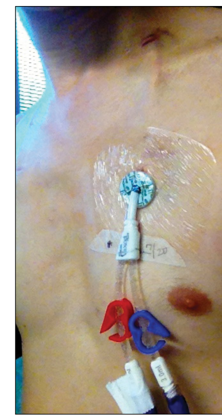
Central-line bundles need a multimodal implementation strategy

Every year, health-care-associated infections (HAIs) affect millions of patients worldwide.[1] In intensive care units (ICUs), 12–15% of all HAIs are bloodstream infections, mostly associated with the use of central lines,[2] and are responsible for excess morbidity, mortality, and use of hospital resources. Central-line-associated bloodstream infections (CLABSIs) are linked to device-related and practice-related risk factors.[3] Extrinsic risks such as femoral or jugular insertion site, number of catheter lumens, or time the device is left in palce can be modified.[4] Maximum sterile barrier precautions, appropriate aseptic technique, and use of alcohol-based chlorhexidine for skin antisepsis are measures to further prevent infection; these are deemed best practice with use of central-line bundles and patient care.[4–6] Best practice interventions allow substantial CLABSI reduction by promotion of groups or bundles of procedures and technology, and by use of a multimodal strategy for education, training, implementation, and dissemination.[6,7]

In this issue of *The Lancet Infectious Diseases*, Erwin Ista and colleagues present the results of their systematic review and meta-analysis[8] about the effect of bundle strategies on CLABSI incidence in 2370 ICUs (including adult, paediatric, and neonatal settings) worldwide. Their review[8] assessed the effectiveness of central-line bundles (insertion and maintenance or both) in preventing CLABSIs. It is the largest—and, in our opinion, the best—completed review in its scientific field. Although the main outcome that bundle strategies significantly reduce CLABSI incidence (incidence risk ratio [IRR] 0·44 [95% CI 0·39–0·50], p<0·001) is not surprising, the review[8] offers some unanticipated and important findings. Variation of baseline incidence has a geographical distribution with lower incidence in high-income countries. Some settings with higher baseline incidence had larger CLABSI reductions, but multi-faceted interventions in hospitals with limited resources (IRR 0·47 [95% CI 0·40–0·54]) were equally effective as in high-income settings (0·44 [0·38–0·51], p=0·77). Ista and colleagues' review[8] also investigated the role of performance indicators and, to little surprise, reported that such information is often missing and, when provided, of rather low quality. The absence of reporting process indicators is a general shortcoming of infection control studies; such information would help to assess the translation of behavioural interventions into practice change at patient bedsides. Finally, the effect of bundle strategies is sustained over time. The reason for sustainability is not quite clear, but culture changes because of the multimodality of CLABSI interventions are probably at the heart of it.

Studies published after 2013 did not contribute further to the knowledge on the effectiveness of central-line bundles in this systematic review.[8] This finding does not mean, however, that new studies might not contribute to the evidence-base of CLABSI prevention—eg, key studies published in the past 2 years have proven the subclavian to be better than the jugular access site,[4] alcohol-based chlorhexidine to be better than alcohol-based iodine,[5] and multimodal strategies to not only work in the ICU but also throughout hospitals.[9] However, when summarising the role of bundles, the authors correctly state that "the question of whether central-line bundles are effective [in CLABSI prevention] is no longer open to debate".[8] Although unquestionably effective, bundles have a major disadvantage—implementation is not easy. Ista and colleagues[8] list education, performance feedback, and checklists as the most frequently used strategies for implementation and briefly discuss the role of written protocols and leadership. This section is the weakest part of their review,[8] but study reports rarely offer details about the implementation process, even if successful. The same strategy can work in one setting,[7] but not in another.[10] The Michigan Keystone and the Matching Michigan programmes in the USA and in England are excellent examples illustrating how much local context affects outcome by interfering with implementation.[11,12] The same intervention that worked in Michigan, USA, did not work in England. At a closer look, the studies reviewed by Ista and colleagues[8] are quite heterogeneous both in bundle composition and implementation strategy.

Success frequently relies on adaption of the strategy to the local context. The authors mention that important factors for success are understanding



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of the complexity of an innovation and culture of a setting. Bundle strategies follow recognised models for infection prevention and control programmes with successful implementation relying on multimodal and multidisciplinary approaches. Use and implementation of infection prevention strategies need to be adapted to patient bedsides. Bundles are no exception. They prevent central-line infections, but their successful implementation needs multimodal approaches adapted to local realities. Evidence-based implementation science with continuous monitoring of performance indicators should be the topic of future studies in central-line infection prevention.

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We declare no competing interests

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Effectiveness of insertion and maintenance bundles to prevent central-line-associated bloodstream infections in critically ill patients of all ages: a systematic review and meta-analysis

Erwin Ista, Ben van der Hoven, René F Kornelisse, Cynthia van der Starre, Margreet C Vos, Eric Boersma, Onno K Helder

Summary

Background Central-line-associated bloodstream infections (CLABSIs) are a major problem in intensive care units (ICUs) worldwide. We aimed to quantify the effectiveness of central-line bundles (insertion or maintenance or both) to prevent these infections.

Methods We searched Embase, MEDLINE OvidSP, Web-of-Science, and Cochrane Library to identify studies reporting the implementation of central-line bundles in adult ICU, paediatric ICU (PICU), or neonatal ICU (NICU) patients. We searched for studies published between Jan 1, 1990, and June 30, 2015. For the meta-analysis, crude estimates of infections were pooled by use of a DerSimonian and Laird random effect model. The primary outcome was the number of CLABSIs per 1000 catheter-days before and after implementation. Incidence risk ratios (IRRs) were obtained by use of random-effects models.

