**Title:** Antimicrobial impregnated central venous catheters for preventing neonatal bloodstream infection: pragmatic, randomised controlled trial (The PREVAIL Trial)

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\*Names and contributions of PREVAIL team given in acknowledgements

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# Summary

**Background**: Bloodstream infection is associated with high rates of mortality and serious morbidity in preterm babies. Evidence from clinical trials shows that antimicrobial-impregnated central venous catheters reduce catheter-related bloodstream infection in adults and children receiving intensive care but evidence from clinical trials is lacking for babies receiving neonatal intensive care.

**Methods:**

This open-label randomised controlled trial was conducted in 18 UK neonatal intensive care units. Newborn babies who needed a peripherally inserted central venous catheter (PICC) were allocated randomly (1:1) to receive either a PICC impregnated with antimicrobials miconazole and rifampicin or a standard (non-impregnated) PICC catheter. We used web-based randomisation stratified for unit. The primary outcome was time to the first microbiologically-confirmed bloodstream or cerebro-spinal fluid (CSF) infection between 24 hours after randomisation and 48 hours after catheter removal or death (International Standard Randomised Controlled Trial Number 81931394).

**Findings**:

We randomised 861 babies (antimicrobial 430; standard 431) over 17 months from August 2015. 754 (87.6%) participants were born before 32 weeks’ gestation. Median time to PICC removal was 8.20 (IQR 4.77-12.13) and 7.86 (IQR 5.00-12.53) days with 46 (10.7%) and 44 (10.2%) babies randomised to miconazole-rifampicin and standard PICCs respectively having a microbiologically-confirmed bloodstream or CSF infection. We did not show a difference in time to infection (hazard ratio 1.11; 95% confidence interval [CI] 0.73, 1.67). 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 did not differ significantly between groups, although rifampicin resistance in positive cultures of PICC tips was higher in the antibiotic group (RR 3.51; 1.16, 10.57). Adverse events were similarly low in both groups.

**Interpretation**: We found no evidence of benefit or harm associated with miconazole-rifampicin impregnated PICCs compared with standard PICCs for newborn babies. Further 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 (12/167/02).

# 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 protective biofilm protecting them from circulating antimicrobial agents and enabling sustained colonisation.2 CVC removal is often needed to clear the infection.

Catheter-related bloodstream infection is reported to occur in up to 30% of neonates, with the highest rates in babies born very preterm (before 32 weeks’ gestation).3,4 The organisms isolated most frequently in preterm babies are coagulase‐negative staphylococci, Gram‐negative bacilli, other Gram‐positive cocci (*Staphylococcus aureus*, 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. A recent large randomised controlled trial involving 1,485 children receiving intensive care in the UK showed that use of antimicrobial-impregnated compared with standard (non-impregnated) CVCsreduced bloodstream infection .1011,12 No recommendations exist, however, for newborn babies due to the lack of antimicrobial-impregnated catheters suitable for preterm babies and lack of evidence from adequately powered randomised trials .13,14 The PREVAIL trial aimed to address thisevidence gapby determining the effectiveness of an antimicrobial-impregnated CVC licensed for newborn infants. We compared use of a miconazole-rifampicin impregnated CVC (Premicath 1 French gauge, Vygon, Swindon, UK) with a standard (non-impregnated) CVC for reducing bloodstream infection, morbidity and mortality in babies receiving intensive care.

# Methods

## Study design and participants

This open-label, 2-arm parallel-group randomised controlled trial was conducted in 18 neonatal units in England. The Research Ethics Committee approval (reference 14-YH-1202), protocol and statistical analysis plan are available online (http://prevailtrial.org.uk/). Local approval and site-specific assessments were obtained from NHS Trusts for trial sites. There were amendments to the trial protocol during the trial. Full details of these changes can be found in the final trial protocol (Version 5.0 (26/04/2017).

All babies requiring a narrow-gauge peripherally inserted central venous catheter (PICC) were eligible to participate (details in Protocol, in supplementary material).. The reason for insertion was not requested, 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 (unpublished data, National Neonatal Research Database, England).

