attribut*[tiab] OR excess[tiab] OR “compared to”[tiab] OR “compared with”[tiab] OR “associated with”[tiab] OR “because of”[tiab] OR “due to”[tiab] OR “caused by”[tiab]) AND (hospital*[tiab] OR inpatient[tiab] OR “Hospital Costs”[mh] OR “intensive care unit”[tiab]) NOT “cost effectiveness”[ti]

Common Search Criteria for Mortality
"Mortality"[mh] OR "Hospital mortality"[mh] OR mortalit*[tiab] OR death*[tiab] OR fatalit*[tiab]) AND (additional[tiab] OR extra[tiab] OR attribut*[tiab] OR excess[tiab] OR “compared to”[tiab] OR “compared with”[tiab] OR “associated with”[tiab] OR “because of”[tiab] OR “due to”[tiab] OR “caused by”[tiab]

Common Exclusions
English[lang] AND United States[pl] AND (2000:2017[dp]

Adverse Drug Events
((“Drug therapy/adverse effects”[mh] OR “drug interactions”[mh] OR “anaphylaxis”[mh] OR “drug overdose”[mh] OR “Drug-related side effects and adverse reactions”[mh] OR “adverse drug event”[tiab] OR “adverse drug events”[tiab] OR “adverse drug reaction”[tiab] OR “adverse drug reactions”[tiab] OR “medication errors”[mh] OR “medication error”[tiab] OR “medication errors”[tiab] OR adverse [tiab] OR “allergic reaction”[tiab] OR “allergic reactions”[tiab] OR “anaphylaxis”[tiab] OR overdose[tiab] OR ((drug[tiab] OR medication[tiab]) AND (harm[tiab] OR injury[tiab]))))
AND
((“anticoagulants”[mh] OR “anticoagulation”[tiab] OR “anticoagulant”[tiab] OR “4- Hydroxycoumarins”[mh] OR “Acenocoumarol”[mh] OR “Ancrod”[mh] OR “Antithrombin III”[mh] OR “Antithrombin Proteins”[mh] OR “Beta 2-Glycoprotein I”[mh] OR “Blood Coagulation Factor Inhibitors”[mh] OR “Citric Acid”[mh] OR “Dabigatran”[mh] OR “Dalteparin”[mh] OR “Dermatan Sulfate”[mh] OR “Dextrans”[mh] OR “Dicumarol”[mh] OR “Edetic Acid”[mh] OR “Enoxaparin”[mh] OR “Ethyl Biscoumacetate”[mh] OR “Fibrin Fibrinogen Degradation Products”[mh] OR “Gabexate”[mh] OR “Heparin”[mh] OR “Heparin Cofactor II”[mh] OR “Heparin, Low-Molecular-Weight”[mh] OR “Heparinoids”[mh] OR “Hirudins”[mh] OR “Nadroparin”[mh] OR “Pentosan Sulfuric Polyester”[mh] OR “Phenindione”[mh] OR “Phenprocoumon”[mh] OR “Protein C”[mh] OR “Protein S”[mh] OR “Rivaroxaban”[mh] OR “Warfarin”[mh] OR “Hirudin Therapy”[mh])
OR
(“analgesics, opioid”[mh] OR opioid*[tiab] OR “Alfentanil”[mh] OR “Alphaprodine”[mh] OR “Buprenorphine”[mh] OR “Buprenorphine, Naloxone Drug Combination”[mh] OR “Butorphanol”[mh] OR “Codeine”[mh] OR “Dextromoramide”[mh] OR “Dextropropoxyphene”[mh] OR “Dihydromorphine”[mh] OR “Diphenoxylate”[mh] OR “Enkephalin, Ala(2)-MePhe(4)-Gly(5)- ”[mh] OR “Enkephalin, D- Penicillamine (2,5)- ”[mh] OR “Ethylketocyclazocine”[mh] OR “Ethylmorphine”[mh] OR “Etorphine”[mh] OR “Fentanyl”[mh] OR “Heroin”[mh] OR “Hydrocodone”[mh] OR “Hydromorphone”[mh] OR “Levorphanol”[mh] OR “Meperidine”[mh] OR “Meptazinol”[mh] OR “Methadone”[mh] OR “Methadyl Acetate”[mh] OR “Morphine”[mh] OR “Nalbuphine”[mh] OR “Opiate Alkaloids”[mh] OR “Opium”[mh] OR “Oxycodone”[mh] OR “Oxymorphone”[mh] OR “Pentazocine”[mh] OR “Phenazocine”[mh] OR “Phenoperidine”[mh] OR “Pirinitramide”[mh] OR “Promedol”[mh] OR “Sufentanil”[mh] OR “Tilidine”[mh] OR “Tramadol”[mh]))
AND
(“iatrogenic disease”[mh] OR “nosocomial”[tiab] OR “healthcare associated”[tiab] OR “health care associated”[tiab] OR “hospital acquired”[tiab] OR “inpatient”[tiab] OR "hospitalized"[tiab] OR "hospital related"[tiab] OR "in hospital"[tiab] OR "in hospitals"[tiab] OR “within hospitals”[tiab]))

CAUTI
((("urinary tract infections"[mh] OR "urinary tract infection*"[tiab]) AND (Urinary catheterization[mh] OR urinary catheter*[tiab] OR “catheter associated”[tiab])) OR ("catheter-related infections"[mh] AND "urinary"[tiab]) OR (Urinary Catheterization/adverse effects*[mh) OR “CAUTI”[tiab] OR ((“cross infection”[mh] OR “iatrogenic disease”[mh] OR “nosocomial”[tiab] OR “hospital infection”[tiab] OR “hospital infections”[tiab] OR “healthcare associated”[tiab] OR “health care associated”[tiab] OR “hospital acquired”[tiab] OR "hospital related"[tiab]) AND “urinary”[tiab]))

CLABSI
(((“catheter-related”[tiab] OR “catheter-associated”[tiab] OR "Catheterization, Central Venous/adverse effects"[Mesh] OR “Central Venous Catheters/adverse effects”[mh] OR “Catheters, Indwelling/adverse effects”[mh] OR “umbilical catheter”[tiab] OR central line*[tiab] OR central venous catheter*[tiab]) AND (“bloodstream infection”[tiab] OR “bloodstream infections”[tiab] OR “blood stream infection”[tiab] OR “blood stream infections”[tiab] OR “bacteremia”[tiab] OR “bacteremia”[mh] OR ((Cross infection[mh] OR “cross infection”[tiab] OR “cross infections”[tiab] OR nosocomial[tiab] OR “hospital-acquired infection”[tiab] OR “hospital-acquired infections”[tiab] OR “healthcare-associated infection”[tiab] OR “healthcare-associated infections”[tiab] OR “health care-associated infection”[tiab] OR “health care-associated infections”[tiab]) AND (“bloodstream”[tiab] OR “blood stream”[tiab])))) OR CLABSI[tiab] OR CRBSI[tiab] OR CABSI[tiab] OR CLAB[tiab] OR (“catheter-related infections”[mh] AND (“blood stream”[tiab] OR “bloodstream”[tiab])))

Falls
("Accidental Falls" [mh] OR Falls [tiab] OR Falling [tiab] OR Fall [tiab] OR "Accidental Falls" [tiab] OR "Accidental Fall" [tiab] OR Slip [tiab] OR Faller [tiab])
AND
(hospital*[tiab] OR inpatient*[tiab] OR “Hospital Costs”[mh] OR “intensive care unit”[tiab] OR “acute care setting”[tiab] OR “hospitalization”[mh] OR “inpatients”[mh] OR "Intensive Care Units"[Mesh])

Obstetric Adverse Events
("Inferior Wall Myocardial Infarction"[Mesh] OR "Anterior Wall Myocardial Infarction"[Mesh] OR "Acute Kidney Injury"[Mesh] OR "Respiratory Distress Syndrome, Adult"[Mesh] OR "Embolism, Amniotic Fluid"[Mesh] OR "Aneurysm"[Mesh] OR "Heart Arrest"[Mesh] OR "Ventricular Fibrillation"[Mesh] OR "Disseminated Intravascular Coagulation"[Mesh] OR "Heart Failure"[Mesh] OR "Head Injuries, Closed"[Mesh] OR "Craniocerebral Trauma"[Mesh] OR "Cerebrovascular Trauma"[Mesh] OR "Cerebrovascular Disorders"[Mesh] OR "Pulmonary Edema"[Mesh] OR "Anesthesia, Obstetrical/adverse effects"[Mesh] OR "Anesthesia, Obstetrical/complications"[Mesh] OR "Sepsis"[Mesh] OR "Shock"[Mesh] OR "Anemia, Sickle Cell/complications"[Mesh] OR "Thrombosis/complications"[Mesh] OR "Blood Transfusion"[Mesh] OR "Defibrillators"[Mesh] OR "Interactive Ventilatory Support"[Mesh])

Pressure Ulcers
((“Pressure Ulcer” [MeSH] OR “Pressure Ulcer” [tiab] OR “Bedsore” [tiab] OR “Bed Sores” [tiab] OR “Decubitus Ulcer” [tiab] OR “Pressure Sore” [MeSH] OR “Pressure Sore” [tiab] OR “Suspected Deep Tissue Injury” [tiab] OR “Pressure Ulcer” [MeSH] OR “Pressure Ulcer” [tiab] OR “osteomyelitis” [MeSH] OR “osteomyelitis” [tiab] OR “tunneling” [tiab] OR “fissure” [tiab])
AND
(“hospital acquired” [tiab] OR “healthcare acquired” [tiab] OR “nosocomial” [tiab] OR “hospitalization” [MeSH] OR “hospitalized”[tiab] OR “healthcare associated”[tiab] OR “health care associated”[tiab] OR “health care acquired”[tiab] OR "hospital related"[tiab] OR “inpatient”[tiab] OR "in hospital"[tiab] OR "in hospitals"[tiab] OR “within hospitals”[tiab])

