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Original Article

The preventable proportion of healthcare-associated infections 2005–2016: Systematic review and meta-analysis

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Abstract

Objective: The preventable proportion of healthcare-associated infections (HAIs) may decrease over time as standards of care improve. We aimed to assess the proportion of HAIs prevented by multifaceted infection control interventions in different economic settings.

Methods: In this systematic review and meta-analysis, we searched OVID Medline, EMBASE, CINAHL, PubMed, and The Cochrane Library for studies published between 2005 and 2016 assessing multifaceted interventions to reduce catheter-associated urinary tract infections (CAUTIs), central-line–associated bloodstream infections (CLABSIs), surgical site infections (SSIs), ventilator-associated pneumonia (VAP), and hospital-acquired pneumonia not associated with mechanical ventilation (HAP) in acute-care or long-term care settings. For studies reporting raw rates, we extracted data and calculated the natural log of the risk ratio and variance to obtain pooled risk ratio estimates.

Results: Of the 5,226 articles identified by our search, 144 studies were included in the final analysis. Pooled incidence rate ratios associated with multifaceted interventions were 0.543 (95% confidence interval [CI], 0.445–0.662) for CAUTI, 0.459 (95% CI, 0.381–0.554) for CLABSI, and 0.553 (95% CI, 0.465–0.657) for VAP. The pooled rate ratio was 0.461 (95% CI, 0.389–0.546) for interventions aiming at SSI reduction, and for VAP reduction initiatives, the pooled rate ratios were 0.611 (95% CI, 0.414–0.900) for before-and-after studies and 0.509 (95% CI, 0.277–0.937) for randomized controlled trials. Reductions in infection rates were independent of the economic status of the study country. The risk of bias was high in 143 of 144 studies (99.3%).

Conclusions: Published evidence suggests a sustained potential for the significant reduction of HAI rates in the range of 35%–55% associated with multifaceted interventions irrespective of a country's income level.

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Few studies have estimated the number of infections prevented or lives saved if hospitals applied best practices in infection prevention and control (IPC). More than 30 years ago, the Centers for Disease Control and Prevention's Study on the Efficacy of Nosocomial Infection Control (SENIC) project made such an estimate.[1] The authors concluded that 30%–35% of most healthcare-associated infections (HAIs) were preventable with effective surveillance and control programs. Numerous studies have since examined interventions to reduce the most common HAIs: central-line–associated bloodstream infections (CLABSIs), catheter-associated urinary tract infections (CAUTIs), ventilator-associated pneumonia (VAP) and surgical site infection (SSI). Harbarth *et al*[2] performed a systematic literature review to describe multimodal intervention studies to give a crude estimate of the proportion of potentially preventable nosocomial infections almost 20 years later, in 2004. They concluded that great potential existed to decrease nosocomial infection rates, from a minimum reduction effect of 10% to a maximum effect of 70%, depending on the setting, study design, baseline infection rates, and type of infection. In 2011, a review by Umscheid *et al*[3] confirmed that as many as 65%–70% of cases of CLABSI and CAUTI and 55% of cases of VAP and SSI might be preventable with current evidence-based strategies, with CLABSI having the highest number of preventable deaths and the highest cost impact. Irrespective of these consistent numbers on reported preventable proportions of infections in the past, the effect of interventions that aim to further reduce HAIs may diminish over time as quality initiatives and infection control programs improve, especially in higher income settings—a phenomenon known as the law of diminishing returns.

We therefore aimed to perform a systematic review and meta-analysis on the proportion of preventable HAIs among the adult patient population in different economic settings based on the literature published in 2005–2016.

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Methods

Data sources and searches

For this systematic review and meta-analysis, we performed an electronic search of OVID Medline, EMBASE, CINAHL (The Cumulative Index to Nursing and Allied Health Literature), PubMed, and The Cochrane Library for articles published between January 1, 2005, and October 7, 2016, based on a previously defined protocol. The search strategy was developed with the help of an experienced librarian with expertise in literature searches for systematic reviews and meta-analyses. For the detailed search strategy, see Supplemental Table S1.

Study selection

We included all quasi-experimental studies, cohort studies, case-control studies, and randomized controlled trials evaluating multifaceted interventions to reduce CAUTIs, CLABSIs, SSIs, VAP, and hospital-acquired pneumonia in nonventilated patients (HAP) in acute-care or long-term care settings that reported infection rates as an outcome. Interventions were considered multifaceted if 2 or more interventions (eg, education AND surveillance, preoperative skin decolonization AND changes in the preoperative skin disinfection protocol) with the aim of reducing HAIs were performed. Surveillance of HAIs or audits were only considered interventions if these measures were combined with feedback. There was no restriction by study site, country, or follow-up period. Only studies published in English were considered eligible. Studies were excluded if they were cases series, case reports, outbreak reports, or ecological studies; if they included patients <16 years of age; or if they investigated only 1 specific intervention measure.

Two authors (P.W.S. and S.P.K.) screened the title and abstract of each reference identified by the search and applied the inclusion criteria. For possibly relevant articles, the full-text article was reviewed independently by the 2 authors. Final inclusion of studies was determined by agreement of both reviewers and involvement of a third author (H.S.) in cases of discrepancy. After in-depth discussion of the different opinions, the authors agreed unanimously on the final classification and inclusion of all studies.

Data extraction and quality assessment

Two authors (P.W.S. and S.P.K.) independently extracted data from published reports. In the case of missing data, no attempts were made to contact study authors, and these articles were subsequently excluded. Data extraction was performed using a standardized data collection form. The reviewers extracted data on study design, population and setting, interventions tested, and outcome measurement. Countries were classified by economic income group according to the World Bank list of economies (March 2017 version).[4] The primary outcome measure was the proportion of infected patients or the infection rate. Data were extracted as proportions if results were only reported as probability of events or as rates per number of device days. If rates were not reported per number of device days but were only reported per number of patient days, the latter was extracted.

To assess methodological quality and risk of bias in randomized controlled studies and controlled before-and-after studies, included articles were examined for (1) generation of allocation sequence, (2) concealment of allocation, (3) similarity of baseline outcome measurement, (4) similarity of baseline characteristics, (5) addressing incomplete outcome data, (6) prevention of knowledge of allocated interventions, (7) protection against contamination, (8) freedom of selective outcome reporting, and (9) freedom from other risks of bias.[5,6] For interrupted time-series analyses, we assessed (1) independency of other changes, (2) prespecification of the shape of the intervention effect, (3) likelihood of affection of data collection by the intervention, (4) appropriate analysis, (5) prevention of knowledge of the allocated intervention during the study, (6) addressing incomplete outcome data, (7) freedom of selective outcome reporting, and (8) freedom from other risk of bias.[5,6] Because uncontrolled before-and-after studies are generally considered low quality, no further quality assessment was performed for this type of study.[5]

Data synthesis and analysis

For studies reporting only aggregated data without the possibility to calculate raw numbers, no data synthesis was performed. For studies reporting raw rates, we calculated the natural log of the risk ratio and variance to meta-analyze the extracted data and to obtain pooled risk ratio estimates. Data synthesis was performed using STATA version 11.1 software (StataCorp, College Station, TX). Because heterogeneity was anticipated between studies, random effects models using the method of DerSimonian and Laird, with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model (for meta-analysis of rates) or the Mantel-Haenszel model (for meta-analysis of proportions) were used for all analyses to obtain a summary estimate (incidence rate ratio [IRR] or rate ratio [RR], as appropriate) of the average effect with its 95% confidence interval (CI). A continuity correction of 0.5 to the counts from both groups of the study were added where a study contained a zero count in either the control group or the intervention group.[5,7]

Statistical heterogeneity was initially inspected graphically in a forest plot. We quantified the degree of heterogeneity using the I^2 statistic and defined heterogeneitiy a priori as $I^2 > 60\%$. Subgroup analyses for differences between country economic income categories were performed using fixed-effect models if criteria for heterogeneity were not met. P values <.05 were considered statistically significant.

Publication bias was investigated using a funnel plot in which the standard error of the effect estimate of each study was plotted against the estimate and was quantified using the Egger test.

Results

Study selection

The review process is summarized in Figure 1. Of the 5,226 articles retrieved with our search strategy, 208 were retained for full-text review, and 144 studies met the inclusion criteria and were included in the systematic review and meta-analysis.[8–152] Included studies are described in Table 1. There were 138 quasi-experimental studies (95.8%): 1 controlled before-and-after study, 137 uncontrolled before-and-after studies.[8–15,17–44,46–49,51–59,61–120,122–133,135–140,142–152] The final group of articles also included 3 randomized controlled trials (2.1%),[121,134,141] 2 cluster-randomized controlled trials (1.4%),[50,60] and 1 time-series analysis (0.7%).[45] Moreover, 109 studies (75.7%) were performed in high income settings,[8,10–12,14,15,17,18,20,21,23–30,34–45,47,48,50–53,55–57,60,64–68,72–77,79–82,85–91,93–97,99–101,103–120,122,124–131,134,138,140,143,144,146–152] 26 studies (18.1%) were conducted in upper middle income settings,[9,13,22,31–33,59,61–63,69–71,78,92,98,102,121,123,132,133,135,137,139,141,145] and 9 studies

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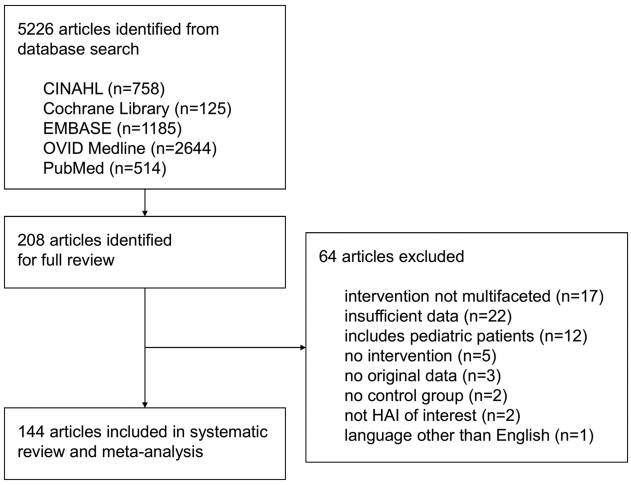

Fig. 1. Study selection. Note. HAI, healthcare-associated infection.