Findings We initially identified 4337 records, and after excluding duplicates and those ineligible, 96 studies met the eligibility criteria, 79 of which contained sufficient information for a meta-analysis. Median CLABSIs incidence were 5·7 per 1000 catheter-days (range 1·2–46·3; IQR 3·1–9·5) on adult ICUs; 5·9 per 1000 catheter-days (range 2·6–31·1; 4·8–9·4) on PICUs; and 8·4 per 1000 catheter-days (range 2·6–24·1; 3·7–16·0) on NICUs. After implementation of central-line bundles the CLABSI incidence ranged from 0 to 19·5 per 1000 catheter-days (median 2·6, IQR 1·2–4·4) in all types of ICUs. In our meta-analysis the incidence of infections decreased significantly from median 6·4 per 1000 catheter-days (IQR 3·8–10·9) to 2·5 per 1000 catheter-days (1·4–4·8) after implementation of bundles (IRR 0·44, 95% CI 0·39–0·50, p<0·0001; I^2=89%).

Interpretation Implementation of central-line bundles has the potential to reduce the incidence of CLABSIs.

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Introduction

Health-care-associated infections are a major problem in intensive care units (ICUs) worldwide.[1] They have been associated not only with impaired immunity of critically ill patients but also with the presence of central lines, urine catheters, and invasive ventilation.[2,3] The true number of health-care-associated bloodstream infections is not known, but 18 000 cases are estimated to have occurred in intensive care in 2009 in the USA, which were associated with a mortality as high as 25%.[4] However, the International Nosocomial Infection Control Consortium (INICC) stated that the pooled incidence of central-line-associated bloodstream infections (CLABSIs) in INICC ICUs (ie, in Africa, Asia, Europe, and Latin America), of 4·9 infections per 1000 central-line-days, is nearly five times higher than that reported from comparable ICUs in the USA.[5] Most hospital-acquired bloodstream infections are associated with the presence of a central-line.[6–8] CLABSIs are the most common health-care-associated infections in paediatric intensive care units (PICUs), and subsequently in neonatal intensive care units (NICUs) and adult ICUs. Furthermore, CLABSIs are responsible for substantial mortality, morbidity, extended duration of stay in hospital, and additional costs to hospitals.[9–13] Evidence suggests that CLABSI prevention is crucial for safe patient care for all age groups.

The Institute for Healthcare Improvement developed so-called bundles to improve patient care. A bundle is a set of evidence-based practices that have been proven to improve patient outcomes, provided they are completed collectively and reliably. In 2006, Pronovost and colleagues wrote a key paper[14] in which they concluded that implementation of central-line insertion bundles significantly reduced CLABSI incidence in adult ICUs. Growing evidence suggests that addition of a maintenance bundle to a central-line insertion bundle might be even more effective in prevention of CLABSIs in children and infants.[15–18] A central-line insertion and maintenance bundle is defined as a combination of interventions, such as full barrier precaution during the insertion of a central line, cleaning of the skin with chlorhexidine, application of appropriate hand hygiene, and prompt removal when the central line is no longer needed.

For more on **INICC** see http://www.inicc.org/

Research in context

Evidence before this study

Health-care associated infections are a large problem in intensive care units (ICUs) worldwide. Risk factors for these infections are associated with both invasive procedures such as insertion and maintenance care of central lines in neonatal, paediatric, and adult ICU patients. Studies have previously investigated the effectiveness of central lines in adult ICUs, including a 2014 systematic review. We focused on effectiveness of the implementation of central-line bundles and the estimated cost savings on the entire lifespan of patients. We searched Embase, MEDLINE, Web-of-Science, Cochrane Library, and PubMed (with no language restriction) using a combination of search terms of "catheterization, central venous/adverse effects", "infection control/methods", "intensive care units", and "quality control". We included literature published between Jan 1, 1990, and June 30, 2015.

Added value of this study

Our study makes an important contribution to clinical practice and shows there is an overwhelming number of publications reporting implementation of central-line bundles are effective in ICU patients, including neonates and children. We show that implementation of central-line bundles are effective in low-income and middle-income countries as well as in high-income countries. Our findings show that central-line bundles are cost saving.

Implications of all the available evidence

Health-care professionals should make efforts to implement central-line bundles in low-income, middle-income, and high-income countries, and stop undertaking new effectiveness studies.

See Online for appendix

CLABSI prevention requires broad practice changes and implementation of multifaceted programmes to improve infection control.[14,19,20] It also requires changes in the behaviour of health-care professionals through education, performance assessments, provision of feedback, use of teamwork, and improvements in the overall safety culture.[21]

A rigorous systematic review and meta-analysis of the effectiveness of central-line bundles has not yet been done in critically ill patients, of all ages, during their entire life span. Robust evidence of bundle effectiveness in individual studies is restricted on account of small sample sizes.[15] Additionally, compliance with the application of bundles is not always consistently assessed. No clear evidence shows that central-line bundles are cost effective. Furthermore, it is unclear what implementation strategy would be best to increase bundle compliance. Our systematic review and meta-analysis aims to assess the effectiveness of the implementation of central-line bundles to prevent CLABSIs in adult, paediatric, and neonatal patients in ICUs.

Methods

Search strategy and selection criteria

We did this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[22] The research protocol was registered in the PROSPERO international prospective register of systematic reviews (CRD42014007303).[23]

We systematically searched for articles published between Jan 1, 1990, and June 30, 2015, in the Embase, MEDLINE OvidSP, Web-of-Science, Cochrane Library, PubMed, and Google Scholar databases using the search terms "catheterization, central venous or adverse effects", "infection control or methods", "intensive care units", and "quality control" (full search strategy is available in the appendix). Additionally, studies were identified from the reference lists of relevant articles. Two authors (EI, OKH) did the literature search and the study selection separately, identifying and scrutinising studies independently for potential inclusion. Disagreements were solved by discussion until consensus was reached.