## Randomisation and masking

Participants were randomised to either an antimicrobial-impregnated or a standard PICC using a secure web based randomisation programme by the PI or delegated other at site, this was controlled centrally by the Clinical Trials Research Centre (University of Liverpool) to ensure allocation concealment. Randomisation sequences were computer-generated by an independent statistician in random blocks of two and four, stratified by site. It was impractical to mask clinicians to PICC allocation because rifampicin caused brown staining of the antimicrobial impregnated PICC. Participant inclusion in analyses and occurrence of outcome events were determined blind to the randomised allocation.

## Procedures

The allocated PICC was inserted within 48 hours of randomisation, thereafter a standard PICC was used. Infection outcomes were captured for all babies until 48 hours after PICC removal or following the last unsuccessful PICC insertion or randomisation (if insertion was not attempted). Follow up for secondary clinical outcomes continued until discharge home, death or 6 months after randomisation, whichever occurred soonest. Follow up for all deaths continued until 6 months after randomisation.

Trial participants were allocated to receive either a:

• miconazole-rifampicin impregnated PICC (PremistarTM, Vygon, Swindon, UK)

• or standard (non-impregnated) PICC (PremicathTM, Vygon, Swindon, UK)

PICC insertion was according to standard unit policy and practice. Miconazole is an anti-fungal agent, which is effective against systemic fungal infection.8 Rifampicin is an antibacterial agent previously evaluated as rifampicin–minocycline CVC impregnation in adults and children (see panel). The manufacturer, Vygon, reported continuing elution from the CVC of rifampicin and miconazole over 21 days.15 The antimicrobial impregnated PICC was marketed after appropriate certification under the Conformité Européenne (CE) process in December 2012 (Certificate number Z/12/02895).

## Outcomes

The primary outcome was time from randomisation to first bloodstream or cerebro-spinal fluid (CSF) infection defined as a microbiologcal culture of a bacteria or fungus from bloodor CSF sampled for clinical reasons. We use the term bloodstream infection (BSI) to mean this combined outcome. The time window for sampling for primary and secondary outcomes was 24 hours post randomisation until 48 hours after PICC removal or death (or 48 hours 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 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 hours 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 hours apart.

Secondary outcomes related to infection were:

1. type of organism isolated from bloodstream infection meeting primary outcome criteria
2. rate of bloodstream infection (including recurrent bloodstream infection) per 1000 PICC days
3. occurrence of 1 or more bloodstream infections
4. rate of catheter-related bloodstream infection (defined by isolation of the same organism from the PICC tip and blood or CSF) per 1000 PICC days
5. rifampicin resistance in any isolate from blood or CSF culture
6. rifampicin resistance in any isolate from PICC tips
7. rifampicin resistance in any isolate from blood or CSF culture or from the PICC tip (this outcome, combining outcomes v) and vi) was added after study close by the chief investigators, prior to seeing any unblinded data).

Outcomes measured to detect potential biases in sampling or treatment based on knowledge of PICC allocation were:

1. rate of blood or CSF culture sampling per 1000 PICC days
2. duration of antimicrobial exposure from randomisation up to 48 hours after line removal
3. time to PICC removal

Clinical secondary outcomes were:

i) chronic lung disease: respiratory support (mechanical ventilation or continuous positive pressure via endotracheal tube or nasal tube), or supplemental oxygen at 36 weeks’ postmenstrual age;

ii) necrotizing enterocolitis (NEC): Bell’s stage II or III;

iii) treatment for retinopathy of prematurity (medical or surgical);

iv) abnormalities on cranial ultrasound (periventricular leukomalacia or intracranial haemorrhage; worse grade of 1 to 4 used in analyses)

v) time from randomisation to full milk feeds (150 mls/kg/day)

vi) total duration of parenteral nutrition from randomisation until discharge from neonatal care

vii) death before discharge home from neonatal care

Death within 6 months of randomisation and time to death (added as a secondary outcome after trial commencement because…) 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 hours after PICC removal (http://prevailtrial.org.uk/).

