Impregnated central venous catheters for prevention of bloodstream infection in children (the CATCH trial): a randomised controlled trial

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Summary

Background Impregnated central venous catheters are recommended for adults to reduce bloodstream infections but not for children because there is not enough evidence to prove they are effective. We aimed to assess the effectiveness of any type of impregnation (antibiotic or heparin) compared with standard central venous catheters to prevent bloodstream infections in children needing intensive care.

Methods We did a randomised controlled trial of children admitted to 14 English paediatric intensive care units. Children younger than 16 years were eligible if they were admitted or being prepared for admission to a participating paediatric intensive care unit and were expected to need a central venous catheter for 3 or more days. Children were randomly assigned (1:1:1) to receive a central venous catheter impregnated with antibiotics, a central venous catheter impregnated with heparin, or a standard central venous catheter with computer generated randomisation in blocks of three and six, stratified by method of consent, site, and envelope storage location within the site. The clinician responsible for inserting the central venous catheter was not masked to allocation, but allocation was concealed from patients, their parents, and the paediatric intensive care unit personnel responsible for their care. The primary outcome was time to first bloodstream infection between 48 h after randomisation and 48 h after central venous catheter removal with impregnated (antibiotic or heparin) versus standard central venous catheters, assessed in the intention-to-treat population. Safety analyses compared central venous catheter-related adverse events in the subset of children for whom central venous catheter insertion was attempted (per-protocol population). This trial is registered with ISRCTN number, ISRCTN34884569.

Findings Between Nov 25, 2010, and Nov 30, 2012, 1485 children were recruited to this study. We randomly assigned 502 children to receive standard central venous catheters, 486 to receive antibiotic-impregnated catheters, and 497 to receive heparin-impregnated catheters. Bloodstream infection occurred in 18 (4%) of those in the standard catheters group, 7 (1%) in the antibiotic-impregnated group, and 17 (3%) assigned to heparin-impregnated catheters. Primary analyses showed no effect of impregnated (antibiotic or heparin) catheters compared with standard central venous catheters (hazard ratio [HR] for time to first bloodstream infection 0·71, 95% CI 0·37–1·34). Secondary analyses showed that antibiotic central venous catheters were better than standard central venous catheters (HR 0·43, 0·20–0·96) and heparin central venous catheters (HR 0·42, 0·19–0·93), but heparin did not differ from standard central venous catheters (HR 1·04, 0·53–2·03). Clinically important and statistically significant absolute risk differences were identified only for antibiotic-impregnated catheters versus standard catheters (–2·15%, 95% CI –4·09 to –0·20; number needed to treat [NNT] 47, 95% CI 25–500) and antibiotic-impregnated catheters versus heparin-impregnated catheters (–1·98%, –3·90 to –0·06, NNT 51, 26–1667). Nine children (2%) in the standard central venous catheter group, 14 (3%) in the antibiotic-impregnated group, and 8 (2%) in the heparin-impregnated group had catheter-related adverse events. 45 (8%) in the standard group, 35 (8%) antibiotic-impregnated group, and 29 (6%) in the heparin-impregnated group died during the study.

Interpretation Antibiotic-impregnated central venous catheters significantly reduced the risk of bloodstream infections compared with standard and heparin central venous catheters. Widespread use of antibiotic-impregnated central venous catheters could help prevent bloodstream infections in paediatric intensive care units.

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Introduction

Bloodstream infections are important causes of adverse clinical outcomes and costs to health services. Paediatric intensive care units have one of the highest reported rates of hospital-acquired bloodstream infections of any clinical specialty, with central venous catheters being a frequent cause of bloodstream infections.[1,2] US studies[3–5] report the success of improved aseptic practices during insertion and maintenance of central venous catheters for reducing rates of catheter-related bloodstream infections. The Department of Health in England invested in similar infection reduction initiatives,

Research in context

Evidence before this study

We searched PubMed on Sept 1, 2014, initially for systematic reviews or meta-analyses, using the clinical queries filter for therapy studies or terms for meta-analysis and (catheter* OR central OR venous OR intravenous), (impregnated OR bonded OR coated OR antibiotic OR heparin), and infection, with no language restrictions. We identified five systematic reviews published since 2008. The two most recent reviews were both published in the Cochrane Library. One included any type of central venous catheter impregnation, but excluded children (consisting of 56 randomised controlled trials, five studies of antibiotic-impregnated catheters *vs* standard catheters, and 1 study of heparin-impregnated catheters *vs* standard catheters). The other compared heparin bonded with standard central venous catheters in children (two trials). All the trials assessed in these two reviews were included in an earlier systematic review and network meta-analysis that comprised direct and indirect mixed treatment comparisons of 45 randomised controlled trials assessing catheter-related bloodstream infections (consisting of six studies of antibiotic-impregnated catheters *vs* standard catheters—none of these studies were in children; and three studies of heparin-impregnated catheters vs standard catheters, two of which were in children). For antibiotic (minocycline–rifampicin) compared with standard central venous catheters, a pooled odds ratio (OR) for catheter-related bloodstream infection of 0·18 (95% CI 0·08–0·34) was reported. We identified one subsequent randomised controlled trial which compared antibiotic (minocycline and rifampicin) and standard central venous catheters for children undergoing heart surgery. The trial of 288 participants was terminated early because of a low event rate (three catheter-associated bloodstream infections in each group). The mixed treatment comparison for heparin-bonded versus standard central venous catheters produced a pooled OR of 0·20 (0·06–0·44), and for antibiotic-impregnated catheters compared with heparin central venous catheters (indirect comparisons only), OR 1·18 (0·28–3·29). A previous cost-effectiveness analysis based on trials in adults estimated that impregnated central venous catheters would be cost effective even at baseline risks of bloodstream infection as low as 0·2%.

