European Journal of Internal Medicine 99 (2022) 70–81

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Antiseptic barrier caps in central line-associated bloodstream infections: A systematic review and meta-analysis

Sofía Tejada [a,b,1,*], Marta Leal-dos-Santos [c,1], Yolanda Peña-López [a,d], Stijn Blot [e,f], Emine Alp [g], Jordi Rello [a,b,h]

[a] Clinical Research/Epidemiology in Pneumonia & Sepsis (CRIPS), Vall d'Hebron Institut of Research (VHIR), Barcelona, Spain
[b] Centro de Investigación Biomédica En Red de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain
[c] Hospital de Curry Cabral, Lisbon, Portugal
[d] Paediatric Critical Care Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain
[e] Department of Internal Medicine & Paediatrics, Ghent University, Ghent, Belgium
[f] Burns, trauma & Critical Care Research Centre, Faculty of Medicine, Brisbane, Australia
[g] Ankara Yıldırım Beyazit University, Ankara, Turkey
[h] Clinical Research in the ICU, Anaesthesia Department, CHU Nimes, Universite de Nimes-Montpellier, France

ARTICLE INFO

Keywords:
Antiseptic barrier cap
Catheter-associated bloodstream infection
CLABSI infection control
Infection reduction rates

ABSTRACT

Objectives: To evaluate the evidence concerning the effectiveness of antiseptic barrier caps vs. manual disinfection in preventing central line-associated bloodstream infection (CLABSI).

Methods: The protocol of this systematic review and meta-analysis was pre-registered in PROSPERO (CRD42021259582). PubMed, Cochrane Library and Web of Science databases were searched from 2011 to 2021. Randomized-controlled trials (RCT) and observational studies on hospitalized patients of any age were included.

Results: Fourteen studies were included. Compared with manual disinfection, antiseptic barrier caps significantly reduced CLABSI rate per 1000 line-days (Standardized Mean Difference [SMD]: -0.02; 95%CI: -0.03 to -0.01) and number of CLABSI per patient (RR: 0.60; 95%CI: 0.41–0.89). Subgroup analysis showed that antiseptic barrier caps were more effective in reducing CLABSI rate per 1000 line-days in ICU (SMD: -0.02; 95%CI: -0.03 to -0.01) and non-ICU patients (SMD: -0.03; 95%CI: -0.05 to -0.01), adults (SMD: -0.02; 95%CI: -0.04 to -0.01), as in observational studies (SMD: -0.02; 95%CI: -0.02 to -0.01). Antiseptic barrier caps also significantly reduce CLABSI risk in ICU patients (RR: 0.65, 95%CI: 0.42–1.00), adults (RR: 0.50, 95%CI: 0.29–0.86), and observational studies (RR: 0.54; 95%CI: 0.32–0.91). No differences were found when only children or RCTs were taken into account. Median cost savings amongst studies were $21,890 [IQR 16,350–45,000] per CLABSI.

Conclusions: Antiseptic barrier caps appear to be effective in reducing CLABSI. The real-world impact needs to be confirmed by RCTs.

1. Introduction

Central venous access devices are indispensable in modern healthcare but their use come with an inherent patient safety risk [1,2]. Catheter-associated bloodstream infections represent 10%-20% of all nosocomial infections [3], and central line-associated bloodstream infections (CLABSI) are associated with both over-hospitalization and additional costs [4]. Microorganisms can intraluminally access a central venous catheter via its hub, particularly in those containing propofol and parenteral nutrition [5]. Effective prevention should focus on aseptic technique during insertion and hub manipulation.

Since 1997, studies have addressed the need for a disinfection hub, initially with a needle system [6,7]. Needleless connectors were introduced to reduce the risk of needlestick injuries to healthcare workers. However, some designs increase the risk of catheter-associated bloodstream infections [8] and CLABSI [9] in patients. Recommended products for needleless connectors decontamination include wipes that contain either chlorhexidine gluconate in 70% isopropyl alcohol or 70%

* Corresponding author at: Vall d'Hebron Institut de Recerca, Ps Vall d'Hebron 119 AMI-14th floor, 08035 Barcelona, Spain.
E-mail address: stmagraner@gmail.com (S. Tejada).
[1] ST and ML contributed equally as first author.

https://doi.org/10.1016/j.ejim.2022.01.040
Received 22 September 2021; Received in revised form 24 January 2022; Accepted 31 January 2022
Available online 10 February 2022

isopropyl alcohol alone[10].

To protect the hub from contamination an antiseptic barrier cap was developed. This device optimizes needleless connectors disinfection through continuous contact with the disinfectant, avoiding the need for cleaning the catheter hub with active scrubbing [11]. Currently, central line maintenance bundles only recommend manual disinfection, although some briefly mention the potential benefit of antiseptic barrier cap use [10,12,13].

Our hypothesis was that antiseptic barrier cap use reduce CLABSI compared to manual disinfection and hence the necessity to include the antiseptic barrier cap to central line maintenance bundles. The study's main aim was to perform a systematic review and meta-analysis (SRMA) to evaluate the value of antiseptic barrier cap effectiveness in the prevention of CLABSI, compared with manual disinfection of needleless connectors. Secondarily, we aimed to evaluate differences between intensive care unit (ICU) vs. non-ICU settings, adult vs. children populations, as well as randomized-controlled trials (RCT) vs. observational studies.

2. Methods

2.1. Registration and protocol

We performed a SRMA according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations [14]. The PRISMA checklist is detailed in supplemental e-table 1. The review protocol was registered in PROSPERO (CRD42021259582).

2.2. Data sources and search strategy

Two reviewers (ML and ST) performed the search through PubMed, Cochrane Library Database and Web of Science database from 2011 to 2021. Also searched the ClinicalTrials.gov and clinicaltrialsregister.eu registers were to identify ongoing trials. Further details of the search strategy can be found in supplemental e-Table 2. No restriction on language of publication was applied. First search was performed in June 2021.

2.3. Selection criteria

The clinical question under the PICO format (Population-Intervention-Comparison-Outcome) was: Do antiseptic caps, in comparison with traditional manual disinfection, prevent central line-associated bloodstream infections?

We used the following inclusion criteria: (i) study design of RCTs and observational studies; (ii) hospitalized patients of any age; (iii) antiseptic barrier cap in preventing CLABSI as intervention; (iv) manual disinfection as comparator. There was no restriction on cap device, both *Curos*® (3 M, St. Paul, MN) and *SwabCap*® (Excelsior Medical, Neptune City, NJ) were included. Primary outcomes were CLABSI rate per 1000 line-days and number of CLABSI per patient; secondary outcomes were compliance with antiseptic cap use, total length of stay, and reported economic differences.

CLABSI is a primary bloodstream infection in a patient that had a central line within the 48-hour period before the development of the primary bloodstream infection and it does not have to be related to an infection at another site [10]. Post-intervention was defined as intervention or antiseptic barrier cap. Pre-intervention was defined as control or manual disinfection. Definitions of studies' type and catheter's type inclusion are detailed in supplemental e-Table 3.

2.4. Data extraction and study selection process

Two authors (ML and ST) analysed independently all the articles that were retrieved by reading and assessing titles, abstracts, and full text. If a consensus between the two reviewers could not be reached for articles, a

Table 1
Main characteristics of included studies.

Study	Location	Type of study	Control Length, months	Type	Intervention Length, months	Type	Type of Line
Inchingolo 2018 [21]	Italy	RCT	9	2% CHG wipe	9	Alcohol impregnated cap (*Curos*)	CVAD and PICC
Rickard 2021 [30]	Australia	RCT	1	70% alcohol wipe + 2% CHG in 70% IPA	1	Alcohol impregnated cap (*SwabCap*)	CVAD
Wright 2013 [29]	USA	Non-RCT	3–6	70% alcohol wipe	6	Alcohol impregnated cap (*SwabCap*)	CVAD and PICC
Ramirez 2012 [26]	USA	Pre/post interventional study	12	70% alcohol wipe	12	Alcohol impregnated cap (*Curos*)	CVAD
Sweet 2012 [28]	USA	Pre/post interventional study	12	70% alcohol wipe	6	Alcohol impregnated cap (*Curos*)	CVAD and PICC
DeVries 2014 [19]	USA	Pre/post interventional study	21	70% alcohol wipe	21	Alcohol impregnated cap (*SwabCap*)	CVAD and PICC
Merrill 2014 [24]	USA	Pre/post interventional study	12	70% alcohol wipe	12	Alcohol impregnated cap (*Curos*)	CVAD
Stango 2014 [27]	USA	Pre/post interventional study	21	70% alcohol wipe	21	Alcohol impregnated cap (*SwabCap*)	CVAD and PICC
Kamboj 2015 [22]	USA	Pre/post interventional study	16	70% alcohol wipe	16	Alcohol impregnated cap	CVAD
Cameron-Watson 2016 [17]	UK	Pre/post interventional study	6	70% alcohol wipe	6	Alcohol impregnated cap (*Curos*)	CVAD, PICC, PIV, arterial catheter[1]
Pavia and Mazza 2016 [25]	USA	Pre/post interventional study	18	70% alcohol wipe	3	Alcohol impregnated cap	CVAD
Martino 2017 [23]	USA	Pre/post interventional study	6	70% alcohol wipe	24	Alcohol impregnated cap (*Curos*)	CVAD
Cooney 2020 [18]	USA	Pre/post interventional study	60	CHG or 70% alcohol wipe	60	Alcohol impregnated cap	CVAD
Helder 2020 [20]	Netherlands	Pre/post interventional study	24	70% alcohol + 10% IPA wipes	12	Alcohol impregnated cap (*Curos*)	CVAD, PICC and PIV[2]