Venous Thromboembolism
((“pulmonary embolism/economics”[MeSH Terms]) OR (“Upper Extremity Deep Vein Thrombosis”[MeSH Terms]) OR (“venous thromboembolism/economics”[MeSH Terms]) OR (“venous thrombosis/economics”[MeSH Terms]) OR ("Pulmonary Infarction"[Mesh]) OR ((“deep venous”[tiab] OR “deep vein”[tiab] OR “pulmonary”[tiab]) AND (thrombos*[tiab] OR embolism*[tiab] OR thromboembolism*[tiab])))
AND
(“iatrogenic disease”[mh] OR “nosocomial”[tiab] OR “healthcare associated”[tiab] OR “health care associated”[tiab] OR “hospital acquired”[tiab] OR “inpatient”[tiab] OR "hospitalized patients"[tiab] OR "hospital related"[tiab] OR "in hospital"[tiab] OR "in hospitals"[tiab] OR “within hospitals”[tiab])

Surgical Site Infections
("cross infection"[mh] OR “hospital acquired” [tiab] OR “healthcare acquired” [tiab] OR “nosocomial” [tiab] OR “hospitalized”[tiab] OR “healthcare associated”[tiab] OR “hospital associated”[tiab] OR “health care associated”[tiab] OR “health care acquired”[tiab] OR "hospital related"[tiab] OR “inpatient”[tiab] OR "in hospital"[tiab] OR "in hospitals"[tiab] OR “within hospitals”[tiab])
AND
(“surgical wound infection/economics”[mh] OR “surgical procedures, operative/adverse effects”[mh] OR (“surgical wound infection”[mh] AND prognosis[mh]) OR ((“surgical wound infection*”[tiab] OR “surgical site infection*”[tiab]) AND outcome*[tiab]))

Ventilator Associated Pneumonia
((“Pneumonia, Ventilator-Associated/economics”[mh]) OR (“Ventilator Associated Pneumonia”[tiab] OR “Ventilator-Associated Pneumonia”[tiab] OR “Ventilators, Mechanical/adverse effects”[mh]) OR ((“Respiration, Artificial/economics"[mh] OR “Artifical respiration”[tiab]) AND (mechanically ventilat*[tiab] OR mechanical ventilat*[tiab] OR intubat*[tiab] OR ventilator associated*[tiab]))
AND
("cross infection"[mh] OR “iatrogenic disease”[mh] OR “hospital acquired” [tiab] OR “healthcare acquired” [tiab] OR “nosocomial” [tiab] OR “healthcare associated”[tiab] OR “hospital associated”[tiab] OR “health care associated”[tiab] OR “health care acquired”[tiab] OR "hospital related"[tiab] OR “inpatient”[tiab] OR "in hospital"[tiab] OR "in hospitals"[tiab]))

***Clostridium difficile* Infections**
((“Clostridium difficile” [Mesh] OR “Clostridium difficile*” [tiab] OR “C diff”[tiab] OR “Colitis” [Mesh] OR “Colitis” [tiab] OR CDAD[tiab]) AND(“cross infection” [Mesh] OR “bacteremia” [Mesh] OR “iatrogenic disease”[MeSH] OR “nosocomial”[tiab] OR “healthcare associated”[tiab] OR “health care associated”[tiab] OR “hospital acquired”[tiab] OR “hospital infection*”[tiab] OR “inpatient”[tiab]))

Appendix B. Excess Mortality Calculations

We define excess mortality as an estimate of additional deaths due to the hospital-acquired condition (HAC). These are expressed as the percentage of HAC cases who die as a result of the HAC.

Calculation: $P(D|E) - P(D|not\ E)$

Where $P(D|E)$ indicates the probability of death in those with HAC and $P(D|not\ E)$ indicates the probability of death in those at risk for, but do not acquire, the HAC.

	Died	Alive
HAC group	a	b
Non-HAC group	c	d

Meta-analysis Method for Estimating Excess Mortality

We calculate the pooled relative risk using meta-analysis and then calculate excess mortality using the pooled RR and an estimate of the underlying mortality rate:

$$Excess\ Mortality = Pr(D|E) - Pr(D|E') = \frac{\Pr(D|E) - \Pr(D|E')}{\Pr(D|E')} * \Pr(D|E') = (RR - 1) * \Pr(D|E')$$

where RR = $\frac{\Pr(D|E)}{\Pr(D|E')}$ indicates the pooled relative risk estimate from our meta-analysis, and $\Pr(D|E')$ represents the underlying mortality in patients at risk for the HAC.

When the underlying mortality was not available from other literature, we used an estimate of the general inpatient mortality rate. This rate, 2 percent, can be thought of as the overall mortality rate among all hospitalized patients, HAC and non-HAC patients. This rate was used for falls and VTE. For all other HACs, the underlying mortality rate was drawn from the published literature. Exhibit B1 shows the underlying mortality rates and a description of the underlying population alongside the meta-analysis-based estimates of excess mortality.

Exhibit B1. Underlying Mortality Rates

HAC	Underlying Population Description	Underlying Mortality Rate	RR (range)	Pooled RR (95% CI)	Excess Mortality Estimate (95% CI)
ADE	Hospitalized patients who are given anticoagulants, hypoglycemic agents, and opioids during hospitalization	0.02[a]	0.68–3.09	1.61 (1.14, 2.27)	0.012 (0.003–0.025)
CAUTI	Hospitalized patients with urinary catheters	0.071[b]	1.28–1.97	1.50 (1.06, 2.11)	0.036 (0.004–0.079)
CLABSI	Hospitalized patients with central lines	0.086[b]	1.86–4.88	2.72 (1.81, 4.10)	0.15 (0.070–0.27)
Falls	All hospitalized patients who are at risk to fall in the hospital	0.02[a]	3.50	3.50 (2.73, 4.48)	0.050 (0.035–0.070)
OBAE	Estimate was not based on RR and underlying mortality; please see report for details				0.0049 (0.0030–0.013)
Pressure Ulcer	All hospitalized patients who are at risk to have pressure ulcer	0.018[c]	2.42–5.06	3.26 (1.71, 6.17)	0.041 (0.013–0.093)
SSI	All hospitalized postsurgical patients	0.0114[d]	1.75–5.70	3.32 (1.79, 6.18)	0.026 (0.009–0.059)
VAP	Hospitalized patients with ventilator	0.3[e]	0.52–4.90	1.48 (0.64, 3.42)	0.14 (-0.11–0.73)
VTE	All hospitalized patients who are at risk to get VTE	0.02[a]	1.01–13.63	3.15 (2.02, 4.91)	0.043 (0.040–0.078)
CDI	All hospitalized patients who are at risk to get CDI	0.073[f]	1.17–9.60	1.60 (1.38, 1.87)	0.044 (0.028–0.064)

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Appendix C. Meta-Analysis Citation List

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Appendix D. Key Study Characteristics

Exhibit D1. Adverse Drug Events

		Kessler (2013)	Oderda (2007)	Suh (2000)	Classen (2010)	Alexander (2005)	LaPointe (2007)	Seigerman (2014)
Study	Study Year	2009-2010	1990-1999	1998	2004	2004	2005	2009-2010
	Population	Patients with a primary surgical procedure	Adult surgical patients (>17 y) in a single Utah hospital	All patient (≥2 y) admissions to a single New York hospital	Medicare beneficiaries	Patients with NSTE ACS	Patients with NSTE ACS	Patients with cardiac surgery
	Study Design	Retrospective cohort	Matched cohort	Retrospective matched control	Retrospective cohort	Prospective observational	Prospective observational	Retrospective cohort
	Data Source(s)	Hospital administrative data	Hospital clinical and surveillance data	Hospital pharmacy and medical record reporting systems	MPSMS	CRUSADE National Quality Improvement Initiative Registry	CRUSADE National Quality Improvement Initiative Registry	HCUP-NIS
	Number of Cases	4,537	1,586	131	172	22,480[g]	13,803	560
	Definition of HAC	ICD-9	Hospital surveillance criteria and Noranjo criteria	WHO	Medication-specific algorithms	Recommended dosing categories	Recommended dosing categories	Non-specified diagnosis
Cost	Cost or Charges Reported	Cost	Cost	Cost				
	Attributable	Y	Y	Y				
	Year of Cost Data	Not specified	Not specified	Not specified				
	Mean Attributable Cost Calculated	$6,721.00	$786.00	$5,483.00				
	Standard Error	$347.54	$151.79	$1,959.00				
Mortality	Matched Control Sample	Y	Y		N	N	N	N
	Adjusted RR/OR	3.39 (2.42–4.74)	Not reported		Not used in analysis	1.50 (1.03-2.17)	1.31 (0.99-1.73)	1.47 (1.30-1.67)

[g] Represents the number of instances of a major bleed in the presence of drug therapy administration; some patients received more than one drug therapy.