Studies were included if they reported about implementation of a central-line bundle (insertion or maintenance or both) in an ICU setting (adult, paediatric, or neonatal) with documentation of the CLABSI incidence expressed per 1000 catheter-days; made a comparison (ie, with and without intervention) using a randomised or non-randomised study design, or an interrupted times series (ITS); and described an intervention (ie, education or feedback) to improve the care process in addition to implementation of a central-line bundle. Reviews, editorials, congress abstracts, or studies that did not report CLABSI incidence were excluded. We used no language restrictions. Studies were included in the meta-analysis if the number of CLABSIs and catheter-days were provided.

In this systematic review and meta-analysis, we defined an "insertion bundle" to include at least maximal sterile barrier precautions (eg, surgical mask, sterile gloves, hat, sterile gown, and large sterile drape) and chlorhexidine-based solution for cleaning patient's skin, and a "maintenance bundle" to include at least hand hygiene, daily evaluation of central-line need, and disinfection before central-line manipulation.

Data extraction and quality assessment

Data from included studies were extracted with use of a standardised template of our own. The following information were collected from all studies: design, setting (eg, number of ICU beds), country, population (adult, paediatric, or neonatal), number of patients (if available), sex, age, severity of illness score, description of the bundle elements, definition of CLABSI, implementation strategies, number of infections and catheter-days, compliance measures, and costs. Implementation strategies were classified on the basis of the Cochrane Effective Practice and Organization of Care (EPOC) group classification system (appendix).[24] Authors were contacted to verify the data abstraction form and to provide, if any, missing information.

We assessed the methodological quality of every trial for risk of bias by use of specific criteria and a scoring system (maximum nine points for randomised controlled trials and eight points for observational non-randomised studies [one point for meeting a criterion point; multicentre criteria not included in scoring]), established by the Dutch Institute for Healthcare Improvement CBO in collaboration with the Dutch Cochrane library (appendix).[25] The major criteria are: method of random allocation, allocation concealment, consecutive patients chosen, outcomes clearly defined, comparable groups, and other potential sources of bias (confounding). Furthermore, studies were rated on adequate measures in the analysis to control for confounding factors (eg, patient characteristics, line days, and device use) or secular trend in infections incidence. Studies assigned a low-quality score (<4) or those with no control of confounding were not excluded, because we aim to provide an overview of effect of implementation of bundles in different circumstances.

Outcomes

The primary outcome of this study was the number of CLABSIs per 1000 catheter-days before and after implementation. Our prespecified secondary outcomes were compliance rate (percentage of intensive care patients with a central line for whom all elements of the insertion, or maintenance, or both, bundle were documented) to central-line bundles, implementation strategies, and estimated cost reduction of the intervention.

Statistical analysis

Study characteristics were summarised as frequencies or percentages. We calculated the incidence risk ratio (IRR) with 95% confidence interval on the basis of the number of infections per catheter-days. For the meta-analysis, crude estimates of infections were pooled by use of a DerSimonian and Laird random effect model.[26] We used cumulative meta-analysis by updating the pooled estimate of the IRR with data from studies added one at the time in chronological order according to date of publication.[27] We tested the heterogeneity among studies using the Cochrane Q test and the inconsistency index (I^2).[28] Heterogeneity was classified as low (25–50%), moderate (50–75%), or high (>75%) on the basis of an I^2 statistic, according to the method suggested by Higgins and colleagues.[29] Funnel plots were drawn to visually assess the possibility of publication bias. A symmetrical funnel arises from a well balanced dataset, whereas an asymmetrical funnel plot suggests publication bias.[30,31]

We did subgroup analyses of studies offering an adjusted analysis (eg, confounding, analysis for secular trend in infection incidence). Furthermore, we did subgroup analyses by meta-regression for baseline CLABSI incidence less than or more than 5·0 per 1000 catheter-days, most effective insertion and maintenance bundle elements for CLABSI reduction, and most effective implementation strategy. Sensitivity analyses by study characteristics were completed to test the robustness of our findings. Results with two-sided p values less than 0·05 were deemed statistically significant. Analyses were completed with Microsoft Excel 2013, and IBM SPSS (version 21.0).