[1]number of arterial catheters was not reported. [2] PIV results were excluded as it did not constitute a central venous access device
CHG: chlorhexidine gluconate; CVAD: central venous access device; IPA: isopropyl alcohol; PICC: peripherally inserted central catheter; PIV: peripheral intravenous access; RCT: Randomized controlled trial.

Table 2
Characteristics of included population.

Study	Population[1]	Sex (male %)	Mean age[2]	Hospital description	Departments
ICU					
Ramirez 2012 [26]	Adults	NR	NR	214-bed community hospital	Only ICU
Wright 2013 [29]	Adults	Phase 1: 46 Phase 2: 43.7 Phase 3: 41	Phase 1: 67.5 Phase 2: 65.5 Phase 3: 61.8	931-bed hospital	Only ICU
Stango 2014 [27]	Adults	NR	NR	520-bed acute care institution	First ICU and later extended to hospital wide
Helder 2020 [20]	Children	NICU Control: 55.7 Intervention: 56.8 PICU Control: 56.2 Intervention: 56.7	NICU (weeks) Control: 30.3 Intervention: 29.3 PICU (months) Control: 10 Intervention: 8	200-bed paediatric hospital	NICU and PICU
Non-ICU					
Inchingolo 2018 [21][3]	Adults	Control: 51.2 Intervention 1: 84 Intervention 2: 42.9	Control: 68 Intervention 1: 75 Intervention 2: 72	1575-bed hospital	Respiratory semi-ICU
DeVries 2014 [19]	Adults	NR	NR	634-bed hospital	Hospital wide
Merrill 2014 [24]	Adults and children	NR	NR	430-bed trauma centre	Hospital wide. Excluded ED, ambulatory care, surgical, labour and delivery, and well-baby nursery and postpartum
Pavia and Mazza 2016 [25]	Children	NR	3y/o	97-bed paediatric hospital, short bowel syndrome specialised	Hospital wide
Martino 2017 [23]	Adults	NR	Control: 42 ± 16 Time 1: 44 ± 18 Time 2: 46 ± 19 Time 3: 45 ± 19	450-bed hospital, burn specialised	Hospital wide
Rickard 2021 [30]	Adults	Control: 61.4 Intervention: 38.5	Control: 61 Intervention: 63	929-bed women's hospital and 750-bed hospital	Hospital wide
Sweet 2012 [28]	Adults	Control: 48.9 Intervention: 49	Control: 56.3 Intervention: 56.4	690-bed hospital	Oncology and haematology units
Kamboj 2015 [22]	Adults	NR	NR	470-bed cancer centre	High risk units and secondarily general oncology
Cameron-Watson 2016 [17]	Adults	NR	NR	1084-bed hospital	Oncology ward, acute care of the elderly, critical care, and surgical ward.
Cooney 2020 [18]	Adults	NR	NR	665-bed hospital	Dialysis floor

[1] Year range not reported
[2] Years unless otherwise stated
[3] RCT
ED: emergency department; ICU: intensive care unit; NICU: neonatal intensive care unit; NR: Not reported; PICU: paediatric intensive care unit

third reviewer (EA) was consulted to resolve differences. For each individual study, the data extracted consisted of: study design, number, and type of patients, setting, and length of pre- (manual disinfection) and post- (antiseptic barrier cap) intervention phases, sample size, types of lines, CLABSI rates and infection reduction rates. Population size and line-days were retrieved when available.

2.5. Quality assessment

The quality assessment was performed for each included study independently by two reviewers (ML and ST), with a third author (YP) consulted for consensus.

The quality of observational and non-RCT studies were assessed using the Newcastle Ottawa Scale [15]. It score ranges from low to high-quality. The scale evaluates 3 domains of study methodology: the selection of study groups, the comparability of study groups, and the quality of determining the outcomes of interest. The three domains include nine questions: representativeness of the exposed cohort; selection of the non-exposed cohort; ascertainment of exposure; demonstration that outcome of interest was not present at start of study; comparability of cohorts based on the design or analysis; assessment of outcome; adequacy of cohorts follow-up and its duration for outcomes to occur.

The quality of RCTs were assessed using the Cochrane Handbook of SR of Interventions [16], and using the Cochrane Review Manager 5.3 risk of bias tool which takes account of allocation sequence generation, concealment of allocation, masking of participants and investigators, incomplete outcome reporting, selective outcome reporting, or other sources of bias. Each potential source of bias was graded to determine whether studies were considered at high, low, or moderate risk of bias.

2.6. Statistical analysis

The meta-analysis was performed when sufficient data for each outcome was reported. All statistical analyses were performed using Review Manager (RevMan) version 5.3 (Cochrane Collaboration, London, UK). Dichotomous outcomes were presented as risk ratios (RR). For ease of interpretation, continuous outcomes were computed as Standardized Mean Differences (SMD) and then translated into original variable units. All statistical measures were calculated with 95% confidence interval (CI). Results were presented in a forest plot. A rate per event of CLABSI analysis was planned; however, it could not be conducted because the required information was not available in the papers selected. Results were analysed by random-effects model and presented in a forest plot.

The Higgins I^2 statistics, representing the percentage of variation

Table 3
Results of eligible studies.

Study	Population and setting	CLABSI rate reduction (%)	Intervention					Control				
			Cases, n	Patients, n	Line-days	CLABSI rate[1]	Compliance, %	Cases, n	Patients, n	Line-days	CLABSI rate[1]	Compliance, %
Pre/post interventional study												
Sweet 2012 [28]	Adults Non-ICU	85.8	1	282	3005	0.33	NR	16	472	6851	2.33	NR
Ramirez 2012 [26]	Adults ICU	73.7	NR	NR	NR	0.5	73	NR	NR	NR	1.9	NR
Cameron-Watson 2016 [17]	Adults Non-ICU	69	8	1094	5333	1.5	80	26	NR	NR	4.3	27
Martino 2017 [23]	Adults Non-ICU	68	3	153	1272	2.36	NR	5	107	673	7.43	NR
Cooney 2020 [18]	Adults Non-ICU	65	5	NR	9787	0.5	NR	11	NR	7568	1.45	NR
Pavia and Mazza 2016 [25]	Children Non-ICU	54.7	NR	25	NR	3.89	NR	NR	25	NR	8.59	NR
Stango 2014 [27]	Adults ICU	50	19	NR	22,891	Total: 0.83 ICU: 1.11 Other Units: 0.64	ICU: 60 Other units: 85	38	NR	25,000	Total: 1.52 ICU: 2.22 Other Units: 1.09	NR
DeVries 2014 [19]	Adults Non-ICU	49.3	NR	NR	NR	0.038/ 100 patient days	NR	NR	NR	NR	0.075/ 100 patient days	NR
Merrill 2014 [24]	Adults and children Non-ICU	> 40	NR	NR	NR	0. 88	NR	NR	NR	NR	1.5	NR
Kamboj 2015 [22]	Adults Non-ICU	34 (combined)	83 86	[2]	34,630 49,029	Phase 3: 2.40 Phase 4: 1.75	NR	124 100	[2]	43,716 40,711	Phase 1: 2.84 Phase 2: 2.46	NR
Helder 2020 [20]	Children ICU	22	18	766	7366	Total: 2.4 NICU: 2.1 PICU: 2.6	NICU: 95.2 PICU: 89	48	1482	15,225	Total: 3.2 NICU: 3.1 PICU: 3.2	NR
Randomized controlled trials												
Inchingolo 2018 [21]	Adults Non-ICU	83	4	46	2857	1.4	NR	10	86	1162	8.6	NR
Rickard 2021 [30]	Adults Non-ICU	-23	1	57	588	1.70	NR	1	66	724	1.38	NR
Non randomized controlled trials												
Wright 2013 [29]	Adults ICU	49	9	364	12,221	Phase 2: 0.74	NR	14 7	435	9677 5354	Phase 1: 1.45 Phase 3: 1.31	NR

CLABSI: Central line-associated bloodstream infection; **ICU:** intensive care unit; **NICU:** neonatal intensive care unit; **NR:** Not reported; **PICU:** paediatric intensive care unit

[1] presented in CLABSI per 1000 line-days, unless otherwise stated

[2] total patients=691

across studies due to heterogeneity rather than chance, was used to describe heterogeneity between studies and was calculated as previously described [16]. Results were categorized as low (0%-25%), moderate (25%-50%), and high (50%-100%) as recommended by the Cochrane handbook. Publication bias was assessed with Egger's test and funnel plot, if existing. Planned subgroup analyses were ICU vs. non-ICU, adults vs. children, and RCT vs. observational studies.