## 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. We hypothesised a similar effect of miconazole-rifampicin impregnation to that of minocycline-rifampicin. We considered a 50% reduction to be conservative, given results of a network meta-analysis by Wang et al for catheter-related BSI (mean odds ratio 0.18 and upper 95% CI 0.34),18 and the results of the CATCH trial .Catch ref To detect a reduction in the proportion of babies experiencing a bloodstream infection from 14% in the standard arm, which was expected based on audit data from three participating neonatal units, to 7% in the antimicrobial-impregnated arm, 79 events were required from 816 babies (408 in each arm), totalling 858 allowing for a 5% loss to follow-up.

Outcome data were analysed according to the intention-to-treat principle. Babies who were randomised but had no PICC inserted were assessed for infection related outcomes until 48 hours after the last attempted insertion or 48 hours after randomisation. Safety analyses excluded babies for whom a PICC was not inserted with the analysis undertaken using groups defined by the PICC used. All statistical tests were two-sided and performed using a 5% significance level. 95% confidence intervals were used throughout. All analyses were conducted with SAS software version 9.4. Results from the primary outcome and safety analyses were validated by independent programing by another statistician from the point of raw data.

The primary outcome and secondary survival outcomes were analysed using the log rank test. We used Kaplan-Meier curves to present the numbers at risk and Cox regression to calculate hazard ratios. Binary outcomes were analysed using Fisher’s exact test and relative risks presented with 95% confidence intervals. Continuous outcomes were analysed using the Mann-Whitney U test and medians for each group were presented with interquartile ranges. Rate outcomes were analysed using Poisson regression and rate ratios were presented with 95% confidence intervals. Descriptive results only are presented for the type of organisms isolated from bloodstream infections and related adverse and serious adverse events.

Four sensitivity analyses of the primary outcome were pre-specified:

i) time to serious bloodstream infection, defined as treatment with antimicrobials for ≥72 hours or death during treatment;

ii) time from PICC insertion to first bloodstream

iii) time to first bloodstream infection excluding samples obtained via arterial cannulas or CVCs and

Iv) time to first bloodstream infection excluding skin organisms (define- does that include CoNS?)

For comparability with published studies we also report bloodstream infection rates per 1000 PICC days between randomisation and PICC removal.

After seeing the results, we specified an additional analysis of the primary outcome to investigate whether the treatment effect varied by gestational age at birth (before 28 weeks 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 (DMC) who made recommendations to the Trial Steering Committee (TSC) . An internal pilot was conducted to demonstrate feasibility of recruitment after the first 6 months and an interim analysis of the primary outcome took place after approximately half of the babies were randomised.

**Trial registration** ISRCTN registry: https://doi.org/10.1186/ISRCTN81931394.

## Role of funding source

The funder appointed independent members to the TSC and DMC, 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 (RG) had full access to all outputs from the data in the study and had final responsibility for the decision to submit for publication.

# Results

We assigned 861 babies to receive an antimicrobial impregnated (430 babies) or standard PICC (431 babies) between August 12, 2015 and January 11, 2017 (Figure 1). Recruitment ended prematurely because the recruitment target was met. Clinical follow up continued until May 30, 2017. Table 1 shows characteristics at randomisation in the trial arms. 83% (715/861) of babies were enrolled into the trial before 7 days of age and 88% (754/861) were born before 32 weeks’ gestation. Slightly more babies randomised to the antimicrobial-impregnated PICC arm did not have the allocated PICC inserted (Table 2). Endpoints for follow up are also shown in Table 2.

*Insert Tables 1 and 2 here.*

The primary outcome did not differ between groups (Hazard Ratio (HR): 1.11, 95% confidence interval [CI]: 0.73-1.67; Table 3 and Figure 2). This finding did not change in sensitivity analyses (Table 3). There was no evidence of a difference in treatment effect for babies with a gestational age of less than 28 weeks compared to 28 weeks or more (p = 0.28). 46/430 (10.7%) babies in the antimicrobial arm had one bloodstream infection and three of these babies had two infection episodes. Corresponding numbers for the standard arm were 44/431 (10.2%) babies with a first bloodstream infection, one of whom had a second infection episode.

