White Rose Research Online

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk
Universities of Leeds, Sheffield and York

Deposited via The University of York.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/id/eprint/145760/

Version: Published Version

Article:
Gilbert, Ruth, Brown, Michaela, Rainford, Naomi et al. (2019) Antimicrobial-impregnated central venous catheters for prevention of neonatal bloodstream infection (PREVAIL): an open-label, parallel-group, pragmatic, randomised controlled trial. The Lancet. Child & adolescent health. pp. 381-390. ISSN: 2352-4650

https://doi.org/10.1016/S2352-4642(19)30114-2

Reuse
This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here: https://creativecommons.org/licenses/

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

UNIVERSITY OF LEEDS
University of Sheffield
UNIVERSITY of York

Antimicrobial-impregnated central venous catheters for prevention of neonatal bloodstream infection (PREVAIL): an open-label, parallel-group, pragmatic, randomised controlled trial

*Ruth Gilbert, Michaela Brown, Naomi Rainford, Chloe Donohue, Caroline Fraser, Ajay Sinha, Jon Dorling, Jim Gray, William McGuire, Carrol Gamble, Sam J Oddie, on behalf of the PREVAIL trial team**

Summary

Background Bloodstream infection is associated with high mortality and serious morbidity in preterm babies. Evidence from clinical trials shows that antimicrobial-impregnated central venous catheters (CVCs) reduce catheter-related bloodstream infection in adults and children receiving intensive care, but there is a paucity of similar evidence for babies receiving neonatal intensive care.

Methods This open-label, parallel-group, pragmatic, randomised controlled trial was done in 18 neonatal intensive care units in England. Newborn babies who needed a peripherally inserted CVC (PICC) were allocated randomly (1:1) to receive either a PICC impregnated with miconazole and rifampicin or a standard (non-antimicrobial-impregnated) PICC. Random allocation was done with a web-based program, which was centrally controlled to ensure allocation concealment. Randomisation sequences were computer-generated in random blocks of two and four, and stratified by site. Masking of clinicians to PICC allocation was impractical because rifampicin caused brown staining of the antimicrobial-impregnated PICC. However, participant inclusion in analyses and occurrence of outcome events were determined following an analysis plan that was specified before individuals saw the unblinded data. The primary outcome was the time from random allocation to first microbiologically confirmed bloodstream or cerebrospinal fluid (CSF) infection between 24 h after randomisation and 48 h after PICC removal or death. We analysed outcome data according to the intention-to-treat principle. We excluded babies for whom a PICC was not inserted from safety analyses, as these analyses were done with groups defined by the PICC used. This trial is registered with ISRCTN, number 81931394.

Findings Between Aug 12, 2015, and Jan 11, 2017, we randomly assigned 861 babies (754 [88%] born before 32 weeks of gestation) to receive an antimicrobial-impregnated PICC (430 babies) or standard PICC (431 babies). The median time to PICC removal was 8·20 days (IQR 4·77–12·13) in the antimicrobial-impregnated PICC group versus 7·86 days (5·00–12·53) days in the standard PICC group (hazard ratio [HR] 1·03, 95% CI 0·89–1·18, p=0·73), with 46 (11%) of 430 babies versus 44 (10%) of 431 babies having a microbiologically confirmed bloodstream or CSF infection. The time from random allocation to first bloodstream or CSF infection was similar between the two groups (HR 1·11, 95% CI 0·73–1·67, p=0·63). Secondary outcomes relating to infection, rifampicin resistance in positive blood or CSF cultures, mortality, clinical outcomes at neonatal unit discharge, and time to PICC removal were similar between the two groups, although rifampicin resistance in positive cultures of PICC tips was higher in the antimicrobial-impregnated PICC group (relative risk 3·51, 95% CI 1·16–10·57, p=0·018). 60 adverse events were reported from 49 (13%) patients in the antimicrobial-impregnated PICC group and 50 events from 45 (10%) babies in the standard PICC group.

Interpretation We found no evidence of benefit or harm associated with miconazole and rifampicin-impregnated PICCs compared with standard PICCs for newborn babies. Future research should focus on other types of antimicrobial impregnation of PICCs and alternative approaches for preventing infection.

Funding UK National Institute for Health Research Health Technology Assessment programme.

Copyright © 2019 The Author(s). Published by Elsevier Ltd. This is an Open Access license under the CC BY 4.0 license.

Lancet Child Adolesc Health 2019

Published Online
April 27, 2019
http://dx.doi.org/10.1016/S2352-4642(19)30114-2

See Online/Comment
http://dx.doi.org/10.1016/S2352-4642(19)30120-8

*Members are listed at the end of the paper

UCL Great Ormond Street Institute of Child Health, London, UK (Prof R Gilbert MD, C Fraser MSc); **Health Data Research UK, London, UK** (Prof R Gilbert); **Clinical Trials Research Centre, Department of Biostatistics, University of Liverpool, Liverpool, UK** (M Brown MSc, N Rainford MSc, C Donohue BSc, Prof C Gamble PhD); **Barts Health NHS Trust, London, UK** (A Sinha MD); **Blizard Institute, Queen Mary University of London, London, UK** (A Sinha); **Division of Neonatal-Perinatal Medicine, Dalhousie University IWK Health Centre, Halifax, NS, Canada** (Prof J Dorling MD); **Birmingham Women's and Children's NHS Foundation Trust, Birmingham, UK** (J Gray MBBS); **Centre for Reviews and Dissemination, University of York, York, UK** (Prof W McGuire MD, S J Oddie MBBS); **and Bradford Institute for Health Research, Bradford Royal Infirmary, Bradford, UK** (S J Oddie)

Correspondence to:
Prof Ruth Gilbert, UCL Great Ormond Street Institute of Child Health, London WC1N 1EH, UK
r.gilbert@ucl.ac.uk

Introduction

Bloodstream infection is the most common serious complication associated with the use of central venous catheters (CVCs) in newborn babies. Microbial pathogens adhere to the catheter material and secrete a biofilm[1] that protects them from circulating antimicrobial drugs, enabling sustained colonisation.[2] CVC removal is often needed to clear the infection.