3. Results

A total of 566 studies were identified: 94 studies in PubMed, 451 in Web of Science and 21 in Cochrane Library databases. Two additional articles were identified through a Pubmed alert. Fourteen studies [17–30] in the qualitative synthesis were included. The PRISMA flow diagram is showed in Fig. 1.

3.1. Eligible studies and characteristics

Amongst fourteen studies included, two were RCTs [21,30], one was non-RCT [29], and eleven were prospective observational studies [17-20,22-28] designed as manual disinfection and antiseptic barrier cap. Length periods varied widely, ranging from 1 month to 5 years. All studies included central venous access devices. Seven studies concomitantly included peripherally inserted central catheter. Two studies [17, 20] also included peripheral intravenous access and, one [17] of them included arterial catheters. Only data relating to central venous access devices was used. Antiseptic barrier cap was detailed in eleven studies (79%), four of them used *SwabCap*® and seven used *Curos*®. Manual disinfection was a 70% alcohol wipe in ten studies, chlorhexidine gluconate or alcohol wipe in one study, 70% alcohol wipes plus 10% isopropyl alcoholwipes in one study, and 2% chlorhexidine gluconate wipes in one study. One study did not specify the comparator. Study characteristics are detailed in Table 1.

Eleven studies involved adult patients [17-19,21-23,26-30], whereas

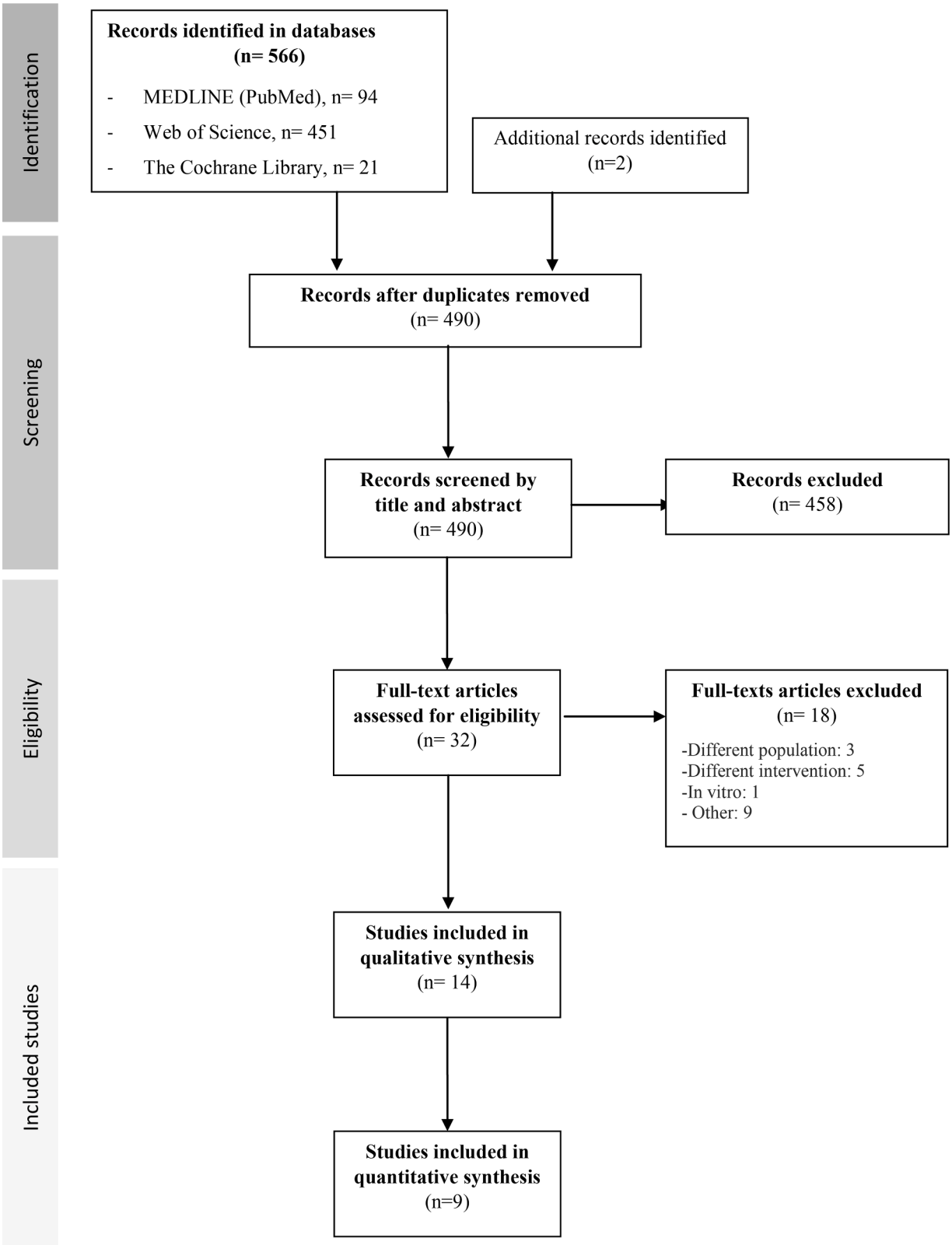

Fig. 1. Flow diagram of study selection (PRISMA).

the remaining two studies involved children [20,25], or both [24]. Four studies were conducted in the ICU [20,26,27,29], and one of them was conducted in a neonatal and paediatric ICU. Ten more studies were conducted in non-ICU settings: six included a wider population [17,19, 23-25,30], either by reporting hospital wide results or including distinct departments, two were made in haematology/oncology units [22,28], one in a dialysis ward [18], and one in a respiratory semi-ICU [21]. None of the studies detailed if they had a previous protocol regarding the change of needleless connectors. Population characteristics are detailed in Table 2.

Distribution of CLABSI rate reduction by average catheterization (days) is detailed in supplemental e-Fig. 1.

3.2. Effect of intervention

Results of eligible studies are detailed in Table 3 and Fig. 2.

3.2.1. Primary outcomes

Nine studies reported CLABSI rate per 1000 line-days [18,20-23,27-30]. The overall mean difference of CLABSI rate per 1000 line-days was significantly reduced (SMD: -0.02; 95%CI: -0.03 to -0.01; I^2=42%) with antiseptic barrier caps compared with manual disinfection (Fig. 3). Egger's test suggested that publication bias existed (supplement e-Fig. 2). In subgroup analysis, ICU patients (SMD: -0.02; 95% CI: -0.03 to -0.01; I^2=0%) and non-ICU patients (SMD: -0.03; 95%CI: -0.05 to -0.01; I_2=61%) have a significantly reduced CLABSI rate per 1000 line-days, both in favour of antiseptic barrier caps (Fig. 3A). Antiseptic barrier caps reduced the CLABSI rate per 1000 line-days in adult patients (SMD: -0.02; 95%CI: -0.04 to -0.01; I^2=48%), and in observational studies (SMD: -0.02; 95%CI: -0.02 to -0.01; I^2=0%). When exclusively, paediatric studies or RCTs were taken into account in the subgroups analyses, no difference in CLABSI rate was observed (Fig. 3B and 3C, respectively). Six studies reported the number of patients with CLABSI [20,21,23,28-30]. Pooled results showed a significant reduction in number of CLABSI when using antiseptic barrier caps (RR: 0.60, 95% CI: 0.41–0.89; I^2=0%) compared with manual disinfection (Fig. 4). Egger's test suggested that publication bias existed (supplement e-Fig. 3). Subgroup analysis showed that antiseptic barrier caps were more effective than manual disinfection in reducing the number of CLABSI in ICU (RR: 0.65, 95%CI: 0.42–1.00; I^2=0%; Fig. 4A), but not in non-ICU patients. Although CLABSI rates were low across all studies (1.9% (18/902) amongst adults and 2.3% (18/766) amongst children), the value of antiseptic barrier caps was only observed amongst adults (RR: 0.50, 95%CI: 0.29–0.86; I^2=0%; Fig. 4B). Furthermore antiseptic barriers caps proved to reduce CLABSI risk in observational studies (RR: 0.54; 95%CI: 0.32–0.91; I^2=23%), but not when only RCTs were considered (Fig. 4C).