*Insert Table 3 here.*

The secondary infection-related outcomes did not differ between the trial arms except for rifampicin resistance from PICC tip cultures (Relative risk [RR]: 3.51; 95% CI: 1.16-10.57; p=0.02). There was no significant difference when comparing rifampicin resistance from blood, CSF or PICC tip cultures combined (RR: 1.80; 95% CI: 0.84-3.86; p=0.13; Table 3). Appendix Table A1 lists the organisms isolated during the primary outcome time window, which were predominantly coagulase negative staphylococci in both trial arms. Appendix Table A2 lists rifampicin resistant isolates by type of organism. Measures of blood or CSF sampling are shown in Table 3. Fewer than half the babies in each arm had one or more blood or CSF samples taken because of signs of infection. The rate of blood sampling for suspected infection was significantly higher in the antimicrobial arm than the standard arm (98/1000 PICC days vs. 80/1000 PICC days respectively; Rate ratio: 1.23; 95% CI: 1.05-1.45; p-value=0.01). There were no differences in the median time to PICC removal (8 days in both groups; p-value=0.73) or in the median duration of antimicrobial treatment (3 days in both groups; p-value=0.25; Table 3). There were no significant differences in any clinical outcomes measured at discharge from the neonatal unit or in mortality within six months of randomisation (Table 3).

Summary data of the most frequent adverse events are listed in Table 4. 60 events were reported from 49 patients (13%) in the antimicrobial-impregnated PICC arm and 50 events from 45 (11%) babies in the standard PICC arm. One serious adverse event involving supraventricular tachycardia following PICC placement was reported in the antimicrobial-impregnated PICC arm.

*Insert Table 4 here.*

# Discussion

We found no evidence of benefit or harm from miconazole-rifampicin impregnated PICCs in babies receiving intensive care (pedantic point- not all infants will have received “intensive care”, or been in an intensive care unit). The 95% confidence interval 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. Sensitivity analyses did not change these results. We found no differences in mortality at 6 months, or clinical outcomes recorded at discharge home from the neonatal unit including difference duration of antibiotic use or of PICC insertion

Strengths of the trial include the large sample size and 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 80% of babies participating in the trial were born before 32 weeks of gestation, the trial provides important new evidence for a group at high risk of infection, with 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 based on positive cultures taken as part of clinical practice in response to suspected infection to guide antibiotic treatment, ensured relevance to routine practice.

We used central web based randomisation to ensure allocation concealment, achieved near complete follow up and assessment for the primary outcome, adhered to a pre-specified 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 arm received the allocated PICC, probably because the randomised PICC had to be inserted within 48 hours, thereafter the standard PICC was used. The proportion of babies with bloodstream infection (10.5%) was lower than expected (14%) but there was sufficient power to exclude a moderate reduction in the risk of bloodstream infection. The 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 arm, but the proportions of babies with at least one sample or any PICC tip culture were similar and there were no differences in the timing of PICC removal between trial arms.

A limitation was the lack of 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 were tested for rifampicin resistance. The risk of rifampicin resistance in isolates from positive blood or CSF cultures did not differ between trial arms, but was significantly increased in positive tip cultures from antimicrobial impregnated PICCs. Selection of rifampicin resistant Gram-positive bacteria during treatment, when rifampicin is used as the sole antibacterial agent, is well recognised.19 Emergence of resistant organisms was considered by the investigators, the TSC and the DMC, but the risk of adverse events arising was viewed as low as the limited 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-rifampicin impregnation did not reduce bloodstream infection in new-born babies. This result is consistent with findings in one randomised controlled trial (RCT) in adults and one small RCT in new-born infants published as an abstract (see panel, and appendix 3).14,20,21 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-rifampicin-impregnated CVCs compared with standard CVCs.10,22,23 Several explanations could account for these differences. Firstly, miconazole-rifampicin may be less effective than minocycline-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.24 However, rifampicin may 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 such as minocycline, especially against methicillin-resistant strains.19,25