Catheter-related bloodstream infection has been reported to occur in up to 30% of neonates, with the

Research in context

Evidence before this study

We searched Cochrane Central Register of Controlled Trials, Embase, and MEDLINE on March 29, 2018, and ClinicalTrials.gov and WHO International Clinical Trials Registry Platform on April 3, 2018, for studies evaluating the effectiveness of antimicrobial-impregnated central venous catheters (CVCs) compared with any other type of CVC for reducing bloodstream infection in newborn infants, children, and adults. We included systematic reviews or meta-analyses of randomised controlled trials of miconazole and rifampicin-impregnated or minocycline and rifampicin-impregnated CVCs published since 2008 and randomised controlled trials in children or newborn infants published since the searches conducted by the systematic reviews that were included in our evidence review. We used search terms related to CVCs, antimicrobial impregnation, and infection (see appendix for full search terms). We identified 11 randomised controlled trials of central venous catheters (CVCs) impregnated with rifampicin combined with another antimicrobial agent (appendix). Two trials compared miconazole and rifampicin-impregnated CVCs and standard CVCs. One of these trials involved newborn infants and was published only as an abstract. Neither trial reported a significant difference in bloodstream infection. Nine randomised controlled trials of minocycline and rifampicin-impregnated CVCs compared with standard CVCs found consistent evidence of reduced catheter-related bloodstream infection in children and adults. One trial reported reduced bloodstream infection from any cause in children (appendix). A 2015 Cochrane review of antimicrobial-impregnated CVCs in newborn babies concluded that, given the paucity of evidence, a large, simple, and pragmatic randomised controlled trial of this intervention was needed to guide policy and practice.

Added value of this study

The PREVAIL trial showed that use of miconazole and rifampicin-impregnated, percutaneously inserted CVCs compared with use of standard CVCs did not reduce the risk of any bloodstream infection or catheter-related bloodstream infection, other morbidity, or mortality in newborn infants. To our knowledge, this is the largest trial to date of this intervention and the validity is enhanced by the methodological quality and power. The findings of this study are broadly applicable to newborn infants cared for in facilities in well-resourced health-care services.

Implications of all the available evidence

The PREVAIL trial findings contrast with those of previous randomised controlled trials of antimicrobial-impregnated CVCs, which reported substantial reductions in bloodstream infection in older children and adults. A possible explanation for this difference is that the trials involving children and adults assessed CVCs impregnated with minocycline and rifampicin rather than the miconazole and rifampicin combination used in this trial. Rifampicin might be more effective when combined with a synergistic antibacterial (minocycline) rather than an antifungal (miconazole) and a simple, pragmatic randomised controlled trial of minocycline and rifampicin-impregnated percutaneously inserted CVCs in newborn infants might now be warranted.

See Online for appendix

highest rates in babies who are born very prematurely (before 32 weeks of gestation).[3,4] The organisms most frequently isolated from preterm babies are coagulase-negative staphylococci, Gram-negative bacilli, other Gram-positive cocci (*Staphylococcus aureus* and enterococci), and fungi (predominantly *Candida* species).[5] Bloodstream infection increases the risk of death and serious morbidity in very preterm babies,[6,7] and is associated with long-term adverse neurodevelopmental outcomes.[8,9]

Use of antimicrobial-impregnated CVCs is recommended in US and UK national guidelines for patients at high risk of infection.[10,11] A randomised trial involving 1485 children (aged 1 week to 18 years) receiving paediatric intensive care in the UK showed that use of antimicrobial-impregnated CVCs versus standard (non-impregnated) CVCs reduced bloodstream infection.[12] However, there are no recommendations for newborn babies because few antimicrobial-impregnated catheters are narrow enough for preterm babies and there is a paucity of evidence from adequately powered randomised trials.[13,14] The PREVAIL trial aimed to address this evidence gap by determining the effectiveness of an antimicrobial-impregnated CVC licensed for newborn infants. We compared use of a miconazole and rifampicin-impregnated CVC with a standard (non-impregnated) CVC for reduction of bloodstream infection, morbidity, and mortality in newborn babies receiving intensive care.

For more on the **PREVAIL trial** see http://prevailtrial.org.uk/

Methods

Study design and participants

This open-label, parallel-group, pragmatic, randomised controlled trial was done in 18 neonatal units in England. Full details of the amended trial protocol (version 5.0; published April 26, 2017), research ethics approval (from Yorkshire and the Humber—Sheffield—Health Research Authority reference no 14-YH-1202), and statistical analysis plan are available online.

All babies requiring a narrow-gauge (French gauge 1) peripherally inserted CVC (PICC) were eligible to participate. The reason for insertion was not requested by the trial team, but PICCs are usually used for parenteral nutrition and drug administration—70% of babies in neonatal units born before 32 weeks of gestation have a PICC inserted (Fraser C, National Neonatal Research Database, England, personal communication). Babies who had previously entered this trial and those who had a known allergy or hypersensitivity to rifampicin or miconazole were excluded.

The parent or legal representative of the baby gave written informed consent for inclusion in the trial.

Randomisation and masking

Participants were randomly assigned (1:1) to receive either an antimicrobial-impregnated PICC or a standard PICC, by use of a secure web-based randomisation programme by the principal investigator or a delegated other individual at the site. Enrolment was done by the principal investigator or a delegated other individual at the site. The randomisation programme was centrally controlled by the Clinical Trials Research Centre (University of Liverpool, Liverpool, UK) to ensure allocation concealment. Randomisation sequences were computer-generated by an independent statistician in random blocks of two and four and stratified by site. Masking of clinicians to PICC allocation was impractical because rifampicin caused brown staining of the antimicrobial-impregnated PICC. However, participant inclusion in analyses and occurrence of outcome events were determined by following an analysis plan that was specified before individuals saw unblinded data.

Procedures

Trial participants were randomly allocated to receive either a miconazole and rifampicin-impregnated PICC (Premistar; Vygon, Swindon, UK) or standard (non-impregnated) PICC (Premicath; Vygon).

PICC insertion was done according to standard unit policy and practice. Miconazole is an anti-fungal agent, which is effective against systemic fungal infection. Rifampicin is an antibacterial agent that has been previously evaluated in rifampicin and minocycline CVC impregnation in adults and children. Vygon reported continuing elution from the CVC impregnated with rifampicin and miconazole over 21 days.[15] The antimicrobial-impregnated PICC was marketed after appropriate certification under the Conformité Européenne process in December, 2012 (certificate number Z/12/02895).

The allocated PICC was inserted within 48 h of random assignment, and thereafter a standard PICC was used. Infection outcomes were captured for all babies until 48 h after PICC removal or following the last unsuccessful PICC insertion or random assignment (if insertion was not attempted). Follow-up for secondary clinical outcomes continued until the infant was discharged to go home, death, or 6 months after randomisation, whichever occurred first. Follow-up for all deaths continued until 6 months after randomisation.