(6.3%) were conducted in lower middle income countries.[19,46,49,54,58,83,84,136,142]

Catheter-associated urinary tract infection

One cluster-randomized controlled trial reported an IRR of 0.644 (95% CI, 0.456–0.910) associated with a multifaceted intervention to reduce CAUTI rates (Supplementary Fig. S1a).[50] Data from 18 before-and-after studies were available for meta-analysis.[20,26,32,46,52,58,61,71,78,79,83,102,116,129,135,137,142,149] Compared to standard of care, multifaceted interventions were associated with a pooled IRR of 0.543 (95% CI, 0.445–0.662), with overall heterogeneity of $I^2 = 78.9\%$. Significant reductions in CAUTI incidence could be observed in all country economic income groups, although differences between subgroups could not be explored due to high heterogeneity (Fig. 2). The 7 studies reporting aggregated data on CAUTI rates demonstrated between 100% reduction and a statistically insignificant

Table 1. Study Characteristics

First Author [Reference] Year	Country Economic Income Group	Study Design	Study Setting	Healthcare-Associated Infection	Main Components of Intervention Bundle
Abbasinia[141] 2016	Iran Upper middle income	RCT	ICU	VAP	Oral subgluteal space suctioning before each position change, regulating cuff pressure in the range 25 cm H_2O, head elevation to 45°
Abboud[139] 2016	Brazil Upper middle income	UBA	Cardiac surgery ICU	CLABSI SSI (various specialties) VAP	Alcohol gel at bedside, daily bathing with CHG-impregnated wash cloths, surface disinfection with CHG 3 times per day
Allen[138] 2014	USA High income	UBA	ICU	CLABSI	Simulation training, standardized insertion kits, electronic medical record-based documentation
Alp[137] 2014	Turkey Upper middle income	UBA	ICU	CLABSI CAUTI VAP	CAUTI bundle, CLABSI bundle, VAP bundle, surveillance and feedback, daily CHG bathing
Alsadat[136] 2012	Syria Lower middle income	UBA	4 tertiary-care teaching hospitals	VAP	VAP bundle: head elevation to 30–45°, daily sedation vacation, daily assesssment of readiness to wean, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis
Amine[142] 2014	Egypt Lower middle income	UBA	Medical ICU	CAUTI	Lectures (HH, aseptic catheter insertion), posters, alcohol-based hand rub personal bottles, audits (catheter insertion and maintenance)
Andrioli[135] 2014	Brazil Upper middle income	UBA	Tertiary-care teaching hospital	CAUTI	Observation of catheter insertion technique, maintenance care and removal practices, professional knowledge evaluation, training, feedback
Anthony[134] 2011	USA High income	RCT	Teaching hospital	SSI (colorectal)	Omission of mechanical bowel preparation, supplemental oxygen during and after surgery, preoperative and intraoperative warming, intravenous fluid restriction, use of a surgical wound protector
Apisarnthanarak[133] 2007	Thailand Upper middle income	UBA	Tertiary-care university hospital	CAUTI	Indication list, nurse-generated daily reminders used by an intervention team
Apisarnthanarak[132] 2010	Thailand Upper middle income	UBA	Tertiary-care center	CLABSI	HH education, education on maximal barrier precautions during insertion, chlorhexidine-based skin preparation, optimization of insertion practices, daily reassessment of the need for CVC
Ban[131] 2011	Korea High income	UBA	University hospital ICU	VAP	Education, pamphlets, hand cultures and postings of results, quiz, posters, reminders, performance feedback

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Table 1. (*Continued*)

First Author [Reference] Year	Country Economic Income Group	Study Design	Study Setting	Healthcare-Associated Infection	Main Components of Intervention Bundle
Barchitta[130] 2012	Italy High income	UBA	20 surgical departments of a teaching hospital	SSI (various specialties)	Educational program, guidelines, posters and leaflets, seminars and workshops, training in handwashing, introduction of alcohol-based antiseptic gel, enhanced cleaning and disinfection of medical equipment, single-patient medical instruments. improvement of timing and documentation of antimicrobial prophylaxis
Bell[129] 2016	USA High income	UBA	Single medical center	CAUTI	Education, mandatory prompts and reminders in the electronic medical record, daily patient tracking, resident quality champion, urine retention protocol
Berenholtz[128] 2011	USA High income	UBA	112 ICUs in Michigan	VAP	CUSP Ventilator bundle: semirecumbent positioning, stress ulcer prophylaxis, prophylaxis to decrease deep venous thrombosis, adjustment of sedation, daily assessment of readiness to extubate
Bion[143] 2013	England High income	UBA	196 adult ICUs	CLABSI	CUSP CLABSI bundle: insertion, catheter site selection, maintenance
Bird[127] 2010	USA High income	UBA	2 surgical ICUs in tertiary-care trauma center	VAP	Head-of-bed elevation >30°, daily sedation break, daily extubation assessment, peptic ulcer prophylaxis, deep vein thrombosis prophylaxis
Bouadma[126] 2010	France High income	UBA	Medical ICU in teaching hospital	VAP	Multidisciplinary task force, educational session, observations with performance feedback, technical improvements, reminders
Bukhari[125] 2014	Saudi Arabia High income	UBA	ICU of secondary acute healthcare facility	CLABSI	HH, maximal barrier precautions upon insertion, skin antisepsis, optimum site selection, daily review of line necessity
Bull[124] 2011	Australia High income	UBA	Acute tertiary-care referral hospital	SSI (colorectal)	Temperature ≥36°C peri- and postoperatively, fraction of inspired oxygen ≥0.8, systolic blood pressure ≥90 mmHg, blood sugar level ≤10 mmol/L, appropriate antibiotic prophylaxis
Cachecho[144] 2012	USA High income	UBA	Shock trauma unit of single hospital	VAP	Team building, culture change Ventilator bundle: head-of-bed elevation 30–45°, oral hygiene with CHG, peptic ulcer prophylaxis, daily assessment of weaning, daily assessment of sedation appropriateness
Castagna[123] 2016	Brazil Upper middle income	UBA	Medical-surgical inpatient wards of tertiary-care, private hospital	CLABSI	Evidenced-based central-line bundle: HH, maximal barrier precautions on insertion, CHG skin antisepsis, optimal catheter site selection, prompt removal of unnecessary lines Education, process and outcome surveillance, feedback reports, establishment of organizational goal, HH campaign, infusion therapy team
Ceppa[122] 2013	USA High income	UBA	University hospital	SSI (hepato-pancreato-biliary)	Feedback of surgeon-specific SSI rates, standardization of preoperative nutrition, glucose control, oxygenation, drain management, perioperative antibiotic management, surgical technique and wound protection, blood transfusions, glycemic control, temperature control
Chen[120] 2014	Taiwan High income	UBA	Medical and surgical ICU of university teaching hospital	VAP	Electronic reminders on evaluation of sedative use, assessing readiness for extubation, peptic ulcer prophylaxis, head-of-bed elevation to 30–45°, deep venous thrombosis prophylaxis, oral decontamination with 0.2% CHG, tube-cuff pressure control (target, 20–30 cm H_2O)
Chen[121] 2016	China Upper middle income	RCT	ICU	VAP	Subglottic secretion drainage every 2 h, head-of-bed elevation to 30–45°
Cherifi[119] 2013	Belgium High income	UBA	5 intensive care units	CLABSI	Repeated staff meetings, audit of process measures (insertion site and care process), performance and outcome feedback reports

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Table 1. (*Continued*)