Secondly, it is possible that, although the most effective type of antimicrobial impregnation in systematic reviews26,27, minocycline-rifampicin impregnated CVCs might not effectively reduce overall rates of bloodstream infection or sepsis.28 Trials in adults show beneficial effects of antimicrobial impregnation for catheter-related bloodstream infection, but few trials measure the effect on any bloodstream infection. Catheter-related infection requires the same isolates from blood and CVC tip and could be biased due to inhibition of positive tip cultures by leaching of antimicrobial from the tip during plating out for culture. Only the large CATCH trial in children used any clinically indicated bloodstream infection as the primary outcome and found a 57% reduction in time to infection (Appendix 3)10. A smaller trial compared catheter-related bloodstream infection in children randomised to minocycline-rifampicin impregnated or standard CVC, found no difference but detected few infection events (three in each group; Appendix 3).29 Thirdly, the reductions in infection rates in neonatal units associated with improved catheter asepsis practices and shorter duration of PICC use may have narrowed the potential for further benefits from antimicrobial impregnation.30 It is also possible that PICCs are not an independent risk factor for infection in sick preterm babies because of their high susceptibility to infection from multiple sources, including numerous invasive procedures and devices, gut permeability and immune immaturity.31

Since 2012, the Premistar PICC has been the only antimicrobial impregnated PICC available for preterm babies in Europe. Its use has been reported in Germany and Italy, 14 but use in the UK was limited to the PREVAIL trial. The trial findings do not support the use of miconazole-rifampicin PICCs in newborn infants because we found no evidence that antimicrobial impregnated PICCs reduce bloodstream infection and they cost more 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 10 babies in the PREVAIL trial had a bloodstream infection and some may suffer serious life-long neurodevelopmental impairment or lung disease as a result. More large trials are therefore urgently needed to reduce the risks of bloodstream infection and their long-term consequences. Viewed against existing evidence for the effectiveness of rifampicin-minocycline impregnated CVCs in adults and children, our findings have implications for manufacturers of these devices and for clinicians. Firstly, to consider trialling alternative types of antimicrobial impregnated PICCs for evaluation in newborn babies as well as other interventions to prevent bloodstream infection in neonatal intensive care. Secondly, to consider further randomised controlled trials to determine whether previous evidence of the effectiveness of antibiotic impregnated central venous catheters in adults is sustained in the context of effective infection control practices.

## Contributions

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

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**Figure 1: CONSORT flow diagram showing numbers of trial participants**

Lost to follow-up (n = 3)

* Withdrew from follow-up after completing trial treatment (n = 0)
* Discontinued intervention (n = 0)
* Lost to follow-up after primary outcome time window complete (n = 3)
* Lost to follow-up during primary outcome time window (n = 0)

Not approached (n = 487)

*Note: these reasons are not mutually exclusive*

* Parents not available to consent (n =163 )
* Parents lack of understanding (n = 8)
* Parents do not understand English/Urdu (n = 18)
* Consultant preference (n = 22)
* Missed by clinical team (n = 134)
* Baby previously entered into PREVAIL (n = 10)
* No reason given (n = 5)
* Not approached for other reason (n = 148)

Approached (n = 1404)

Excluded (n = 543)

* Declined consent (n = 467)
* Consented but not randomised (n = 76)

Analysed (n = 430)

* Excluded from analysis (n = 0)

Allocated to antimicrobial PICC (n = 430)

* Received allocated PICC (n = 373)
* Received non allocated 1FR\* PICC (n = 23)
* Received 2FR\* PICC (n = 5)
* Did not receive any PICC (n = 29)
  + Attempted insertion (n = 17)
  + Did not attempt insertion (n = 12)

Allocated to standard PICC (n = 431)

* Received allocated PICC (n = 407)
* Received non allocated 1FR\* PICC (n = 1)
* Received 2FR\* PICC (n = 7)
* Did not receive any PICC (n = 16)
  + Attempted insertion (n = 9)
  + Did not attempt insertion (n = 7)