Outcomes

The primary outcome was the time from random allocation to first bloodstream or cerebrospinal fluid (CSF) infection, defined as a microbiological culture of a bacteria or fungus from the blood or CSF sampled for clinical reasons. We use the term bloodstream infection to mean this combined outcome. The time window for sampling for primary and secondary outcomes was 24 h after randomisation until 48 h after PICC removal or death (or 48 h after randomisation if PICC not inserted). We imposed a-priori decision rules to avoid counting pre-existing bloodstream infection. We excluded microbial cultures within the assessment time window if the same organism was isolated from blood or CSF and samples were taken less than 14 days apart, or if a different organism was isolated and samples were less than 24 h apart. Multiple infection episodes within the time window were considered as distinct infection episodes if positive samples for each episode involved the same organism and occurred more than 14 days apart or involved different organisms and occurred more than 24 h apart.

Secondary outcomes related to infection were as follows: the type of organism isolated from bloodstream infection meeting primary outcome criteria, the rate of bloodstream infection (including recurrent bloodstream infection) per 1000 days with PICC, occurrence of one or more bloodstream infections, rate of catheter-related bloodstream infection (defined by isolation of the same organism from the PICC tip and blood or CSF) per 1000 days with PICC, rifampicin resistance in any isolate from blood or CSF culture, rifampicin resistance in any isolate from PICC tips, and rifampicin resistance in any isolate from blood or CSF culture or from the PICC tip (this was added as an additional analysis in version 2.0 of the statistical analysis plan, which was approved on March 7, 2018, before database lock [study closure]).

Outcomes measured to detect potential biases in sampling or treatment on the basis of knowledge of PICC allocation were as follows: rate of blood or CSF culture sampling per 1000 days with PICC, duration of antimicrobial exposure from randomisation up to 48 h after line removal, and time to PICC removal.

Clinical secondary outcomes were as follows: chronic lung disease, defined as requiring respiratory support (mechanical ventilation or continuous positive pressure via endotracheal tube or nasal tube) or supplemental oxygen at 36 weeks' postmenstrual age, necrotising enterocolitis (Bell stage 2 or 3), treatment for retinopathy of prematurity (medical or surgical), abnormalities on cranial ultrasound (periventricular leukomalacia or intracranial haemorrhage; worst grade of 1 to 4 used in analyses), time from random allocation to full milk feeds (150 mL/kg per day), total duration of parenteral nutrition from random allocation until discharge from neonatal care, and death before discharge to go home from neonatal care.

Death within 6 months of randomisation and time to death were recorded from linked death registration data. We recorded occurrence of related adverse events for all babies who had a PICC successfully inserted until 48 h after PICC removal. For all babies who had a PICC successfully inserted, we recorded occurrence of any expected or unexpected adverse events considered to be related to the PICC until 48 h after PICC removal.

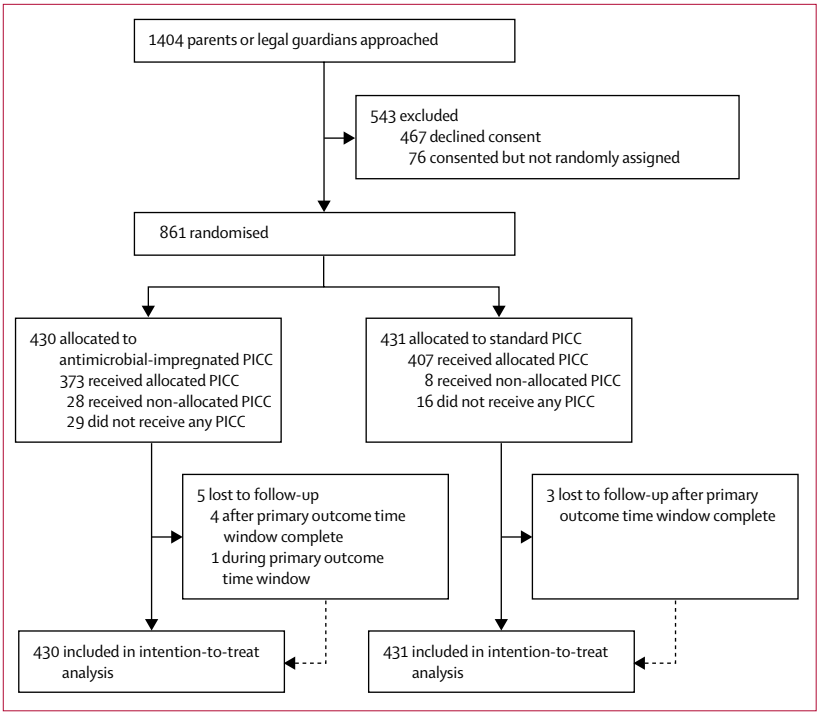


Figure 1: **Trial profile**
PICC=peripherally inserted central venous catheter.

Statistical analysis

The sample size calculation for the primary outcome was based on the log-rank test for equality of survival curves, with a 5% significance level and 90% power to detect a difference between the treatment groups. We considered a 50% reduction in bloodstream infection to be conservative, given the results of a network meta-analysis by Wang and colleagues[16] of catheter-related bloodstream infections (mean odds ratio 0·18, upper 95% CI 0·34), and the results of the CATCH trial.[10] To detect a reduction in the proportion of babies with a bloodstream infection from 14% in the standard CVC group, which was expected based on audit data from three participating neonatal units, to 7% in the antimicrobial-impregnated CVC group, 79 events were required from 816 babies (408 in each group); allowing for 5% loss to follow-up, we planned to recruit 858 neonates in total.

We analysed the primary outcome and secondary survival outcomes with the log-rank test. We used Kaplan-Meier curves to present the numbers at risk and Cox regression to calculate hazard ratios (HRs). We analysed binary outcomes with Fisher's exact test and presented relative risks (RRs) with 95% CIs. We analysed continuous outcomes with the Mann-Whitney *U* test and presented medians with IQRs for each group. We analysed rate outcomes using Poisson regression and presented rate ratios with 95% CIs. Descriptive results only are presented for the type of organisms isolated from bloodstream infections, related adverse events, and serious adverse events.

We analysed outcome data according to the intention-to-treat principle. Babies who were randomly assigned but had no PICC inserted were assessed for infection-related outcomes until 48 h after the last attempted insertion or 48 h after randomisation. We excluded babies for whom a PICC was not inserted from safety analyses, as these analyses were undertaken with groups defined by the PICC used.

All statistical tests were two-sided, with a 5% significance level. All analyses were done with SAS software, version 9.4. Results from the primary outcome and safety analyses were validated by independent programming by another independent statistician from the point of raw data.

We did four prespecified sensitivity analyses of the primary outcome as follows: time to serious bloodstream infection, defined as treatment with antimicrobials for 72 h or longer or death during treatment; time from PICC insertion to first bloodstream infection; time to first bloodstream infection, excluding samples obtained via arterial cannulas or CVCs; and time to first bloodstream infection, including clearly pathogenic organisms and excluding skin organisms (eg, coagulase-negative staphylococci). For comparability with published studies we also reported bloodstream infection rates per 1000 days with PICC between randomisation and PICC removal.

