**TITLE PAGE**

Care bundles to reduce central line-associated bloodstream infections in the neonatal unit: A systematic review and meta-analysis.

V Payne1, Dr Mike Hall2, Dr Jacqui Prieto3, Dr Mark Johnson 2,5

1.

Advanced Neonatal Nurse Practitioner and Visiting Fellow

University of Southampton and University Hospital Southampton NHS Foundation Trust

Faculty of Health Sciences  
Princess Anne Hospital F- 120

Southampton, UK  
Tel: [02381 208 677](tel:02381%20208%20677)

Email: vp1m14@soton.ac.uk  
  
2.

University Hospital Southampton NHS Foundation Trust

Department of Neonatal Medicine  
Southampton, UK

3.

University of Southampton and University Hospital Southampton NHS Foundation Trust  
Southampton, UK

4.

University of Southampton and University Hospital Southampton NHS Foundation Trust,

NIHR Southampton Biomedical Research Centre  
Southampton, UK

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*What is already known:*

Care bundles have been successful in reducing CLABSIs in adult ICUs, though replication in paediatric ICUs has been less successful.

Zero-CLABSI rates have been reported following the introduction of care bundles in some US NNUs

*What this paper adds:*

There is a substantial body of quasi-experimental evidence that care bundles may reduce CLABSIs in the NNU, though the magnitude of effect is variable.

There is widespread variation in the bundled elements used, though having a dedicated skin preparation protocol and education were the two most commonly used bundled elements.

**ABSTRACT**

**BACKGROUND**

CLABSIs are associated with increased mortality, prolonged hospitalisation and increased healthcare costs. Care bundles have reduced CLABSIs in adult ICUs but replication in paediatric ICUs has had inconsistent outcomes. A systematic review was performed to assess the evidence for the efficacy of care bundles in reducing CLABSIs in the neonatal unit.

**METHODS**

MEDLINE, CINAHL and EMBASE were searched from January 2010 up to January 2017. The Cochrane Library, Web of Science, Zetoc and Ethos were searched for additional studies. RCTs, quasi-experimental and observational studies were eligible. The primary outcome measure was CLABSI rates per 1000 central line, or patient, days. A meta-analysis was performed using random effects modelling.

**RESULTS**

Twenty-four studies were eligible for inclusion; 6 were performed in Europe, 12 were in North America, 2 in Australia and 4 were in developing countries. Five were observational studies and 19 were before and after quality improvement (QI) studies. No RCTs were found. Meta-analysis revealed a statistically significant reduction in CLABSIs following the introduction of care bundles (Rate Ratio = 0.40 [CI 0.31-0.51], p < 0.00001), which equates to a 60% reduction in CLABSI rate.

**CONCLUSION**

There is a substantial body of quasi-experimental evidence to suggest that care bundles may reduce CLABSI rates in the NNU, though it is not clear which bundle elements are effective in specific settings. Future research should focus on determining what processes promote the effective implementation of infection prevention recommendations, and which elements represent essential components of such care bundles.

**INTRODUCTION**

Neonatal late-onset sepsis (LOS) is associated with increased mortality and morbidity and prolonged hospitalisation ([1-3](#_ENREF_1)), with substantial additional healthcare costs ([2](#_ENREF_2)). Neonates are especially susceptible to episodes of LOS due to an immature immune system, and they frequently require invasive devices, including central lines, to deliver life-saving medications and parenteral nutrition. The use of such devices significantly increases the risk of infection, and central line-associated bloodstream infections (CLABSIs) are an important cause of LOS ([4](#_ENREF_4)). Whilst there is some uncertainty regarding the impact of CLABSIs on neurological outcomes ([1](#_ENREF_1)), recent evidence suggests that reductions in coagulase-negative staphylococcal (CoNS) infections may reduce cognitive disability in preterm infants ([5](#_ENREF_5)).