Analysed (n = 431)

* Excluded from analysis (n = 0)

Allocation

Randomised (n = 861)

Enrolment

Lost to follow-up (n = 5)

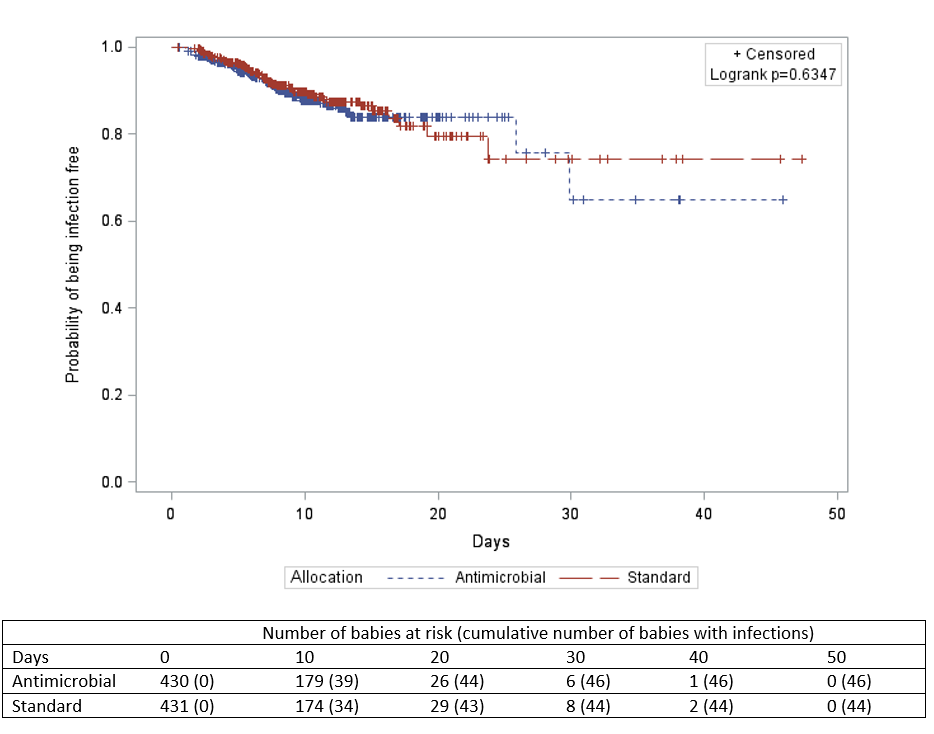
* Withdrew from follow-up after completing trial treatment (n = 0)
* Discontinued intervention (n = 0)
* Lost to follow-up after primary outcome time window complete (n = 4)
* Lost to follow-up during primary outcome time window (n = 1)

Follow-Up

Analysis

**Figure 2: Kaplan-Meier curve showing time to first bloodstream infection for newborn babies randomised to antimicrobial or standard PICC**