After seeing the results of the primary analysis, we specified an additional post-hoc analysis of the primary outcome to investigate whether the treatment effect varied by gestational age at birth (before 28 weeks of gestation or at 28 weeks or more of gestation) using a Cox proportional hazards model, including an interaction between treatment and gestational age.

The study was monitored by an independent Data Monitoring Committee who made recommendations to the Trial Steering Committee. An internal pilot study was done to show the feasibility of recruitment after the first 6 months and an interim analysis of the primary outcome was done after around half of the babies had been randomly assigned.

The trial is registered with ISRCTN, number 81931394.

Role of the funding source

The funder appointed independent members to the Trial Steering Committee and Data Monitoring Committee, approved all protocol amendments, and monitored study progress against agreed milestones. The funder had no involvement in data interpretation or writing of the report. The corresponding author had full access to all outputs from the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 12, 2015, and Jan 11, 2017, we randomly assigned 861 babies to receive an antimicrobial-impregnated PICC (430 babies) or standard PICC (431 babies) (figure 1). Parents of 487 babies who received

	Antimicrobial-impregnated PICC (n=430)	Standard PICC (n=431)
Baseline characteristics		
Sex		
Male	214 (50%)	225 (52%)
Female	216 (50%)	206 (48%)
Birthweight (g)	962·5 (729–1220)	960·0 (770–1250)
<750	119 (28%)	92 (21%)
750 to <1000	110 (26%)	140 (32%)
1000 to <1250	102 (24%)	91 (21%)
1250 to <1500	52 (12%)	62 (14%)
1500 to <1750	27 (6%)	27 (6%)
1750 to <2000	8 (2%)	7 (2%)
≥2000	12 (3%)	12 (3%)
Gestational age at birth (weeks)	27·90 (25·78–29·94)	28·06 (26·23–30·14)
<26	115 (27%)	93 (22%)
26 to <28	101 (23%)	110 (26%)
28 to <30	103 (24%)	102 (24%)
30 to <32	54 (13%)	76 (18%)
32 to <34	28 (7%)	15 (3%)
34 to <36	7 (2%)	9 (2%)
36 to <38	5 (1%)	3 (1%)
≥38	7 (2%)	11 (3%)
Missing	10 (2%)	12 (3%)
<32	373 (87%)	381 (88%)
Major congenital anomaly		
Yes	21 (5%)	27 (6%)
No	408 (95%)	404 (94%)
Missing data	1 (<1%)	0
Age (days)	4·12 (2·04–5·93)	3·90 (1·90–6·12)
<2	106 (25%)	113 (26%)
2 to <7	256 (60%)	240 (56%)
7 to <14	39 (9%)	52 (12%)
14 to <21	6 (1%)	11 (3%)
21 to <28	3 (1%)	5 (1%)
≥28	20 (5%)	10 (2%)
Apgar score at 5 min		
0–3	23 (5%)	19 (4%)
4–7	138 (32%)	140 (32%)
8–10	247 (57%)	249 (58%)
Missing data	22 (5%)	23 (5%)
Delivery characteristics		
Location of birth		
Born in study hospital	340 (79%)	367 (85%)
Transferred after birth	90 (21%)	64 (15%)
Mode of delivery		
Vaginal	196 (46%)	198 (46%)
Caesarean	234 (54%)	233 (54%)
Membrane rupture >24 h before delivery		
Yes	111 (26%)	104 (24%)
No	299 (70%)	310 (72%)
Missing data	20 (5%)	17 (4%)
Maternal antenatal corticosteroids		
Yes	375 (87%)	381 (88%)
No	53 (12%)	50 (12%)
Missing data	2 (<1%)	0
Maternal antibiotics ≤12 h before delivery		
Yes	135 (31%)	102 (24%)
No	275 (64%)	310 (72%)
Missing data	20 (5%)	19 (4%)
Neonatal care		
Surgery before randomisation		
>6 days before	2 (<1%)	3 (1%)
≤6 days before	15 (3%)	10 (2%)
No surgery	413 (96%)	418 (97%)
Positive blood culture <72 h before randomisation		
Yes	29 (7%)	19 (4%)
No	401 (93%)	412 (96%)
Antibiotics or antifungals <72 h before randomisation (excluding prophylaxis)		
Yes	367 (85%)	363 (84%)
No	63 (15%)	68 (16%)
Respiratory support <72 h before randomisation		
Invasive ventilation	262 (61%)	257 (60%)
Non-invasive ventilation	122 (28%)	133 (31%)
Oxygen only	9 (2%)	7 (2%)
None	37 (9%)	34 (8%)
Devices in situ at randomisation		
<4	370 (86%)	390 (90%)
≥4	60 (14%)	41 (10%)
Randomly assigned PICC		
PICC insertion site		
No PICC inserted	29 (7%)	16 (4%)
Lower limb	207 (48%)	220 (51%)
Upper limb	191 (44%)	190 (44%)
Scalp	3 (1%)	3 (1%)
Other	0	1 (<1%)
Missing	0	1 (<1%)

Data are n (%) or median (IQR). PICC=peripherally inserted central venous catheter.

Table 1: **Baseline characteristics, clinical condition at randomisation, and details of the intervention according to random PICC allocation**

a PICC (French gauge 1) and who would have been eligible for inclusion in the study were not approached for consent (appendix). Recruitment ended earlier than planned (Jan 11, 2017) because the recruitment target was met. Clinical follow-up continued until May 30, 2017.

715 (83%) of 861 babies were enrolled in the trial before 7 days of age and 754 (88%) were born before 32 weeks of gestation (table 1). Slightly more babies randomised to

	Antimicrobial-impregnated PICC (n=430)	Standard PICC (n=431)
PICC status		
Allocated PICC inserted	373 (87%)	407 (94%)
Non-allocated PICC inserted	28 (7%)	8 (2%)
No PICC inserted	29 (7%)	16 (4%)
PICC insertion attempted	17 (4%)	9 (2%)
PICC insertion not attempted	12 (3%)	7 (2%)
End of follow-up for outcomes that required samples		
48 h after PICC removal	387 (90%)	398 (92%)
Death with PICC in situ	13 (3%)	18 (4%)
48 h after randomisation	29 (7%)	15 (3%)
Lost to follow-up	1 (<1%)	0
End of follow-up for outcomes that did not require samples		
Discharge to home from neonatal care	383 (89%)	385 (89%)
Transfer to non-participating site	4 (1%)	3 (1%)
Death before discharge	36 (8%)	33 (8%)
6 months after randomisation	6 (1%)	10 (2%)

Data are n (%). PICC=peripherally inserted central venous catheter.