Added value of this study

To our knowledge, this is the first trial to assess antibiotic and heparin-impregnated central venous catheters in children and in the context of low bloodstream infection rates associated with improved asepsis practices. We add new evidence of effectiveness of antibiotic central venous catheters for any bloodstream infection, showing a 57% reduction compared with standard central venous catheters in children.

We confirmed the effectiveness of antibiotic central venous catheters identified in systematic reviews of trials in adults, with a 75% reduction in the risk of catheter-related bloodstream infections (HR 0·25, 0·07–0·90) compared with standard central venous catheters, for the first time in children. We also report for the first time that antibiotic central venous catheters are superior to heparin central venous catheters. These results are based on secondary analyses so need to be interpreted with caution. Our results are consistent with previous studies showing no effect of antibiotic impregnation on mortality or adverse effects.

By contrast with evidence from systematic reviews, we identified no significant effect for heparin-bonded versus standard central venous catheters. The lack of effectiveness of heparin central venous catheters might relate to the low baseline event rate noted in this study, which was done after implementation of central venous catheter care bundles in paediatric intensive care units to improve asepsis procedures during central venous catheters insertion and maintenance. Another potential explanation could be emergence of resistance to benzalkonium chloride, the bonding agent used for heparin, which is widely used in hand hygiene products.

Implications of the available evidence

When combined with previous systematic reviews, our findings establish the effectiveness of antibiotic-impregnated central venous catheters compared with standard central venous catheters and extend this evidence for paediatric use. Widespread use of antibiotic-impregnated central venous catheters could help prevent bloodstream infections in paediatric intensive care units.

including the Saving Lives central venous catheter care bundle and the Matching Michigan scheme.[6–8]

Use of central venous catheters that are impregnated, for example with antibiotics, chlorhexidine, or heparin, has been recommended as part of these infection reduction initiatives in the USA and the UK, but only for adults at high risk of bloodstream infections.[7,9] Impregnated central venous catheters have not been recommended for children.[10] The evidence for reduced rates of catheter-related bloodstream infections with impregnated compared with standard central venous catheters derives from trials predominantly of adults. Systematic reviews[11–15] draw on evidence from 56 randomised controlled trials. A network meta-analysis[14] of direct and indirect comparisons of impregnated and standard central venous catheters identified that heparin-bonded or antibiotic-impregnated central venous catheters were the most effective options, with an associated 70–80% reduction in the risk of catheter-related bloodstream infections.

Despite the large number of randomised controlled trials, uncertainty remains about the strength of the evidence for using impregnated central venous catheters, particularly for children. First, inherent biases exist in the use of catheter-related bloodstream infections (the primary outcome used in all previous trials) as a primary outcome because this could overestimate benefits of antibiotic impregnation.[11,16] Criteria for catheter-related

bloodstream infection require positive cultures of the same organism in the central venous catheter tip and in blood. This requirement might favour reduced catheter-related bloodstream infection in antibiotic-impregnated central venous catheters because antibiotics in the catheter tip might inhibit bacterial growth in culture media.[17] Second, few studies[6,7,18] have been done in the context of the low infection rates associated with improved asepsis programmes. Third, very few of these trials were in children.[19–21] Compared with adults, children need narrower central venous catheters, which thrombose more readily. Standard, non-impregnated central venous catheters are still used for most children in UK paediatric intensive care units.[10] However, there could be substantial benefits for children's health and health-care costs if impregnated central venous catheters could be shown to reduce rates of bloodstream infections.

We aimed to establish the effectiveness of any type of impregnation (antibiotic or heparin) compared with standard central venous catheters for prevention of bloodstream infections in children needing intensive care. A secondary aim was to establish which of the three types of central venous catheter was most effective. We also investigated the effectiveness of type of central venous catheter on catheter-related bloodstream infections, duration of care, and safety, including mortality and adverse events, such as antibiotic resistance.

Methods

Study design and population

The CATCH trial was a pragmatic, three-group, randomised controlled trial of children admitted to 14 paediatric intensive care units in England between December, 2010, and November, 2012. Children younger than 16 years were eligible if they were admitted or being prepared for admission to a participating paediatric intensive care unit and were expected to need a central venous catheter for 3 or more days. For children admitted to paediatric intensive care units after elective surgery, we sought prospective written parental consent during preoperative assessment. For children who needed a central venous catheter as an emergency, we sought written parental consent after randomisation and stabilisation (deferred consent) to avoid delaying treatment. Parents consented to the use of their child's data for the trial, to follow-up using routinely recorded clinical data, and to an additional 0·5 mL of blood being collected for PCR testing whenever a blood culture was clinically needed (appendix). The Research Ethics Committee for South West England approved the study protocol (reference number 09/H0206/69). The protocol and the statistical analysis plan are available online and the full statistical analysis report is available on request from the authors.

Randomisation and masking

Children were randomly assigned (1:1:1) at the bedside or in theatre (operating room) immediately before central venous catheter insertion to receive a central venous catheter impregnated with antibiotics, a central venous catheter impregnated with heparin, or a standard central venous catheter. The clinician or research nurse opened a pressure-sealed, sequentially numbered, opaque envelope containing the central venous catheter allocation. Randomisation sequences were computer generated by an independent statistician in random blocks of three and six, stratified by method of consent, site, and envelope storage location within the site to help with easy access to envelopes (eg, for insertion in theatre and in paediatric intensive care unit).

The clinician responsible for inserting the central venous catheter was not masked to allocation (because of the different colour of strips for antibiotic and heparin central venous catheters), but because central venous catheters looked identical while in situ, allocation was concealed from patients, their parents, and the paediatric intensive care unit personnel responsible for their care. Labels identifying the type of central venous catheter received were held securely in a locked drawer in case unmasking was needed. Participant inclusion in analyses and occurrence of outcome events were established before release of the randomisation sequence for analysis and for the data monitoring committee.