First Author [Reference] Year	Country Economic Income Group	Study Design	Study Setting	Healthcare-Associated Infection	Main Components of Intervention Bundle
Chien[118] 2014	Taiwan High income	UBA	National University Hospital	SSI (sternal wound)	Preoperative CHG showering, PVP iodine paint before bathing, improvement of antibiotic prophlyaxis management, change of surgical gloves
Cima[117] 2013	USA High income	UBA	Tertiary-care hospital	SSI (colorectal)	Establishment of multidisciplinary team, standards in patient cleansing, antibiotic administration, closing protocol at time of fascia closure, postoperative HH and patient hygiene, dressing removal and posthospitalization process
Clarke[116] 2013	USA High income	UBA	Community hospital	CAUTI	Exclusive use of silver alloy catheters, securing device to limit movement, repositioning catheter tubing if touching the floor, catheter removal on postoperative day 1 or 2
Collignon[115] 2007	Australia High income	UBA	Tertiary-care referral hospital	CLABSI	Weekly team meetings, outcome surveillance and feedback, review of associated preventable factors, assistance to implement targeted interventions
Corcoran[114] 2013	Ireland High income	UBA	Tertiary-care referral maternity hospital	SSI (caesarean section)	Nonabsorbable sutures for skin closure, clippers instead of razors, 2% CHG for skin disinfection before incision
DeLuca[113] 2016	USA High income	UBA	Academic emergency department	VAP	Head-of-bed elevation to 30–45°, oral care every 2 h, subglottic suctioning, sedation titration, sedation vacations and spontaneous breathing trials, stress ulcer prophylaxis, deep venous thrombosis prophylaxis, education and training, VAP supply carts, nurse champion for real-time mentoring and feedback
Ding [112] 2013	USA High income	UBA	9 academic ICUs	VAP	IHI VAP bundle: head-of-bed elevation to ≥30°, daily sedation vacation, daily assessment of readiness to extubate, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis
Dumyati[111] 2014	USA High income	UBA	37 non-ICU wards at 6 hospitals	CLABSI	Engagement of nursing staff and leadership, nursing education on line care maintenance, competence evaluation, audits of line care, feedback on CLABSI rates
Dyrkorn[110] 2012	Norway High income	UBA	Maternity clinic	SSI (ceasarean section)	Establishment of improvement team, advice against hair removal by patients prior to delivery, antibiotic-coated absorbable sutures, sterile gown for midwive; highly absorbent wound dressing, double gloving, strengthening of adherence to preoperative surgical hand washing and aseptic techniques
Entesari-Tatafi [109] 2015	Australia High income	UBA	Tertiary-care ICU	CLABSI	Care bundle: standard line insertion procedure and novel line maintenance procedure comprising biopatch, sterile line access, daily body wash with 2% CHG, daily line review with early removal, liaison nurse follow-up of central lines, bedside audits with stopping rules
Exline[108] 2013	USA High income	UBA	Tertiary-care medical ICU	CLABSI	Central-line insertion checklist, daily line necessity checklist, demonstration of competencies for line maintenance and access, quality rounds by nursing leadership, heightened staff accountability
Frankel[107] 2005	USA High income	UBA	Surgical ICU of academic tertiary-care referral center	CLABSI	Barrier precaution kits, new policies for catheter changes over guide wires, adoption of a new site-preparation antiseptic, direct attending supervision of catheter insertions, video training for housestaff, and increased frequency of dressing changes, CHG-silver catheters selectively for high-risk patients
Freixas[106] 2013	Spain High income	UBA	Non-ICU wards of 11 hospitals	CLABSI	Evidence-based bundle of practices relating to catheter insertion: HH, site selection, full barrier precautions, 2% CHG alcohol for skin antisepsis Maintenance bundle: disinfectrion of the connector before access, proper maintenance, daily review Training program for healthcare workers, prevalence surveys for adherence to recommendations, feedback reports

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Table 1. (*Continued*)

First Author [Reference] Year	Country Economic Income Group	Study Design	Study Setting	Healthcare-Associated Infection	Main Components of Intervention Bundle
Frenette[104] 2016	Canada High income	UBA	Tertiary-care public teaching institution	SSI (cardiac)	2% CHG washcloths, hair removal with clippers, identification and treatment of infections, preoperative MRSA screening, CHG alcohol skin disinfection, nonocclusive dressing, improvements in surgical technique, daily assessment of drains and chest tubes, improvement of antibiotic prophylaxis
Frenette[105] 2016	Canada High income	UBA	Tertiary-care public teaching institution	SSI (solid organ transplantation and hepatobiliary)	Individual feedbacks of SSI rates, 2% CHG washcloths, improvement of antibiotic prophylaxis
Galpern[103] 2008	USA High income	UBA	Surgical ICU	CLABSI	Maximal barrier precautions, HH, skin antisepsis with CHG, central line cart, avoidance of femoral lines
Gao[102] 2015	China Upper middle income	UBA	ICU	CLABSI CAUTI VAP	CLABSI bundle: HH, aseptic technique, minimum number of ports, CHG for skin disinfection, maintenance recording, dressing changes CAUTI bundle: check catheterization bag, choice of the right catheter, aseptic technique at catheter insertion, proper fixation and maintenance, daily review VAP bundle: daily assessment of ventilation necessity, head-of-bed elevation 30–45°, oral care with CHG, aseptic technique, cleaning and disinfection, sterile water for humidification, daily assessment of sedation use
Garcia[101] 2009	USA High income	UBA	University-affiliated medical ICU	VAP	Oral cavity assessment, toothbrushing twice daily, deep suctioning every 6 h, oral tissue cleaning every 4 h
Ghuman[100] 2015	Canada High income	UBA	Academic institution	SSI (colorectal)	Colorectal closure bundle: change in gown and gloves, redraping, wound lavage, and new set of instruments for closure
Grigonis[99] 2016	USA High income	UBA	30 long-term acute-care hospitals	CLABSI	Education, alcohol-based central-catheter caps, CHG dressings, formation of a central-catheter team of nurses, process monitoring
Guanche-Garcell[98] 2013	Cuba Upper middle income	UBA	ICU	VAP	Bundle of infection control interventions (HH, head-of-bed elevation to 30–45°, daily assessment of readiness to wean, oral care with antiseptic solution, noninvasive ventilation whenever possible, orotracheal instead of nasotracheal intubation, endotracheal cuff pressure ≥20 cm H_2O, removal of condensate from ventilator circuits, no regular changes of ventilator circuit, avoidance of gastric overdistention, avoidance of histamine antagonists or proton pump inhibitors, sterile water to rinse reusable respirator equipment), education, HH surveillance, feedback of VAP rates and HH
Guerin[97] 2010	USA High income	UBA	ICU of a university-affilitated acute-care teaching hospital	CLABSI	Training, HH and full barrier precautions, 2% CHG alcohol scrub for the insertion site, head-to-toe sterile drape of the patient during insertion, time-out before performing the procedure, avoidance of the femoral insertion site
Halperin[96] 2016	USA High income	UBA	Neuro ICU	CAUTI	Daily review of urinary catheter use, education in catheter insertion and maintenance, urinary catheter insertion kit, mobile CT in neuro ICU
Hawe[95] 2009	UK High income	UBA	Surgical/medical ICU	VAP	Education VAP bundle: head-of-bed elevation to 30–45°, daily sedation breaks, daily assessment of readiness to wean and tubing management, oral antisepsis with CHG, subglottic suction/drainage tubes Process measurement and feedback, outcome measurement and feedback

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Table 1. (*Continued*)

First Author [Reference] Year	Country Economic Income Group	Study Design	Study Setting	Healthcare-Associated Infection	Main Components of Intervention Bundle
Hedrick[94] 2007	USA High income	UBA	Tertiary-care center	SSI (colorectal)	Prophylactic antibiotics 0–60 minutes before incision, continued antibiotic administration for ≤24 h postoperatively, maintenance of intraoperative normothermia (≥36°C), improved glycemic control (goal <200 mg/dL 48 h postoperatively) in diabetic patients, placement of penrose drains in the subcutaneous space of patients with a BMI ≥ 25 kg/m^2
Hewitt[93] 2017	USA High income	UBA	University hospital	SSI (colorectal)	Education, smoking cessation counseling, preoperative oral neomycin/metronidazole, home use of 2% CHG washcloths before surgery, abdominal irrigation with antibiotic saline solution, donning of fresh gowns and gloves before closure, unused closing tray for fascial/skin closure
Higuera[92] 2005	Mexico Upper middle income	UBA	2 adult ICUs in public university hospital	CLABSI	Education, observation, performance feedback of HH and catheter care (compliance with gauze on CVC insertion sites, dates on intravenous administration sets, and maintenance of gauze dressings on catheter sites)
Hill[91] 2015	USA High income	UBA	Surgical department	SSI (hepatic)	Antibiotic prophylaxis change and redosing, CHG body wash the night prior to and the morning of surgery, Ioban drape, instillation of neomycin/polymixin B/bacitracin prior to case completion and closure
Hiramatsu[90] 2016	Japan High income	UBA	Cancer hospital	HAP	Breathing exercises, respiratory muscle-stretching exercises, professional oral cleaning, cleaning of teeth and tongue, nutritional control, smoking cessation
Hocking[89] 2013	New Zealand High income	UBA	Critical care unit	CLABSI	HH and use of CHG 2% and alcohol to cleanse the skin prior to insertion, site selection, full barrier precautions, full body drape, sterile technique during insertion, central line insertion pack, daily review for necessity, infusing intravenous nutrition via a dedicated lumen, daily checking for insertion site inflammation and cleaning of all ports with 2% CHG/alcohol prior to access, chlorhexidine impregnated dressings and/or antibiotic impregnated catheters for high-risk patients
Hogle[88] 2014	USA High income	UBA	Academic health center	SSI (cardiac)	Education modules, limitation of operating room traffic, CHG/alcohol skin preparation, equipment cleaning resource book, education about and enhancement of environmental cleaning, glucose control, performance-improvement team and surgeon champion, reduce/eliminate flash steam sterilization, real-time analysis of complications, speaking up
Hong[87] 2013	USA High income	UBA	17 ICUs	CLABSI	CUSP
Hsu[86] 2016	USA High income	UBA	University medical center	SSI (caesarean section)	Education Infection control policies: jewellery restriction, attire policy, alcohol dispensers, antibiotic prophylaxis, CHG skin preparation, operating room traffic, education, HH monitoring, patient and family education Presurgical checklist: electronic clippers, CHG skin preparation, antibiotic prophylaxis, cord traction to remove placenta, closure of deep subcutaneous layer, subcuticular suture for skin closure
Hutchins[85] 2009	USA High income	UBA	ICU of private acute care hospital	VAP	Oral care every 4 h: teeth brushed with cetylpyridinium chloride or CHG using a suction toothbrush, oral cavity cleansed with suction swabs treated with hydrogen peroxide, application of mouth moisturizer, deep oropharyngeal suctioning, suction catheters to control secretions
Jaggi[83] 2012	India Lower middle income	UBA	Tertiary-care private hospital	CAUTI	Training, CAUTI bundle and checklist, audits

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Table 1. (*Continued*)