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the

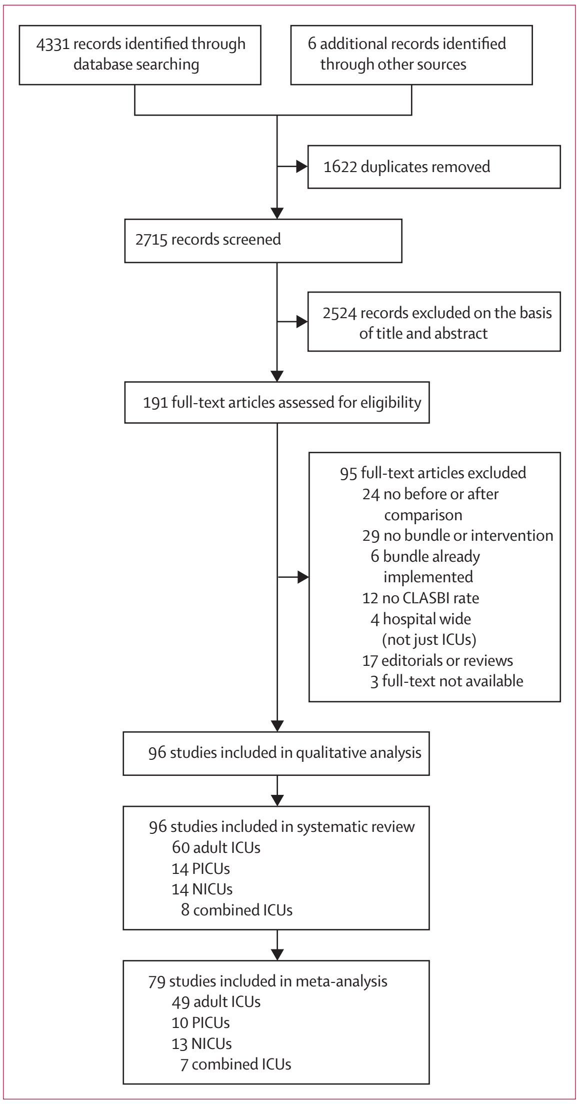

Figure 1: **Flow diagram of study selection**
CLABSI=central-line-associated bloodstream infections. ICU=intensive care unit. PICU=paediatric ICU. NICU=neonatal ICU.

study and had final responsibility for the decision to submit for publication.

Results

We initially identified 4337 records. After removal of duplicates, the search strategy yielded 2715 unique publications, 191 of which were deemed relevant based on the title and abstract and were retrieved. Of these, and after full-text reading, 96 records were used in the systematic review (figure 1), which included 60 records in adult ICUs,[32–91] 14 in PICUs,[16,17,92–103] 14 in NICUs,[104–117] and eight in combined settings.[118–125] 46 (48%) authors returned the data abstraction form with approval, or provided supplemental or missing data. 79 records were used for the meta-analysis, which included 49 in adult ICUs,[32,35,37,39–41,43,45–61,63–67,70–83,85–90] ten in PICUs,[93–98,100–103] 13 in NICUs,[104–109,111–117] and seven combined records.[118–121,123–125] Four of seven combined records provided separate data for children[118,119,124,125] and neonates,[124] which made subgroup analysis possible.

The 96 selected records described a total of 2370 ICUs (ie, 2216 adult, 79 paediatric, and 75 neonatal ICUs). Most studies were undertaken in the USA (55 [57%]), followed by Europe (13 [14%]), Latin America (12 [12%]),

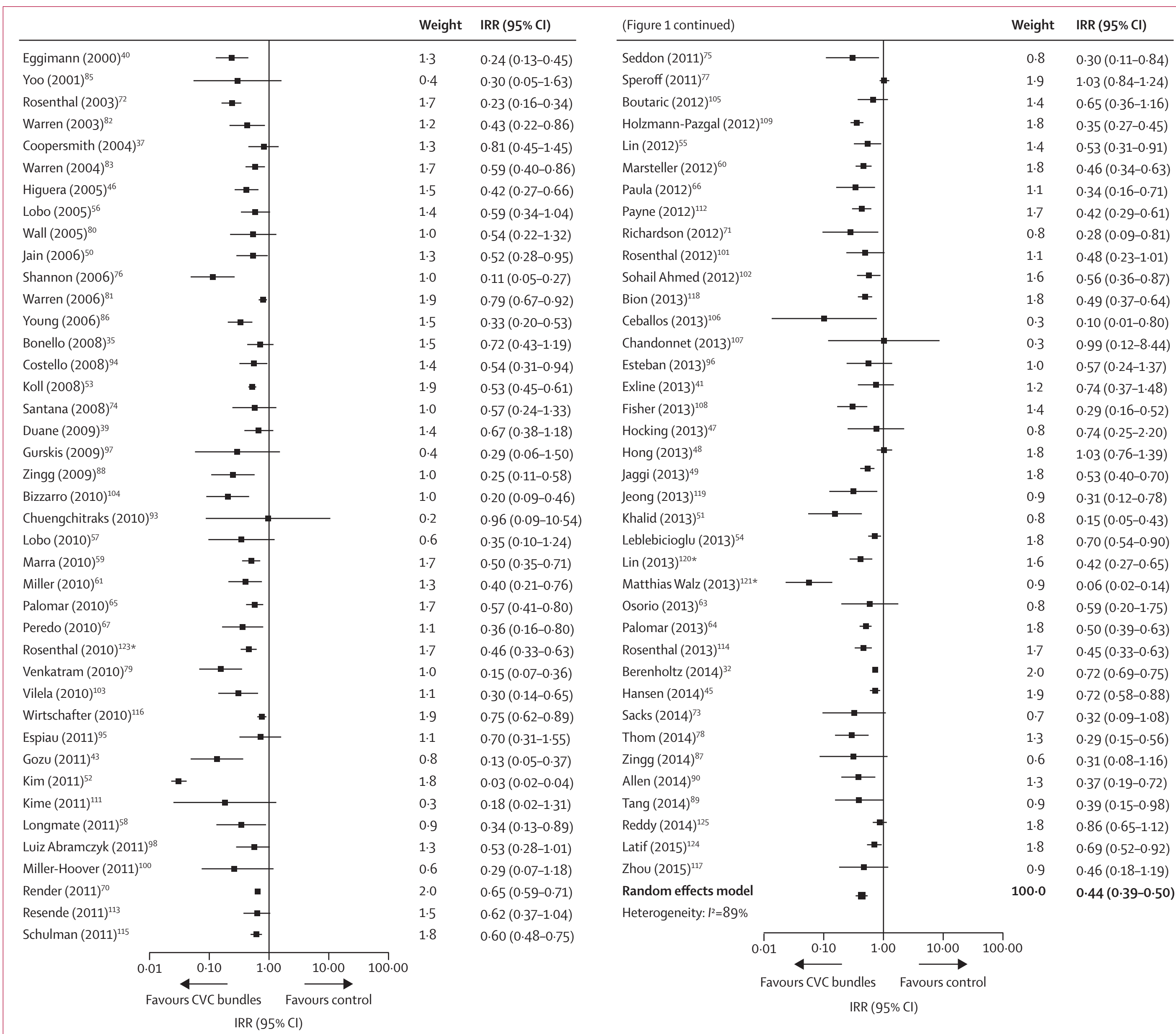

***Figure 2:* Forest plot of IRR for CLABSI, comparing implementation central-line bundles versus none (all 79 studies)**
CLABSI=central-line-associated bloodstream infections. IRR=incidence risk ratio. CVC=central venous catheter. *Undertaken in various ICUs, findings cannot be separated by intensive care unit types.