Table 2: **PICC insertion status and endpoint of follow-up**

	Antimicrobial-impregnated PICC (n=430)		Standard PICC (n=431)	
	Total samples or babies with positive culture	Babies sampled or with positive culture tested	Total samples or babies with positive culture	Babies sampled or with positive culture tested
Culture samples taken*				
Blood or CSF	379	198 (46%)	329	190 (44%)
Peripheral venous blood	321	183 (43%)	268	178 (41%)
CSF	40	33 (8%)	38	34 (8%)
Other	18	16 (4%)	23	20 (5%)
PICC tip	314	313 (73%)	310	310 (72%)
Babies with rifampicin resistance tested in positive cultures†				
Blood or CSF	48	21 (44%)	46	25 (54%)
Peripheral venous blood	44	21 (48%)	42	23 (55%)
CSF	0	0	3	1 (33%)
Other	5	0	3	2 (67%)
PICC tip	47	32 (68%)	90	61 (68%)

PICC=peripherally inserted central venous catheter. CSF=cerebrospinal fluid. *Data are total samples taken (n) and the babies from whom samples were taken (n [%]) as a proportion of the total number of babies with antimicrobial-impregnated PICCs or standard PICC. †Data are total babies with positive culture (n) and the proportion of babies with at least one positive culture tested (n [%]).

Table 3: **Sampling for primary and secondary endpoints**

the antimicrobial-impregnated PICC group did not have the allocated PICC inserted (table 2). Endpoints for follow-up are shown in tables 2, 3.

The time from random allocation to first bloodstream or CSF infection was similar between the two groups (HR 1·11, 95% CI 0·73–1·67; table 4, figure 2). The Kaplan-Meier curves crossed when the numbers at risk were low. A time varying coefficient was added to the model to check the assumption of proportional hazards, and this was not significant (p=0·62; data not shown). We observed similar results to our primary outcome findings in our sensitivity analyses (table 4).

We found no evidence of a difference in treatment effect for babies with a gestational age of less than 28 weeks compared with 28 weeks or more (p=0·28; appendix). 46 (11%) of 430 babies in the antimicrobial-impregnated PICC group had one or more bloodstream infections, and three (7%) of these babies had two infection episodes. 44 (10%) of 431 babies in the standard PICC group had one or more bloodstream infections, and one (2%) of these had a second infection episode.

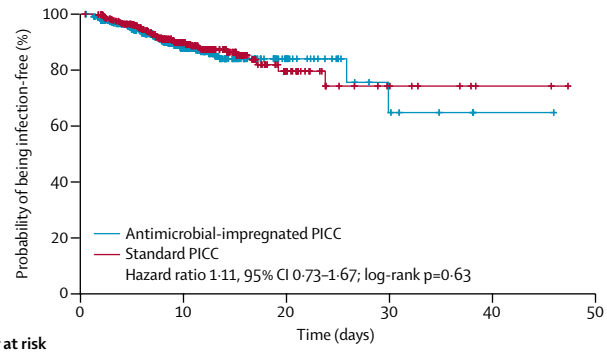
Secondary infection-related outcomes were similar between the trial groups, with the exception of rifampicin resistance from PICC tip cultures (RR 3·51, 95% CI 1·16–10·57; p=0·018). We found no significant difference when comparing the two groups for rifampicin resistance from blood, CSF, or PICC tip cultures combined (RR 1·80, 0·84–3·86; p=0·13; table 4). We noted the organisms isolated during the primary outcome time window, which were predominantly coagulase-negative staphylococci in both trial groups (appendix). We also recorded rifampicin-resistant isolates by type of organism (appendix). Measures of blood or CSF sampling are shown in table 4. Fewer than half of the babies in each trial group had one or more blood or CSF samples taken (table 3). The rate of blood sampling for suspected infection was significantly higher in the antimicrobial-impregnated PICC group than in the standard PICC group (97·90 per 1000 days with antimicrobial-impregnated PICC *vs* 79·64 per 1000 days with standard PICC; rate ratio 1·23, 95% CI 1·05–1·45; p=0·012; table 4). We found no significant differences in the median time to PICC removal (8·20 days [IQR 4·77–12·13] in the antimicrobial-impregnated PICC group *vs* 7·86 days [5·00–12·53] days in the standard PICC group; HR 1·03, 95% CI 0·89–1·18, p=0·73) or in the median duration of antimicrobial treatment (3 days [IQR 2–6] in both groups; p=0·25; table 4). We found no significant differences in any clinical outcomes measured at discharge from the neonatal unit or in mortality within 6 months of randomisation (table 4).

We recorded summary data of the most frequent adverse events (table 5). 60 events were reported from 49 (13%) babies in the antimicrobial-impregnated PICC group and 50 events were reported from 45 (10%) babies in the standard PICC group. One serious adverse event involving supraventricular tachycardia following PICC placement was reported in the antimicrobial-impregnated PICC group.