3.2.2. Secondary outcomes

Reduction in the length of hospital stay, as well as cost savings, were assessed in various forms depending on population size. The calculations were made using estimates from secondary literature. Nevertheless, three studies showed reduction in the length of hospital stay [17,24,29] (not showed) and six [17,22,24,26,27,29] provided the estimated savings made by antiseptic barrier cap use. Results of costs savings are summarized in Table 4.

3.3. Quality assessment

Risk of bias of eleven observational studies and one non-RCT were assessed by the Newcastle Ottawa Scale tool (supplemental e-Table 4A). Eight studies showed moderate quality and four studies were low quality. Mainly the shortage wuality was due to issues in selection with inability to show ascertainment of exposure and lack of demonstration that outcome of interest was not present at start of study.

The risk of bias of the two RCTs was assessed by the Cochrane risk of bias tool (supplemental e-table 4B), resulting in high risk mainly due to comparability and outcome reporting.

4. Discussion

Our results showed that the use of antiseptic barrier caps may be associated with lower risk of CLABSI and a lower CLABSI rate per 1000 line-days compared with manual disinfection. Furthermore, the compliance with antiseptic barrier cap use was high and the costs were lower. Our findings suggest that adults and ICU patients are the population to obtain greater benefit. However, the evidence is weak because it is based mainly on observational studies.

Differences between CLABSI reduction rates in the paediatric population could be misleading, since only two studies [20,25] were included. Both studies comprised neonatal and paediatric patients and the critically and non-critically ill patients. A systematic review [31]

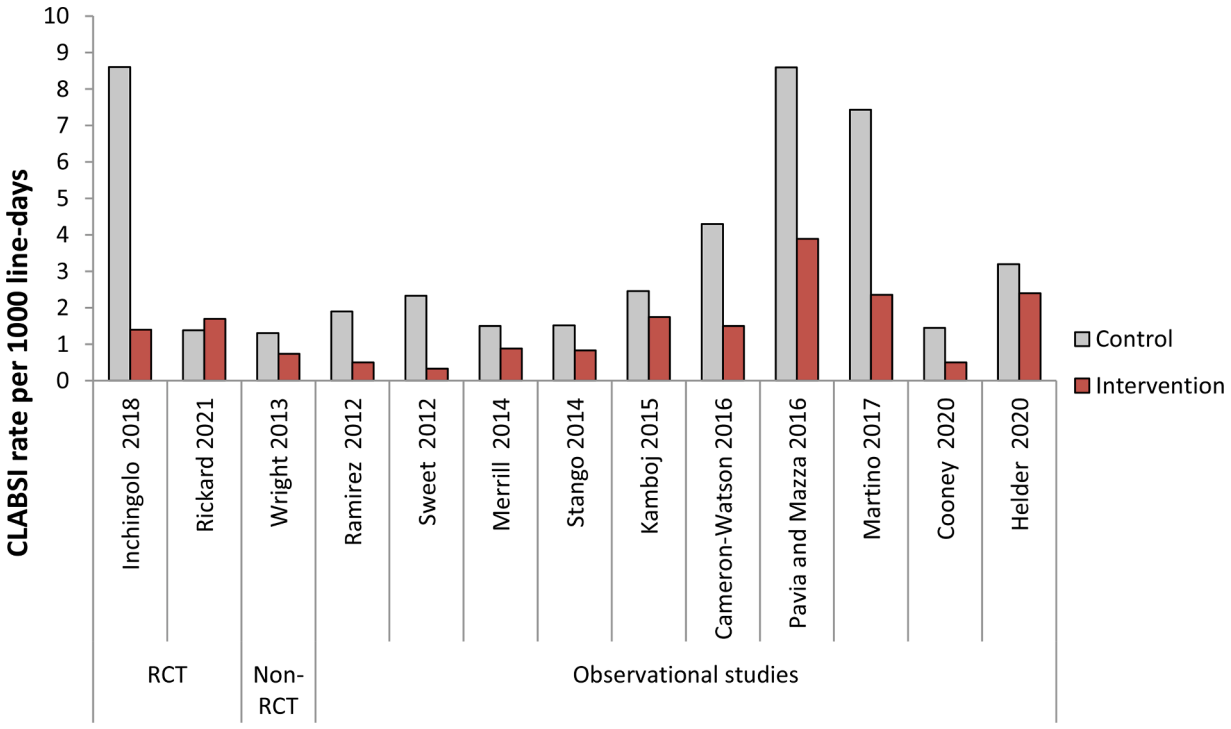

Fig. 2. Graphic of CLABSI rate per 1000 line-days for control and intervention groups
Devries 2014 did not report CLABSI rate per 1000 line-days. The study only reported 0.075/100 patient days (control) and 0.038/100 patient days (intervention).

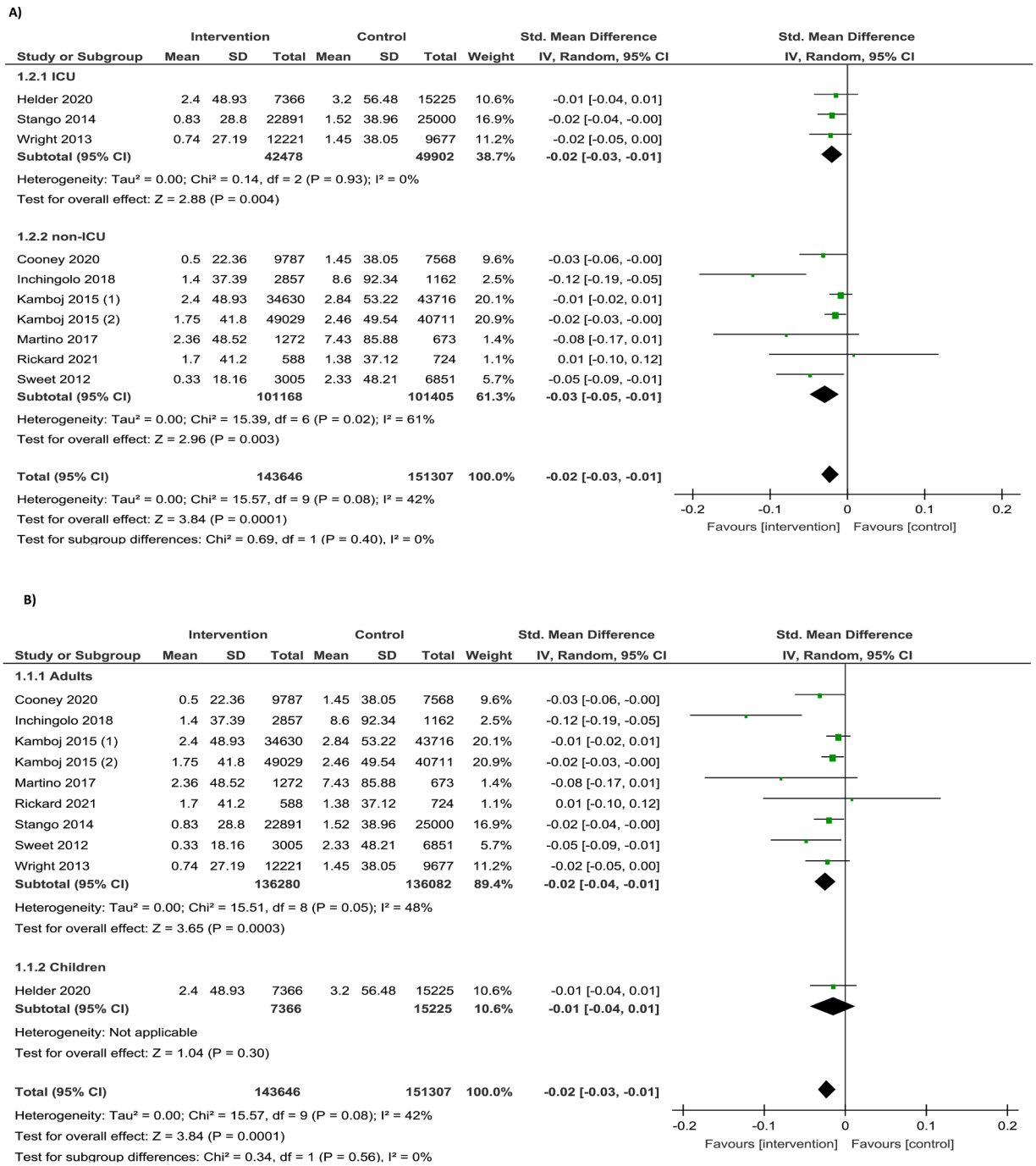

Fig. 3. Forest plot of CLABSI rate per 1000 line-days: A) ICU vs. non-ICU patients; B) adults vs. children; C) Randomized-controlled trials vs. observational studies. Mean refers to mean CLABSI rate. Total refers to number of line-days. I=Heterogeneity index; CI= Confidence Interval.