	SE(logRR)/SE(logOR)	0.161	0.321		0.314	0.190	0.142	0.064

Exhibit D2. Catheter-Associated Urinary Tract Infection

		Glied (2016)	**Yi (2014)**	**Byrn (2015)**	**Dasenbrock (2016)**	**Goudie (2015)**	**Sammon (2013)**	**Murthy (2016)**
Study	**Study Year**	2006-2012	2009	2006-2012	2008-2011	2009-2011	1999-2009	2002-2011
	Population	All patients, New York City hospital network	Medicare beneficiaries with ESRD	Patients with colorectal resection	Patients with aneurysmal subarachnoid hemorrhage	Patients 1-17 years of age	Patients with any of 8 surgical oncology procedures	Patients with nontraumatic intracerebral hemorrhage
	Study Design	Matched retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Matched retrospective cohort	Retrospective	Retrospective cohort
	Data Source(s)	Hospital clinical and administrative data	MedPAR, Beneficiary Annual Summary File	University hospital database	HCUP-NIS	HCUP-NIS	HCUP-NIS	HCUP-NIS
	Number of Cases	8,048	884	18	1,793	1,513	105,113	40,018
	Definition of HAC	Lab results and ICD-9	CDC-NHSN	NHSN; NSQIP; ICD-9	ICD-9	ICD-9	ICD-9	ICD-9
Cost	**Cost or Charges Reported**	Charges	Payment	Cost	Charges	Cost		
	Attributable	Y	Y	N	N	Y		
	Year of Cost Data	2012	2009	2012	2011[h]	2011		
	Mean Attributable Cost Calculated	$20,857.50	$5,877.13	$11,587.10	$27,858.50	$7,200.00		
	Standard Error	$2,365.07	$1,644.05	$5,531.84	$2,164.43	$2,538.82		
Mortality	**Matched Control Sample**	Y	Y				N	N
	Adjusted RR/OR	1.28	1.37 (1.04-1.80) ICU; 1.17 (0.62-2.23) non-ICU				1.97 (1.85-2.10)	1.42 (1.10-1.94)
	SE(logRR)/SE(logOR)	0.054	0.311				0.032	0.145

[h] The year of cost data is not specified; the last year of the study period was used for the purpose of this analysis.

Exhibit D2. Catheter-Associated Urinary Tract Infection continued

		Kilgore (2008)
Study	Study Year	2001-2006
	Population	All hospitalized patients
	Study Design	Retrospective cohort
	Data Source(s)	Cardinal Health MedMined database
	Number of Cases	18,930
	Definition of HAC	Lab results
Cost	Cost or Charges Reported	Cost
	Attributable	Y
	Year of Cost Data	2007
	Mean Attributable Cost Calculated	$3,936.00
	Standard Error	$1,961.26
Mortality	Matched Control Sample	
	Adjusted RR/OR	
	SE(logRR)/SE(logOR)	

Exhibit D3. Central-Line Associated Bloodstream Infections

		Dimick (2001)	Glied (2016)	Warren (2006)	Cohen (2010)	Dasenbrock (2016)	Goudie (2014)	Wilson (2014)
Study	Study Year	1998-1999	2006-2012	1998-2000	2006-2007	2008-2011	2008-2011	2008-2011
	Population	Surgical ICU patients in single Maryland hospital	All patients, New York City hospital network	All ICU patients, suburban St. Louis Missouri hospital	All ICU patients,single Chicago-area hospital	Patients with aneurysmal subarachnoid hemorrhage	Patients under 18 years of age	Pediatric hematology and oncology patients in Mid-Atlantic hospital
	Study Design	Prospective cohort	Matched retrospective cohort	Prospective cohort	Case-control	Retrospective cohort	Matched case-control	Matched prospective cohort
	Data Source(s)	Hospital administrative data	Patients' electronic medical record and other digital sources	Hospital clinical and administrative data	Hospital administrative data	HCUP-NIS	HCUP-NIS	Hospital clinical and administrative data
	Number of Cases	9	3,603	41	12	77	1,339	60
	Definition of HAC	Catheter colonization	Lab results and ICD-9	CDC-NHSN	ICD-9	ICD-9	AHRQ PQI	Lab results
Cost	Cost or Charges Reported	Cost	Charges	Cost	Cost	Charges	Cost	Cost
	Attributable	Y	Y	Y	Y	N	Y	Y
	Year of Cost Data	1998	2012	2000	2008	2011[i]	2011	2011[j]
	Mean Attributable Cost Calculated	$56,167.00	$17,197.00	$11,971.00	$82,005.00	$40,983.42	$55,646.00	$69,332.00
	Standard Error	$39,340.52	$4,425.38	$2,964.34	$15,687.02	$7,366.13	$8,602.71	$17,443.43
Mortality	Matched Control Sample	N	Y	N				
	Adjusted RR/OR	4.3 (0.9-19.9)	2.49	Not reported				
	SE(logRR)/SE(logOR)	0.322	0.063	0.160				

[i] The year of cost data is not specified; the last year of the study period was used for the purpose of this analysis.

[j] The year of cost data is not specified; the last year of the study period was used for the purpose of this analysis.

Exhibit D3. Central-Line Associated Bloodstream Infections continued

		Mendizabal (2016)	Sammon (2013)	Stevens (2014)
Study	Study Year	2000-2010	1999-2009	2008-2010
	Population	Adult patients with epilepsy	Patients with any of 8 surgical oncology procedures	All patients, single tertiary-care hospital
	Study Design	Retrospective cohort	Retrospective	Retrospective cohort
	Data Source(s)	HCUP-NIS	HCUP-NIS	Hospital clinical and administrative data
	Number of Cases	Not reported	47,551	197
	Definition of HAC	AHRQ PSI	ICD-9	CDC-NHSN
Cost	Cost or Charges Reported			
	Attributable			
	Year of Cost Data			
	Mean Attributable Cost Calculated			
	Standard Error			
Mortality	Matched Control Sample	N	N	N
	Adjusted RR/OR	4.88 (4.02-5.93)	17.29 (16.33-18.31)	2.27 (1.15-4.46)
	SE(logRR)/SE(logOR)	0.099	0.015	0.346

Exhibit D4. Falls

		Memtsoudis (2012)	Bates (1995)	Wong (2011)
Study	Study Year	1998-2007	1987-1991	2004-2006
	Population	Postoperative hip and knee surgery patients	All patients in a single Massachusetts hospital	Adult inpatients in 3 Midwest hospitals
	Study Design	Retrospective cohort	Retrospective case-control	Retrospective case-control
	Data Source(s)	HCUP-NIS	Hospital clinical data	Hospital incident reporting system
	Number of Cases	9,198	62	57
	Definition of HAC	ICD-9	Patient reported as having fallen	Serious fall-related injury
Cost	Cost or Charges Reported	Cost	Charges	Cost
	Attributable	N	Y	Y
	Year of Cost Data	2007[k]	1991[l]	2009
	Mean Attributable Cost Calculated	$2,247	$3,802	$13,806
	Standard Error	$90.57	$2,262.97	$6,031.23
Mortality	Matched Control Sample	N		
	Adjusted RR/OR	Not reported		
	SE(logRR)/SE(logOR)	0.126		

[k] The year of cost data is not specified; the last year of the study period was used for the purpose of this analysis.

[l] The year of cost data is not specified; the last year of the study period was used for the purpose of this analysis.

Exhibit D5. Obstetric Adverse Events

		Zhan (2003)	Hunt (2016)	Callaghan (2008)	Callaghan (2012)	Creanga (2014)	Grobman (2014)
Study	**Study Year**	2000	2010	1991-2003	1998-2009	2008-2010	2008-2011
	Population	Women with delivery-related discharge	Women with delivery-related discharge in New York	Women with delivery-related discharges	Women with delivery-related discharges	Women with delivery-related discharges in 7-state sample	Women who delivered ≥23 weeks gestations in any of 25 cohort hospitals
	Study Design	Retrospective cohort	Retrospective cohort	Retrospective	Retrospective	Retrospective	Retrospective cohort
	Data Source(s)	HCUP-NIS	State-level inpatient database	National Hospital Discharge Survey	HCUP-NIS	HCUP-NIS	*Eunice Kennedy Shriver* National Institute of Child Health & Human Development Maternal-Fetal Medicine Units Network cohort
	Number of Cases	64,879	1,053	257,000	597,920	74,720	332
	Definition of HAC	AHRQ PSI	ICD-9	ICD-9	ICD-9	ICD-9	Geller et al. (2004) morbidity scoring system
Cost	**Cost or Charges Reported**	Charges	Cost				
	Attributable	Y	Y				
	Year of Cost Data	2000	2010				
	Mean Attributable Cost Calculated	$8.35	$1,091.34				
	Standard Error	$28.344	$30.20				
Mortality	**Matched Control Sample**			N	N	N	N
	Adjusted RR/OR			Alternative estimation method used	Alternative estimation method used	Alternative estimation method used	Alternative estimation method used
	SE(logRR)/SE(logOR)			-	-	-	-

Exhibit D6. Pressure Ulcers

		Bauer (2016)	Spector (2016)	Goudie (2015)	Zhan (2003)	Mendizabal (2016)	Lyder (2012)
Study	Study Year	2008-2012	2011–2012	2009-2011	2000	2000-2010	2006-2007
	Population	General hospitalized patients	Adult patients with surgery	Patients 1-17 years of age	General hospitalized patients	Adult patients with epilepsy	Medicare beneficiary FFS sample
	Study Design	Retrospective	Matched retrospective cohort	Matched retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective
	Data Source(s)	HCUP-NIS	HCUP-SID and MPSMS	HCUP-NIS	HCUP-NIS	HCUP-NIS	MPSMS
	Number of Cases	676,435	534	120	843	Not reported	2,313
	Definition of HAC	ICD-9	MPSMS chart review	ICD-9	ICD-9	AHRQ PSI	ICD-9
Cost	Cost or Charges Reported	Charges	Cost	Cost	Charges		
	Attributable	N	Y	Y	Y		
	Year of Cost Data	Not specified	2011	2011	2000		
	Mean Attributable Cost Calculated	$19,900.00	$8,251.00	$19,740.00	$5,422.50		
	Standard Error	$149.72	$11,553.78	$11,553.78	$184.00		
Mortality	Matched Control Sample	N				N	N
	Adjusted RR/OR	Not reported				2.42 (2.20-2.66)	2.81 (2.44-3.23)
	SE(logRR)/SE(logOR)	0.004				0.048	0.072