First Author [Reference] Year	Country Economic Income Group	Study Design	Study Setting	Healthcare-Associated Infection	Main Components of Intervention Bundle
Jaggi[84] 2013	India Lower middle income	UBA	16 adult ICUs of 11 hospitals	CLABSI	Bundle of interventions: HH, use and maintain sterile dressing, early catheter removal, administration set change every 96 h, CHG-based antiseptic for skin preparation, site selection, all-inclusive catheter kit, maximal sterile barrier precautions, single use vials, disinfection of hubs and connectors Education, outcome surveillance, process surveillance, feedback on CLABSI rates and consequences, performance feedback
Jeong[82] 2013	Korea High income	UBA	ICU	CLABSI	Task force team, posters and educational programs and materials, regular feedback on unit-level compliance and CLABSI incidence CLABSI bundle, including checklist: HH, maximal barrier precautions, CHG/alcohol skin antisepsis, site selection
Jiang[145] 2016	China Upper middle income	UBA	University-affiliated hospital	SSI (neurosurgery)	Education and training, HH, antibiotic prophylaxis, aseptic draping and dressing, hair removal, skin desinfection
Johnson[81] 2013	USA High income	UBA	Neuroscience ICU	VAP	Education, head-of-bed elevation to >30°, CHG mouth wash twice daily and oral care every 2 h, subglottic suctioning, suction catheter change every 24 h, early tracheostomy, HH, gastric ulcer prophylaxis, VAP diagnosis using quantitative cultures obtained via bronchoscopic or blind bronchoalveolar lavage
Johnson[80] 2016	USA High income	UBA	Academic center	SSI (gynecologic cancer)	Sterile closing tray, staff glove change for fascia and skin closure, dressing removal at 24–48 h, dismissal with 4% CHG, follow-up nursing phone call
Kachare[79] 2014	USA High income	UBA	Academic surgical oncology unit	CAUTI	Guidelines and training, indication list, HH, Foley bundle (including daily assessment for necessity, securement of device, maintenance)
Kanj[78] 2013	Lebanon Upper middle income	UBA	Medical-surgical ICU of a tertiary-care university hospital	CAUTI	Active surveillance Infection control bundle: education and training on insertion, care maintenance, alternatives, insertion only when needed, early removal Education, outcome surveillance and feedback, process surveillance and feedback
Kazaure[146] 2014	USA High income	UBA	Noncardiac surgical patients on general surgical ward	HAP	Education, coughing and deep-breathing exercises, oral hygiene with CHG, pain control, head-of-bed elevation to at least 30°, quarterly discussions for nursing staff, bundle documentation, physician pneumonia prevention order set
Keenan[77] 2014	USA High income	UBA	Academic tertiary-care referral center	SSI (colorectal)	Patient education, preoperative CHG shower, mechanical bowel preparation with oral antibiotics, antibiotic prophylaxis within 1 h of incision, skin preparation with CHG/alcohol, fascial wound protector, gown/glove change before fascial closure, wound closure tray, limited operation room traffic, glucose control, normothermia, removal of sterile dressing within 48 h, daily washing of incisions with CHG
Kellie[76] 2014	USA High income	UBA	Medical ICU of tertiary-care referral academic center	VAP CLABSI	Staff and patient educational campaign on hand hygiene, daily rounds CLABSI bundle: HH, full sterile attire, biopatch, CHG wash, site selection, insertion checklist, companion insertion kit VAP bundle: head-of-bed elevation, oral care with CHG, daily sedation vacation, daily assessment of readiness to wean, checklist, random chart audits
Khan[75] 2016	Saudi Arabia High income	UBA	ICU	VAP	Head-of-bed elevation 30–45°, daily sedation vacation and assessment for extubation, peptic ulcer disease prophylaxis, deep vein thrombosis prophylaxis, oral care with CHG, endotracheal intubation with in-line suction and subglottic suctioning, and maintenance of endotracheal tube cuff pressure at 20–30 mmHg

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Table 1. (*Continued*)

First Author [Reference] Year	Country Economic Income Group	Study Design	Study Setting	Healthcare-Associated Infection	Main Components of Intervention Bundle
Kim[74] 2011	USA High income	UBA	ICUs	CLABSI	Line removal after 24 h if placed in the emergency room CLABSI bundle and checklist: time-out, site selection, full barrier precautions, ultrasound guidance, sterile insertion technique, safe sharps disposal, x-ray to confirm position, central line cart, daily review, education, feedback of process and outcome
Konishi[147] 2006	Japan High income	UBA	University hospital	SSI (colorectal surgery)	Surveillance, optimization of antibiotic prophylaxis, replacement of surgical instruments and gloves before closure of abdominal wall, improvement of peritoneal and subcutaneous lavage method
Landrum[73] 2008	USA/Iraq High income	UBA	ICU of a military hospital	VAP	HH, contact barrier precautions, patient and staff cohorting, CHG oral care, reduction of surgical prophylaxis, periodic cleaning and disinfection, education
Le[72] 2014	USA High income	UBA	Neurosurgery department	SSI (neurosurgery)	Perioperative vancomycin, barrier dressing for 3 d after surgery, then postoperative wound decolonization with CHG
Leblebicioglu[70] 2013	Turkey Upper middle income	UBA	ICUs of hospitals in 8 cities in Turkey	CLABSI	Infection control bundle: HH, sterile dressing, early removal, change of administration set every 96 h, CHG-based antiseptic, site selection, catheter cart or kit, maximal sterile barrier precautions, single-use vials, disinfection of line hubs Education, outcome surveillance, process surveillance, feedback
Leblebicioglu[71] 2013	Turkey Upper middle income	UBA	ICUs of hospitals in 10 cities in Turkey	CAUTI	Infection control bundle: HH, insertion only when needed and removal when unnecessary, indication list, alternatives when appropriate, to use as small as possible catheters, insert catheters by use of aseptic technique and sterile equipment, appropriate management, maintain unobstructed urine flow, keep the collecting bag below the level of the bladder at all times, empty the collecting bag regularly, cleaning of the meatal area Education, outcome surveillance, process surveillance, feedback
Leblebicioglu[69] 2013	Turkey Upper middle income	UBA	ICUs of hospitals in 10 cities in Turkey	VAP	Infection control bundle: HH, head-of-bed elevation to 30–45°, daily assessment of readiness to wean, oral care with antiseptic solution, nonivasive ventilation whenever possible, orotracheal instead of nasotracheal intubation, cuff pressure ≥20 cm H_2O, ventilator circuit management, avoidance of gastric overdistention, avoidance of antacids, sterile water to rinse reusable equipment Education, outcome surveillance, process surveillance, feedback
Liau[68] 2010	Singapore High income	UBA	Tertiary-care hospital department of surgery	SSI (gastrointestinal and hernia)	Guideline implementation: clippers instead of shavers for hair removal, standardized prophylactic antibiotic regimen, antibiotic administration within 30 min before incision; standardized glucose monitoring for diabetics; maintenance of postoperative normothermia
Lipke[67] 2010	USA High income	UBA	2 community hospitals	SSI (caesarean section, gastric bypass and banding, orthopedic)	MRSA screening, patient education, intranasal mupirocin, skin antisepsis with 2% CHG cloth (all patients)
Longmate[66] 2011	UK High income	UBA	ICU of general hospital	CLABSI	Insertion bundle: aseptic technique, maximal barrier precautions, CHG-alcohol for skin antisepsis, site selection, insertion checklist Maintenance bundle: HH, early removal, clean injection ports, avoid 3-way taps, daily dressing inspection, dedicated lumen for total parenteral nutrition, avoid blood sampling, avoid guide wire exchange Education, organizational change

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Table 1. (*Continued*)

First Author [Reference] Year	Country Economic Income Group	Study Design	Study Setting	Healthcare-Associated Infection	Main Components of Intervention Bundle
Lutfiyya[65] 2012	USA High income	UBA	300-bed hospital	SSI (colorectal)	Education Colorectal surgery bundle: patient education, smoking cessation, CHG wipes, mechanical bowel preparation with oral antimicrobials, glucose control, clippers for hair removal, normothermia, antibiotic prophylaxis, CHG-alcohol for skin preparation, ≥80% fraction of inspired oxygen, pulse lavage of subcutaneous tissues, silver-impregnated dressing
Maric[64] 2014	Croatia High income	UBA	Medical ICU	CLABSI VAP CAUTI	Education, HH intervention, improvement of isolation management, improvement in environmental cleaning, device-specific bundles, audits
Marra[62] 2009	Brazil Upper middle income	UBA	Medical-surgical ICU of private tertiary-care hospital	VAP	IHI ventilator bundle: head-of-bed elevation, daily sedation vacation and assessment of readiness to extubate, peptic ulcer prophylaxis, deep venous thrombosis prophylaxis, oral decontamination with CHG, continuous aspiration of subglottic secretions, ventilator circuit management Education, performance monitoring
Marra[63] 2010	Brazil Upper middle income	UBA	Medical-surgical ICU and 2 step-down units of private tertiary-care hospital	CLABSI	IHI central-line bundle: insertion cart, HH, maximal barrier precautions, CHG skin antisepsis, site selection, daily review of line necessity with prompt removal Education, performance monitoring
Marra[61] 2011	Brazil Upper middle income	UBA	Medical-surgical ICU and 2 step-down units of private tertiary-care hospital	CAUTI	IHI bladder bundle: catheter insertion cart, HH, CHG skin and meatal antisepsis, sterile field and sterile gloves, only 1 attempt at insertion allowed for each catheter, adequate balloon inflation, daily review of necessity with prompt removal if no longer needed Education, performance monitoring
Marsteller[60] 2012	USA High income	Cluster-RCT	45 ICUs form 35 hospitals	CLABSI	CUSP CLABSI bundle: HH, full barrier precautions, site selection, CHG for disinfection, early removal
Martinez-Resendez[59] 2014	Mexico Upper middle income	UBA	2 ICUs in tertiary-care teaching hospital	VAP CAUTI CLABSI	Daily bathing with 2% CHG wipes, HH, training, supervision and feedback
Mathur[58] 2015	India Lower middle income	UBA	Level 1 trauma center of tertiary-care hospital	VAP CLABSI CAUTI	Education, monitoring, surveillance and feedback CLABSI bundle: HH, maximal barrier precautions, CHG skin antisepsis, site selection, daily review of line necessity with prompt removal VAP bundle: head-of-bed elevation, daily sedation vacations, assessment of readiness to extubate, peptic ulcer disease prophylaxis, deep venous thrombosis prophylaxis CAUTI bundle: aseptic insertion and proper maintenance, alternatives to catheter, avoiding indwelling catheter, early removal through reminders or stop orders, dependent drainage
Matocha[57] 2013	USA High income	UBA	Community teaching hospital	CLABSI	Education, surveillance, evidence-based policies and protocols, product selection
Matsen[56] 2016	USA High income	UBA	Mid-size community hospital	SSI (total joint arthroplasty)	Education, training, operating room traffic reduction, eliminating lint producing materials und unneccessary items, occlusive antimicrobial dressing, combination antibiotic prophylaxis, preoperative decolonization withouth screening, change to postoperative aspirin prophylaxis instead of low-dose warfarin, dilute betadine irrigation at completion of surgery, postponing arthroplasty for patients at high risk
McDonald[55] 2015	USA High income	UBA	Community hospital	SSI (total joint arthroplasty)	Patient education, *Staphylococcus aureus* screening and decolonization, combined antibiotic prophylaxis, alcohol agents for skin disinfection