The reported incidence of CLABSIs in neonates ranges from 3.2 to 21.8 CLABSIs per 1000 central line days ([6](#_ENREF_6)). The disparity in incidence possibly reflects the diverse definitions of CLABSIs which is demonstrated in Table 1. There are also variations in aspects of care and infection prevention practices and it seems that the variations in rates cannot be wholly explained by case mix between centres, with similar centres having differing CLABSI rates ([7](#_ENREF_7), [8](#_ENREF_8)). This suggests that studying the practice patterns of different neonatal units (NNUs) may provide insights into possible preventative strategies ([9](#_ENREF_9)).

Care bundles, structured packages of evidence based practices aimed at improving the processes of care and patient outcomes, have been shown to be effective in reducing CLABSIs in adult ICUs. The Michigan Keystone project ([10](#_ENREF_10)), a US state-wide quality improvement project in adult ICUs, introduced bundled evidence-based interventions alongside a patient safety programme, and was considered a major success, reporting zero CLABSI rates post-implementation. Matching Michigan, a UK 2-year, four-cluster, stepped non-randomised study conducted in adult and paediatric ICUs,

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| **Table 1. Three definitions of central line-associated bloodstream infection** | | | |
| Source | Definition | Clinical signs | Laboratory Markers |
| NEO-KISS  ([11](#_ENREF_11)) | Laboratory-confirmed bloodstream infection (LCBI) with coagulase negative staphylococcus (CoNS) isolated as sole pathogen  AND 2 clinical signs AND 1 laboratory parameter  OR Pathogen isolated from blood or cerebrospinal fluid culture, not related to infection at another site AND 2 clinical signs  LCBI with non-CoNS pathogen isolated in blood culture or cerebrospinal fluid, and pathogen not related to infections at other site AND two clinical signs  Clinical sepsis without proof of pathogen  No pathogens isolated from blood or culture not taken  Physician prescribes antimicrobials for at least 5 days  No apparent infection at another site  AND  2 clinical signs, without other recognised cause | Fever > 38 oC or temperature instability (frequent incubator adjustment) or hypothermia <36.5 oC  Unexplained metabolic acidosis BE > -10  Tachycardia >200bpm and/or bradycardia <80bpm  New or more frequent apnoeas  Recapillarisation time >2 secs  New hyperglycaemia >140mg/dl  Other signs of infection:  Colour (when recapillarisation time not use), apathy, CRP, interleukin, increased oxygen requirement (intubation) or unstable condition | C-Reactive Protein  > 2,0mg/dl  Thrombocytes <100/nl  I/T ratio >0/2 \*  Leukocytes <5/nl (without erythroblasts)  \*immature granulocytes/total granulocytes |
| NNAP  ([12](#_ENREF_12)) | The growth of a recognised pathogen in pure culture OR in the case of a mixed growth, or growth of skin commensal, the added requirement for 3 or more of 10 predefined clinical signs | Tachypnoea/clinically relevant increase in oxygen or ventilation support  Clinically relevant increase in apnoea, Bradycardias  Hypotension  Hypo or hyper-glycaemia  Impaired peripheral perfusion, pallor, mottling, Capillary refill time >3 secs, toe-core gap >2  Lethargy, irritability, poor handling  Temperature instability  Ileus, feed intolerance  Reduced urine output  Metabolic acidosis Base Excess >-10 | N/A |
| CDC  ([13](#_ENREF_13)) | A laboratory- confirmed bloodstream infection (LCBI) where central line or umbilical catheter was in place for >2 calendar days on the date of event, with the day of device placement being Day 1, AND the line was also in place on the date of event or the day before.  LCBI: Patient of any age has a recognised pathogen identified AND organism identified in blood is not related to an infection at another site OR  Patient <1 year of age has at least one clinical sign AND organism identified from blood is not related to an infection at another site AND the same common commensal is identified from 2 or more specimens. | Fever  Hypothermia  Apnoea, or bradycardia | N/A |

attempted to replicate this success and despite a 48% reduction in paediatric CLABSIs, this did not reach statistical significance ([14](#_ENREF_14)). This was attributed to small numbers, large variations in paediatric CLABSI rates, and difficulties in outperforming the temporal trend. There was a failure to demonstrate, with confidence, that improvements were directly attributed to the intervention, with notable differences in team engagement ([15](#_ENREF_15)). These differences highlight the importance of understanding how various elements work to deliver improvements ([16](#_ENREF_16)).