	Antimicrobial-impregnated PICC (n=430)	Standard PICC (n=431)	HR (95% CI), rate ratio (95% CI), or RR (95% CI)*	p value
Primary outcome				
Time to first bloodstream infection†	46 (11%)	44 (10%)	1·11 (0·73–1·67)	0·63
Sensitivity analyses				
Assessed for time to first clinically serious bloodstream infection	42 (10%)	40 (9%)	1·11 (0·72–1·71)	0·65
Assessed for time to first bloodstream infection (from insertion)	45 (10%)	44 (10%)	1·08 (0·71–1·64)	0·72
Assessed for time to first bloodstream infection, excluding arterial or PICC samples	45 (10%)	43 (10%)	1·11 (0·73–1·68)	0·64
Assessed for time to first bloodstream infection, excluding skin organisms	16 (4%)	9 (2%)	1·90 (0·84–4·31)	0·12
Secondary outcomes				
Rate of bloodstream infection, per 1000 days with PICC	13·15	10·87	1·21 (0·78–1·88)	0·40
Sensitivity analysis				
Rate of bloodstream infection (when line is in situ), per 1000 days with PICC‡	12·57	11·21	1·12 (0·73–1·12)	0·60
Rate of catheter-related bloodstream infection, per 1000 days with PICC	1·84	2·35	0·78 (0·27–2·25)	0·65
Sensitivity analysis				
Rate of catheter-related bloodstream infection (when line is in situ), per 1000 days with PICC‡	1·71	2·46	0·70 (0·25–1·96)	0·49
Rate of blood or CSF culture sampling, per 1000 days with PICC	97·90	79·64	1·23 (1·05–1·45)	0·012
Sensitivity analysis				
Rate of blood or CSF sampling (line in situ), per 1000 days with PICC‡	93·72	82·01	1·14 (0·98–1·34)	0·095
Occurrence of one or more bloodstream infections	46 (11%)	44 (10%)	1·05 (0·71–1·55)	0·82
Rifampicin resistance from blood or CSF culture	4 (1%)	7 (2%)	0·57 (0·17–1·94)	0·55
Rifampicin resistance from PICC tip culture	14 (3%)	4 (1%)	3·51 (1·16–10·57)	0·018
Rifampicin resistance from blood or CSF or PICC tip culture§	18 (4%)	10 (2%)	1·80 (0·84–3·86)	0·13
Chronic lung disease	190 (44%)	178 (41%)	1·07 (0·92–1·25)	0·41
Necrotising enterocolitis (Bell stage 2 or 3)	41 (10%)	46 (11%)	0·89 (0·59–1·32)	0·57
Treatment for retinopathy of prematurity	40 (9%)	30 (7%)	1·34 (0·85–2·11)	0·21
Abnormality on cranial ultrasound	166 (39%)	150 (35%)	1·11 (0·93–1·33)	0·26
Death before discharge	36 (8%)	33 (7%)	1·09 (0·70–1·72)	0·71
Death within 6 months of randomisation	36 (8%)	35 (8%)	1·03 (0·66–1·61)	0·90
Time to PICC removal, days‡	8·20 (4·77–12·13)	7·86 (5·00–12·53)	1·03 (0·89–1·18)	0·73
Time to full milk feeds, days	9·51 (6·37–17·26)	9·40 (6·32–16·37)	0·99 (0·86–1·14)	0·85
Time to death within 6 months of randomisation†	NA	NA	1·06 (0·67–1·70)	0·79
Antimicrobial treatment, days	3·00 (2·00–6·00)	3·00 (2·00–6·00)	NA	0·25
Parenteral nutrition, days	11·00 (7·00–19·00)	10·00 (7·00–18·00)	NA	0·83

Data are n (%) or median (IQR), unless otherwise indicated. For all outcomes that relate to samples, events were only considered on samples taken between 24 h after randomisation until 48 h after removal. PICC=peripherally inserted central venous catheter. HR=hazard ratio. RR=relative risk. CSF=cerebrospinal fluid. NA=not applicable. *HRs (95% CIs) are given for primary outcome data and time to event data; rate ratios (95% CIs) are given for secondary outcomes pertaining to rate data; and RRs (95% CIs) are given for all other data. †Median time to event not reported as not enough babies had an event. ‡Only includes babies where PICC was successfully inserted (antimicrobial-impregnated PICC: 401 babies; standard PICC: 415 babies). §Outcome not prespecified in protocol but requested by investigators and included in statistical analysis plan before any unmasked data were seen.

Table 4: **Primary and secondary outcomes in babies randomised to antimicrobial or standard PICC (intention-to-treat analysis)**



Number at risk (number censored)						
Antimicrobial-impregnated PICC	430 (0)	179 (39)	26 (44)	6 (46)	1 (46)	0 (46)
Standard PICC	431 (0)	174 (34)	29 (43)	8 (44)	2 (44)	0 (44)

Figure 2: **Time to first bloodstream infection for newborn babies randomised to antimicrobial-impregnated PICC or standard PICC**
PICC=peripherally inserted central venous catheter.

	Antimicrobial-impregnated PICC (n=374)		Standard PICC (n=430)	
	Events	Babies	Events	Babies
Any adverse event	60	49 (13%)	50	45 (10%)
Evidence of catheter blockage	15	15 (4%)	15	15 (3%)
Extravasation	11	11 (3%)	11	11 (3%)
Swelling or haematoma at line site	10	10 (3%)	7	7 (2%)
Clinically evident thrombophlebitis	4	4 (1%)	7	7 (2%)
Difficulty removing stylet	8	8 (2%)	1	1 (<1%)
Catheter damage	3	3 (1%)	4	4 (1%)

Data are n or n (%). PICC=peripherally inserted central venous catheter.

Table 5: **Adverse events in babies with PICC inserted**

Discussion

We found no evidence of benefit or harm from miconazole and rifampicin-impregnated PICCs in babies receiving intensive care. The 95% CI for the primary outcome excluded a 27% reduction or 67% increase in the time to bloodstream infection associated with using an antimicrobial-impregnated PICC compared with a standard PICC, and similar results were found in the sensitivity analyses. We found no differences between the two groups for mortality at 6 months or clinical outcomes recorded at discharge home from the neonatal unit.

The strengths of the trial are the large sample size and the multicentre, nationally representative sample of babies admitted for neonatal intensive care, which was adequately powered to detect a halving of the bloodstream infection risk. As 754 (88%) babies participating in the trial were born before 32 weeks of gestation, this trial provides important new evidence for a group at high risk of infection, who have frequent use of PICCs, but for whom trial evidence is lacking.[13,14] The pragmatic trial design, with no additional sampling, and use of a primary outcome on the basis of positive cultures taken as part of clinical practice in response to suspected infection to guide antibiotic treatment, ensured relevance to routine practice. Although blood culture is relatively insensitive, we found no difference in clinical outcomes such as duration of antibiotics or PICC insertion.

We used central web-based randomisation to ensure allocation concealment, achieved almost complete follow-up and assessment of the primary outcome, adhered to a prespecified statistical analysis plan for intention-to-treat analyses, and halted recruitment once the sample size was achieved. Baseline characteristics were well balanced at randomisation. Slightly fewer babies in the antimicrobial-impregnated PICC group received the allocated PICC, probably because the randomly assigned PICC had to be inserted within 48 h; thereafter, the standard PICC was used. The proportion of babies in the standard PICC group with bloodstream infection (44 [10%] of 431 babies) was lower than expected (14%) but we had sufficient power to exclude a moderate reduction in the risk of bloodstream infection. We based the sample size and statistical analyses on the proportional hazards assumption. We checked this assumption and believe it is reasonably upheld, but acknowledge that there could be an impact on study power if this is not the case. This study was open label, so clinicians could distinguish the type of PICC. We found a slightly increased rate of blood culture sampling in the antimicrobial-impregnated PICC group, but the proportions of babies with at least one blood or CSF culture or any PICC tip culture were similar and there were no differences in the timing of PICC removal between trial groups.