Procedures

Participation in the trial did not involve any changes to standard clinical care or data collection apart from collection of an additional 0·5 mL of blood whenever a blood culture sample was taken. The sample was sent for PCR testing for 16S ribosomal RNA (rRNA) of bacterial ribosome protein to detect bacterial infection. All randomly assigned and consented participants were followed up until 48 h after central venous catheter removal or attempted central venous catheter insertion. The research nurse assessed routinely recorded daily hospital records up until 48 h after catheter removal to assess primary and secondary outcomes. To corroborate data and to measure admissions, discharges, or death more than 48 h after catheter removal, we linked the child's hospital administrative records, death certification records, and records from the national Paediatric Audit Network (PICANet[22]) for 6 months after randomisation to the child's trial record. We extracted the Paediatric Index of Mortality[23] at admission to intensive care from the PICANet database.

Both types of impregnation involved internal and external surfaces. We used polyurethane central venous catheters manufactured by Cook Medical Incorporated, IN, USA. Sizes used were French gauge 4 (double lumen), 5, or 7 (triple lumen). Cook reports a concentration of 503 µg/cm minocycline and 480 µg/cm rifampicin for their antibiotic-impregnated central venous catheters, which reduces biofilm formation.[24] Heparin bonding reduces thrombus and thereby biofilm formation and uses benzalkonium chloride as an anti-infective bonding agent.[16,25]

See Online for appendix

For the **protocol** see http://www.nets.nihr.ac.uk/projects/hta/081347

Outcomes

The primary analysis for the trial compared any impregnated central venous catheters (antibiotic or heparin) with standard central venous catheters. Secondary analyses involved pairwise comparisons for the three types of central venous catheters for the primary outcome.

The primary outcome was time to the first bloodstream infection based on blood cultures taken between 48 h after randomisation and 48 h after central venous catheter removal (or before death). All blood culture samples included in the primary outcome were clinically indicated, defined by recorded evidence of infection (one or more of: temperature instability, change in inotrope requirements, haemodynamic instability, or poor perfusion) or removal of the central venous catheter because of suspected infection. Blood cultures were

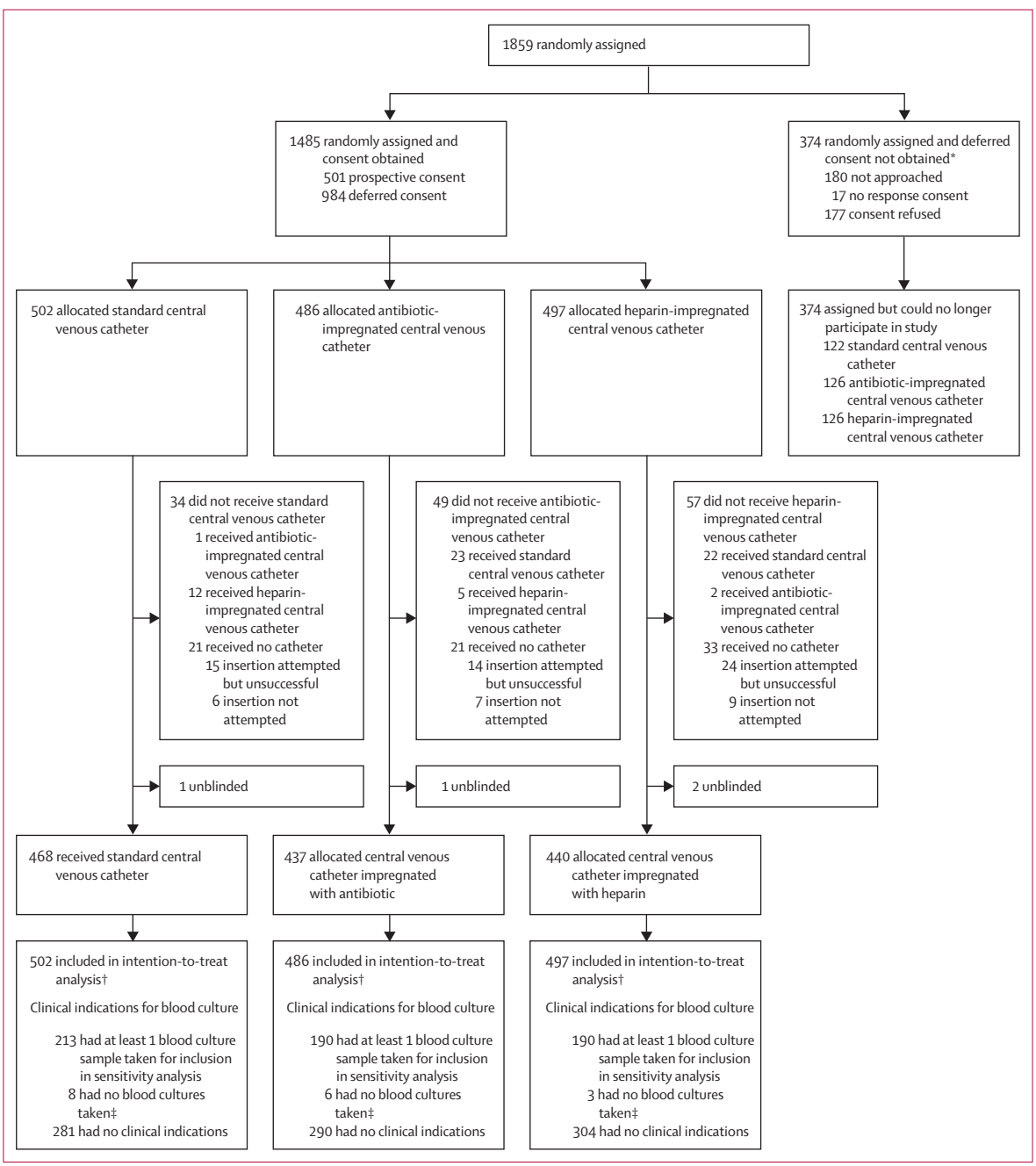

Figure 1: **Trial profile**

*Further details reported elsewhere.[27] †Based on a clinically indicated blood culture sample taken at least 48 h after randomisation and less than 48 h after central venous catheter removal. ‡Samples used in sensitivity analysis.