\*FR=French gauge



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

|  |  |  |  |
| --- | --- | --- | --- |
| Baseline characteristics |  | **Antimicrobial (n=430)** | **Standard (n=431)** |
| Gender | Male | 214 (49.8%) | 225 (52.2%) |
|  | Female | 216 (50.2%) | 206 (47.8%) |
| Birth weight (grams) | Median (IQR) | 962.5 (729-1220) | 960 (770-1250) |
|  | <750 | 119 (27.7%) | 92 (21.3%) |
|  | 750 - <1000 | 110 (25.6%) | 140 (32.5%) |
|  | 1000 - <1250 | 102 (23.7%) | 91 (21.2%) |
|  | 1250 - <1500 | 52 (12.1%) | 62 (14.4%) |
|  | 1500 - <1750 | 27 (6.3%) | 27 (6.3%) |
|  | 1750 - <2000 | 8 (1.9%) | 7 (1.6%) |
|  | ≥2000 | 12 (2.8%) | 12 (2.8%) |
| Gestational age at birth (weeks) | Median (IQR) | 27.90 (25.78-29.94) | 28.06 (26.23-30.14) |
| <26 | 115 (26.7%) | 93 (21.6%) |
| 26 - <28 | 101 (23.5%) | 110 (25.5%) |
| 28 - <30 | 103 (24.0%) | 102 (23.7%) |
| 30 - <32 | 54 (12.6%) | 76 (17.6%) |
| 32 - <34 | 28 (6.5%) | 15 (3.5%) |
| 34 - <36 | 7 (1.6%) | 9 (2.1%) |
| 36 -<38 | 5 (1.2%) | 3 (0.7) |
| ≥38 | 7 (1.6%) | 11 (2.6%) |
| Missing | 10 (2.3%) | 12 (2.8%) |
| < 32 | 373 (86.7%) | 381 (88.4%) |
| Major congenital anomaly | Yes | 21 (4.9%) | 27 (6.3%) |
|  | No | 408 (94.9%) | 404 (93.7%) |
|  | Missing | 1 (0.2%) | 0 (0.0%) |
| Age (days) | Median (IQR) | 4.12 (2.04-5.93) | 3.90 (1.90-6.12) |
|  | <2 | 106 (24.7%) | 113 (26.2%) |
|  | 2 - <7 | 256 (59.5%) | 240 (55.7%) |
|  | 7 - <14 | 39 (9.1%) | 52 (12.1%) |
|  | 14 - <21 | 6 (1.4%) | 11 (2.6%) |
|  | 21 - <28 | 3 (0.7%) | 5 (1.2%) |
|  | ≥28 | 20 (4.7%) | 10 (2.3%) |
| Apgar score at 5 minutes | 0-3 | 23 (5.3%) | 19 (4.4%) |
|  | 4-7 | 138 (32.1%) | 140 (32.5%) |
|  | 8-10 | 247 (57.4%) | 249 (57.8%) |
|  | Missing | 22 (5.1%) | 23 (5.3%) |
| **Delivery characteristics** |  |  |  |
| Location of birth | Born in study hospital | 340 (79.1%) | 367 (85.2%) |
|  | Transferred after birth | 90 (20.9%) | 64 (14.8%) |
| Mode of delivery | Vaginal | 196 (45.6%) | 198 (45.9%) |
|  | Caesarean | 234 (54.4%) | 233 (54.1%) |
| Membrane rupture >24h before delivery | Yes | 111 (25.8%) | 104 (24.1%) |
| No | 299(69.5%) | 310 (71.9%) |
| Missing | 20 (4.7%) | 17 (3.9%) |
| Maternal antenatal corticosteroids | Yes | 375 (87.2%) | 381 (88.4%) |
| No | 53 (12.3%) | 50 (11.6%) |
| Missing | 2 (0.5%) | 0 (0%) |
| Maternal antibiotics ≤ 12h before delivery | Yes | 135 (31.4%) | 102 (23.7%) |
| No | 275 (64.0%) | 310 (71.9%) |
| Missing | 20 (4.7%) | 19 (4.4%) |
| **Neonatal care** | |  |  |
| Surgery before randomisation | >6 days | 2 (0.5%) | 3 (0.7%) |
| ≤6 days | 15 (3.5%) | 10 (2.3%) |
| No surgery | 413 (96.0%) | 418 (97.0%) |
| Positive blood culture <72 hours prior to randomisation | Yes | 29 (6.7%) | 19 (4.4%) |
| No | 401 (93.3%) | 412 (95.6%) |
| Antibiotics/antifungals <72 hours prior to randomisation (excluding prophylaxis) | Yes | 367 (85.3%) | 363 (84.2%) |
| No | 63 (14.7%) | 68 (15.8%) |
| Respiratory support <72 hours prior to randomisation | Invasive ventilation | 262 (60.9%) | 257 (59.6%) |
| Non-invasive ventilation | 122 (28.4%) | 133 (30.9%) |
| Oxygen only | 9 (2.1%) | 7 (1.6%) |
| None | 37 (8.6%) | 34 (7.9%) |
| Devices in situ at randomisation | <4 | 370 (86.0%) | 390 (90.5%) |
| ≥4 | 60 (14.0%) | 41 (9.5%) |
| **Randomised PICC** |  |  |  |
| PICC insertion site | No PICC inserted | 29 (6.7%) | 16 (3.7%) |
|  | Lower limb | 207 (48.1%) | 220 (51.0%) |
|  | Upper limb | 191 (44.4%) | 190 (44.1%) |
|  | Scalp | 3 (0.7%) | 3 (0.7%) |
|  | Other | 0 (0.0%) | 1 (0.2%) |
|  | Missing | 0 (0.0%) | 1 (0.2%) |