Exhibit D7. Surgical Site Infections

		Glied (2016)	Kim (2012)	Boltz (2011)	de Lissovoy (2009)	Eagye (2009)	Sammon (2013)
Study	Study Year	2006-2012	2001-2008	2007-2009	2005	2005-2007	1999-2009
	Population	All patients, New York City hospital network	Adults undergoing radical cystectomy for bladder cancer	Adult general and vascular surgical patients in single hospital	Surgical patients	Patients with ECS procedures in single Connecticut hospital	Patients with any of 8 surgical oncology procedures
	Study Design	Matched retrospective cohort	Retrospective cohort	Retrospective cohort	Matched retrospective cohort	Prospective cohort and case-control	Retrospective
	Data Source(s)	Patients' electronic medical record and other digital sources	HCUP-NIS	Hospital clinical data	HCUP-NIS	Hospital administrative data	HCUP-NIS
	Number of Cases	1,292	381	186	6,891	46	80,086
	Definition of HAC	Lab results and ICD-9	ICD-9	NSQIP; CDC NNIS	ICD-9	ICD-9	ICD-9
Cost	Cost or Charges Reported	Charges	Cost	Cost	Cost	Cost	
	Attributable	Y	N	Y	Y	N	
	Year of Cost Data	2012	2008	Not specified	2005	Not specified	
	Mean Attributable Cost Calculated	$34,813.00	$36,454.00	$10,497.00	$20,842.00	$21,228.07	
	Standard Error	$7,274.19	$2,530.06	$3,532.46	$971.19	$3,844.11	
Mortality	Matched Control Sample	Y	N				N
	Adjusted RR/OR	Not reported	5.70 (3.94–8.24)				3.78 (3.56-4.02)
	SE(logRR)/SE(logOR)	0.129	0.188				0.031

Exhibit D8. Venous Thromboembolism

		Hennessey (2012)	Kim (2012)	Goudie (2015)	Ali (2011)	Gephart (2012)	Mendizabal (2016)	Nguyen (2008)
Study	Study Year	2003-2008	2001-2008	2009-2011	2005	2002-2008	2000-2010	1998-2004
	Population	Patients with head or neck cancers	Adults undergoing radical cystectomy for bladder cancer	Patients 1-17 years of age	Patients with cirrhosis	Adult patients with thoracic/thoraco-lumbar spinal fusion	Adult patients with epilepsy	Patients with inflammatory bowel disease
	Study Design	Retrospective cohort	Retrospective case control	Matched retrospective cohort	Retrospective cross sectional	Retrospective cohort	Retrospective cohort	Retrospective cohort
	Data Source(s)	HCUP-NIS	HCUP-NIS	HCUP-NIS	HCUP-NIS	HCUP-NIS	HCUP-NIS	HCUP-NIS
	Number of Cases	1,860	219	1,563	8,231	162	Not reported	1,934
	Definition of HAC	ICD-9	ICD-9	ICD-9	ICD-9	ICD-9	AHRQ PSI	ICD-9
Cost	Cost or Charges Reported	Cost	Cost	Cost				
	Attributable	Y	N	Y				
	Year of Cost Data	2011	2008	2011				
	Mean Attributable Cost Calculated	$10,313.28	$27,387	$27,686.00				
	Standard Error	$1,159.73	$3,024.31	$8,443.52				
Mortality	Matched Control Sample	N	N		N	N	N	N
	Adjusted RR/OR	3.08 (1.56 – 6.12)	5.85 (3.61 – 9.48)		1.01 (0.83, 1.23)	13.63 (6.37-29.16)	3.09 (2.64-3.62)	2.50 (1.83 – 3.43)
	SE(logRR)/SE(logOR)	0.349	0.246		0.100	0.388	0.081	0.160

Exhibit D8. Venous Thromboembolism continued

		Satahoo (2015)	Trinh (2014)	Wu (2010)
Study	Study Year	2005-2009	1999-2009	1998-2006
	Population	Patients with burn injuries	Patients with major cancer surgery	Patients with liver cirrhosis
	Study Design	Retrospective cohort	Retrospective cohort	Retrospective cohort
	Data Source(s)	HCUP-NIS	HCUP-NIS	HCUP-NIS
	Number of Cases	297	33,409	Not reported
	Definition of HAC	ICD-9	ICD-9	ICD-9
Cost	Cost or Charges Reported			
	Attributable			
	Year of Cost Data			
	Mean Attributable Cost Calculated			
	Standard Error			
Mortality	Matched Control Sample	N	N	N
	Adjusted RR/OR	1.88 (1.147 – 3.075)	5.30 (4.88 – 5.76)	2.30 (2.06 – 2.57)
	SE(logRR)/SE(logOR)	0.252	0.042	0.056

Exhibit D9. Ventilator-Associated Pneumonia

		Cocanour (2005)	Kollef (2012)	Rello (2002)	Restrepo (2010)	Warren (2003)	Apisarnthanarak (2003)	Gupta (2015)
Study	Study Year	2002-2003	2008-2009	1998-1999	2002-2006	1998-1999	2000-2001	2009
	Population	ICU patients with shock trauma in a single Texas tertiary-care hospital	Adults ICU patents, ≥1 day in ICU with mechanical ventilation ≥2 days	All patients admitted to ICU who received mechanical ventilation for >24h	Hospitalized patients in 54 medical centers, nationwide	All patients admitted to ICU in a single Missouri medical center	Extremely pre-term neonates in Missouri hospital	Mechanically ventilated patients <18 y across 16 geographically diverse PICUs
	Study Design	Matched retrospective cohort	Matched retrospective cohort	Matched retrospective cohort	Matched retrospective cohort	Prospective cohort	Prospective and nested cohort	Prospective cohort
	Data Source(s)	Hospital administrative data	Premier Healthcare Informatics Database	MediQual Profile database	NASCENT study	Hospital clinical and administrative data	Hospital clinical data	Hospital CXR
	Number of Cases	93	2,144	816	30	127	19	108
	Definition of HAC	NNIS guideline	ICD-9	ICD-9	ICD-9 and lab results	NNIS criteria	CDC-NNIS	CDC-NHSN
Cost	Cost or Charges Reported	Cost	Cost	Charges	Cost	Cost		
	Attributable	Y	Y	N	N	Y		
	Year of Cost Data	2003	2009	1999	2005	1999		
	Mean Attributable Cost Calculated	$57,158.00	$39,828.00	$20,647.00	$44,331.50	$11,897.00		
	Standard Error	$1,045.59	$2,250.00	$1,730.21	$6,731.00	$5,344.23		
Mortality	Matched Control Sample	Y	Y	Y	Y		Y	N
	Adjusted RR/OR	Not reported	Not reported	Not reported	Not reported		3.4 (1.2, 12.3)	3.07 (1.36 – 6.90)
	SE(logRR)/SE(logOR)	0.414	0.052	0.062	0.435		0.594	0.414

Exhibit D9. Ventilator-Associated Pneumonia continued

		Josephson (2010)	Klompas (2011)	Klompas (2012)	Sammon (2013)
Study	Study Year	2006-2007	2006-2007	Not specified	1999-2009
	Population	Patients with neurovascular disease in a California hospital	Mechanically ventilated patients >18 y in 3 geographically diverse hospitals	8 U.S. hospital ICUs	Patients with any of 8 surgical oncology procedures
	Study Design	Retrospective	Retrospective matched control	Retrospective	Retrospective cohort
	Data Source(s)	Hospital clinical and administrative	Hospital clinical data	Hospital clinical data	HCUP-NIS
	Number of Cases	24	55	Not reported	87,594
	Definition of HAC	CDC-NHSN	CDC-NHSN	Candidate surveillance definitions	ICD-9
Cost	Cost or Charges Reported				
	Attributable				
	Year of Cost Data				
	Mean Attributable Cost Calculated				
	Standard Error				
Mortality	Matched Control Sample	N	Y	Y	N
	Adjusted RR/OR	1.11 (0.37 – 3.30)	1.1 (0.5 – 2.4)	2.1 (1.3 – 3.3)	4.90 (4.64 – 5.17)
	SE(logRR)/SE(logOR)	0.558	0.395	0.238	0.028

Exhibit D10. *Clostridium difficile* Infections

		Donnelly (2015)	Glance (2011)	Kim (2012)	Lagu (2014)	Pakyz (2011)	Sundaram (2014)	Tabak (2013)
Study	Study Year	2012-2014	2005-2006	2001-2008	2004-2010	2002-2007	2008-2011	2007-2008
	Population	Patients with solid organ transplant	Trauma patients LOS >3 days	Adults undergoing radical cystectomy for bladder cancer	Adult, non-surgical patients with sepsis	Adult patients	Adult patients with primary diagnosis of alcoholic hepatitis	Adult patients in six Pennsylvania hospitals
	Study Design	Retrospective cohort	Retrospective	Retrospective cohort	Retrospective cohort	Retrospective	Retrospective	Retrospective
	Data Source(s)	University Health System Consortium Clinical Database	HCUP-NIS	HCUP-NIS	Premier Healthcare Informatics Database	University Health System Consortium Clinical Database	HCUP-NIS	Clinical research database
	Number of Cases	1,109	768	73	2,368	10,857	177	282
	Definition of HAC	ICD-9	ICD-9	ICD-9	ICD-9, lab results, and treatment codes	ICD-9 and treatment codes	ICD-9	Toxin Assay
Cost	Cost or Charges Reported	Cost	Cost	Cost	Cost	Cost	Charges	Cost
	Attributable	Y	Y (ratio)	N	Y	N	N	Y
	Year of Cost Data	2014	2011[m]	2008	2010	2007	2011	2013[n]
	Mean Attributable Cost Calculated	$27,890.65	$14,905.00	$22,634.00	$4,924.00	$27,160.00	$3,894.00	$6,117.00
	Standard Error	$1,617.07	$1,147.00	$3,346.00	$1,244.00	$249.00	$1,382.00	$2,274.00
Mortality	Matched Control Sample	N	N	N	Y	Y	N	Y
	Adjusted RR/OR	1.22 (0.9-1.65)	1.87 (1.31-2.66)	2.11 (1.04-4.28)	Not reported	Not reported	1.75 (1.01-3.03)	1.61
	SE(logRR)/SE(logOR)	0.155	0.181	0.361	0.060	0.037	0.280	0.214

[m] The year of cost data is not specified; the last year of the study period was used for the purpose of this analysis.