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Table 1. (*Continued*)

First Author [Reference] Year	Country Economic Income Group	Study Design	Study Setting	Healthcare-Associated Infection	Main Components of Intervention Bundle
Mehta[54] 2013	India Lower middle income	UBA	21 ICUs from 10 cities	VAP	Education, outcome and process surveillance, feedback of outcomes and performance VAP bundle: HH, head-of-bed elevation 30–45°, daily assessments of readiness to wean, oral care with antiseptic soluation, noninvasive ventilation whenever possible, orotracheal instead of nasotracheal intubation, cuff pressure ≥20 cm H_2O, ventilator circuit management, avoidance of gastric overdistention, no peptic ulcer prophylaxis, sterile water to rinse ventilator equipment
Micik[53] 2013	Australia High income	UBA	Cardiothoracic ICU	VAP	Education, limit use of mechanical ventilation (sedation vacation, readiness to wean, noninvasive ventilation), prevent aspiration of secretions (head-of-bed elevation 30°, avoid gastric overdistension, cuff pressure ≥20 cm H_2O), prevent nasal and oropharyngeal colonisation (mupirocin ointment, oral hygiene, oral cavity assessment), prevent use of contaminated equipment (HH, equipment change), early mobilization
Miller[52] 2016	USA High income	UBA	2 ICUs of community-based academic healthcare system	CLABSI CAUTI VAP	CUSP CLABSI bundle: education, training, surveillance, root cause analysis, central-line cart, insertion checklist, inclusion of nurses in placement process, IHI central line bundle: hand hygiene, maximal sterile barriers, CHG skin asepsis, optimal catheter site selection, review of line necessity Changes in dressing, line maintenance, scrub the hub, culture improvement CAUTI bundle: surveillance, root cause analysis, education, reinforcement of use of leg straps, assessment of need and early removal VAP bundle: data collection, monitoring, and daily round discussion, elevation, teeth brushing, and oral suctioning
Miyahara[51] 2014	Japan High income	UBA	Municipal hospital	SSI (sternal wound infection in cardiovascular surgery)	Standardization of surgical technique, MRSA screening and nasal decolonization, preoperative shower with soap, CHG-alcohol and PVP iodine skin disinfection, standardization of surgical hand antisepsis, double gloving, clipping, euglycemia, inspired oxygen >80%, antibiotic prophylaxis with cefazoline, normal saline wound irrigation, standardized wound dressing
Mody[50] 2015	USA High income	Cluster RCT	12 community-based nursing homes	CAUTI	Education on key prevention practices, preemptive barrier precautions, active surveillance with data feedback
Mohamed[49] 2014	Egypt Lower middle income	UBA	Surgical and medical ICU	VAP	Head-of-bed elevation >30°, daily sedation break, assessment for extubation, peptic ulcer prophylaxis, deep venous thrombosis prophylaxis
Morris[48] 2011	Scotland High income	UBA	Medical-surgical teaching hospital ICU	VAP	Head-of-bed elevation, oral CHG gel, sedation vacation, weaning protocol
Narang[47] 2008	Oman High income	UBA	ICU	VAP	Head-of-bed elevation to 30–45°, daily sedation vacation and assessement of readiness to extubation, peptic ulcer prophylaxis, deep venous thrombosis prophylaxis
Navoa-Ng[46] 2013	Philippines Lower middle income	UBA	4 ICUs of 2 hospitals	CAUTI	Education CAUTI bundle: HH, unobstructed urine flow, collection bag below level of bladder at all times, empty collecting bag regularly Surveillance and feedback, process monitoring and feedback
Ng[45] 2015	Canada High income	ITS	Community hospital	SSI (caesarean section)	Prenatal education and posters on self-hair removal, hair removal optimization, timing of antibiotic prophylaxis, surgical safety checklist, CHG-alcohol surgical skin preparation
Omrane[44] 2007	Canada High income	UBA	Tertiary-care teaching hospital ICU	VAP	Education, nutrition, patient positioning, HH, stress ulcer prophylaxis, ventilator circuit optimization

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Table 1. (*Continued*)

First Author [Reference] Year	Country Economic Income Group	Study Design	Study Setting	Healthcare-Associated Infection	Main Components of Intervention Bundle
O'Neil[43] 2016	USA High income	CBA	General medicine wards of teaching hospital	CLABSI	Maintenance bundle: education, update of hospital policies, visual aids, competence assessement, process monitoring, progress reports, consolidation of supplies
Palomar[42] 2013	Spain High income	UBA	192 ICUs	CLABSI	CUSP, insertion and maintenance bundle: HH, full-barrier precautions, CHG skin disinfection, site selection, removal of unneccessary catheter
Parisi[41] 2016	Greece High income	UBA	ICU	VAP	Education and posters VAP bundle: HH, head-of-bed elevation, daily sedation vacation and assessment of readiness to extubate, peptic ulcer prophylaxis, deep venous thrombosis prophylaxis; Sodium bicarbonate-based oral hygiene protocol
Parry[40] 2013	USA High income	UBA	Community teaching hospital	CAUTI	Nurse-directed removal protocol, indication documentation, device-specific charting module, unit-specific feedback of catheter use
Perez-Granda[140] 2014	Spain High income	UBA	ICU	VAP	Training program, subglottic aspiration, inclinometer to record semirecumbent position, reinforcement of oral care with CHG
Prieto[39] 2016	Uruguay High income	UBA	Liver transplant unit	SSI (liver transplant)	Antibiotic prophylaxis policy, surgical skin preparation policy
Pronovost[38] 2008	USA High income	UBA	103 ICUs	CLABSI	CUSP, catheter bundle: HH, full barrier precautions, CHG skin disinfection, site selection, removal of unnecessary catheters
Rauk[37] 2008	USA High income	UBA	University teaching hospital	SSI (caesarean section)	Education and training, CHG wash cloths, CHG-alcohol skin preparation, modified instrument sterilization techniques
Reddy[36] 2014	UAE High income	UBA	2 ICUs of tertiary-care hospital	CLABSI	Central-line insertion and maintenance bundle: HH, CHG for skin antisepsis, full barrier precautions, site selection, daily assessement of line necessity, line site care, tubing care, hub care Central-line insertion checklist, central-line trolleys, education for insertion and maintenance, empowerment of nurses, surveillance and feedback, CUSP
Rello[35] 2013	Spain High income	UBA	5 ICUs	VAP	Oral care with CHG every 8 h, HH, intracuff pressure control, sedation control protocol, ventilator circuit management
Remington[148] 2016	USA High income	UBA	Burn-trauma ICU of university medical center	CLABSI	Line insertion checklist, daily assessment of need, central line insertion pack, alcohol-impregnated caps, updated care standards, expanded central-line documentation
Render[34] 2011	USA High income	UBA	174 ICUs	CLABSI	HH, maximal barrier precautions, CHG site disinfection, site selection, timely catheter removal, recruiting leadership, benchmarked feedback, learning tools, selective mentoring
Rosenthal[33] 2006	Argentina Upper middle income	UBA	ICUs of 2 hospitals	VAP	Educational sessions, active surveillance and feedback
Rosenthal[31] 2012	14 developing countries Upper middle income	UBA	44 ICUs in 38 hospitals	VAP	Education, outcome and process surveillance and feedback Infection control bundle: HH, head-of-bed elevation to 30–45°, daily assessment of readiness to wean, weaning protocols, oral care with antiseptic solutions, noninvasive ventilation whenever possible, orotracheal instead of nasotracheal intubation, cuff pressure $\geq$20 cm H_2O, ventilator circuit management, avoidance of gastric overdistention, avoidance of peptic ulcer prophylaxis, sterile water to rinse equipment
Rosenthal[32] 2012	15 developing countries Upper middle income	UBA	57 ICUs	CAUTI	Infection control bundle: education and training on insertion, care maintenance, alternatives, insertion only when needed, early removal Education, surveillance and feedback, process monitoring and feedback

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Table 1. (*Continued*)