	Standard CVC (n=502)	Antibiotic-impregnated CVC (n=486)	Heparin-impregnated CVC (n=497)
Emergency (deferred consent)	333 (66%)	320 (66%)	331 (67%)
Elective (prospective consent)	169 (34%)	166 (34%)	166 (33%)
Sex			
Male	285 (57%)	291 (60%)	277 (56%)
Female	217 (43%)	195 (40%)	220 (44%)
Age			
<3 months	159 (32%)	159 (33%)	175 (35%)
3–12 months	129 (26%)	123 (25%)	116 (23%)
1–10 years	174 (35%)	154 (32%)	174 (35%)
≥11 years	40 (8%)	50 (10%)	32 (6%)
Weight at admission (kg)			
<3	41 (8%)	38 (8%)	56 (11%)
3–10	278 (55%)	280 (58%)	273 (55%)
>10	183 (36%)	166 (34%)	168 (34%)
Data missing	0	2 (<1%)	0
Admitted for surgery	174 (35%)	171 (35%)	181 (36%)
PICU assessment (from linked PICANet data)	479 (95%)	456 (94%)	473 (95%)
Primary reason for admission*			
Cardiovascular	235 (49%)	233 (51%)	250 (53%)
Endocrine or metabolic	30 (6%)	34 (7%)	30 (6%)
Infection	39 (8%)	30 (7%)	31 (7%)
Cancer	9 (2%)	6 (1%)	8 (2%)
Respiratory	102 (21%)	86 (19%)	84 (18%)
Neurological	22 (5%)	31 (7%)	29 (6%)
Trauma	18 (4%)	10 (2%)	18 (4%)
Other	24 (5%)	26 (6%)	22 (5%)
Unknown	0	0	1 (<1%)
Paediatric Index of Mortality (PIM2) score*			
<1%	54 (11%)	48 (11%)	48 (10%)
1–5%	264 (55%)	236 (52%)	247 (52%)
5 to <15%	116 (24%)	123 (27%)	119 (25%)
15 to <30%	34 (7%)	31 (7%)	39 (8%)
>30%	11 (2%)	18 (4%)	20 (4%)
Clinical condition <72 h before randomisation			
CVC in situ	95 (19%)	91 (19)	83 (17%)
Anticoagulants received	50 (10%)	59 (12)	61 (12%)
Antibiotics received	286 (57%)	276 (57%)	284 (57%)
Positive blood culture	40 (8%)	25 (5%)	36 (7%)
Clinical condition at randomisation			
Infection suspected	214 (43%)	181 (37%)	199 (40%)
Immune compromised	44 (9%)	31 (6%)	29 (6%)
Inserted CVCs	481 (96%)	465 (96%)	464 (93%)
Deferred consent, CVC inserted†	314 (65%)	301 (65%)	302(65%)
CVC inserted at same hospital†			
Intensive care unit	276 (57%)	264 (57%)	259 (56%)
Operating theatre	5 (1%)	4 (<1%)	7 (2%)
Other	2 (<1%)	3 (<1%)	1 (<1%)
CVC inserted at other hospital†‡			
Intensive care unit	5 (1%)	6 (1%)	3 (<1%)
Operating theatre	3 (<1%)	8 (2%)	7 (2%)
Other	23 (5%)	16 (3%)	23 (5%)
Data missing	0	0	2 (<1%)
Prospective consent, CVC inserted†	167 (35%)	164 (35%)	162 (35%)
CVC inserted at same hospital†			
Intensive care unit	15 (3%)	23 (5%)	16 (3%)
Operating theatre	152 (32%)	141 (30%)	144 (31%)
Other	0	0	1 (<1%)
Triple lumen CVC†	450 (94%)	421 (91%)	422 (91%)
CVC inserted into femoral vein†	253 (53%)	217 (47%)	235 (51%)

Data are n (%). PICU=paediatric intensive care unit. PICANet=Paediatric Intensive Care Audit Network. CVC=central venous catheter. *n=479 for standard CVCs, n=456 for antibiotic-impregnated CVCs, and n=497 for heparin-impregnated CVCs. †n=481 for standard CVCs, n=465 for antibiotic-impregnated CVCs, and n=464 for heparin-impregnated CVCs. ‡CVCs were inserted by the retrieval team before to transfer to PICU.

Table 1: **Baseline characteristics**

recorded as positive for the primary outcome if any organism was isolated that was not a skin commensal bacterium or if coagulase-negative staphylococci (or other skin commensal bacteria) were isolated and there were two or more positive cultures of the same organism within 48 h of each other. A clinical committee reviewed all primary outcomes involving positive cultures without knowledge of central venous catheter allocation status. A sensitivity analysis assumed that the primary outcome occurred for those with a record of clinical indication but no blood culture taken in the primary outcome time window.