[n] The year of cost data is not specified; the last year of the study period was used for the purpose of this analysis.

Exhibit D10. *Clostridium difficile* Infections continued

		Damle (2014)	O'Brien (2007)	Flagg (2014)	Keshavamurthy (2014)	Lemaire (2015)	Lesperance (2011)	Luo (2015)
Study	Study Year	2008-2012	1999-2003	2004-2008	2005-2011	2002-2009	2004-2006	2005-2011
	Population	Adult patients with colorectal resection and malignancy	All hospitalizations in a single Massachusetts hospital database with primary or secondary diagnosis of CDAD	Patients who underwent cardiac surgery	Patients who underwent cardiac surgery in a single Ohio hospital	Patients who underwent coronary artery bypass grafting and valvular surgery	Patients who underwent colonic resection during hospital admission	Adult patients with leukemia
	Study Design	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort	Retrospective cohort
	Data Source(s)	University Health System Consortium Database	Hospital database	HCUP-NIS	Hospital clinical data and REDCap database	HCUP-NIS	HCUP-NIS	HCUP-NIS
	Number of Cases	1,266	3,692	2,581	145	Not reported	10,077	42,438
	Definition of HAC	ICD-9	ICD-9	ICD-9	Lab testing	ICD-9	ICD-9	ICD-9
Cost	Cost or Charges Reported	Cost	Cost					
	Attributable	Y	Y					
	Year of Cost Data	2008	2005					
	Mean Attributable Cost Calculated	$14,130.00	$13,675.00					
	Standard Error	$465.00	$583.00					
Mortality	Matched Control Sample			Y	Y	N	N	N
	Adjusted RR/OR			Not reported	Not reported	2.0 (1.65-2.35) (CABG) 1.9 (1.51-2.39) VS	1.19 (1.11-1.29)	1.17 (1.13-1.22)
	SE(logRR)/SE(logOR)			0.089	0.276	0.095	0.038	0.02

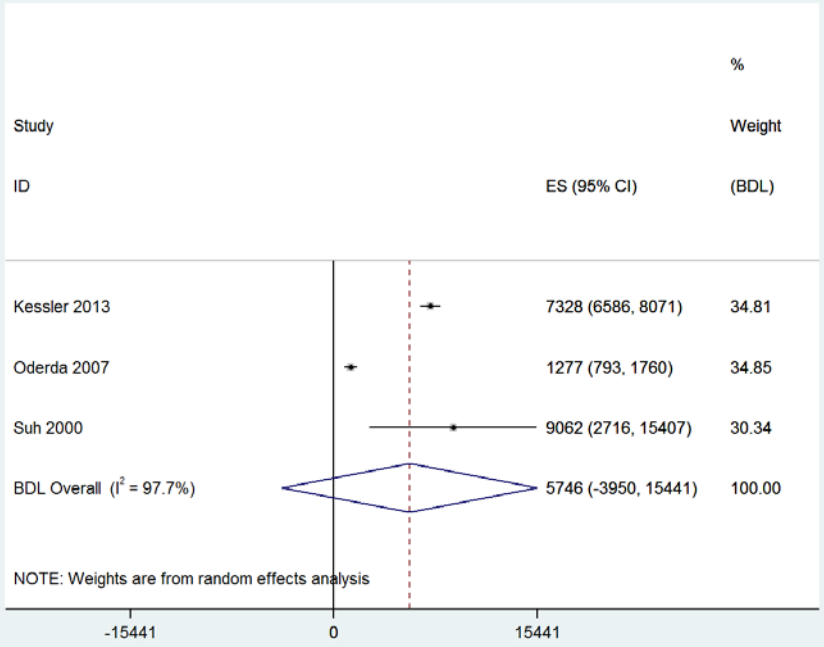
Exhibit D10. *Clostridium difficile* Infections Ccontinued

		Skovrlj (2014)
Study	Study Year	2002-2011
	Population	Patients with lumbar spine surgery for degenerative diagnoses
	Study Design	Retrospective
	Data Source(s)	HCUP-NIS
	Number of Cases	2,867
	Definition of HAC	ICD-9
Cost	Cost or Charges Reported	
	Attributable	
	Year of Cost Data	
	Mean Attributable Cost Calculated	
	Standard Error	
Mortality	Matched Control Sample	N
	Adjusted RR/OR	9.6 (5.17-17.83)
	SE(logRR)/SE(logOR)	0.316