First Author [Reference] Year	Country Economic Income Group	Study Design	Study Setting	Healthcare-Associated Infection	Main Components of Intervention Bundle
Saint[149] 2016	USA and Puerto Rico High income	UBA	926 units (ICU and non-ICU) in 603 hospitals	CAUTI	CUSP, surveillance and feedback, education, daily assessments of the presence and need for urinary catheter, alternative urine-collection methods, emphasis on aseptic technique during insertion and maintenance, addressing gaps in knowledge of urinary management processes
Salama[30] 2016	Kuwait High income	UBA	ICU	CLABSI	HH, maximal barrier precautions, 2% CHG alcohol skin preparation, site selection, daily reassessment of necessity
Salim[29] 2011	Israel High income	UBA	Single academic institution	SSI (caesarean secction)	Antibiotic prophylaxis, education and training on aseptic and scrub technique, observation and feedback
Sen[28] 2016	USA High income	UBA	Burn ICU	VAP	Nurse champions VAP bundle: head-of-bed elevation to 30°, CHG oral care daily, sedation interruption and assessment for readiness to wean, stress ulcer prophylaxis, deep venous thrombosis prophylaxis
Shitrit[27] 2015	Israel High income	UBA	Geriatric hospital ward	VAP	VAP bundle: HH, head-of-bed elevation to >30°, CHG oral care in each shift, tracheostomy cannula balloon pressure at 20–30 cm H_2O, measuring nasogastric food remnants before each meal Process monitoring and feedback
Sutherland[26] 2015	USA High income	UBA	Academic medical center	CAUTI	Task force formation, staff education on appropriate catheterization and aseptic technique, electronic order sets with decision support and daily reminders for evaluation, surveillance, and feedback
Talbot[25] 2015	USA High income	UBA	6 academic medical center ICUs	VAP	Real-time computerized bundle compliance dashboard VAP bundle: head-of-bed elevation to 30–45°, routine oral care, daily sedation managment and assessment of readiness to extubate, deep venous thrombosis prophylaxis, stress ulcer prophylaxis
Tang[24] 2014	Taiwan High income	UBA	5 adult ICUs at regional teaching hospital	CLABSI	Education CLABSI insertion and maintenance bundle: HH, maximal barrier precautions, CHG skin antisepsis, site selection, dressing changes, aseptic technique, daily review of necessity Process monitoring, outcome surveillance
Tanner[23] 2016	UK High income	UBA	2 teaching hospitals	SSI (open colorectal surgery)	MRSA screening and decolonization, preoperative showering, hair removal with clippers, glucose control for diabetic patients, normothermia, antibiotic prophylaxis, CHG-alcohol for skin preparation, antiseptic impregnated incisive drapes, supplemental oxygen in early postoperative phase, process and outcome monitoring and feedback
Tao[22] 2012	China Upper middle income	UBA	3 ICUs of university hospital	VAP	Education VAP bundle: HH, oral care with CHG twice daily, head-of-bed elevation to 30–45° Process and outcome surveillance and feedback
Taylor[21] 2017	USA High income	UBA	Academic medical center	SSI (genecologic oncology)	Patient education, preoperative antibiotic soap, appropriate antibiotic prophylaxis, glove and instrument change at closure, surgical dressing for 48 h, postdischarge phone call with SSI education and assessment
Ternavasio[20] 2016	Spain High income	UBA	Internal medicine department of university hospital	CAUTI	Training, catheterization reminders, observations and feedback, awareness-raising campaign
Thompson[150] 2011	USA High income	UBA	Academic health center	SSI	Revision of order sets, assignment of responsibilty for antibiotic delivery, enhancement of electronic medical record, postoperative normothermia, clippers instead of razors, *Staphylococcus aureus* decolonization and perioperative skin cleansing, antibiotic redosing, dose adaptation for obese patients, standardized skin preparation. HH, improving operating room environment, traffic, attire

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Table 1. (*Continued*)

First Author [Reference] Year	Country Economic Income Group	Study Design	Study Setting	Healthcare-Associated Infection	Main Components of Intervention Bundle
Tillekeratne[19] 2014	Kenya Lower middle income	UBA	Medical wards	CAUTI	Education, reminder signs for daily assessment, indication list, weekly rounds by nurse matrons
Titsworth[18] 2012	USA High income	UBA	Neurological ICU of tertiary-care medical center	CAUTI	Multidisciplinary team CAUTI bundle: avoidance of insertion, maintenance of catheter sterility, product standardization, timely removal Catheter rounds, education
Trussell[17] 2008	USA High income	UBA	Single institution	SSI (coronary artery bypass grafting)	Timely peri-incisional antibiotic administration, tight glucose control, hair removal with clippers
van der Slegt[15] 2013	The Netherlands High income	UBA	Teaching hospital	SSI (vascular surgery)	Multidisciplinary team, process monitoring and feedback SSI bundle: normothermia, hair removal with clippers, antibiotic prophlyaxis policy, reduction of operation room door openings
van Kasteren[14] 2005	The Netherlands High income	UBA	13 hospitals	SSI (orthopedic, vascular, gynecological and intestinal surgery)	Antibiotic policy: antibiotic choice, unit dosage, number of postoperative doses, timining of first and subsequent doses Performance feedback, education
Viana[13] 2013	Brazil Upper middle income	UBA	Medical ICU of private general hospital	VAP	Education VAP bundle: head-of-bed elevation >30°, daily sedation vacation, peptic ulcer prophylaxis, deep venous thrombosis prophylaxis, standardized oral care
Wahl[12] 2010	USA High income	UBA	Trauma and burn surgical ICU	VAP CLABSI	Education VAP bundle: head-of-bed elevation >30°, glucose control, enforcement of daily weaning parameters and sedation vacations
Warren[151] 2006	USA High income	UBA	12 ICUs and 1 bone-marrow transplant unit at 6 academic medical centers	CLABSI	Review and update of policies, education (prefer subclavian site, maximal sterile barrier precautions, keep dressings clean, dry and intact and properly dated)
Wick[11] 2012	USA High income	UBA	Academic medical center	SSI (colorectal surgery)	Surgery-based CUSP SSI bundle: standardization of skin preparation, preoperative CHG showers, selective elimination of mechanical bowel preparation, normothermia, encanced sterile technique for skin and fascial closure, antibiotic prophylaxis policy
Yamamoto[10] 2015	Japan High income	UBA	Single center	SSI (emergency colorectal surgery)	SSI bundle: triclosan-coated antimicrobial sutures, irrigation with warm normal saline solution, cyanoacrylate tissue adhesive coating, no subcutaneous drain, antibiotic prophylaxis timing policy
Yavuz[9] 2013	Turkey Upper middle income	UBA	Teaching hospital	SSI (open heart surgery)	Administrative support, MRSA screening and decolonization, HH, preoperative CHG shower, intranasal mupirocin perioperatively for all patients, antibiotic prophylaxis policy, normoglycemia, skin preparation with CHG alcohol Education, surveillance and feedback
Youngquist[152] 2007	USA High income	UBA	2 ICUS of a single hospital with two campuses	VAP	HH campaign, oral care protocol, head-of-bed elevation, daily sedation vacation along with a readiness to wean assessment, peptic ulcer disease prophylaxis, deep vein thrombosis prophylaxis
Zingg[8] 2014	Switzerland High income	UBA	University-affiliated tertiary-care hospital	CLABSI	Interdisciplinary study group, CLABSI bundle: insertion checklist, e-learning, CVC carts and single-use insertion kits, insertion training

Abbreviations: CLABSI, central-line–associated bloodstream infection; CAUTI, catheter-assoicated urinary tract infection; VAP, ventilator-associated pneumonia; UBA, uncontrolled before-and-after design; CBA, controlled before-and-after desgn; ICU, intensive care unit; ITS, interrupted time-series study; RCT, randomized controlled trial; VA, Veterans Administration; HH, hand hygiene; CVC, central venous catheter, CUSP, comprehensive unit-based safety program, including education and training, culture change, learning from experience, observation, implementation of evidence-based practice; CHG, chlorhexidine gluconate; IHI, Institute for Healthcare Improvement; MRSA, methicillin-resistant *Staphylococcus aureus*; PVP, polyvinylpyrolidone.

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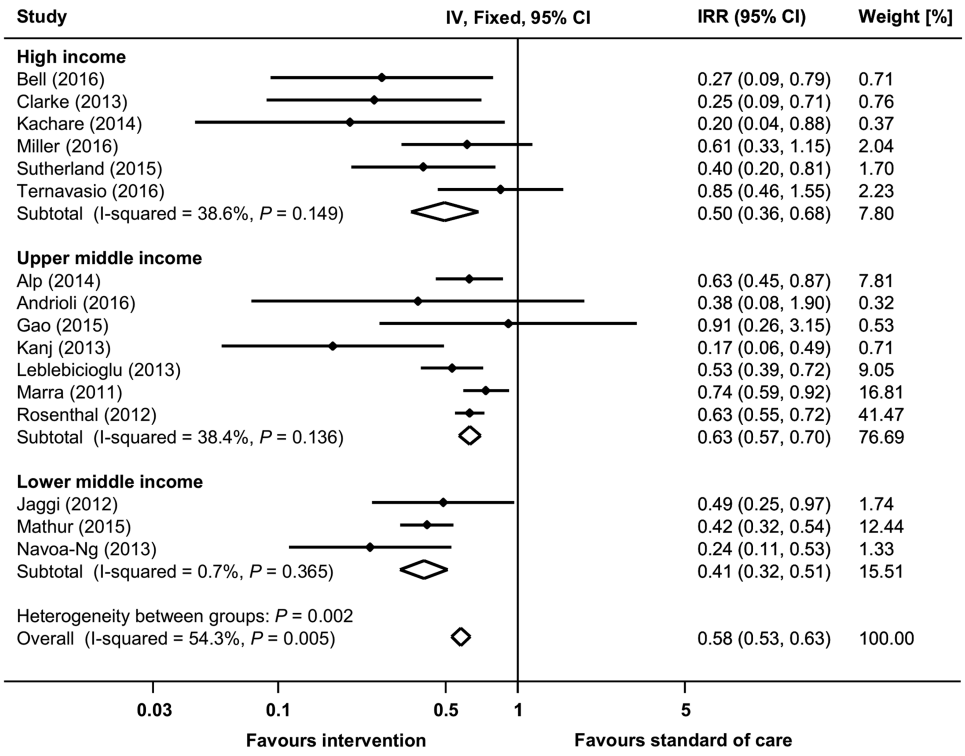

Fig. 2. Incidence rate ratios (IRRs) from fixed effects models for catheter-associated urinary tract infection (CAUTI) in uncontrolled before-and-after studies stratified by country economic income status. Data markers indicate IRRs and error bars indicate 95% confidence intervals (95% CI). Note. IV, inverse variance.