Asia (nine [9%]), and other regions (seven [7%]). The most used study design was a before-test and an after-test design with or without a control group (n=88 [92%]) or interrupted time series design (n=5 [5%]; appendix).

No general consensus was used for the definition of bloodstream infection, although most studies used the US Centers for Disease Control and Prevention (CDC) definition, if relevant adapted for age.

The baseline CLABSI incidence ranged from 1·2[122] to 46·3[46] per 1000 catheter-days (median 5·7, IQR 3·1–9·5) on adult ICUs, from 2·6[93] to 31·1[98] (5·9, 4·8–9·4) on PICUs, and from 2·6[107] to 24·1[113] (8·4, 3·7–16·0) on NICUs (appendix). After implementation of the central-line bundles the incidences ranged from 0[33] to 19·5[46] per 1000 catheter-days (2·0, 1·1–3·7) on adult ICUs, from 0[119] to 16·5[98] (4·3, 2·4–6·1) on PICUs, and from 0[111] to 14·9[113] (2·6, 1·7–7·6) on NICUs. Duration of the studies ranged from 6 months to 108 months, with a median of 32 months (IQR 22–39; appendix).

Sustained effects, established through a second post-test measurement at median 12 months (IQR 10–17) after implementation of central-line bundles, were reported in 24 (25%) studies.[16,17,39,41,45,47,51,56,58,61,62,66,75,76,91,92,94,96,102,103,106,107,117,123] The median CLABSI incidence in the second post-test measurement was 2·27 per 1000 catheter-days (IQR 1·00–4·44), which means that the reduction was sustained during this period.

Compliance of health-care professionals with bundle elements was determined in 23 (24%) studies[37,46,47,51,54,56,57,72,75,88–90,92,94,96,101,106,108,111,114,119,122,123] before and after implementation and in 11 (11%) studies[16,17,41,43,59,63,66,70,93,107,112] only after implementation of the bundle. In 12 (12%) studies,[16,17,41,47,51,63,66,94,108,112,119,122] the absolute compliance with the full insertion bundle had a 7% improvement[94] and up to 45%[47] after implementation compared with the median 82% before measurement. With respect to compliance with separate elements, maximal barrier precaution was noted in 11 studies[37,56,57,59,88–90,92,93,119,123] and the compliance after implementation ranged from 65% to 100%. Hand hygiene compliance (reported in 15 studies) ranged from 30% to 100% after implementation. Absolute compliance for the maintenance bundle improved by 14%,[16,94] up to 24%[108] after implementation.

Costs savings were described in 12 studies, including two NICU[107,108] and one PICU[16] studies. All studies reported cost savings in high-income countries (11 in the USA,[16,33,36,38,39,71,78,86,90,106,108] one in New Zealand[75]). In one study,[39] the cost savings were based on a reduced duration of ICU stay, as context-independent cost-indicator. In nine studies the cost savings were extrapolated from the number of prevented CLABSIs with fixed costs per prevented