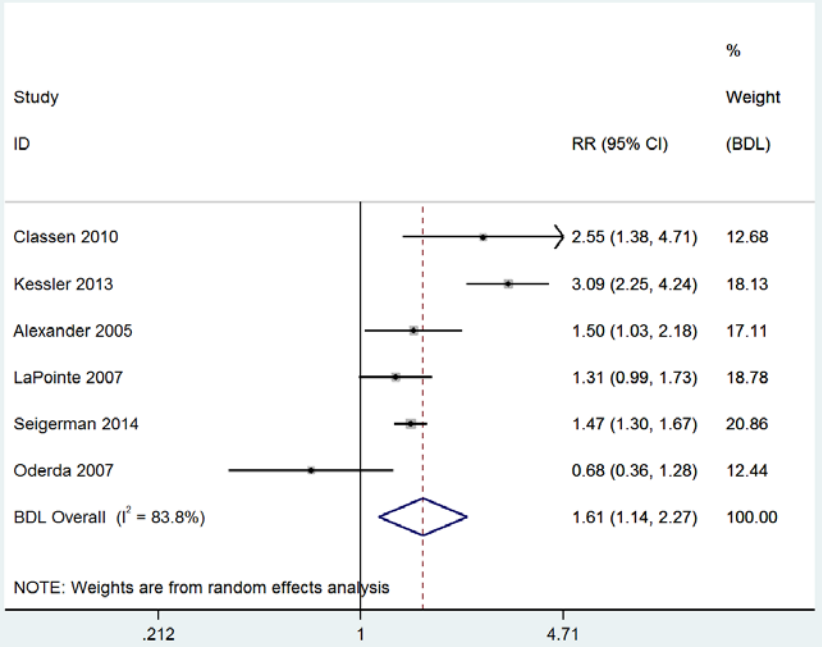
Appendix E. Forest Plots

Adverse Drug Events

Additional Costs

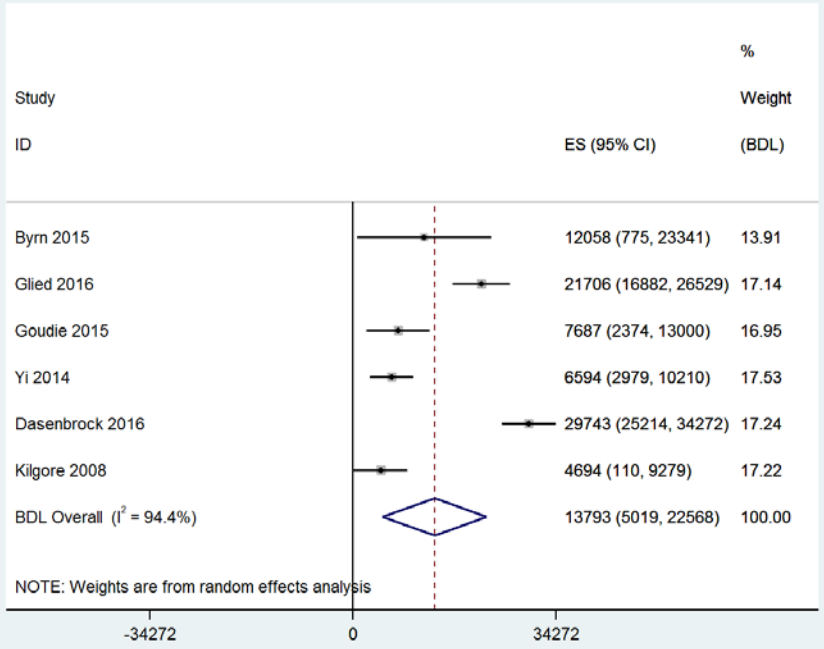


Excess Mortality



Catheter-Associated Urinary Tract Infection

Additional Costs



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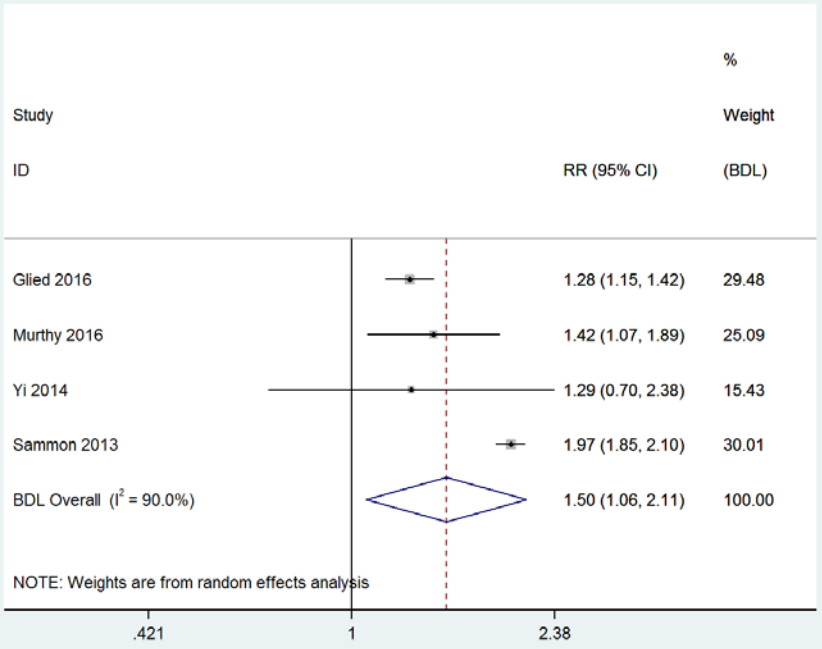
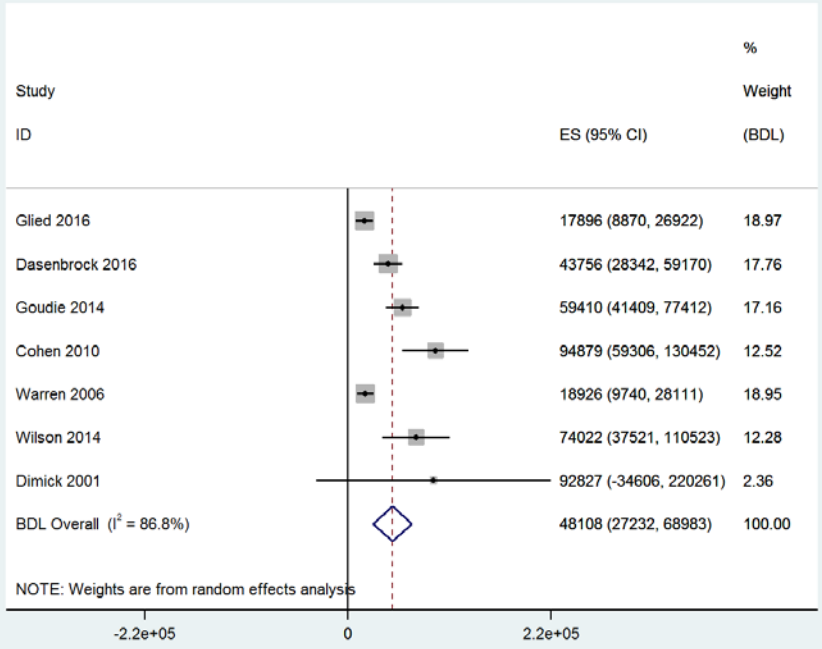


Central-Line Associated Bloodstream Infections

Additional Costs



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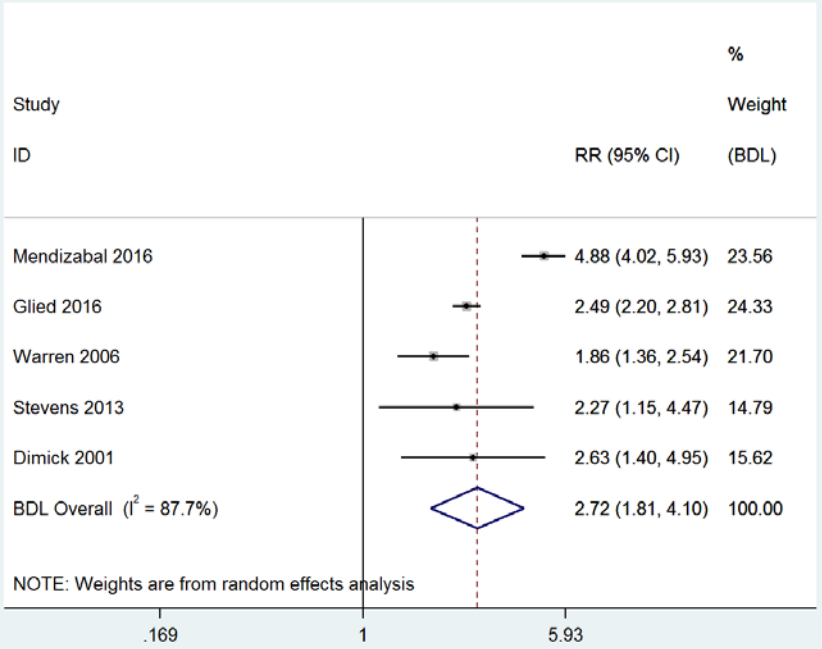
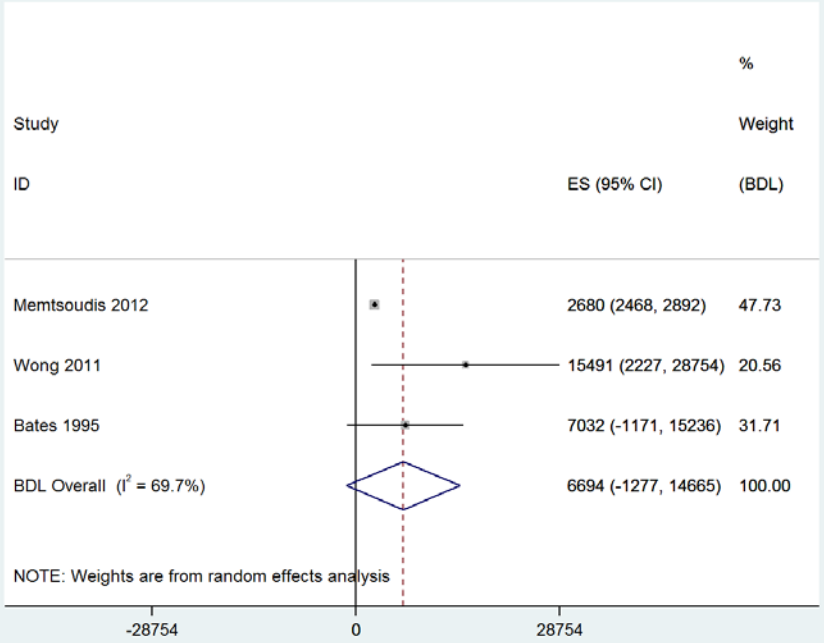


Falls

Additional Costs



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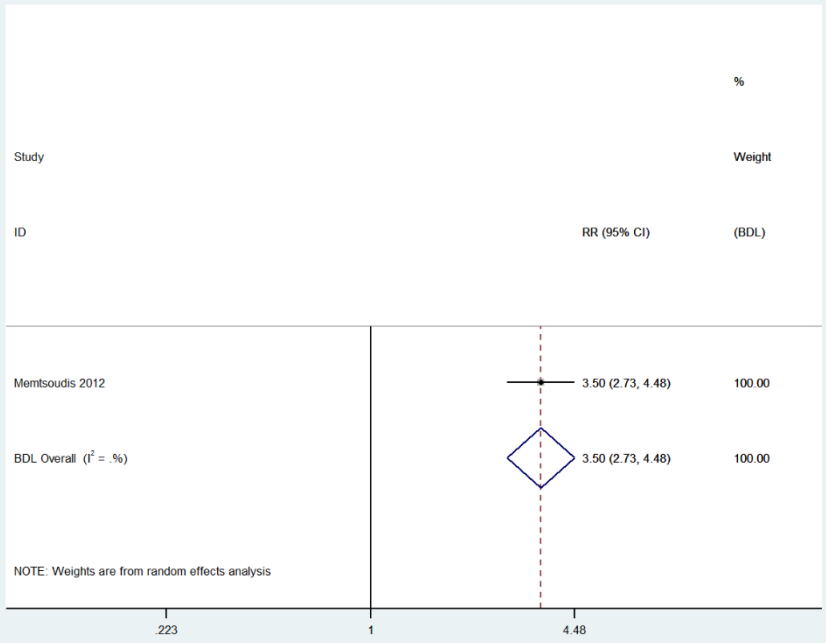
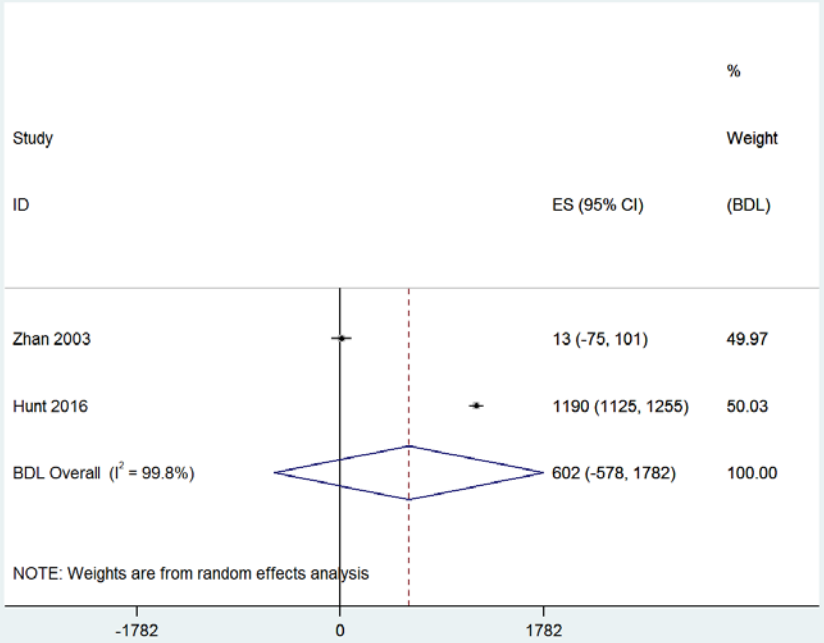