A limitation of this study was the insufficient power to detect significant differences in rifampicin-resistant organisms isolated from blood or CSF cultures. The low number of resistant organisms was due to few positive cultures, and because only 44–54% of these cultures were tested for rifampicin resistance. The risk of rifampicin resistance in isolates from positive blood or CSF cultures did not differ between the trial groups but was significantly increased in positive tip cultures from antimicrobial-impregnated PICCs. Selection of rifampicin-resistant Gram-positive bacteria during treatment—if rifampicin is used as the sole antibacterial agent—is well recognised.[17] Emergence of resistant organisms was considered by the investigators, the Trial Steering Committee, and the Data Monitoring Committee, but the risk of adverse events arising was viewed as low because the restricted release of rifampicin from the catheter surface would be unlikely to affect bacteria at any site other than the catheter itself. Even if rifampicin-resistant Gram-positive bacteria did cause infection in an individual patient, routine antibiotic use would be unaffected because rifampicin is rarely used for treatment in the neonatal setting.

We found that miconazole and rifampicin impregnation did not reduce bloodstream infection in newborn babies. This result is consistent with findings from a randomised controlled trial in adults and a small randomised

controlled trial in newborn infants published as an abstract (appendix).[14,18,19] However, our findings contrast with evidence of reduced catheter-related bloodstream infection in adults and reductions in any bloodstream infection in children randomised to minocycline and rifampicin-impregnated CVCs versus standard CVCs.[10,20,21] Several explanations could account for these differences. First, miconazole and rifampicin might be less effective than minocycline and rifampicin impregnation. Miconazole is used to prevent invasive fungal infection in preterm babies, which is rare in the UK, but has a very high mortality.[8] Few babies in our trial had fungal bloodstream infection, consistent with a recent UK study.[22] However, rifampicin might be less effective when used as the sole antibacterial agent combined with miconazole. Rifampicin is more active against Gram-positive than against Gram-negative bacteria and has synergistic action against staphylococci when combined with another antibacterial drug—eg, minocycline—especially against methicillin-resistant strains.[17,23]

Second, although the combination of minocycline and rifampicin has been reported as the most effective type of antimicrobial impregnation in systematic reviews,[24,25] it is possible that minocycline and rifampicin-impregnated CVCs might not effectively reduce overall incidence of bloodstream infection or sepsis.[26] A network meta-analysis of seven randomised trials in adults showed beneficial effects of antimicrobial impregnation for catheter-related bloodstream infection,[25] but few trials have measured the effect on any bloodstream infection.[10] Catheter-related infection requires the same isolates from blood and CVC tip and could be prone to bias because of inhibition of positive tip cultures by leaching of antimicrobial from the tip during plating out for culture. Only the large CATCH trial[10] in children used any clinically indicated bloodstream infection as the primary outcome and found a 57% reduction in time to infection (appendix). A smaller trial[27] compared catheter-related bloodstream infection in children randomly assigned to minocycline and rifampicin-impregnated CVC or standard CVC and found no difference in the rate of catheter-acquired bloodstream infection, but detected few infection events (three in each group; appendix).[27] Third, reductions in infection rates in neonatal units associated with improved catheter asepsis practices and shorter duration of PICC use might have narrowed the potential for further benefits from antimicrobial impregnation.[28] PICCs also might not be an independent risk factor for infection in sick preterm babies because of their high susceptibility to infection from multiple sources, due to numerous invasive procedures and devices, gut permeability, and immune immaturity.[29]

Since 2012, the Premistar PICC has been the only antimicrobial-impregnated PICC available for preterm babies in Europe. Use of Premistar has been reported in Germany and Italy,[14] but, to our knowledge, use in the UK has been limited to the PREVAIL trial. The trial findings do not support the use of miconazole and rifampicin-impregnated PICCs in newborn infants, as we found no evidence that antimicrobial-impregnated PICCs reduced bloodstream infections and such PICCs are more expensive than standard PICCs. However, the serious life-long consequences of bloodstream infection mean that even interventions with relatively small effects might be clinically important. One in ten babies in the PREVAIL trial had a bloodstream infection and some might have serious life-long neurodevelopmental impairment or lung disease as a result. Therefore, more large trials are urgently needed to reduce the risks of bloodstream infection and their long-term consequences. Viewed against existing evidence on the effectiveness of rifampicin and minocycline-impregnated CVCs in adults and children, our findings have implications for the manufacturers of these devices and for clinicians. First, alternative types of antimicrobial-impregnated PICCs should be considered for evaluation in newborn babies, along with other interventions to prevent bloodstream infection in the neonatal intensive care unit. Second, further randomised controlled trials should be considered to determine whether previous evidence on the effectiveness of antibiotic-impregnated CVCs in adults is sustained in the context of effective infection control practices.

Contributors
All authors contributed to the design and conduct of the study. RG and SJO (co-chief investigators), MB, and CG conceived and designed the study, with input from AS, WM, and JD. CD, SJO, AS, JD, WM, and RG implemented the trial. NR and MB did the statistical analyses, overseen by CG. RG, MB, CF, WM, and SJO wrote the paper. All authors commented on the manuscript and approved the final version.

The PREVAIL trial team
Rachel Wane (Bradford Teaching Hospitals NHS Foundation Trust); Marie Hubbard, Rosalind Astles (University Hospitals of Leicester NHS Trust); Andrew K Ewer, Rachel Jackson (Birmingham Women's and Children's NHS Foundation Trust); Ranganath Ranganna, Nicola Booth (Manchester University NHS Foundation Trust); Phani Kiran Yajamanyam, Karen Harvey (Liverpool Women's NHS Foundation Trust); Narendra Aladangady, Asha Mathew (Homerton University Hospital NHS Foundation Trust); Elizabeth Pilling, Pauline Bayliss (Sheffield Teaching Hospitals NHS Foundation Trust); Natasha Maddock, Louise Woodhead (The Pennine Acute Hospitals NHS Trust); MaySze Chang, Imdad Ali, Ivone Lancoma-Malcolm (Barts Health NHS Trust); Sandeep Dharmaraj, Claire Lodge (Lancashire Teaching Hospitals NHS Foundation Trust); Helen Navarra (Nottingham University Hospitals NHS Trust); Charles Roehr, Sheula Barlow (Oxford University Hospitals NHS Foundation Trust); Mahesh Yadav, Claire Abbott (Bolton NHS Foundation Trust); Kathryn Johnson (The Leeds Teaching Hospitals NHS Trust); Dushyant Batra, Yvonne Hooton (Nottingham University Hospitals NHS Trust); Pamela Cairns, Jennifer Chapman (University Hospitals Bristol NHS Foundation Trust); Bal Krishnan Sharma, Helen Smith (Barking, Havering and Redbridge University Hospitals NHS Trust); Berit Muller-Pebody (Public Health England); Katie Harron (University College London); Tracy Moitt (Clinical Trials Research Centre, University of Liverpool).