This systematic review was performed in order to assess the evidence for the efficacy of care bundles to reduce CLABSIs in infants with indwelling central lines in the NNU, compared to standard care, and to determine which bundled elements were most commonly used.

**METHODS**

The search protocol was registered in the PROSPERO international prospective register of systematic reviews (42016045321), and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines have been followed ([17](#_ENREF_17)). MEDLINE, CINAHL and EMBASE databases were searched from January 2010 up to January 2017. The Cochrane Library, Web of Science, Zetoc and Ethos were searched for additional studies, and reference lists of relevant articles were searched. Two authors (VP, MJ) performed the search and selection process separately, and disagreements were resolved by discussion.

Studies were eligible for inclusion if they investigated the effect of a care bundle and were performed in an NNU of any care level. A care bundle was defined as any intervention with multiple interacting components, and included both central line insertion and maintenance care bundles. Randomised controlled trials (RCT), non-randomised interventional studies and observational studies were all eligible for inclusion. Studies were excluded if they investigated a single intervention, were performed in adult or paediatric populations or were focused on a specific pathogen outbreak. Studies not published in English, and conference abstracts, were excluded.

**OUTCOMES**

The primary outcome was the number of CLABSIs per 1000 central line or patient days. This denominator was chosen in order to reflect any potential changes in unit acuity or central line exposure that may result following the introduction of a bundle. The secondary outcome was to identify the frequency with which bundled technical and non-technical elements were used, the latter classified according to the Cochrane Effective Practice and Organisation of Care (EPOC) system.

**DATA EXTRACTION AND RISK OF BIAS ASSESSMENT**

Data were extracted using a standardised template. Study characteristics were collected including setting, study design, bundled elements, definition of CLABSI, change in CLABSI rate and measures of compliance. CLABSI rates were extracted from the published studies. Studies were categorised as observational or quality improvement (QI) based upon the classification provided in the original studies. The methodological quality of observational studies was assessed using the Newcastle-Ottawa Scale (NOS) ([18](#_ENREF_18)). The Standards for Quality Improvement Reporting Excellence (SQUIRE) 18-item checklist was used for QI studies ([19](#_ENREF_19)).

**STATISTICAL ANALYSIS**

The bundled elements were summarised as frequencies and percentages. The rate ratio (RR) for the number of infections per 1000 central line days or patient days was calculated with 95% Confidence Intervals (CI), with a correction of 0.5 applied to zero rates as per the methods in the Cochrane Handbook ([20](#_ENREF_20)). This results in a more conservative estimate of the effect size. A meta-analysis was performed using random effects modelling ([21](#_ENREF_21)). Heterogeneity between studies was assessed using the *I*2 test, with values >30% considered to represent moderate heterogeneity, >50% substantial heterogeneity, and >75% considerable heterogeneity ([20](#_ENREF_20)). There were no *a priori* sub-group analyses planned, other than according to study design.

**RESULTS**

The search initially identified 439 articles, and following the removal of duplicates, 259 unique studies remained (Figure 1). Titles and abstracts were screened for relevance, and 40 full-text studies were assessed.

**Study characteristics**

Twenty-four studies were eligible for inclusion (Table 2). Twelve studies (50%) were performed in North America, 6 (25%) in Europe, 2 in Australia (8%) and 4 (17%) in developing countries. Sixteen (67%) were single centre, whilst 8 (33%) were multi-centre. Whilst 5 studies described themselves as observational studies, all 24 studies were non-randomised intervention studies. No RCTs were found.