Secondary bloodstream infection-related outcomes were catheter-related bloodstream infection based on the same organisms cultured from blood and the central venous catheter tip between 48 h after randomisation and 48 h after central venous catheter removal, differential positivity of cultures from several central venous catheter lumens on two or more occasions, or exit site infection or central venous catheter removed for infection; rate of bloodstream infection per 1000 central venous catheter-days based on one or more bloodstream infections between randomisation and central venous catheter removal; and time to a composite measure of bloodstream infection comprising the primary outcome or a negative blood culture combined with a positive

	Standard (n=502)	Antibiotic (n=486)	Heparin (n=497)
Primary outcome			
Bloodstream infection	18 (4%)	7 (1%)	17 (3%)
Median time to first bloodstream infection (days)	7·5 (4·5–11·2)	6·9 (6·0–8·0)	4·2 (3·1–8·4)
Type of organism			
Non-skin	15* (3%)	6 (1%)	16 (3%)
Skin	3 (<1%)	1 (<1%)	1 (<1%)
Organism group†			
Gram positive‡	10 (2%)	3 (<1%)	10 (2%)
Gram negative	6 (1%)	4 (<1%)	5 (1%)
Candida	2 (<1%)	0	3 (<1%)
Secondary outcomes			
Catheter-related bloodstream infection	12 (2%)	3 (<1%)	10 (2%)
Bloodstream infection rate per 1000 central venous catheter-days	8·24 (4·72–11·77)	3·31 (1·01–5·60)	8·78 (5·03–12·55)
Number of bloodstream infections per 1000 days	21/2·547	8/2·389	21/2·421
Bloodstream infection or culture negative infection§	112 (22%)	103 (21%)	102 (21%)
Thrombosis	125 (25%)	126 (26%)	105 (21%)
Median time to central venous catheter removal (days)	4·28 (2·30–6·97)	4·31 (2·13–7·0)	4·20 (2·24–6·97)
Mortality ≤30 days after randomisation	42 (8%)	39 (8%)	28 (6%)
Post-hoc analyses			
Median time to PICU discharge (days)	5·1 (2·8–10·0)	4·4 (2·2–9·3)	4·9 (2·3–8·9)
Median time to hospital discharge (days)	12·0 (6·4–25·6)	12·0 (6·7–22·7)	12·1 (6·4–22·5)
Safety analyses¶			
Central venous catheter-related adverse events	9 (2%)	13 (3%)	9 (2%)
Mortality ≤30 days after randomisation	45 (8%)	35 (8%)	29 (6%)

Data are n (%), median (IQR), or rate (95% CI), unless otherwise specified. PICU=paediatric intensive care unit. *Includes one mixed bloodstream infection pathogen and skin organism. †Groups add to more than total number of organism groups because multiple types of organisms were isolated on the same occasion in some patients. ‡Includes six bloodstream infections due to coagulase negative staphylococci. §Composite measure of bloodstream infection including the primary outcome or a negative blood culture combined with a positive 16S PCR result for bacterial DNA, removal of the central venous catheter because of suspected infection, or a start of antibiotics or change in type of antibiotics on the same or next day. ¶For the safety analysis, n=533 for the standard central venous catheter group, n=451 for the antibiotic-impregnated catheter group, and n=479 for heparin-impregnated catheter group.

***Table 2*: Endpoint frequency according to central venous catheter allocation (intention-to-treat analyses) and central venous catheter received (safety analyses)**

For the **protocol** see http://www.catchtrial.org.uk

16S PCR result for bacterial DNA, removal of the central venous catheter because of suspected infection, or a start of antibiotics or change in type of antibiotics on the same or next day.

Other secondary outcomes included time to central venous catheter removal and time to central venous catheter thrombosis (defined by two episodes within 5 days of each other of difficulty flushing the central venous catheter or drawing back blood from the central venous catheter, one episode of swollen limb, central venous catheter removal because of thrombosis, or a positive ultrasound indicating thrombosis). We also compared the time to paediatric intensive care unit discharge, hospital discharge, and death within 30 days of randomisation between groups. Deaths were recorded by the research team or by linkage to death certification data from the Office of National Statistics. Cost-effectiveness analyses based on linked hospital resource data for 6 month follow-up will be reported elsewhere.

Safety analyses compared central venous catheter-related adverse events (including unexplained thrombocytopenia after insertion of central venous catheter), mortality, and antibiotic resistance to minocycline (>0·5 μg/mL) or rifampicin (>1·0 μg/mL) based on etest strips (bioMérieux, USA) applied to organisms isolated from bloodstream infections. Incomplete laboratory testing and reporting limited analyses of resistance in positive blood cultures and prevented analysis of resistance in cultures from the central venous catheter tip (protocol).

Statistical analysis

We based the sample size calculation for the primary analysis on relative risk (RR). We assumed that detection of a RR of 0·5 in patients with a baseline risk of 10% would change policy. We assumed that the RR would remain constant across baseline risks whereas the absolute risk difference would be more variable. 1200 children in a 2:1 ratio (impregnated:standard) were needed to achieve 80% power to detect an RR of 0·5 at a 5% level of significance, based on an estimated bloodstream infection rate of 10% and allowing for 5% loss to follow-up. A lower than expected bloodstream infection rate of 5% would have 62% power to detect a RR of 0·5 or 80% power for a RR of 0·32.

The independent data monitoring committee recommended continuation of the study until Nov 30, 2012, after reviewing the first 209 children, an interim analysis of 650 children using the Peto-Haybittle stopping rule for the primary outcome had occurred, recruitment had reached the original target of the 1200 preschedule in June, 2012, and there were no safety concerns. The recommendation for continuation aimed to exhaust available funding.

Outcome data were analysed according to the intention-to-treat principle. Safety analyses included the subset of children for whom central venous catheter insertion was attempted, grouped by the subset in whom central venous catheters were actually received. A p value of 0·05 was considered statistically significant and 95% CIs were used throughout. Absolute risk differences were calculated for proportions. Time-to-event outcomes were analysed using Kaplan-Meier curves and log-rank tests. Cox regression was used to adjust primary and secondary analyses of time to first bloodstream infection for prospective or deferred consent type and suspected infection at baseline. In a post-hoc sensitivity analysis, we used cumulative incidence curves to assess competing risks from death for time to first bloodstream infection. We applied Gray's test