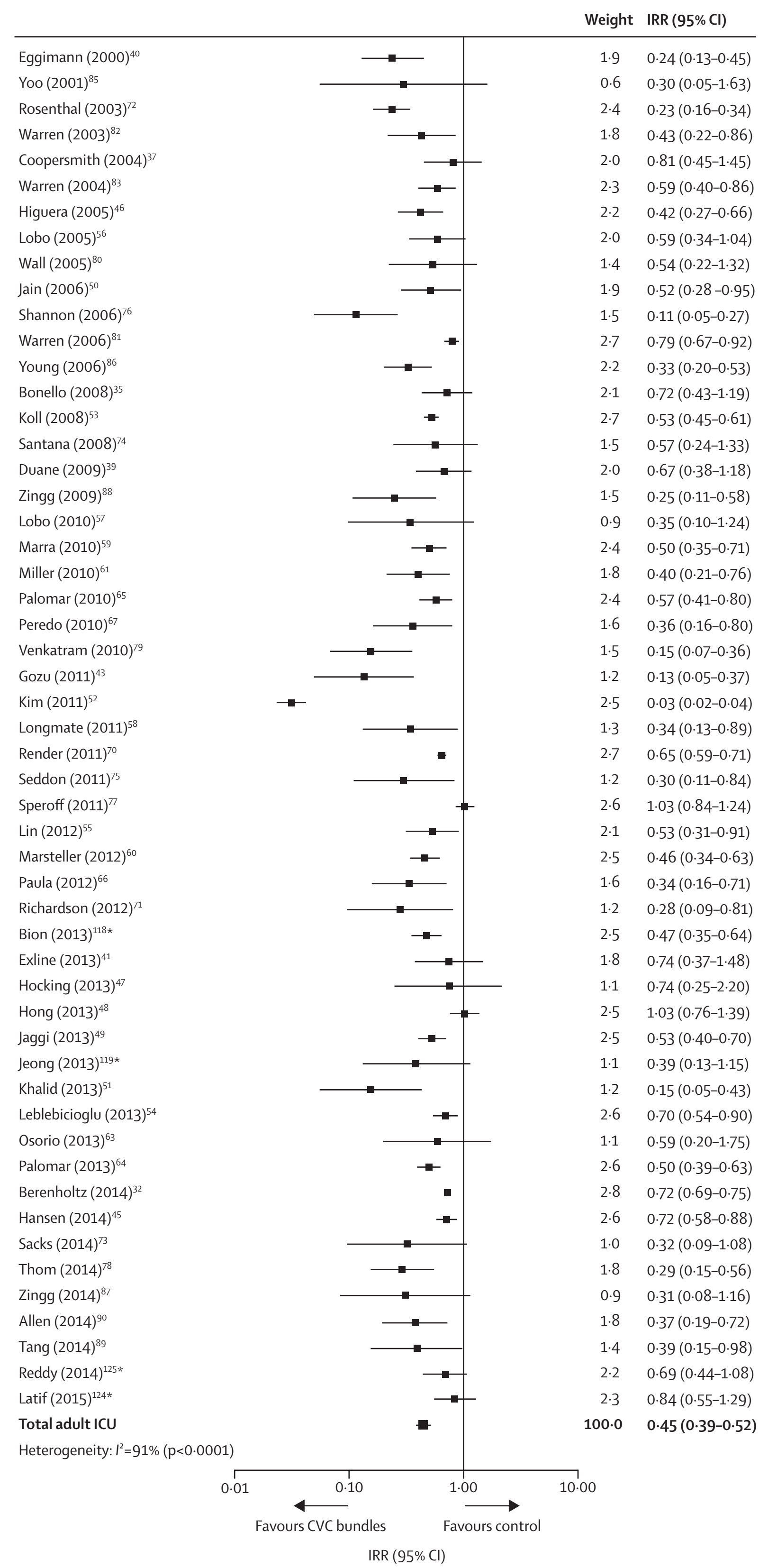

Figure 3: Forest plot of incidence risk ratio for CLABSI, comparing implementation central-line bundles versus none in adult ICUs
CLABSI=central-line-associated bloodstream infections. CVC=central venous catheter. *Undertaken in various ICUs, using only the study's adult ICU data.

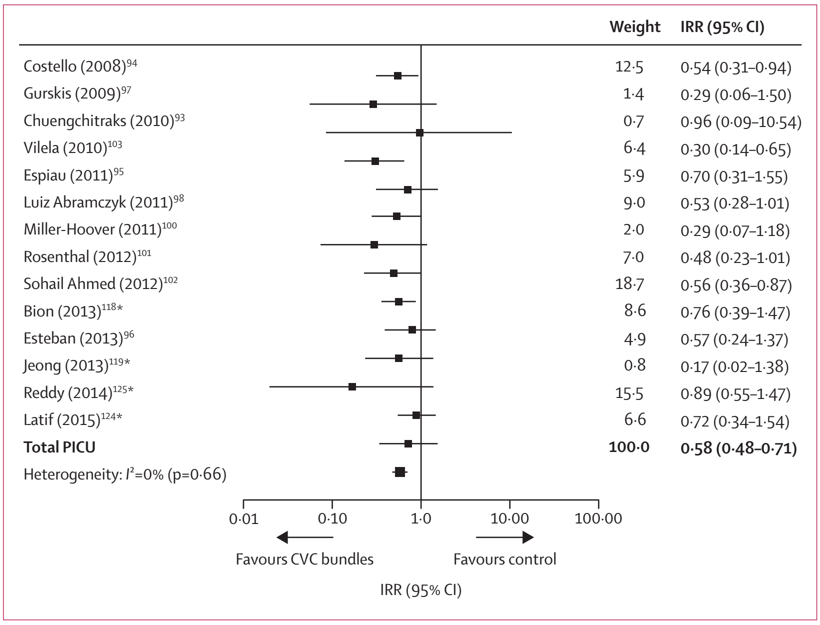

Figure 4: **Forest plot of incidence risk ratio for CLABSI, comparing use of implementation central-line bundles versus none in PICUs**
CLABSI=central-line-associated bloodstream infections. PICU=paediatric intensive care unit. IRR=incidence risk ratio. CVC=central venous catheter. *Undertaken in various ICUs, using only the study's PICU data.

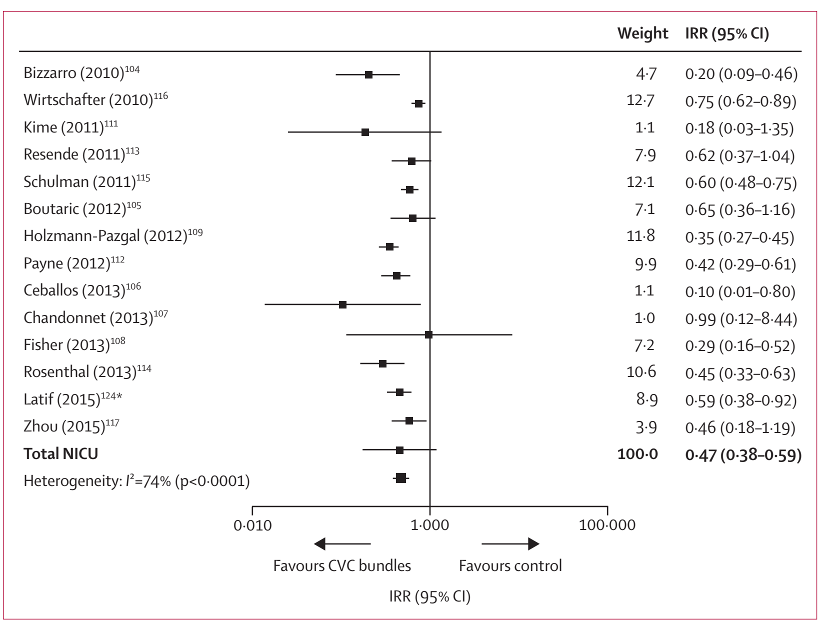

Figure 5: **Forest plot of incidence risk ratio for CLABSI, comparing implementation central-line bundles versus none in NICUs**
CLABSI=central-line-associated bloodstream infections. NICU=neonatal intensive care unit. IRR=incidence risk ratio. CVC=central venous catheter. *Undertaken in various intensive care units, using only the study's NICU data.

infection. Overall, median estimated cost savings per one prevented CLABSI were US$42 609 (IQR 19 000–46 739).