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| **Table 2. Study Characteristics** | | | | | |
| Author (date) | Setting | Location | Described Study Design | Definition | Results |
| Almeida (2016)([22](#_ENREF_22)) | Tertiary NICU | Portugal | Before/After | NEO-KISS | 14.1 to 10.4 |
| Arnts (2015) ([23](#_ENREF_23)) | Tertiary NICU | Netherlands | Prospective Cohort | CDC | 12.9 to 4.7  (CI 1.25–11.23) |
| Bizzarro (2010) ([24](#_ENREF_24)) | Level IIIc 54 bed NICU | US | Before/After | CDC | 8.44 to 1.7  (CI 0.08-0.45) |
| Bowen (2016) ([25](#_ENREF_25)) | 8 NICUs  <29 weeks only | Australia | Before/After | BSI infection where a central line was in situ or within 48 hours of removal of the central line, unless clearly identified source of infection. | 9.9 – 5.4 |
| Ceballos (2013)([26](#_ENREF_26)) | Level IIIb 50 bed NICU | US | Before/After | CDC | 6.9-0.5 |
| Chandonnet (2012)([27](#_ENREF_27)) | Level IIIc 24 bed NICU | US | Before/After | CDC | 2.6 to 0.8 |
| Erdei (2015) ([28](#_ENREF_28)) | Level IIIc NICU | US | Before/After | CDC | 4.1 to 0.94 |
| Fisher (2013) ([29](#_ENREF_29)) | 13 NNUs:  3 Level II  10 Level III | US | Before/After | CDC | 3.94- 1.16 |
| Kime (2011) ([30](#_ENREF_30)) | Level III NICU | US | Before/After | CDC | 15.6-0.5 |
| McMullan (2016) ([31](#_ENREF_31)) | Level V NICU | Australia | Retrospective cohort | Proven BSI associated with a central venous line, when a central line has been in use 48 hours before signs and symptoms of infection. | 8.5 to 2.3 |
| Piazza (2016)([32](#_ENREF_32)) | 17 IIIc NICUs  >25 beds | US | Before/After | CDC | 1.33-1.076 |
| Rallis (2016)([33](#_ENREF_33)) | Level III NICU | Greece | Before/After | CDC | 12-3.4 |
| Resende (2011) ([34](#_ENREF_34)) | NICU | Brazil | Before/After | CDC | 24.1-14.9 |
| Rosenthal (2013) ([35](#_ENREF_35)) | 4 NICUs | El Salvador, Mexico,Phillipines, Tunisia | Before/After | CDC | 21.4-9.7 |
| Salm ([36](#_ENREF_36)) | 34 NICUs | Germany | Cohort study | NEO-KISS | 2.63-1.98 |
| Schulman (2011) ([37](#_ENREF_37)) | 18 NICUs | US | Prospective cohort | CDC  Definition change during study | 3.5-2.1 |
| Shepherd (2015) ([38](#_ENREF_38)) | 8 NICUs | US | Before/After | CDC | 6-0.68 |
| Sinha (2016) ([39](#_ENREF_39)) | Level III NICU | UK | Before/After | BSI > 48 hours after birth, with central line in situ, or 48 hours previously | 31.6-4.3 |
| Steiner (2015) ([40](#_ENREF_40)) | NICU | Austria | Before/After | NEO-KISS | 13.9-4.7 |
| Ting (2013) ([41](#_ENREF_41)) | NICU Level III | Canada | Before/After | Canadian Nosocomial Infection Surveillance Program or NHSN | 7.9-2.2 |
| Wang (2015)([42](#_ENREF_42)) | NICU  110 VLBW | China | Case-Control | Not provided | 3.1 control  0 intervention. |
| Wilder (2016) ([43](#_ENREF_43)) | NICU, Level IV, 36 beds | US | Before/After | Not provided | 3.9-0.3 |
| Wirtschafter (2010) ([44](#_ENREF_44)) | 13 NICUs | US | Before/After | CDC | 4.3-3.2 |
| Zhou (2015)([45](#_ENREF_45)) | NICU | China | Before/After | CDC | 16.7-5.2 |