	Any impregnated *vs* standard (primary analysis)			Antibiotic-impregnated *vs* standard (secondary analysis)			Heparin-impregnated *vs* standard (secondary analysis)			Antibiotic-impregnated *vs* heparin-impregnated (secondary analysis)		
	Risk difference (95% CI)	Hazard ratio (95% CI)	p value	Risk difference (95% CI)	Hazard ratio (95% CI)	p value	Risk difference (95% CI)	Hazard ratio (95% CI)	p value	Risk difference (95% CI)	Hazard ratio (95% CI)	p value
Primary outcome												
First bloodstream infection	−1·14 (−3·04 to 0·75)	0·71 (0·37 to 1·34)	0·29	−2·15 (−4·09 to −0·20)	0·43 (0·20 to 0·96)	0·04	−0·17 (−2·45 to 2·12)	1·04 (0·53 to 2·03)	0·90	−1·98 (−3·90 to −0·06)	0·42 (0·19 to 0·93)	0·03
Secondary outcomes												
Catheter-related bloodstream infection	−1·07 (−2·58 to 0·45)	0·55* (0·25 to 1·21)	0·13	−1·77 (−3·28 to −0·27)	0·25* (0·07 to 0·90)	0·03	−0·38 (−2·20 to 1·44)	0·84* (0·36 to 1·96)	0·68	−1·39 (−2·81 to 0·02)	0·30* (0·08 to 1·11)	0·09
Rate of bloodstream infection per 1000 central venous catheter days	−2·21 (−6·36 to 1·94)	0·73† (0·40 to 1·34)	0·31	−4·94 (−9·14 to −0·73)	0·40† (0·17 to 0·97)	0·04	0·55 (−4·60 to 5·70)	1·07† (0·55 to 2·06)	0·85	−5·49 (−9·89 to −1·08)	0·38† (0·16 to 0·89)	0·03
First bloodstream infection or culture-negative infection	−1·46 (−5·90 to 2·98)	0·95 (0·75 to 1·20)	0·65	−1·12 (−6·26 to 4·03)	0·94 (0·72 to 1·23)	0·73	−1·79 (−6·87 to 3·30)	0·95 (0·73 to 1·25)	0·67	0·67 (−4·41 to 5·75)	0·99 (0·75 to 1·25)	0·93
Central venous catheter thrombosis	−1·40 (−6·02 to 3·22)	0·98 (0·79 to 1·22)	0·88	1·03 (−4·40 to 6·46)	1·09 (0·85 to 1·40)	0·49	−3·77 (−8·99 to 1·44)	0·88 (0·68 to 1·14)	0·34	4·80 (−0·50 to 10·10)	1·24 (0·96 to 1·60)	0·11
Time to central venous catheter removal	..	1·04 (0·93 to 1·16)	0·53	..	1·02 (0·90 to 1·17)	0·67	..	1·05 (0·92 to 1·19)	0·51	..	0·99 (0·87 to 1·13)	0·87
Mortality ≤30 days after randomisation	..	0·80* (0·54 to 1·20)	0·28	..	0·96* (0·61 to 1·51)	0·85	..	0·65* (0·40 to 1·07)	0·09	..	1·46* (0·88 to 2·42)	0·14
Post-hoc analyses												
Time to PICU discharge	..	1·08 (0·97 to 1·20)	0·17	..	1·07 (0·95 to 1·22)	0·27	..	1·08 (0·96 to 1·23)	0·21	..	0·98 (0·86 to 1·11)	0·73
Time to hospital discharge	..	1·04 (0·93 to 1·16)	0·47	..	1·03 (0·91 to 1·16)	0·68	..	1·05 (0·93 to 1·19)	0·42	..	0·98 (0·87 to 1·11)	0·77

Risk difference is based on the risk of the outcome during follow-up and displayed as percentage. PICU=paediatric intensive care unit. *Risk ratios. †Rate ratios.

Table 3: **Risk differences and relative effect measures by central venous catheter allocated (intention-to-treat analyses)**

to detect whether there was a difference between impregnated and standard central venous catheters for the primary outcome.[26] For secondary outcomes, binary outcomes were analysed using the chi squared χ^2 test and continuous outcomes analysed using the Mann-Whitney *U* test. The rate of bloodstream infection (defined as the total number of bloodstream infections per 1000 central venous catheter-days occurring between randomisation and central venous catheter removal) was analysed using Poisson regression. All analyses were done with SAS software version 9.2. This trial is registered with ClinicalTrials.gov, number NCT01029717.

Role of the funding source

The manufacturer and the funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

Results

Between Nov 25, 2010, and Nov 30, 2012, 1859 children were randomly assigned (501 prospective, 1358 emergency) to one of the central venous catheter groups. 984 (72%) of the emergency patients subsequently provided deferred consent, leaving 1485 participants for final analysis (figure 1). Reasons for not providing consent are reported in figure 1. Of the 1485 randomly assigned participants, 75 (5%) did not receive a central venous catheter. In 53 of these participants, insertion was attempted but unsuccessful and in 22, central venous catheter insertion was not attempted (16 no longer required a central venous catheter, five reason unknown, and one patient died).

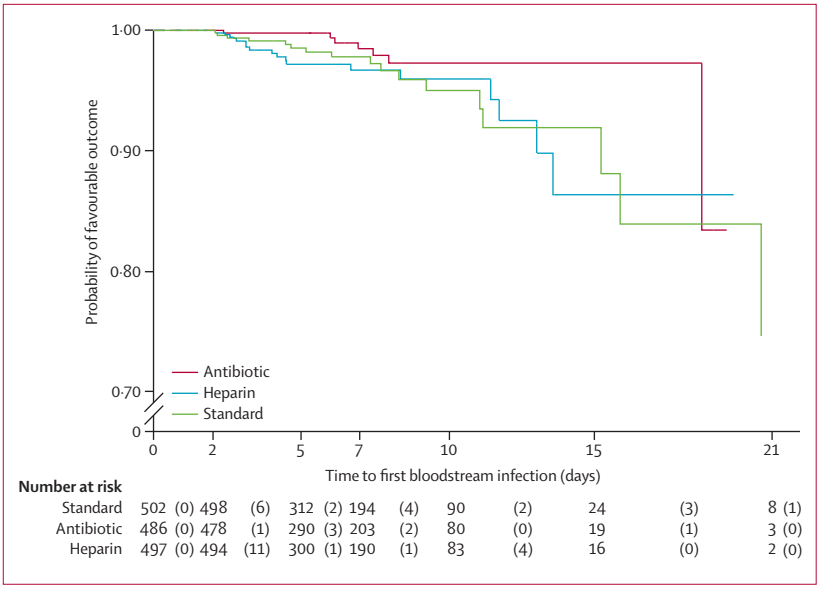

Figure 2: **Kaplan-Meier curve for time to first bloodstream infection by central venous catheter allocation**