Median number of implementation strategies per study was 5 (IQR 4–7) for non-controlled studies (eg, before-after studies) and 5 (4–6) for controlled studies (eg, RCTs). The most used strategies were education (93 [97%] of 96 studies), performance feedback (71 [74%]), organisational changes 62 [66%]), and checklists (59 [61%]; appendix).

The median quality score was 4 for both the controlled studies (IQR 4–5·75), and the non-controlled studies (IQR 3–5). Overall, methodological quality of 53 (55%) studies was moderate to high. In 44 (46%) of 96 studies the CLABSI incidence was controlled for confounding factors.

79 studies were included in a meta-analysis to assess the effect of implementation of bundles on the incidence of CLABSI. Overall, the result of the analysis was consistent with a significant reduction in the CLABSI incidence (IRR 0·44, 95% CI 0·39–0·50, p<0·0001; I^2=89%; figure 2). The analyses for the three different types of ICUs (adult, paediatric, and neonatal) yielded significant reductions in CLABSI incidence (figures 3–5; table). No significant differences were noted in risk reduction between the three types of ICUs (p=0·67).

Subgroup analysis showed a significantly higher risk reduction in studies with a CLABSI incidence of five per 1000 catheter-days or higher at baseline (IRR 0·37, 95% CI 0·29–0·48) than in studies with a lower baseline infection incidence (0·59, 0·53–0·65, p=0·008). The risk reduction in studies of low-income and middle-income countries (n=20; 0·47, 0·40–0·54) did not significantly differ from studies of high-income countries (n=59; 0·44, 0·38–0·51, p=0·77). Risk reduction in studies that corrected for confounding (n=38) did not differ from that in studies that did not correct for confounding (n=41; IRR 0·97, 95% CI 0·78–1·21, p=0·81). Risk ratio reduction did not differ between low-quality studies (0·53, 0·41–0·70) and high-quality studies (0·44, 0·33–0·60; p=0·38). Finally, the risk reduction in studies that reported catheter-related bloodstream infections (n=13; IRR 0·30, 95% CI 0·13–0·66) did not differ (p=0·21) from studies that reported CLABSIs (n=66; 0·51, 0·46–0·56). The number of newly published studies per year about this topic was accelerating with time. However, studies published in 2013 and after contributed very little to the already proven effectiveness of central-line bundles (appendix).

Our meta-regression analysis (appendix) showed that the implementation strategy associated with large CLABSI risk reductions was having the support of opinion leaders (p=0·041). Separate bundle elements were analysed for their contributions to CLABSI risk reduction. With respect to the insertion bundle, addition of hand hygiene (p=0·003) to the bundle resulted in significantly reduced CLABSIs in adult ICUs. Other clinically important items were having a central venous catheter kit (p<0·0001) and proper selection of insertion vein (p=0·03) in PICUs. With respect to the maintenance bundle, clinically important items were hand hygiene (p=0·022) in the adult ICU, and minimising of central-line access (p=0·019) in the NICU.

Sensitivity analysis was done for all studies and separately for the studies on the three types of ICUs (appendix). Analysis of all studies, but without the low-quality studies, yielded a reduction of the I^2 from 92% (with low-quality studies included) to 77% (p<0·0001; appendix). For publication bias of all studies and the adult ICU before and after studies the funnel plots showed an asymmetry due to heterogeneity, but these were symmetrical for the NICU and PICU studies (appendix). The plots did not suggest reporting bias. Investigators seem to have mainly reported small studies with large effects and large studies with small effects.

	Number of studies	Random effects model		Heterogeneity (I^2)	
		ln (IRR [95% CI])	IRR (95% CI)	I^2 (%)	p value
Overall ICUs	79 (100%)	−0·81 (−0·93 to −0·69)	0·44 (0·39 to 0·50)	89%	<0·0001
Adult ICUs	53 (67%)	−0·80 (−0·95 to −0·65)	0·45 (0·38 to 0·52)	91%	<0·0001
NICUs	14 (18%)	−0·75 (−0·97 to −0·53)	0·47 (0·38 to 0·59)	74%	<0·0001
PICUs	14 (18%)	−0·54 (−0·74 to −0·42)	0·58 (0·48 to 0·71)	0%	0·66

CLABSI=central-line-associated bloodstream infections. ln=natural log. IRR=incidence rate ratio. I^2=inconsistency index. ICU=intensive care unit. NICU=neonatal ICU. PICU=paediatric ICU.

Table: **Effect of implementation of CLABSI bundle in adult, paediatric, and neonatal ICUs**

Discussion

The main finding of this systematic review and meta-analysis of 2370 ICUs, is a significant association between implementation of central-line insertion and maintenance bundles and reduction of the incidence of CLABSIs in all ICU settings. The risk reduction was more conspicuous in studies with a CLABSI incidence of five or higher per 1000 catheter-days at baseline than in studies with a CLASBSI incidence lower than five per 1000 catheter-days.