**Risk of Bias Assessment**

The mean NOS score across the studies was 7 (range 6-8, see Table 3) from a possible maximum of 9. Lower scores tended to be due to a lack of control for NNU centre and central line days, though all the observational studies controlled for birth weight and gestational age. In general there was limited reporting of data collection and verification processes. Those studies reported as QI studies tended to have longer intervals between the before and after groups, and only two studies used interrupted time series analysis to account for temporal trends ([36](#_ENREF_36), [39](#_ENREF_39)), with a further five using statistical process control ([25](#_ENREF_25), [32](#_ENREF_32), [46-48](#_ENREF_46)).

Using the SQUIRE reporting framework to assess the QI studies revealed that whilst the majority of studies provided detailed descriptions of the setting, the implementation process was not well documented (see supplementary material). Few studies reported if the care bundle was implemented as intended (for instance by measuring compliance with bundle elements), and no studies reported any unintended consequences.

**Reduction in CLABSI rates**

Meta-analysis of all 24 studies revealed a statistically significant reduction in CLABSI rates following the introduction of a care bundle in the NICU (Rate Ratio = 0.40 [CI 0.31-0.51] *p* <0.00001, Figure 2). This equates to a 60% reduction in CLABSI rates. This effect remained for the separate analysis of the QI studies (RR= 0.40, CI 0.30- 0.52) and for the observational studies alone (RR=0.39 CI 0.20-0.79). There was no statistical heterogeneity amongst the studies, with *I*2 = 0%.

Baseline CLABSI rates ranged from 1.33 to 31.6 per 1000 catheter days. Following the introduction of a care bundle, CLABSI rates decreased to between zero and 14.9 per 1000 catheter days, with 7 studies reporting rates <1/1000 catheter days. All studies reported a reduction in CLABSI rates,

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| **Table 3. Assessment of bias using Newcastle Ottawa Scale** | | | | | | | | | | |
|  | **Selection** | | | | **Comparability** | | **Outcome** | | |  |
| Author | Representativeness of cohort | Selection of non-exposed cohort | Ascertainment of exposure | Outcome of interest | Controls for birth weight or gestational age | Controls for NICU centre, central line days | Assessment | Follow up duration  >6months | Completeness of follow up | Total Score |
| Arnts | \* | \* | \* | \* | \* | - | \* | \* | - | 7 |
| McMullan | \* | - | \* | \* | - | - | \* | \* | \* | 6 |
| Salm | \* | - | \* | \* | \* | \* | \* | \* | \* | 8 |
| Schulman | \* | - | \* | \* | \* | \* | \* | \* | \* | 8 |
| Wang | \* | \* | - | \* | \* | - | \* | \* | - | 6 |

though some were not as large as predicted ([32](#_ENREF_32), [49](#_ENREF_49)) and some did not find a reduction in rates in specific sub-groups, including neonates with birth weights <751 grams, 1000-1500grams and >1500 grams([26](#_ENREF_26), [44](#_ENREF_44), [50](#_ENREF_50)). Several centres had starting rates that were already lower than the average National Health Surveillance Network rate ([32](#_ENREF_32)). In one multicentre study, one NNU reported 96% reduction in CLABSI rates, whilst another reported a 187% increase in rates([51](#_ENREF_51)). Similarly, in a multi-centre study across 4 developing countries, only one NNU out of 4 reached a statistically significant reduction in CLABSI rates ([35](#_ENREF_35)).