about paediatric population reported a disparity of CLABSI rates between the different studies. This is frequently explained by the variation of patient's condition, the indication for the central Iine insertion and the catheter dwell-time, more than age per se. Preventive measures implemented amongst adult patients have been also successfully adopted in paediatric and neonatal settings [31]. Therefore, the effect of antiseptic barrier caps do not necessarily have to differ from adults, especially when there is no difference in pathogenic mechanism leading to CLABSI. The Ista et al. [31] study demonstrated that the prompt removal of the central venous catheters in the paediatric ICU population could have limited the protective effect of antiseptic barrier caps, because they have reduced risk of infection due to shorter period of catheterization. Distribution of studies is detailed in supplemental e-Fig. 1. Therefore we cautiously assume a similar beneficial effect of antiseptic barrier caps amongst neonates and children, as in adult patients. The Helder et al. [20] study reported a combined neonatal and paediatric ICU setting population. In the pre-intervention period, nurses disinfected the needleless connectors by short rubbing with gauze impregnated with antiseptic. During the intervention period, an antiseptic barrier cap was introduced. The use of an antiseptic barrier cap did not reduce the CLABSI rate per 1000 line-days when compared with the pre-intervention period. Therefore, providing CLABSI rates disaggregated by gestational age or weight at birth would be preferred in further studies. Heterogeneity did not change when subgroup analyses

C)

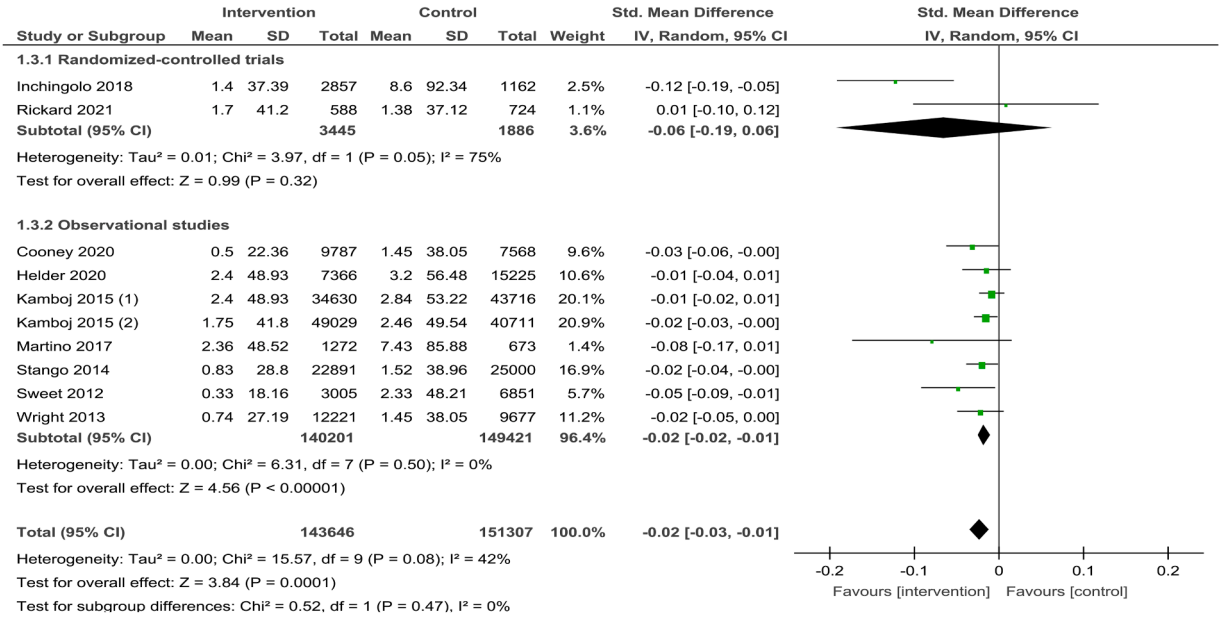

Fig. 3. (*continued*).

were performed (see Figs. 3B and 4B).

The most important difference between the studies was that Pavia y Mazza et al. [25] focuses on chronically ill patients with long term central venous access devices. Simultaneously, they have shown significant heterogeneity regarding setting (neonatal ICU/paediatric ICU vs. short bowel syndromehospital), type of line (central venous access devices vs. central venous access devices/peripherally inserted central catheter) and underlying diseases. Those included in the neonatal ICU/paediatric ICU study [20] often had a cardiac surgery background and ventilatory support, especially in the intervention group; while in the short bowel syndrome study [25], because of higher contamination risk, antiseptic barrier cap's disinfection capacity-plus its ability to protect catheters from touch-airborne-droplet contamination-appears to have made an important contribution. In the study conducted in the paediatric ICU [20], the median [IQR] duration of central venous access devices (in days) was very short (3 days [IQR 2–8]), while it was longer for neonatal ICU patients (8 days [IQR 5–14]). In contrast, the median time from the central venous access devices insertion to CLABSI was 13 days [IQR 4–19] and 9 days [IQR 6–12], respectively. In this study the prompt removal of the central venous access devices could have been important to decrease CLABSI in these units. Additionally, there could be underreporting and difficulty in identifying primary bloodstream infection in infants under 1 year-old since the definition used was that of CDC [20].

We noticed a decrease in the CLABSI reduction rates when analysing the studies chronologically. Inchingolo et al. [21] goes against this trend, its design might account for this difference. Moreover, higher CLABSI reduction rates in older studies [26,28] may be due to recent years' focus on CLABSI prevention even without use of antiseptic barrier caps, with increase in bundle implementation and compliance. The study of Rickard et al. [30] show a non-significant increase in the CLABSI rate. Its design may also account for this difference, since pilot RCTs are not designed to test statistical differences in outcomes or for the effect of potential confounders or covariates such as the type of needleless connector catheter type, or patient factors.

The results of the meta-analyses show a decrease in CLABSI rate per 1000 line-days and in the number of CLABSI per patient in ICU patients. This could be due, along with cap use itself, to the staff's distinct knowledge of catheter maintenance guidelines and subsequent ease to implement changes. Nevertheless, although prior efforts have focused on the identification and prevention of CLABSI in the ICU setting, the importance of CLABSI in non-ICU departments is increasingly recognized [32]. Furthermore, CLABSI rate per line-days also decrease in non-ICU patient. Despite lower device utilization rates, studies have demonstrated greater prevalence of central venous catheter and equivalent rates of CLABSI in non-ICU departments compared with ICU settings [33].

Antiseptic barrier cap use compliance rates were considerably high. However, for most studies, how this was assessed and for how long, was unclear. Additionally, comparison with manual disinfection rates of compliance was only available in one study [17] which raises the potential bias of a high baseline CLABSI rate or seasonal variation, as demonstrated in previous epidemiological studies [34]. Nevertheless, given the mean compliance rate for cap use of 80%, it seems feasible to have it implemented in daily practice.

A previous meta-analysis [11] of nine studies, comparing manual disinfection to antiseptic barrier cap, in patients with central venous catheter, showed that antiseptic barrier caps were effective in reducing CLABSIs ($p<0.001$). They only have reported one study conducted in an ICU setting [26] and one in a paediatric population [25]. The study by Flynn et al. [9] compared the effectiveness of connector decontamination with 70% alcohol wipes, alcoholic chlorhexidine gluconate wipes, or alcohol impregnated caps to prevent CLABSI in ten studies. Five studies [23,28,29,35,36] were analysed in the SRMA reporting that alcohol impregnated caps (RR: 0.43; 95%CI 0.28–0.65) and alcoholic chlorhexidine gluconate wipes (RR: 0.28; 95%CI: 0.20–0.39) were associated with significantly less catheter-associated bloodstream infections than 70% alcohol wipes. Both reviews [9,11] concluded that the cost of antiseptic barrier cap use is surpassed by the costs associated with CLABSI management and allows savings.