Declaration of interests
We declare no competing interests.

Data sharing
Access to fully anonymised participant-level datasets and a data dictionary can be made available by applying to the Clinical Trials

Research Centre, who will liaise with the investigators to approve the proposal and ensure that a signed data access agreement is in place before data are released.

Acknowledgments

We thank the children and families who participated in the PREVAIL trial. We thank the Trial Steering Committee (Mike Sharland [chair], Edmund Juszczak, Win Tin, and Stephanie Chadwick) and the Independent Data Safety and Monitoring Committee (Nicholas Embleton [chair], Alison Balfour, and Louise Stanton) for their oversight of the study. The trial was funded by the UK National Institute for Health Research Health Technology Assessment (NIHR HTA) programme (project number 12/167/02).

References

1 Machado JD, Suen VM, Figueiredo JF, Marchini JS. Biofilms, infection, and parenteral nutrition therapy *JPEN J Parenter Enteral Nutr* 2009; **33:** 397–403.

2 Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. *Lancet* 2001; **358:** 135–38.

3 Garland JS, Alex CP, Sevallius JM, et al. Cohort study of the pathogenesis and molecular epidemiology of catheter-related bloodstream infection in neonates with peripherally inserted central venous catheters. *Infect Control Hosp Epidemiol* 2008; **29:** 243–49.

4 Wong J, Dow K, Shah PS, Andrews W, Lee S. Percutaneously placed central venous catheter-related sepsis in Canadian neonatal intensive care units. *Am J Perinatol* 2012; **29:** 629–34.

5 Stoll BJ, Hansen N, Fanaroff AA, et al. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. *Pediatrics* 2002; **110:** 285–91.

6 Piening BC, Geffers C, Gastmeier P, Schwab F. Pathogen-specific mortality in very low birth weight infants with primary bloodstream infection. *PLoS One* 2017; **12:** e0180134.

7 Stoll BJ, Gordon T, Korones SB, et al. Late-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. *J Pediatr* 1996; **129:** 63–71.

8 Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. *JAMA* 2004; **292:** 2357–65.

9 Mitha A, Foix-L'Hélias L, Arnaud C, et al. Neonatal infection and 5-year neurodevelopmental outcome of very preterm infants. *Pediatrics* 2013; **132:** e372–80.

10 O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control* 2011; **39** (4 suppl 1): S1–34.

11 Loveday HP, Wilson JA, Pratt RJ, et al. epic3: national evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. *J Hosp Infect* 2014; **86** (suppl 1): S1–70.

12 Gilbert RE, Mok Q, Dwan K, et al. Impregnated central venous catheters for prevention of bloodstream infection in children (the CATCH trial): a randomised controlled trial. *Lancet* 2016; **387:** 1732–42.

13 Balain M, Oddie SJ, McGuire W. Antimicrobial-impregnated central venous catheters for prevention of catheter-related bloodstream infection in newborn infants. *Cochrane Database Syst Rev* 2015; **9:** CD011078.

14 Flemmer A, De Maio N, Schubert S, et al. A randomized controlled trial to evaluate antibiotic impregnated percutaneously introduced central (PIC-) lines in preterm infants. *Eur J Pediatr* 2016; **175:** 1477.

15 Rump AF, Güttler K, König DP, Yücel N, Korenkov M, Schierholz JM. Pharmacokinetics of the antimicrobial agents rifampicin and miconazole released from a loaded central venous catheter. *J Hosp Infect* 2003; **53:** 129–35.

16 Wang H, Huang T, Jing J, et al. Effectiveness of different central venous catheters for catheter-related infections: a network meta-analysis. *J Hosp Infect* 2010; **76:** 1–11.

17 Rothstein DM. Rifamycins, alone and in combination. *Cold Spring Harb Perspect Med* 2016; **6:** a027011.

18 Yücel N, Lefering R, Maegele M, et al. Reduced colonization and infection with miconazole-rifampicin modified central venous catheters: a randomized controlled clinical trial. *J Antimicrob Chemother* 2004; **54:** 1109–15.

19 Fraenkel D, Rickard C, Thomas P, Faoagali J, George N, Ware R. A prospective, randomized trial of rifampicin-minocycline-coated and silver-platinum-carbon-impregnated central venous catheters. *Crit Care Med* 2006; **34:** 668–75.

20 Kramer RD, Rogers MA, Conte M, Mann J, Saint S, Chopra V. Are antimicrobial peripherally inserted central catheters associated with reduction in central line-associated bloodstream infection? A systematic review and meta-analysis. *Am J Infect Control* 2017; **45:** 108–14.

21 Wu G, Chen Z, Sun Y, Xiao S, Xia Z. Impregnated central venous catheters in children: a systematic review of randomized controlled trials. *Intensive Care Med* 2017; **43:** 1159–61.

22 Cailes B, Kortsalioudaki C, Buttery J, et al. Antimicrobial resistance in UK neonatal units: neonIN infection surveillance network. *Arch Dis Child Fetal Neonatal Ed* 2018; **103:** F474–78.

23 Segreti J, Gvazdinskas LC, Trenholme GM. In vitro activity of minocycline and rifampin against staphylococci. *Diagn Microbiol Infect Dis* 1989; **12:** 253–55.

24 Lai NM, Chaiyakunapruk N, Lai NA, O'Riordan E, Pau WS, Saint S. Catheter impregnation, coating or bonding for reducing central venous catheter-related infections in adults. *Cochrane Database Syst Rev* 2016; **3:** CD007878.

25 Chong HY, Lai NM, Apisarnthanarak A, Chaiyakunapruk N. Comparative efficacy of antimicrobial central venous catheters in reducing catheter-related bloodstream infections in adults: abridged Cochrane systematic review and network meta-analysis. *Clin Infect Dis* 2017; **64** (suppl 2)**:** S131–40.

26 Niël-Weise BS, Stijnen T, van den Broek PJ. Anti-infective-treated central venous catheters: a systematic review of randomized controlled trials. *Intensive Care Med* 2007; **33:** 2058–68.

27 Cox EG, Knoderer CA, Jennings A, et al. A randomized, controlled trial of catheter-related infectious event rates using antibiotic-impregnated catheters versus conventional catheters in pediatric cardiovascular surgery patients. *J Pediatric Infect Dis Soc* 2013; **2:** 67–70.

28 Payne V, Hall M, Prieto J, Johnson M. Care bundles to reduce central line-associated bloodstream infections in the neonatal unit: a systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2018; **103:** F422–29.

29 Wynn JL, Levy O. Role of innate host defenses in susceptibility to early-onset neonatal sepsis. *Clin Perinatol* 2010; **37:** 307–37.