A high baseline incidence of CLABSIs was associated with geographical distribution; however, the multifaceted, central venous catheter bundles, implementation programmes in low-income and middle-income countries and in hospital settings with restricted resources were as effective as in high-income countries. Furthermore, the effect in the adult ICU and NICU populations seemed to be larger than that in the PICU population, although this difference was not significant. Effects of the implementation of central-line bundles were sustained over time.

The findings of our meta-analysis are unique because the included studies covered the entire life span (from neonatal to adult patients). Previous systematic reviews[126–128] have suggested that implementation of central-line bundles is effective in adult ICUs, but our meta-analysis established this finding not only in adult ICUs,[129] but also in paediatric and neonatal ICUs.

Health professionals' compliance with bundle protocols was measured in no more than a third of the studies and was reported to be suboptimum in all. For that matter, protocol and guideline compliance is a universal problem in health care.[130,131] The question remains whether health-care professionals' perfect compliance with all bundle elements will help reduce catheter-related infections to zero.

Hand hygiene practices were well explained in about half of all included studies. The effect of hand hygiene practices on the results can only be speculated, but good hand hygiene has been noted to contribute to CLABSI reduction in the ICU population.[132]

Various implementation approaches were taken, but implementation was seemingly most successful with the combination of leadership by a recognised authority with strict protocol or checklist compliance, and when nurses were empowered to stop the procedure if a physician breached protocol.[133] In settings in which these aspects are not present, health-care professionals should pay attention to removing potential barriers to successful implementation of central venous catheter bundles. Finally, although we noted associations between type of implementation strategy and clinical outcome, quality improvement and implementation will be more successful with understanding of the complexity of the innovation and a setting's culture.[133,134]

Continuous monitoring of the occurrence of CLABSIs is compulsory in some countries, such as in the USA (more than half of all states), the UK, Germany, France, and the Netherlands.[135] However, this task is very time-consuming because different variables must be collected for the different age groups (adult, paediatric, and neonates) and manually assessed on the CDC's bloodstream infection criteria.[136] Alternatives to document the number of CLABSIs per 1000 catheter-days could be considered—eg, a once every 3 months measure of point prevalence.[137,138] A shift from extensive monitoring (eg, continuously) to smart effective measuring (eg, once every 3 months) could possibly help additionally needed interventions to sustain high protocol compliance, which could eventually lead to sustained infection reductions.

Our study should be interpreted in the context of several limitations. First, a large proportion of studies were single-centre studies in adult ICUs, and most were undertaken in the USA. Furthermore, a possibility is that some studies, from 2010 onwards, included parts of previously published data. We checked this aspect so far as possible, but had to rely on the information provided by the authors.

Second, a clinical and methodological heterogeneity was caused by a moderate variability in bundle compositions. Therefore, we stated that studies could only be included if the insertion bundle contained at least two specified elements. To account for these variations, data were analysed with a random effects model rather than a fixed effects model.[27] On the other hand, the included studies widely differed in study design, characteristics of the population, and baseline measurements. Only a few trials were randomised, interrupted time series, or controlled study designs. Most studies applied a before and after design, which is a weaker model and prone to bias. As a result, these before and after designed studies should report device use and catheterisation duration, which are necessary to assess confounding factors, because increased catheter use for reduced durations leads to intervention effect overestimations. Additionally, analysis of IRR in these studies was based on crude estimates of infections, which could have resulted in an overestimation of treatment effects. Still, sensitivity and subgroup analyses showed quite consistent results. Although we might not be able to estimate the extent of the effect of insertion and maintenance bundles with full certainty, evidently they contribute to a reduction of CLABSIs.

Third, no standard reporting was used for the outcome of bloodstream infections. The definition varied in studies, although the CDC definition was most often used, and if relevant was adapted for age. On the other hand, catheter-associated and related bloodstream infections were reported. Incidence of catheter-related blood stream infections were lower but the effect of the intervention within the studies was similar between studies of CLABSIs and of catheter-related blood stream infections. However, the overall effects are probably overestimated.

Fourth, use of impregnated central venous catheters in combination with the implementation of central venous catheter bundles could affect the risk reduction; however, this was reported in a few studies.

Fifth, all studies were included in our meta-analysis irrespective of methodological quality. Although inclusion of low-quality studies could have affected the intervention effects of high-quality studies, results from the subgroup analysis show that this was not the case here.

Lastly, additional hospital costs caused by bloodstream infections were usually estimated mostly on the basis of fixed costs per bloodstream infection. Therefore, the exact costs or the benefits cannot be accounted for.[139] We assume that cost savings in developed countries, with high salaries and a comparatively expensive health-care system, would be greater than in developing countries. Because of bloodstream infection-related morbidity, especially in children, we expected the sum of all health-care related costs due to bloodstream infections (after hospital discharge) to be much higher than the given hospital costs in the studies.

Our findings might have implications for clinical practice. First, the question of whether central-line bundles are effective is no longer open to debate—we have shown that they are. The number of publications on the effectiveness of insertion and maintenance bundles is overwhelming and seems to accelerate from 2011 onwards. However, studies published in 2013 and after did not contribute to the already established evidence. In our opinion it would be worthwhile to direct efforts to the implementation of central-line insertion and maintenance bundles, including protocol compliance, rather than doing time-consuming, new effectiveness studies. Second, in line with findings from cost-effectiveness studies in Australian and US populations,[10,140] we reported that implementation of central-line bundles is cost saving (estimated at a median $42 609).

Contributors

EI and OKH had full access to all of the data in the study and both take responsibility for the integrity of the data and the accuracy of the data analysis. EI, BvdH, and OKH created the study concept and design, and collected data. EI, EB, and OKH did the data analysis and data interpretation. EI and OKH drafted the manuscript. All authors did a critical revision of the manuscript for important intellectual content. EI did the statistical analysis.

Declaration of interests

We declare no competing interests.

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