This SRMA shows that, despite differences in cost estimation, there are sustained savings amongst the studies that performed an economic evaluation [17,22,24,26,27,29]. However, as stated above, this must be interpreted with caution [11]. The most noticeable differences are in two studies that report significantly lower ($39,050) [26] and higher ($3268,990) cost estimated savings with cap use [22].Overall, median cost savings amongst studies were $21,890 [IQR 16,350–45,000] per CLABSI. Indeed, population size was not reported which could relate to

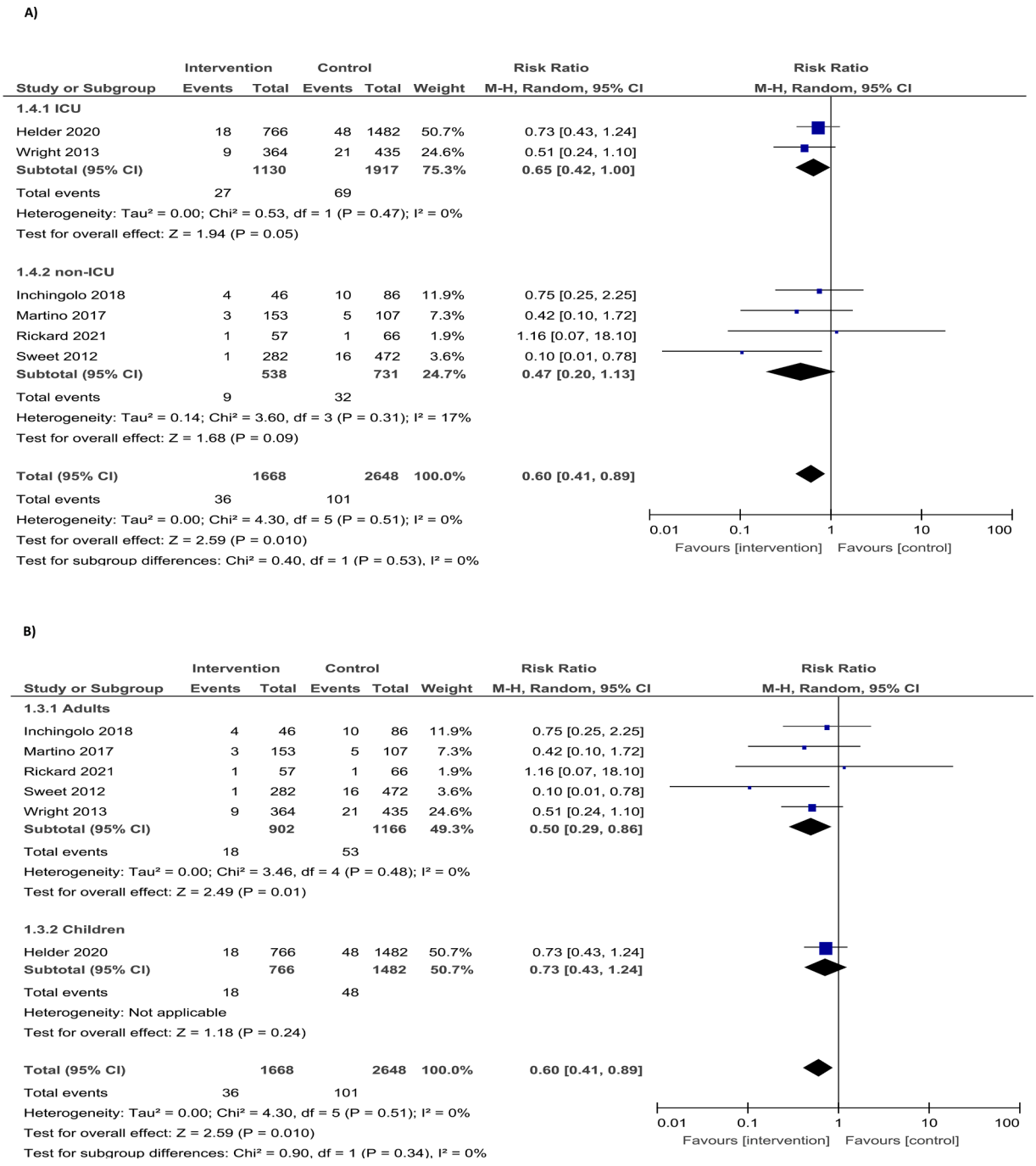

Fig. 4. Forest plot of number of patients with CLABSI: A) ICU vs. non-ICU patients; B) adults vs. children; C) Randomized-controlled trials vs. observational studies. Mean refers to events in number of CLABSI. Total refers to number of patients. I=Heterogeneity index; CI= Confidence Interval.

low estimated savings, and besides, the study was conducted in high-risk units at a cancer centre, hence additional cost could have played a part. Ideally, the total CLABSI cost should be evaluated over the total unit per year. Several potential reasons could account for variability amongst studies including small sample sizes with resultant imprecise estimates, differences in patient populations and foci of infection studied. Perhaps more important is how costs and cost variation are actually determined, for comparable services, internationally and between regions within the same country [11,37]. The Mastrogianni et al. study [38] concludes that it is necessary to improve standardised costing methods in order to make comparisons and succeed in cost-effective management.

Our study differs from previous reviews in several aspects (supplement e-Table 5). We have included 14 studies (2 of these were RCTs) over the last decade (2011–2021) to gather the latest data. Unlike the two previous SR, our study included individual CLABSI reduction rates, demonstrating a median reduction of 50% with antiseptic barrier cap use. Moreover, we have compared the CLABSI rates in ICU and non-ICU settings, as well as in the adult and paediatric populations. Our findings highlight the need for further development of high quality randomised controlled trials.

Though antiseptic barrier caps have been under discussion for several years and SRMAs date back to 2012, they are still not widely used nor recommended. Currently, all clinical guidelines [10,12,13,39,39-47] recommend manual disinfection in central line maintenance.

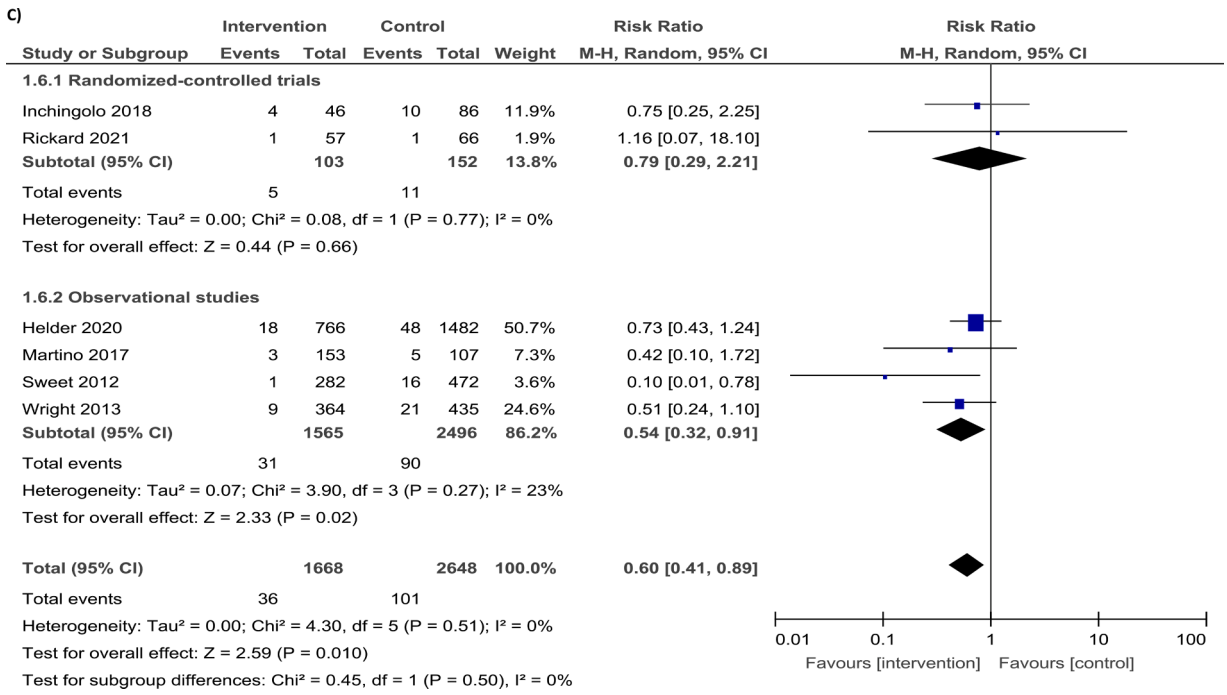

Fig. 4. (*continued*).