Of those who received a central venous catheter, more of those randomly assigned to standard central venous catheter received the allocated type of central venous catheter than those assigned to antibiotic-impregnated or heparin-impregnated catheter (figure 1). Most of the central venous catheters received but not allocated were standard central venous catheters (45 [69%] of 65; figure 1). All randomly assigned and consented participants were followed up until 48 h after central venous catheter removal or attempted central venous catheter insertion.

More than half (57%) of children were aged younger than 12 months at admission, with a third aged less than 3 months (table 1). A third of children had surgery before admission to the paediatric intensive care unit and half had cardiovascular problems as their primary diagnosis at admission. Central venous catheter insertion took place in the operating room for 437 (89%) of 493 participants in the prospective consent (elective) group, but in only 34 (4%) of 917 of the deferred consent (emergency) group.

Clinical indicators of infection were recorded during the primary outcome time interval from 48 h after randomisation up to 48 h after central venous catheter removal for 610 (41%) of 1485 participants, 593 (97%) of whom had blood cultures taken (figure 1). Derivation of the primary outcome and the number of bloodstream infections excluded from the primary outcome is shown in the appendix. The primary outcome of bloodstream infection was recorded for 42 children: 18 (4%) of 502 with standard central venous catheters, 7 (1%) of 486 with antibiotic-impregnated catheters, and 17 (3%) of 497 with heparin-impregnated catheters. Gram-positive organisms accounted for most bloodstream infections (23 [55%] of 42), of which six (14%) were positive for coagulase negative staphylococci (table 2). Details of all organisms isolated in the primary outcomes are given in the appendix. All outcomes are reported by central venous catheter type (table 2).

In the primary comparison, time to bloodstream infection did not differ between impregnated central venous catheters (antibiotic or heparin combined) and standard central venous catheters (hazard ratio [HR] 0·71, 95% CI 0·37–1·34; table 3). In secondary, pairwise comparisons, antibiotic-impregnated central venous catheters reduced the risk of bloodstream infections compared with standard central venous catheters (HR 0·43, 0·20–0·96) and compared with heparin central venous catheters (HR 0·42, 0·19–0·93). Absolute risks of bloodstream infections differed significantly at the 5% level only for antibiotic-impregnated central venous catheters compared with standard central venous catheters (–2·15%) and heparin-impregnated central venous catheters (–1·98%; table 3). The number needed to treat by using antibiotic-impregnated central venous was 47 (95% CI 25–500) compared with standard and 51 (26–1667) compared with heparin central venous catheters.

Figure 2 shows the Kaplan-Meier curve for time to first bloodstream infection. No significant difference was observed in time to first bloodstream infection comparing any impregnated catheters with standard catheters (p=0·9) or heparin-impregnated catheters with standard catheters (p=0·9). The risk of bloodstream infection was reduced for antibiotic-impregnated catheters compared with standard catheters (p=0·04) and for antibiotic compared with heparin-impregnated catheters (p=0·03). The direction of these results was robust to the sensitivity analysis in which the 17 cases with clinical indicators but no blood culture taken were assumed to have a positive bloodstream infection (figure 1). The direction of results did not change in the regression analysis (appendix). Competing risks analyses using Gray's test indicated no difference between impregnated and standard central venous catheters for either competing risk (p=0·29 for bloodstream infection and p=0·89 for death; data not shown).[28]

No significant difference was reported between any impregnated catheter and standard central venous catheters for the risk of catheter-related bloodstream infections (p=0·13). The risk of catheter-related bloodstream infection was significantly lower for antibiotic-impregnated catheters versus standard central venous catheters (p=0·03) and for antibiotic-impregnated catheters versus heparin-impregnated central venous catheters (p=0·03; table 3). The bloodstream infection rate per 1000 central venous catheter-days was lowest in the antibiotic group (table 2). No children had more than one bloodstream infection while the trial central venous catheter was in place. The association between bloodstream infection outcomes is shown by time since randomisation (appendix). The composite measure of bloodstream infection or culture

negative infection did not differ by central venous catheter (table 2, 3). Indicators of infection contributing to the composite measure are shown in the appendix. No other secondary outcomes were associated with type of central venous catheter (table 3).

The cohort for safety analyses (per protocol) was based on children who had a central venous catheter insertion attempted. These analyses comprised more children in the standard group (n=533) than in the antibiotic (n=451) or heparin groups (n=479; table 2; appendix p 2). No central venous catheter-related adverse events (31 events) or mortality (148 events) were attributed to type of central venous catheter received (table 2). Two children developed thrombocytopenia unrelated to the type of central venous catheter. One was allocated to antibiotic and the other to heparin central venous catheter (full statistical analysis report available from the authors).

Testing for antibiotic resistance varied by centre. Only 12 of the 42 children with the primary outcome bloodstream infection had minocycline and rifampicin resistance reported using etest strips; eight of 12 were resistant to one or both antibiotics (three of five in the standard group, two of two in the antibiotic-impregnated group, and three of five in the heparin-impregnated group; appendix). Most resistance occurred in Gram-negative organisms (seven of nine organisms cultured from eight bloodstream infection episodes; appendix). Resistance was detected in two bloodstream infections that were positive for staphylococcal species: one allocated to antibiotic and the other to heparin central venous catheters (appendix).