22% increase from baseline (Supplementary Table S2).[18,19,40,59,64,96,133]

Publication bias was evident from visual inspection of the funnel plot (Supplementary Fig. S1b) and was confirmed using the Egger test ($P = .002$).

Central-line–associated bloodstream infection

In total, 30 before-and-after studies reported raw data on infection rates and were available for meta-analysis (Supplementary Fig. S2a).[24,30,34,42,43,52,57,58,63,66,69,74,76,82,84,87,89,92,97,102,106,108,109,111,119,123,132,137,138,151] The pooled IRR of these studies was 0.459 (95% CI, 0.381–0.554), with an overall heterogeneity of $I^2 = 86.8\%$. Reductions in CLABSI incidence could be observed in all country economic income groups, although differences between subgroups could not be explored due to high heterogeneity (Fig. 3). Changes in CLABSI rates ranged from a reduction of 100% to a statistically insignificant increase of 6% in 15 studies reporting aggregated data only (Supplementary Table S3).[8,12,36,38,59,60,64,99,103,107,115,125,139,143,148]

Visual inspection of the funnel plot (Supplementary Fig. S2b) and the Egger test ($P = 0.071$) revealed no publication bias.

Surgical site infections

Overall, 36 before-and-after studies and 1 RCT reported raw data on infection rates and were available for meta-analysis (Supplementary Fig. S3a).[9–11,14,15,17,21,23,29,37,39,51,55,56,65,67,72,77,80,86,88,91,93,94,100,104,105,110,114,117,118,124,130,134,145,147,150] The pooled RR of the before-and-after studies was 0.461 (95% CI, 0.389–0.546), with an overall heterogeneity of $I^2 = 66.4\%$. A significant increase of SSI rates associated with a multifaceted intervention (RR, 1.565; 95% CI, 1.015–2.412) was reported in 1 RCT.[134] Significant reductions in SSI rates could be observed in all country economic income groups, but differences between subgroups could not be explored due to high heterogeneity (Fig. 4). Supplementary Table S4 lists the 4 studies reporting aggregated SSI rates only. In these studies, SSI reductions ranged from 31% to 84%.[45,68,122,139]

Publication bias was evident from visual inspection of the funnel plot (Supplementary Fig. S3b) and was confirmed using the Egger test ($P = .004$).

Ventilator-associated pneumonia

Raw data from 17 before-and-after studies were used to calculate the pooled IRR for VAP (Supplementary Fig. S4a).[22,25,31,33,44,54,58,62,70,76,81,85,95,98,101,102,137] The pooled IRR of these studies was 0.553 (95% CI, 0.465–0.657), with an overall heterogeneity of $I^2 = 81.0\%$. Significant reductions in VAP incidence could be observed in all country economic income groups, although differences between subgroups could not be explored due to high heterogeneity (Fig. 5). Moreover, 5 before-and-after studies and 2 RCTs reported raw proportions of patients with VAP (Supplementary Fig. S5a).[47,73,112,113,121,126,141] All but 1 of these studies, which was conducted in a upper middle income country,[141] were performed in high income countries. The pooled RR (95% CI) of the before-and-after studies was 0.611 (95% CI, 0.414–0.900). The 2 RCTs showed a pooled RR of 0.509 (95% CI, 0.277–0.937).[121,141] Data from 22 studies with aggregated data for VAP are shown in Supplementary Table S5.[12,13,27,28,35,41,48,49,52,53,59,64,75,120,127,128,131,136,139,140,144,152] Changes in VAP rates or proportions in these reports ranged between 100% reduction and a 17% increase (statistical significance not reported).

Visual inspection of the funnel plots (Supplementary Figures S4b and S5b) and the Egger test ($P = .105$ for studies reporting rates; $P = .560$ for studies reporting proportions) revealed no evidence for publication bias.

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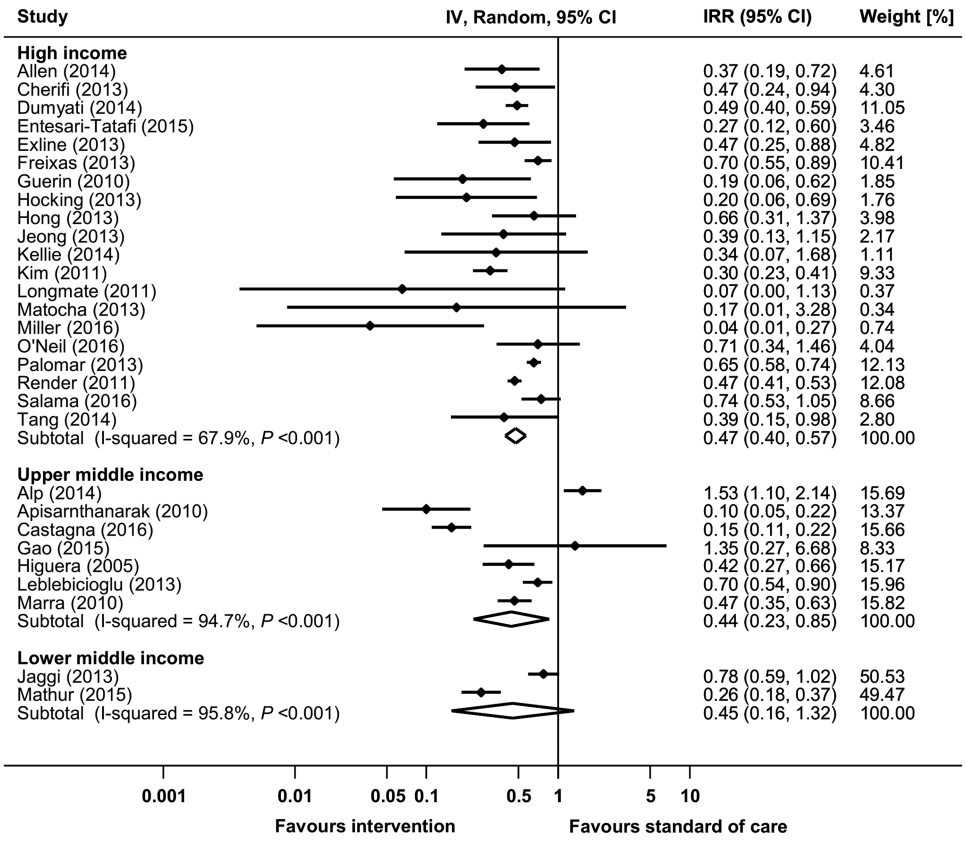

Fig. 3. Incidence rate ratios (IRR) from fixed-effects models for central-line–associated bloodstream infection (CLABSI) in uncontrolled before-and-after studies stratified by country economic income status. Data markers indicate IRRs and error bars indicate 95% confidence intervals (95% CI). Note. IV, inverse variance.

Healthcare-associated pneumonia

Only 2 uncontrolled before-and-after studies on HAP met the inclusion criteria.[90,146] One study showed an adjusted OR of 0.16 (95% CI, 0.01–0.94) associated with a multifaceted intervention for prevention of postoperative pneumonia.[90] Another study reported a significant reduction of 43.6% of HAP rates, from 0.78% (preintervention) to 0.44% (postintervention).[146]

Study quality

The risk of bias in all but 1 of the included studies was high. Uncontrolled before-and-after studies were a priori defined to be at high risk of bias.[8–15,17–44,46–49,51–59,61–120,122–133,135–140,142–152] All 5 randomized controlled trials and the controlled before-and-after study were considered at high risk of bias because study participants and study personnel were unblinded throughout (Supplementary Table S6).[43,50,60,120,134,141] Risk of bias was unclear in the remaining 1 interrupted time-series analysis.[45]

Discussion

In our extensive systematic review of 5,226 screened and 144 included articles published over a 12-year period between 2005 and 2016, the pooled IRRs associated with multifaceted interventions for HAI reduction were 0.543 (95% CI, 0.435–0.662) for CAUTI, 0.459 (95% CI, 0.381–0.554) for CLABSI, and 0.553 (95% CI, 0.465–0.657) for VAP. The pooled RR was 0.461 (95% CI, 0.389–0.546) for interventions aiming at SSI reduction, and for VAP interventions, the pooled RRs were 0.611 (95% CI, 0.414–0.900) for before-and-after studies and 0.509 (95% CI, 0.277–0.937) for randomized controlled trials. Relative reductions of infection rates were independent of country economic income status, indicating that quality improvement projects with multifaceted interventions may result in substantial reducions of infection rates irrespective of the economic setting.