**Bundled Elements**

The technical and professional elements forming the care bundle in the included studies are shown in Table 4. The most common technical elements included the use of a specific skin preparation protocol (79%), maximal standard barrier precautions (71%), and a daily assessment of the need for the central line (67%). The choice of skin disinfectant varied, with chlorhexidine gluconate (CHG) and 70% isopropyl alcohol most commonly used (63%) though the strengths varied. Other preparations included povidone iodine (38%), or were unspecified (25%). Percentages do not total 100% due to some studies specifying multiple agents, determined according to gestational age. Despite hand hygiene resulting in significant reductions in hospital acquired infections ([52](#_ENREF_52)), practices were poorly described, with only four studies specifying a product for hand cleansing([39](#_ENREF_39), [47](#_ENREF_47), [50](#_ENREF_50), [53](#_ENREF_53)), and the remainder making reference only to ensuring appropriate hand hygiene. Hand hygiene audits were reported in only 5 (20%) of studies.

The most common professional elements were education and training (100%), the use of checklists (67%), and audit and feedback (63%). Two studies attempted to associate specific elements with reductions in CLABSI rates, but were unable to isolate one single element ([32](#_ENREF_32), [39](#_ENREF_39)). Bundle

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| **Table 4. Common bundled elements** | | | | | | | | | | | | | | | | | | | | | | | | |
| **Author**  **Technical Element** | **Almeida** | **Arnts** | **Bizzarro** | **Bowen** | **Ceballos** | **Chandonnet** | **Erdei** | **Fisher** | **Kime** | **McMullan** | **Piazza** | **Rallis** | **Resende** | **Rosenthal** | **Salm** | **Schulman** | **Shepherd** | **Sinha** | **Steiner** | **Ting** | **Wang** | **Wilder** | **Wirtschafter** | **Zhou** |
| **Maximal standard barrier precautions** | \* |  |  | \* | \* | \* |  | \* |  | \* | \* | \* | \* | \* | \* | \* |  |  | \* | \* | \* |  | \* | \* |
| **Skin Preparation** | \* |  | \* |  | \* | \* | \* | \* | \* | \* | \* | \* | \* |  | \* | \* | \* | \* |  | \* | \* | \* | \* |  |
| **Daily line need assessment** |  | \* |  | \* |  | \* | \* | \* | \* | \* | \* |  | \* | \* | \* | \* | \* |  |  |  | \* |  | \* | \* |
| **Scrub the hub** | \* | \* |  | \* |  |  | \* | \* | \* |  | \* |  |  | \* |  |  | \* | \* |  | \* |  |  | \* |  |
| **Closed IV tubing** | \* |  | \* |  |  |  |  | \* |  |  |  |  |  |  |  |  |  |  |  |  |  | \* | \* |  |
| **PICC team** |  |  | \* |  |  |  | \* |  |  |  |  |  |  |  |  |  | \* |  |  |  | \* | \* |  | \* |
| **Central line trolley/ kit** |  | \* |  | \* | \* |  | \* |  |  |  |  |  |  | \* |  | \* |  |  | \* | \* |  |  | \* | \* |
| **Dressing protocol** |  |  |  | \* |  | \* |  |  | \* | \* |  | \* |  | \* |  |  | \* |  |  |  | \* | \* |  |  |
| **2 person technique** |  |  |  | \* | \* | \* | \* |  |  | \* |  | \* |  |  |  |  |  |  |  |  |  | \* |  |  |
| **Alcohol impregnated port protectors** |  |  |  |  |  |  | \* |  |  |  |  |  |  |  |  |  | \* |  |  |  |  |  |  |  |
| **Professional Element** |  |
| **Education & training** | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* | \* |
| **Multidisciplinary team** |  | \* | \* | \* | \* |  | \* | \* | \* | \* | \* |  |  |  |  |  | \* |  |  | \* |  | \* | \* | \* |
| **Audit & feedback** |  | \* | \* | \* | \* | \* | \* |  | \* | \* | \* |  |  | \* |  |  | \* | \* |  | \* |  | \* | \* |  |
| **Checklists** |  | \* | \* | \* | \* |  |  | \* | \* | \* | \* | \* |  |  | \* | \* | \* |  | \* | \* | \* |  | \* |  |
| **Opinion leaders** |  |  |  | \* |  |  | \* |  |  |  |  |  | \* |  |  |  |  |  |  |  |  |  |  |  |
| **Rewards** |  |  |  |  |  | \* | \* |  | \* |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Root Cause Analysis** |  |  |  | \* | \* | \* | \* |  | \* |  | \* |  |  |  |  |  | \* |  |  |  |  |  | \* |  |