Obstetric Adverse Events

Additional Costs



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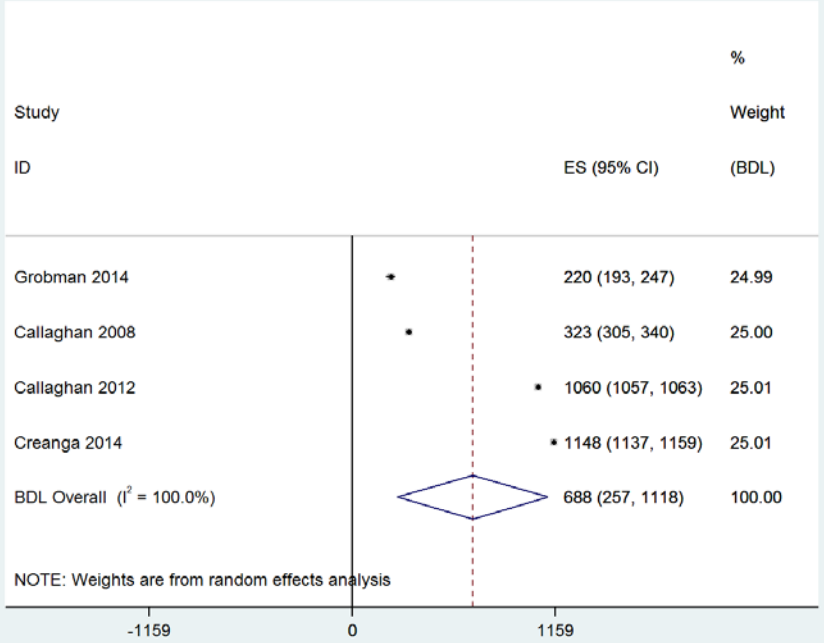
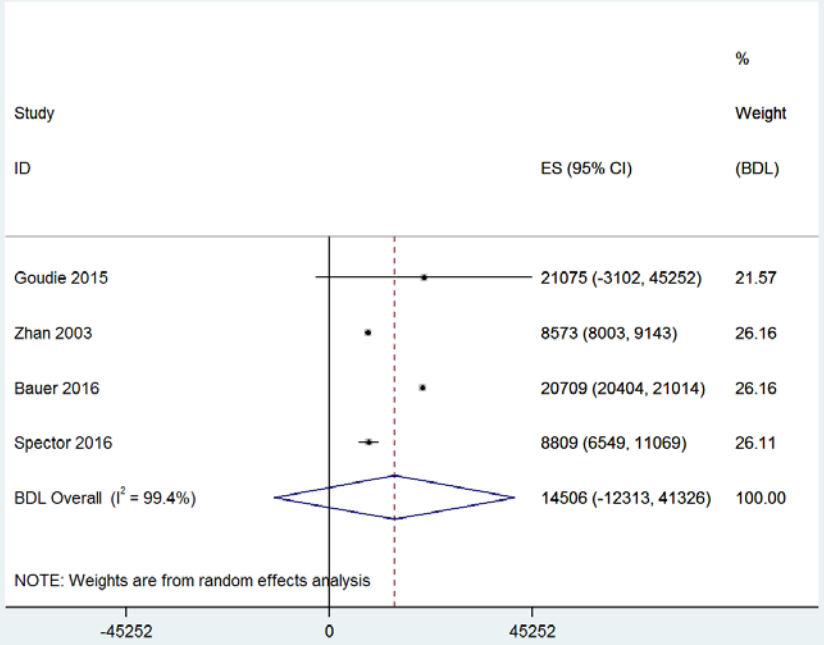


Pressure Ulcers

Additional Costs



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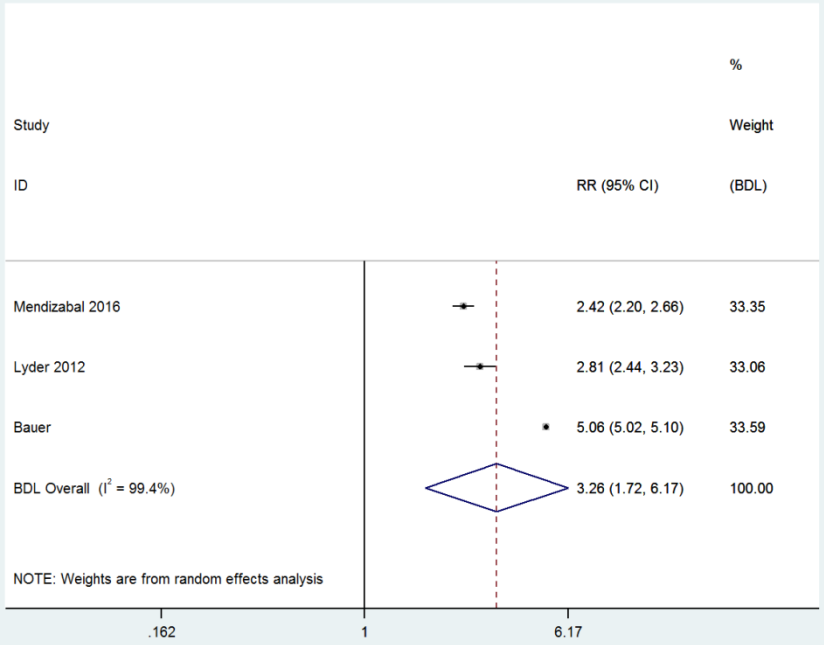
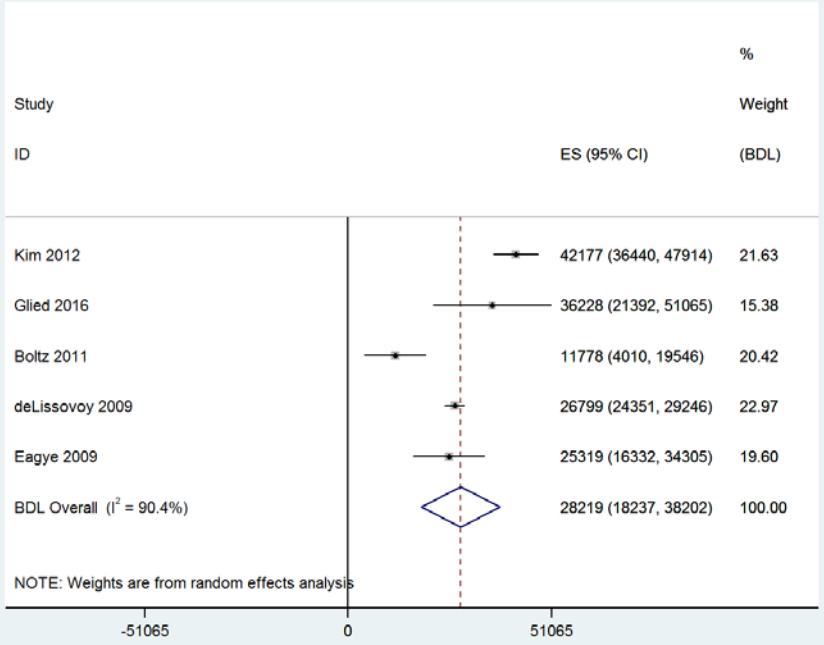


Surgical Site Infections

Additional Costs



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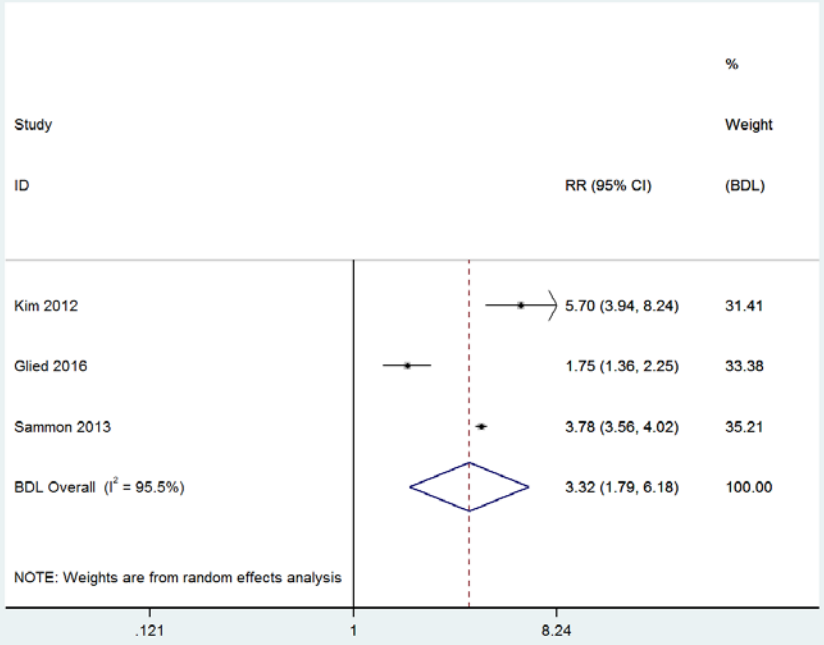
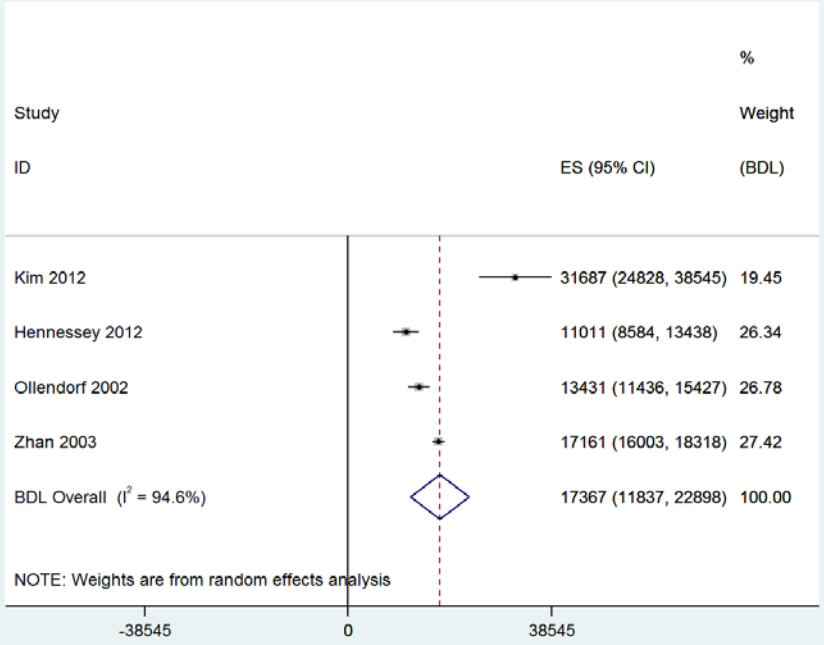