Table 4
Reported results of cost evaluation.

Study	Country	Length considered	Estimated cost considered		Cost of intervention	Estimated savings with cap use	Reduction in length of hospital stay	Details
			Per CLABSI	**Per length considered**				
Ramirez 2012 [26]	USA	Annually	16.350 ($)	NR	10.000 ($)	39.050 ($)	NR	Additional morbidities associated with CLABSI not included
Cameron-Watson 2016 [17]	UK	Six months	21.890 ($)	18.450.786 ($)	9.383 ($)	385.698 ($)	198 bed-days	Savings from not having to treat avoidable infections and the cost of the product for disinfecting needle-free devices on the four wards
Stango 2014 [27]	USA	Annually	45.000 ($)	486.000 ($)	21.560 ($)	464.440 ($)	NR	Considers 10.8 avoided infections per year
Wright 2013 [29]	USA	Annually	30.000 ($)	NR	60.233 ($)	390.617 ($)	56.7 bed-days	Considers cost per catheterized patient-day of $2.07, 21 infections and 4 deaths, and the hospital's ability to increase admissions by 13 per year
Merrill 2014 [24]	USA	Annually	NR	575.000 ($)	192.160 ($)	282.840 ($)	1 day/week	Before intervention estimated cost of CLABSI was 1 050 000 ($)
Kamboj 2015 [22]	USA	Annually	20.754 ($)	NR	202.706 ($)	3.268.990 ($)	NR	Cost savings were calculated by subtracting the annual cost of hospital-wide implementation of disinfection caps from the gross savings associated with CLABSI reduction

CLABSI: Central line-associated bloodstream infection; **NR:** Not reported

Eventhough two of them [10,39] mention the device, they merely state the potential benefit and the lack of substantial data for definite recommendation. The device has shown promise in terms of efficacy and cost savings in current clinical guidelines. In addition, our results show a reduction in the rate of CLABSI. Therefore, introduction of the device deserves to be considered.

There are limitations to this SRMA. Firstly, there are only two RCTs. Twelve out of fourteen eligible studies were observational/non-RCT, with its inherent lower quality and, given their design, the true effect of the interventions may be either overestimate, or underestimated. In fact, when quality assessment was applied nearly all studies show high risk of bias, especially in comparability and outcome reporting. Additionally, none of the observational/non-RCT showed high quality (eight studies showed moderate quality and four studies were low quality). These assessments were mainly due to issues in selection, inability to show ascertainment of exposure and demonstration that outcome of interest was not present at the beginning of the intervention. Five studies were not used in quantitative synthesis, because despite detailing results in CLABSI by catheter days, the number of patients included was not reported (Table 3). Heterogeneity can affect the intervention outcomes and make the results difficult to compare. Across the studies variables leading to substantial heterogeneity between the studies include: population, sample size, type of catheter, study length and compliance assessment, differences in standard of care (compliance to infection prevention), and the fact that the introduction of caps often goes along with the implementation of other interventions. Furthermore, two studies of paediatric population were included. Thirdly, future trials examining these interventions should report catheter days, total length of stay both in hospital and in ICU, and time from catheter insertion to CLABSI to enable a more reliable analysis.

Amongst the strengths, our study was based on the latest evidence regarding the topic while highlighting, yet again, the need for a suitably large RCT to provide evidence for the best approach for the disinfection on needleless connectors. Moreover, our review may help to update clinical practice guidelines.

5. Conclusion

Antiseptic barrier cap use appears to be effective and cost saving. Our findings suggest that adults and ICU patients are the population to obtain greater benefit. Antiseptic barrier caps need robust data to confirm the device's efficacy and should be addressed promptly to consider a possible inclusion in CLABSI prevention guidelines. Our findings suggest that RCTs in various patient settings are urgently needed to definitely confirm the device's potential benefits.

Funding

This work was funded by CIBERES, Instituto de Salud Carlos III, Madrid, Spain (Fondos FEDER) (CB06–06–036).

Authors contribution

JR and SB designed the study. ST and ML abstracted data. YP and EA validated data. ML wrote the first manuscript draft. All authors contributed scientifically to the subsequent versions. All authors approved the final version of the manuscript.

Declaration of Competing Interest

SB received travel support and honoraria for educational activities from 3M. The other authors declare they have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2022.01.040.