compliance was reported in 7 (29%) studies, and ranged from 10-100%. Studies that reported initial lower compliance rates of 10-30% generally reported improvement in rates over time. One study achieved a compliance rate of 55%, speculating this was lower than previously published rates due to anonymous bedside reporting ([46](#_ENREF_46)). One study concluded that CLABSI rate reductions were not associated with reductions in compliance rates ([32](#_ENREF_32)), whilst another study concluded that post-intervention CLABSI rates were better in those units that reported checklist compliance >15 % ([37](#_ENREF_37)). However, in this multicentre study 5 out of 18 units did not submit compliance data.

**DISCUSSION**

This systematic review suggests that care bundles are associated with a statistically significant reduction in CLABSI rates in NNUs. This appears to be supported by a recent meta-analysis by Ista et al ([54](#_ENREF_54)) which was the first systematic review to investigate CLABSI rates across all ages, performing separate sub-group analyses of adult ICU, PICU and NICUs. It found that care bundles statistically reduced CLABSI rates across all age ranges, including 14 neonatal studies (IRR 0.47, 95% CI 0.38-0.59). This is similar to the reduction found in the present study.

The lack of statistical heterogeneity is surprising, given that there is substantial heterogeneity amongst the included studies in terms of CLABSI definitions, setting and intervention. Moderate heterogeneity was found in the neonatal sub-group analysis performed by Ista et al ([54](#_ENREF_54)), with an *I*2 of 74%, though there were fewer studies included in their meta-analysis. Despite several studies being reported as cohort or case-control, the studies were all non-randomised interventional studies, which not only means there are multiple risks of bias, but may also partially explain the lack of statistical heterogeneity. Whilst the lack of statistical heterogeneity found in this study may suggest that the process of introducing a care bundle, regardless of its components, is effective, the absence of any negative studies strongly suggests a risk of publication bias within the literature. To date, no studies published in peer-reviewed journals have reported a negative effect of care bundles on CLABSI rates, and no studies reported unexpected or unintended consequences. Future QI should consider reporting relevant balance measures, such as any potential impact on skin integrity, nursing time, or infant growth.

There was no consensus definition for the primary outcome measure of CLABSI in the studies, although the majority of studies used the Centre for Disease Control (CDC) definition (see Table 1). The importance of a consistent definition cannot be underestimated, as a change in CDC definition in 2008, which required two or more positive cultures for a skin contaminant, drawn on separate occasions ([50](#_ENREF_50)),was associated with a 40% reduction in adjusted CLABSI rates ([37](#_ENREF_37)). The practice of obtaining two cultures following the growth of a skin commensal is likely to vary among neonatal units, due to both local practices and challenges associated with blood sampling, particularly in the extremely low birth weight population. In the case of a single culture of a skin commensal subjective judgement may be required in determining if it is a contaminant or a genuine infection, though arguably the aim should be to reduce the incidence of both genuine CLABSIs and contaminant cultures. Only one definition in Table 1 utilises laboratory markers, though in practice the use of markers such as white cells and C-reactive protein are likely to be used to distinguish genuine infection from contaminants.