Venous Thromboembolism

Additional Costs



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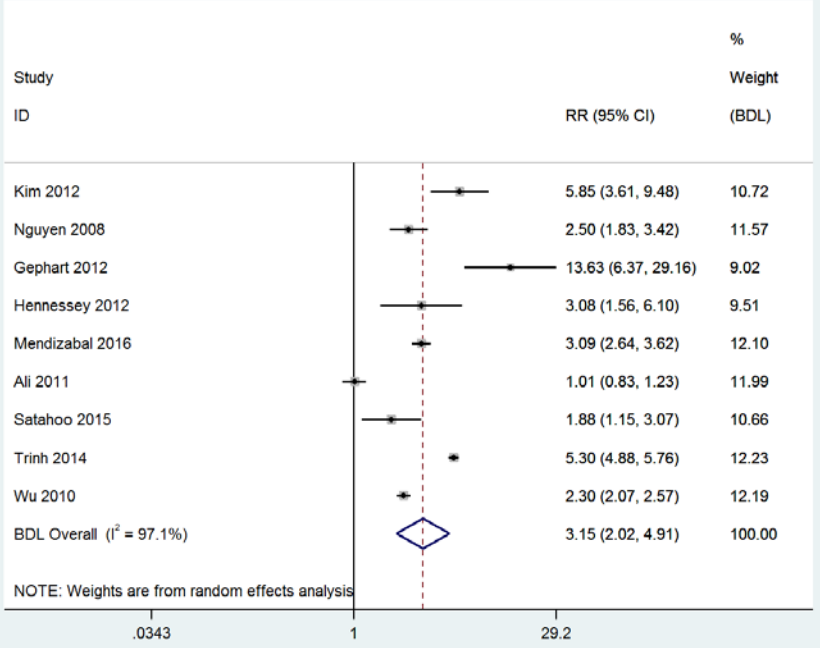
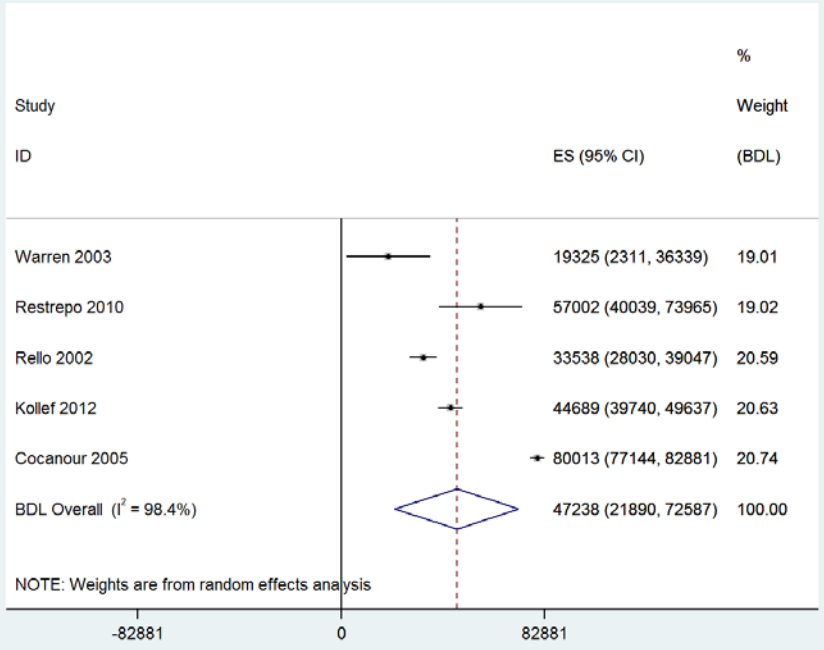


Ventilator-Associated Pneumonia

Additional Costs



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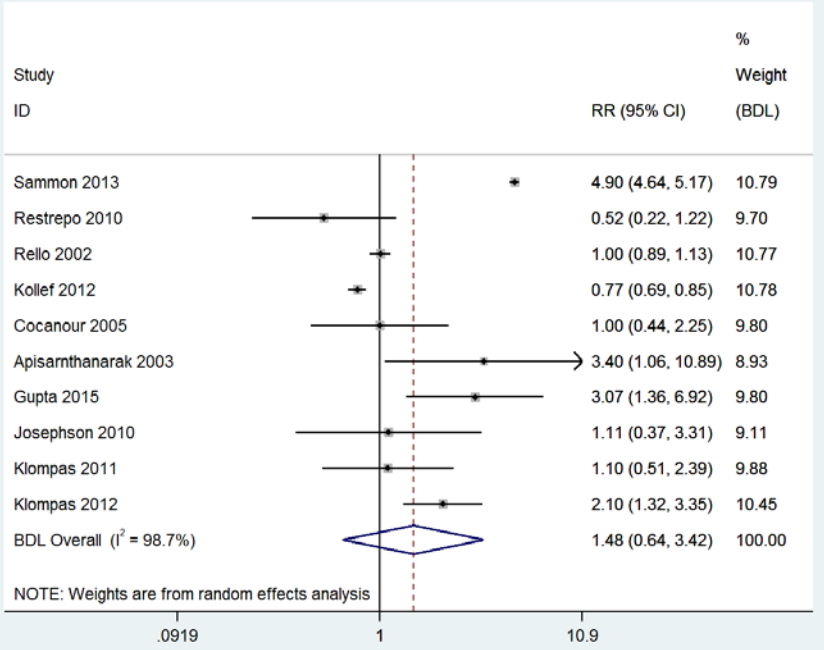
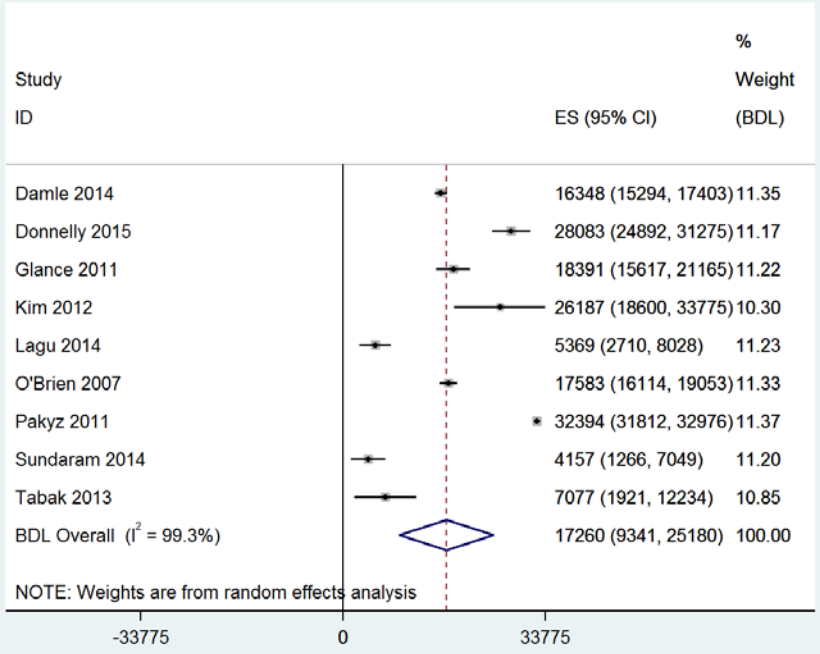


Clostridium difficile Infections

Additional Costs



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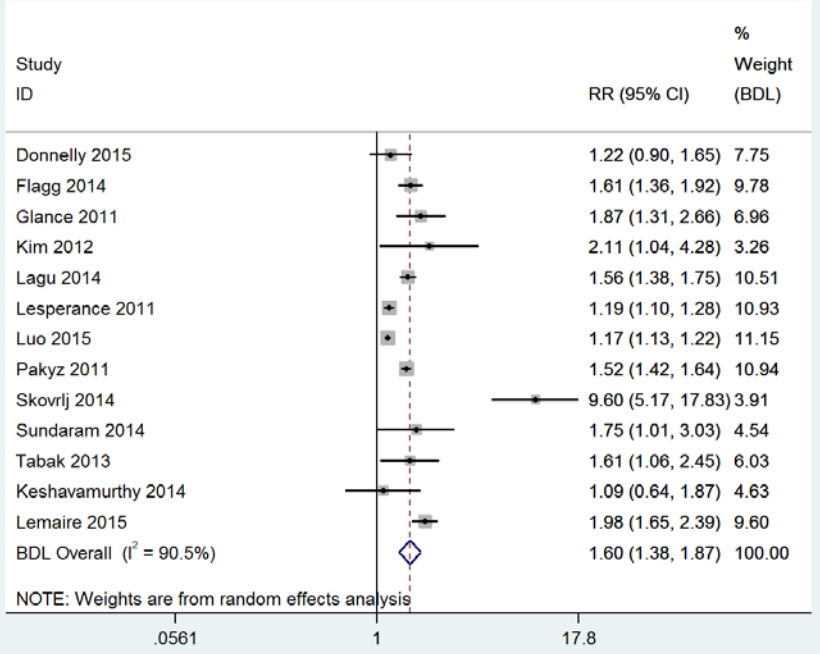

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