References

[1] Conoscenti E, Blot S. A necessary evil: Central venous catheters. Intensive Crit Care Nurs 2020;57:102810. https://doi.org/10.1016/j.iccn.2020.102810.
[2] Huang Z, Chen H, Liu Z. The 100 top-cited systematic reviews/meta-analyses in central venous catheter research: a PRISMA-compliant systematic literature review and bibliometric analysis. Intensive Crit Care Nurs 2020;57:102803. https://doi.org/10.1016/j.iccn.2020.102803.
[3] Labeau SO, Vandijck DM, Rello J, Adam S, Rosa A, Wenisch C, et al. Centers for Disease Control and Prevention guidelines for preventing central venous catheter-related infection: results of a knowledge test among 3405 European intensive care nurses*. Crit Care Med 2009;37:320–3. https://doi.org/10.1097/CCM.0b013e3181926489.
[4] Rello J, Ochagavia A, Sabanes E, Roque M, Mariscal D, Reynaga E, et al. Evaluation of Outcome of Intravenous Catheter-related Infections in Critically Ill Patients. Am J Respir Crit Care Med 2000;162:1027–30. https://doi.org/10.1164/ajrccm.162.3.9911093.
[5] Sitges-Serra A, Pi-Suñer T, Garces JM, Segura M. Pathogenesis and prevention of catheter-related septicemia. Am J Infect Control 1995;23:310–6. https://doi.org/10.1016/0196-6553(95)90062-4.
[6] Sitges-Serra A, Hernández R, Maestro S, Pi-Suñer T, Garcés JM, Segura M. Prevention of catheter sepsis: the hub. Nutrition 1997;13. https://doi.org/10.1016/s0899-9007(97)00220-7. 30S–35S.
[7] Segura M, Alía C, Oms L, Sancho JJ, Torres-Rodríguez JM, Sitges-Serra A. In vitro bacteriological study of a new hub model for intravascular catheters and infusion equipment. J Clin Microbiol 1989;27:2656–9. https://doi.org/10.1128/jcm.27.12.2656-2659.1989.
[8] Flynn JM, Larsen EN, Keogh S, Ullman AJ, Rickard CM. Methods for microbial needleless connector decontamination: a systematic review and meta-analysis. Am J Infect Control 2019;47:956–62. https://doi.org/10.1016/j.ajic.2019.01.002.
[9] Moureau NL, Flynn J. Disinfection of needleless connector hubs: clinical evidence systematic review. Nurs Res Pract 2015;2015:1–20. https://doi.org/10.1155/2015/796762.
[10] O'Grady N.P.. Guidelines for the Prevention of Intravascular Catheter-Related Infections (2011) 2017:80.
[11] Voor in 't holt AF, Helder OK, Vos MC, Schafthuizen L, Sülz S, van den Hoogen A, et al. Antiseptic barrier cap effective in reducing central line-associated bloodstream infections: a systematic review and meta-analysis. Int J Nurs Stud 2017;69:34–40. https://doi.org/10.1016/j.ijnurstu.2017.01.007.
[12] Marschall J, Mermel LA, Fakih M, Hadaway L, Kallen A, O'Grady NP, et al. Strategies to Prevent Central Line-Associated Bloodstream Infections in Acute Care Hospitals: 2014 Update. Infect Control Hosp Epidemiol 2014;35:753–71. https://doi.org/10.1086/676533.
[13] Schiffer CA, Mangu PB, Wade JC, Camp-Sorrell D, Cope DG, El-Rayes BF, et al. Central Venous Catheter Care for the Patient With Cancer. Am Soc Clin Oncol Clin Pract Guideline JCO 2013;31:1357–70. https://doi.org/10.1200/JCO.2012.45.5733.
[14] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700. https://doi.org/10.1136/bmj.b2700.
[15] Wells G., Shea B., O'Connell D., Peterson J., Welch V., Losos M., et al. The Newcastle- Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital Research Institute n.d. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed June 21, 2021).
[16] Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. https://doi.org/10.1136/bmj.d5928.
[17] Cameron-Watson C. Port protectors in clinical practice: an audit. Br J Nurs 2016;25:S25–31. https://doi.org/10.12968/bjon.2016.25.8.S25.
[18] Cooney RM, Manickam N, Becherer P, Harmon LS, Gregg L, Farkas Z, et al. The Use of 3.15% Chlorhexidine Gluconate/70% Alcohol Hub Disinfection to Prevent Central Line-Associated Bloodstream Infections in Dialysis Patients. J Assoc Vasc Access 2019;24:33–6. https://doi.org/10.2309/j.java.2019.004.001.
[19] DeVries M, Mancos PS, Valentine MJ. Reducing Bloodstream Infection Risk in Central and Peripheral Intravenous Lines: initial Data on Passive Intravenous Connector Disinfection. J Assoc Vasc Access 2014;19:87–93. https://doi.org/10.1016/j.java.2014.02.002.
[20] Helder OK, van Rosmalen J, van Dalen A, Schafthuizen L, Vos MC, Flint RB, et al. Effect of the use of an antiseptic barrier cap on the rates of central line-associated bloodstream infections in neonatal and pediatric intensive care. Am J Infect Control 2020;48:1171–8. https://doi.org/10.1016/j.ajic.2019.11.026.
[21] Inchingolo R, Pasciuto G, Magnini D, Cavalletti M, Scoppettuolo G, Montemurro G, et al. Educational interventions alone and combined with port protector reduce the rate of central venous catheter infection and colonization in respiratory semi-intensive care unit. BMC Infect Dis 2019;19:215. https://doi.org/10.1186/s12879-019-3848-z.
[22] Kamboj M, Blair R, Bell N, Son C, Huang Y-T, Dowling M, et al. Use of Disinfection Cap to Reduce Central-Line-Associated Bloodstream Infection and Blood Culture Contamination Among Hematology-Oncology Patients. Infect Control Hosp Epidemiol 2015;36:1401–8. https://doi.org/10.1017/ice.2015.219.
[23] Martino A, Thompson L, Mitchell C, Trichel R, Chappell W, Miller J, et al. Efforts of a Unit Practice Council to implement practice change utilizing alcohol impregnated port protectors in a burn ICU. Burns 2017;43:956–64. https://doi.org/10.1016/j.burns.2017.01.010.
[24] Merrill KC, Sumner S, Linford L, Taylor C, Macintosh C. Impact of universal disinfectant cap implementation on central line-associated bloodstream infections. Am J Infect Control 2014;42:1274–7. https://doi.org/10.1016/j.ajic.2014.09.008.
[25] Pavia M, Mazza M. Adding innovative practices and technology to central line bundle reduces bloodstream infection rate in challenging pediatric population. Am J Infect Control 2016;44:112–4. https://doi.org/10.1016/j.ajic.2015.08.026.
[26] Ramirez C, Lee AM, Welch K. Central Venous Catheter Protective Connector Caps Reduce Intraluminal Catheter-Related Infection. J Assoc Vasc Access 2012;17:210–3. https://doi.org/10.1016/j.java.2012.10.002.
[27] Stango C, Runyan D, Stern J, Macri I, Vacca M. A Successful Approach to Reducing Bloodstream Infections Based on a Disinfection Device for Intravenous Needleless Connector Hubs. J Infus Nurs 2014;37:462–5. https://doi.org/10.1097/NAN.0000000000000075.
[28] Sweet MA, Cumpston A, Briggs F, Craig M, Hamadani M. Impact of alcohol-impregnated port protectors and needleless neutral pressure connectors on central line-associated bloodstream infections and contamination of blood cultures in an inpatient oncology unit. Am J Infect Control 2012;40:931–4. https://doi.org/10.1016/j.ajic.2012.01.025.
[29] Wright M-O, Tropp J, Schora DM, Dillon-Grant M, Peterson K, Boehm S, et al. Continuous passive disinfection of catheter hubs prevents contamination and bloodstream infection. Am J Infect Control 2013;41:33–8. https://doi.org/10.1016/j.ajic.2012.05.030.
[30] Rickard CM, Flynn Julie M, Larsen Emily N, Mihala G, Playford EG, Shaw J, et al. Needleless connector decontamination for prevention of central venous access device infection: a pilot randomized controlled trial. Am J Infect Control 2021:5.
[31] Ista E, van der Hoven B, Kornelisse RF, van der Starre C, Vos MC, Boersma E, et al. 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. Lancet Infect Dis 2016;16:724–34. https://doi.org/10.1016/S1473-3099(15)00409-0.
[32] Rhee Y, Heung M, Chen B, Chenoweth CE. Central Line-Associated Bloodstream Infections in Non-ICU Inpatient Wards: A 2-Year Analysis. Infect Control Hosp Epidemiol 2015;36:424–30. https://doi.org/10.1017/ice.2014.86.
[33] Marschall J, Leone C, Jones M, Nihill D, Fraser VJ, Warren DK. Catheter-Associated Bloodstream Infections in General Medical Patients Outside the Intensive Care

Unit: A Surveillance Study. Infect Control Hosp Epidemiol 2007;28:905–9. https://doi.org/10.1086/519206.
[34] Blot K, Hammami N, Blot S, Vogelaers D, Lambert M-L. Seasonal variation of hospital-acquired bloodstream infections: A national cohort study. Infect Control Hosp Epidemiol 2021:1–7. https://doi.org/10.1017/ice.2021.85.
[35] Pichler J, Soothill J, Hill S. Reduction of blood stream infections in children following a change to chlorhexidine disinfection of parenteral nutrition catheter connectors. Clin Nutr 2014;33:85–9. https://doi.org/10.1016/j.clnu.2013.03.021.
[36] Soothill JS, Bravery K, Ho A, Macqueen S, Collins J, Lock P. A fall in bloodstream infections followed a change to 2% chlorhexidine in 70% isopropanol for catheter connection antisepsis: a pediatric single center before/after study on a hemopoietic stem cell transplant ward. Am J Infect Control 2009;37:626–30. https://doi.org/10.1016/j.ajic.2009.03.014.
[37] Laupland KB, Lee H, Gregson DB, Manns BJ. Cost of intensive care unit-acquired bloodstream infections. J Hosp Infect 2006;63:124–32. https://doi.org/10.1016/j.jhin.2005.12.016.
[38] Mastrogianni M, Galanis P, Kaitelidou D, Konstantinou E, Fildissis G, Katsoulas T. Factors affecting adult intensive care units costs by using the bottom-up and top-down costing methodology in OECD countries: A systematic review. Intensive Crit Care Nurs 2021;66:103080. https://doi.org/10.1016/j.iccn.2021.103080.
[39] Kusek L, Soule BM, Kupka N, Williams S. Preventing Central Line-Associated Bloodstream Infections. J Nurs Care Qual 2012;27:283–7. https://doi.org/10.1097/NCQ.0b013e31825733d1.
[40] Association for Professionals in Infection Control and Epidemiology. Guide to Preventing Central Line-Associated Boodlstream Infections. APIC n.d. https://apic.org/(accessed June 18, 2021).
[41] "Feixe de Intervenções" de Prevenção de Infeção Relacionada com Cateter Venoso Central - Portal das Normas Clínicas n.d. https://normas.dgs.min-saude.pt/2015/12/16/feixe-de-intervencoes-de-prevencao-de-infecao-relacionada-com-cateter-venoso-central/(accessed June 18, 2021).
[42] Ling ML, Apisarnthanarak A, Jaggi N, Harrington G, Morikane K, Thu LTA, et al. APSIC guide for prevention of Central Line Associated Bloodstream Infections (CLABSI). Antimicrob Resist Infect Control 2016;5:16. https://doi.org/10.1186/s13756-016-0116-5.
[43] NIHealth and C Excellence. Healthcare-associated infections: prevention and control in primary and community care 2017:35.
[44] Umang J. How-to Guide: Prevent Central Line-Associated Bloodstream Infections (CLABSI). Cambridge, MA: Institute for Healthcare Improvement 2012:40.
[45] Patient Safety Institute. Prevent central line infection. n.d. https://www.patientsafetyinstitute.ca:443/en/Search/pages/results.aspx?k=prevent+central+line+infections (accessed June 18, 2021).
[46] American Society of Anesthesiologists Task Force on Central Venous Access, SM Rupp, Apfelbaum JL, Blitt C, Caplan RA, Connis RT, et al. Practice guidelines for central venous access: a report by the American Society of Anesthesiologists Task Force on Central Venous Access. Anesthesiology 2012;116:539–73. https://doi.org/10.1097/ALN.0b013e31823c9569.
[47] Practice Guidelines for Central Venous Access 2020 2020;132:8–43. 10.1097/ALN.0000000000002864.