Despite the use of an objective definition, inter-observer variability in the application of standardised definitions has been reported in the adult literature ([15](#_ENREF_15)) ([55](#_ENREF_55)). Uncertainty attributing central lines as the cause of infection, variations in counting line days and logistical challenges in data collection means that this measure of reporting may be subject to measurement bias and local interpretation ([15](#_ENREF_15)). Whilst this study attempted to use a standardised primary outcome measure of bloodstream infections per 1000 line or patient days, selected in order to reflect changes in central line exposure and unit activity, this is not without limitations. However, this is the most frequently reported outcome measure and only two studies were excluded for reporting percentages ([49](#_ENREF_49), [56](#_ENREF_56)).

There was variability within the bundled elements, though the commonest elements included education and training, using checklists, having a specific skin preparation protocol and using maximal standard barrier precautions (Table 4). Other practices potentially affecting the reduction of CLABSIs were not frequently reported, and it should be noted that 5 studies specified removing central lines at 120mls/kg/day enteral feed volumes. The study by Ista et al found minimising central line access significantly contributed to reducing CLABSIs in the NICU ([54](#_ENREF_54)). The authors did not contact the researchers for clarification on bundled elements, and are unable to ascertain if any bundled elements were used but not reported. It is often unclear why specific elements were chosen, and absence of reported elements does not necessarily equate to absence in the neonatal unit. Unlike the study by Ista et al ([54](#_ENREF_54)), this study has not attempted to associate specific bundled elements with reductions in CLABSIs, but instead identified the most frequently reported elements.

It is unclear is how consistently the bundled elements were implemented. None of these studies formally evaluated the implementation process to identify the most effective implementation strategy, though some did consider compliance with particular practices. The implementation of care bundles is often not successful or consistent ([16](#_ENREF_16), [57](#_ENREF_57)). One of the challenges is that it is often uncertain whether the intervention, or the implementation, or both, has contributed to the success or failure of an intervention. It is unlikely that the success of a care bundle in one setting can be simply extrapolated to another ([15](#_ENREF_15), [58](#_ENREF_58)). Several studies retrospectively theorised the possible mechanisms through which care bundles may contribute to healthcare professional behaviour change, including repetitive social interaction, establishing communities of practice and the use of cognitive tools such as checklists and audit ([37](#_ENREF_37), [44](#_ENREF_44), [59](#_ENREF_59)). One study recognised that the implementation of measures not yet introduced, such as checklists, audit and feedback, commonly used in other care bundle studies, may help reduce CLABSI rates further in their unit ([22](#_ENREF_22)).

There are several additional limitations to this study. There were no RCTs, and only 2 studies used interrupted time series analysis to account for temporal trends though a further 5 studies used statistical process control methods. There has been a trend towards reducing CLABSI rates, with a 50% decrease in CLABSI between 2008 and 2014 ([60](#_ENREF_60)), and one of the challenges of QI studies is outperforming temporal trends. Whilst this trend may be as a result of the plethora of QI projects that have been performed during this time, local practice variations and the change in CDC definition may have affected the results. Whilst non-randomised studies are traditionally not meta-analysed, they can provide pragmatic ‘real world’ solutions and can generate important knowledge regarding systems of care, how best to change them, and identify potentially better practices. As future RCTs investigating the impact of a care bundle are unlikely, this study therefore provides a useful insight into current practices in neonatal units though further work should investigate how these bundles are implemented.

**CONCLUSION**

There is now a substantial body of evidence to suggest that care bundles reduce CLABSI rates in the NNU. However, it is not clear what bundle elements are most effective in specific settings, and individual centres should undertake local work to identify areas for improvement. This study highlights the potential effectiveness of a care bundle approach and common bundle elements that neonatal units might use to develop bundles specific to their local settings. Future research should focus on determining what processes promote the effective implementation of infection prevention recommendations, and which bundle elements represent essential components.

**CONTRIBUTORSHIP STATEMENT**

MH and VP contributed to the conception of the research. MJ and VP performed the search and selection process separately, and disagreements were resolved by discussion. VP performed data collection and analysis, and MJ assisted with data analysis. VP drafted the original manuscript. All authors were involved in critical revision of the article and approved the final version for publication.

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Figure 2