The proportion of HAIs that is preventable is still under debate.[3] Our observed ranges of reductions associated with the implementation of multfaceted, evidence-based interventions are in line with previous estimates.[1–3] Our results confirmed the findings by Harbarth *et al*[2] that the largest effect was attributed to interventions targeting CLABSI prevention. Interestingly, the avoidable proportion of HAI does not seem to decrease over time as would be predicted by the law of diminishing returns given the increasingly widespread availability and expected implementation of evidence-based practices for HAI reduction.[153] However, for an accurate comparison, these findings must be considered in the context of changes in epidemiology over time. From 1997 to 2008, an increase of the percentage of the elderly (≥65 years of age) population from 12% to 37% was described in the United States, and a similar increase of this elderly fraction in hospitalized patients was reported.[154] Increasing age is associated with a higher rate of hospitalization.[155] Furthermore, aging predisposes to the development of chronic diseases, increasing the likelihood of multimorbidity.[156] Later studies likely included a larger fraction of older and sicker patients—a vulnerable population prone to HAIs and increased morbidity and mortality resulting from HAIs. Therefore, it would seem that increasing implementation of evidence-based best practies has been met with global trends of aging and multimorbidity, which necessitate additional efforts to

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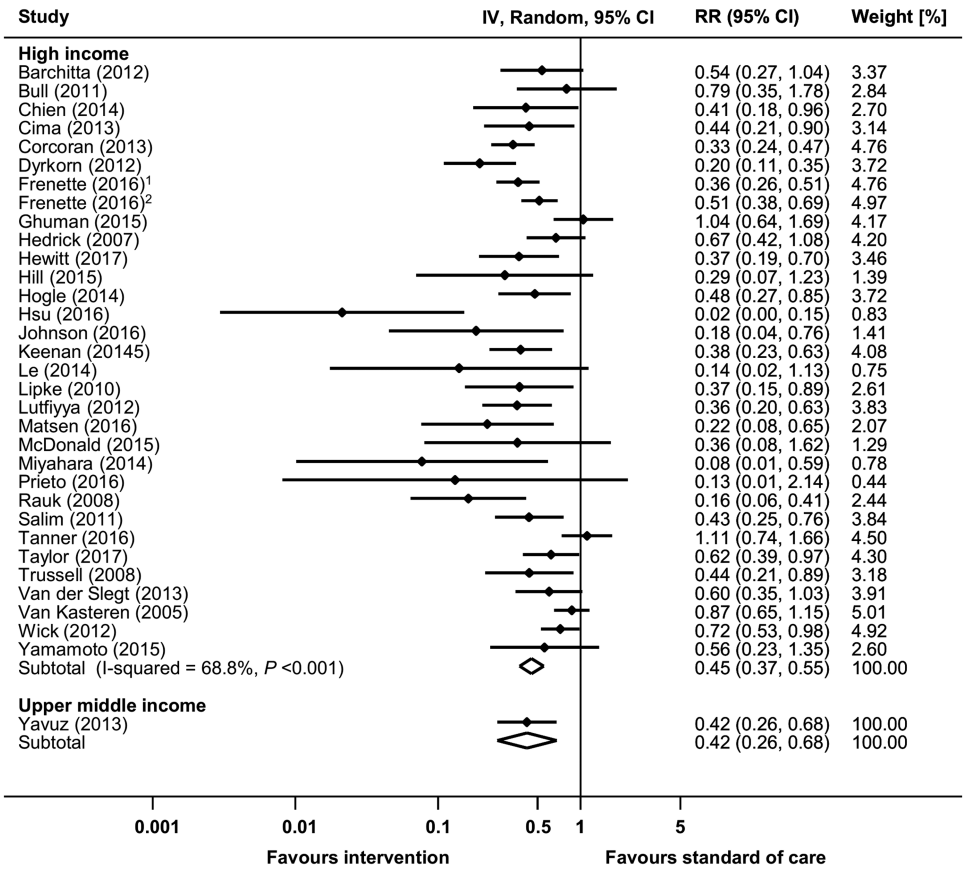

Fig. 4. Risk ratios (RRs) from random-effects models for surgical site infection (SSI) in uncontrolled before-and-after studies stratified by income status. Data markers indicate risk ratios and error bars indicate 95% confidence intervals (95% CI). Note. IV, inverse variance. ([1]Reference #104; [2]Reference #105 in the online supplementary material.)

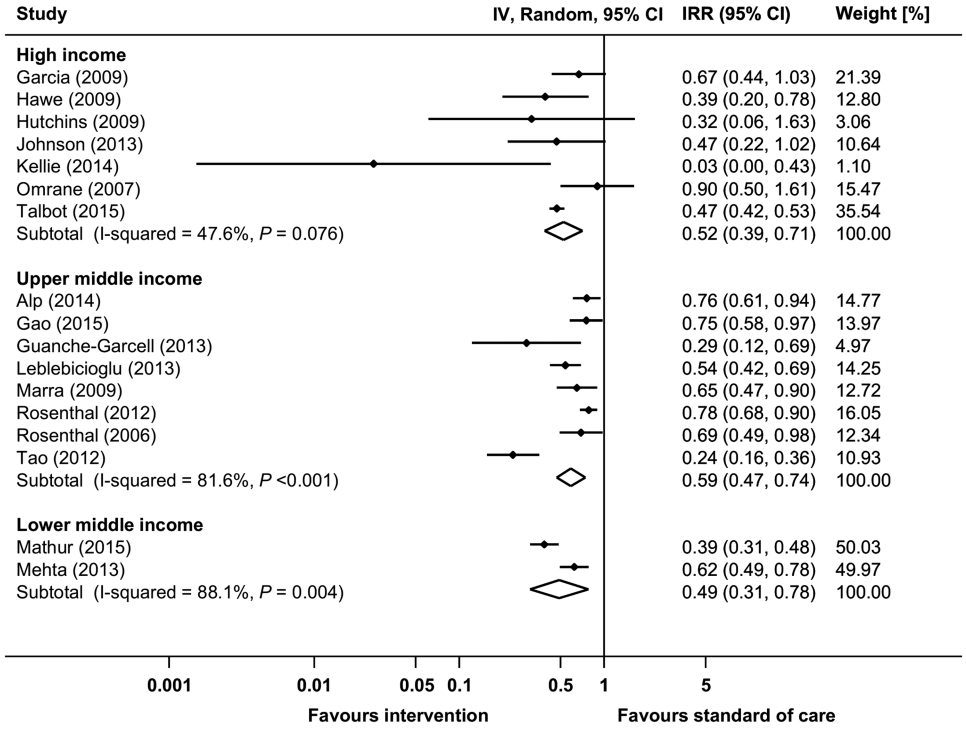

Fig. 5. Incidence rate ratios (IRRs) from random-effects models for ventilator-associated pneumonia (VAP) in uncontrolled before-and-after studies stratified by country economic income status. Data markers indicate IRRs and error bars indicate 95% confidence intervals (95% CI). Note. IV, inverse variance.

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further reduce HAIs. Overall, the HAI target should likely be considered an ever-moving group of individuals at risk who enter and leave the healthcare system.

Our findings demonstrate that even in high income countries, where high adherence to current recommendations may be expected, there remains considerable room for improvment. The persistance of a 30%–50% potential reduction in HAI with the implementation of evidence-based strategies demonstrates that current recommendations have not been sufficiently implemented. Importantly, the quality of infection control measures cannot be inferred on country economic classification alone. However, due to the heterogeneity of studies included in our dataset and lack of information on process indicators, we were unable to determine whether the actual efforts to achieve a reduction of HAI differed between studies from different economies. Although many hospitals, particularly in high income settings, may claim that they adhere to current evidence-based standards, implementation science has demonstrated a large discrepancy between the intention to effect change by employing standard operating procedures and true implementation of such practices into daily practice.[157,158] On the other hand, our results may also indicate that there is room for improvement after implementation of basic infection control measures that reduce HAI rates to levels that do not attract further attention.

Our systematic review and meta-analysis included multifaceted interventions only. Another highly interesting, and until now unresolved, question concerns the individual contribution of the single components of bundled interventions. Although not addressed in the current study, more profound knowledge would help guide bundle development by focusing on the most efficient elements of these interventions.

The studies reviewed in this analysis only covered known measures for IPC. The evolution of risk related to the acquisition of HAIs in medicine, however, is unknown. On one hand, medical innovations may reduce the risk of HAIs due to less invasive techniques (eg, minimal invasive surgery or noninvasive ventilation). On the other hand, novel technologies allowing interventions on patient populations that were previously ineligible for certain treatments due to impaired health status may be associated with an increased risk of HAIs. Even factors that may be perceived as unmodifiable today may be alterable in the future. Therefore, continuous efforts in the field of IPC are needed to keep up with medical progress. Such efforts must consider not only extrinsic factors (including medical devices) but also intrinsic factors (ie, host and microbes). In the future, IPC should and will be integrated more intrinsically in all medical procedures. In addition to the medical duty to prevent harm to patients, recent literature further illustrates that infection prevention programs are cost-effective when factoring in the incremental costs of HAIs to hospitals.[3] This particularly applies to settings were complications are not reimbursed or even associated with penalizations.[159,160]

The fact that we observed publication bias for studies on CAUTI and SSI and that risk of bias was high in 143 of 144 studies (99.3%) needs to be considered. An uncontrolled study design with before-and-after assessment of the intervention effect was used in most studies; thus, bias due to the influence of unmeasured extraneous factors that change over time cannot be excluded. Moreover, blinding was not performed in the 4 randomized controlled trials that were included, which may also have distorted the reported results. As in other fields of medicine, smaller intervention trials with negative results may remain unpublished.[161] The HAIs addressed in this systematic review and meta-analysis mainly consist of device-associated infections. These infections, however, represent only a fraction of all HAIs. Data about the preventable proportion of non–device-associated infections are scarce; only 2 studies on HAP were included in our study. Lastly, the clear majority of the included papers reported on a single HAI or on only 1 type of SSI, which indicates that even though the interventions are multifaceted, their focus is nevertheless narrow. Additional, higher-quality data are clearly required to guide prevention efforts from a governance perspective.

The preventable proportion of HAIs reported by this systematic literature review and meta-analysis of 35%–55% suggests that there remains much to be desired in terms of implementation of evidence-based best practices. Our study findings should motivate healthcare institutions that aim to improve quality of patient care and to reduce infection rates to develop their own customized, multifaceted strategies to improve patient outcomes.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2018.183

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Conflicts of interest. All authors report no competing interests relevant to this article.

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