Discussion

In this first trial to compare two types of impregnated central venous catheters with standard central venous catheters in children our primary analysis showed no evidence of a statistically significant difference between time to first bloodstream infection for any impregnated central venous catheters (antibiotic and heparin combined) compared with standard central venous catheters. However, antibiotic impregnation reduced the risk of bloodstream infection by 57% compared with standard central venous catheters, and by 58% compared with heparin-bonded central venous catheters. Antibiotic-impregnated central venous catheters were associated with an absolute risk reduction of 2·15% compared with standard central venous catheters, meaning 47 children (95% CI 25–500) would need to be treated with an antibiotic-impregnated central venous catheter instead of a standard central venous catheter to prevent one case of bloodstream infection.

The strengths of this study include the use of any bloodstream infections as a clinically important primary outcome thereby avoiding the biases inherent in measuring catheter-related bloodstream infections. A further strength was the restriction to positive blood cultures that were clinically indicated, meaning signs of infection were recorded in the child, thereby recording an outcome that clinicians would regard as potentially serious and needing treatment. Restriction to clinically indicated blood cultures increased the clinical relevance of the primary outcome, but, by contrast with routine blood culture sampling for all study participants, diminished the sensitivity of the study to detect bacteraemia. Only 41% of children had clinical indicators of bloodstream infection recorded during the primary outcome interval but nearly all of these had a blood culture taken. A third strength is the representativeness of the study population in terms of children admitted to the 14 largest paediatric intensive care units (of a total of 24) across the country. We were able to enrol a similar proportion of emergency patients (two-thirds) as seen in practice,[29] enabled by the inclusion of retrieved children and the use of deferred consent.

Limitations of this study include the limited power of the study to detect differences in the primary outcome according to the type of central venous catheter. The trial was based on the best available evidence at the time, which indicated large but equivalent benefits of antibiotic and heparin central venous catheters compared with standard.[11–14] The key question, which determined our primary analysis and sample size, was whether these benefits occurred in children. Secondary, pairwise comparisons addressed which type of impregnated central venous catheter was best, but the trial was not adequately powered to detect the anticipated small differences between antibiotic and heparin central venous catheters. Power was further reduced by the low baseline rate of bloodstream infections.

Another limitation relates to finding that although antibiotic central venous catheters reduced bloodstream infections, we identified no differences in secondary outcomes such as mortality, duration of central venous catheter insertion, or the composite measure of bloodstream infections or culture negative infection. One potential reason is the complex and varied conditions and disease processes affecting patients receiving intensive care. Antibiotic central venous catheters might affect bloodstream infection in these patients but not other outcomes. For example, none of the deaths were deemed to be directly attributable to bloodstream infections. A second reason is the poor specificity of the secondary outcomes. Mortality and duration of central venous catheter placement are affected by a number of treatments, not just central venous catheter impregnation, thereby biasing in favour of a null effect for these secondary outcomes. The reduction in the hazard ratio for antibiotic versus standard central venous catheter was largest for catheter-related bloodstream infections (reduced by 75%), less for bloodstream infections (reduced by 57%), and small and not significant for the composite measure of bloodstream infections or culture negative infection. Of these outcomes, catheter-related bloodstream infection is most specifically affected by antibiotic impregnation,

whereas the composite measure of bloodstream infection is affected by other disease and treatment factors, thereby biasing towards the null effect.

Another factor likely to bias towards the null effect for secondary outcomes is the potential for rescue treatment in response to signs of bloodstream infections. Patients in intensive care units are continuously monitored for changes in their condition and treated promptly. As a result, signs of infection should be less likely to develop into septic shock given good intensive care management. Such responses introduce bias towards the null effect for secondary outcomes such as mortality but are difficult to measure adequately.

A further limitation was the fact that antibiotic catheters had a brown line on the internal part of the catheter, but once inserted, the catheters were identical. We found no evidence of differential blood culture sampling by trial group (figure 1). The number of children who received their allocated central venous catheter was slightly higher for those in the standard group, probably showing the fact that standard central venous catheters were the default catheters used in many units.[10] Lastly, antibiotic resistance testing using etest strips was not done for all positive blood cultures. This represents local laboratory administration and processing, which centralised testing of positive cultures could have mitigated. Where reported, resistance occurred in all trial groups, predominantly in Gram-negative isolates, as expected. The low rates are consistent with previous lack of evidence for the emergence of resistance.[30]

The primary outcome, time to bloodstream infection, did not differ between impregnated and standard central venous catheters. However, secondary, pairwise analyses of the type of central venous catheter, showed that only antibiotic-impregnated central venous catheters reduced the risk of bloodstream infections compared with standard and with heparin-impregnated central venous catheters. The low rate of bloodstream infections in the standard and heparin groups and the multiple, pairwise comparisons, reduced the power of our study. However, when combined with evidence from systematic reviews, our findings establish the effectiveness of antibiotic-impregnated central venous catheters compared with standard central venous catheters and extend this evidence for paediatric use. For the first time, we directly show the effectiveness of impregnation of central venous catheters with antibiotics compared with heparin in this population, even in the context of low rates of bloodstream infections.[31] Widespread use of antibiotic-impregnated central venous catheters could help prevent bloodstream infections in the paediatric intensive care unit. Whether these benefits outweigh the additional costs depends on differential pricing of antibiotic and standard central venous catheters by the manufacturer and the cost benefits of avoiding bloodstream infection.

Contributors
All authors contributed to the design or conduct of the study. REG (Chief Investigator), QM, and CG conceived and designed the study. Statistical analyses were done by KD and CG. Endpoint review for the primary outcome was done by QM, MM, and REG. REG, QM, KD, KH, and CG wrote the paper and all authors commented on the manuscript and approved the final version.

Declaration of interests
We declare no competing interests.

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