n=number of participants

**Table 2: Results showing PICC insertion status, end point of follow up, and sampling for primary and secondary endpoints according to randomised PICC allocation**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Antimicrobial**  **N=430** | | **Standard**  **N=431** | |
| **PICC Status** |  | Babies  n (%) |  | Babies  n (%) |
| Allocated PICC inserted |  | 373 (86.7) |  | 407 (94.4) |
| Non allocated PICC inserted |  | 28 (6.5) |  | 8 (1.9) |
| No PICC inserted |  | 29 (6.7) |  | 16 (3.7) |
| PICC insertion attempted |  | 17 (4.0) |  | 9 (2.1) |
| PICC insertion not attempted |  | 12 (2.8) |  | 7 (1.6) |
| **End of follow up for outcomes that required samples** |  | Babies  n (%) |  | Babies  n (%) |
| 48h after PICC removal |  | 387 (90.0) |  | 398 (92.3) |
| Death with PICC in situ |  | 13 (3.0) |  | 18 (4.2) |
| 48h after randomisation |  | 29 (6.7) |  | 15 (3.5) |
| Lost to follow up |  | 1 (0.2) |  | 0 (0.0) |
| **End of follow up for outcomes that did not require samples** |  | Babies  n (%) |  | Babies  n (%) |
| Discharge home from neonatal care |  | 383 (89.1) |  | 385 (89.3) |
| Transfer to non-participating site |  | 4 (0.9) |  | 3 (0.7) |
| Death before discharge |  | 36 (8.4) |  | 33 (7.7) |
| 6 months after randomisation |  | 6 (1.4) |  | 10 (2.3) |
| **Culture samples taken** | Samples  n | Babies  n (%) | Samples  n | Babies  n (%) |
| Blood or CSF | 379 | 199 (46.3) | 329 | 190 (44.1) |
| Peripheral venous blood | 321 | 183 (42.6) | 268 | 178 (41.3) |
| CSF | 40 | 33 (7.7) | 38 | 34 (7.9) |
| Other | 18 | 16 (3.7) | 23 | 20 (4.6) |
| PICC tip | 314 | 313 (72.8) | 310 | 310 (71.9) |
| **Rifampicin resistance tested in positive cultures\*** | Babies with positive culture\*\*  n | Babies with positive culture tested  n (%) | Babies with positive culture\*\*  n | Babies with positive culture tested  n (%) |
| Blood or CSF | 48 | 21 (43.8) | 46 | 25 (54.3) |
| Peripheral venous blood | 44 | 21 (47.7) | 42 | 23 (54.8) |
| CSF | 0 | 0 (0.0) | 3 | 1 (33.3) |
| Other | 5 | 0 (0.0) | 3 | 2 (66.7) |
| PICC tip | 47 | 32 (68.1) | 90 | 61 (67.8) |

\*only performed on positive cultures

\*\*any positive sample after randomisation and up to 48 hours after PICC removal

**Table 3: Primary and secondary outcomes in babies randomised to antimicrobial or standard PICC (intention to treat analysis)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Antimicrobial (n=430)** | **Standard**  **(n=431)** | **Antimicrobial vs. Standard** | |
| **Primary outcome\*** | **Number of babies with BSI\***  **n (%)** | | **Hazard Ratio (95% CI)** | **p-value** |
| Time to first BSI | 46 (10.7) | 44 (10.2) | 1.11 (0.73-1.67) | 0.63 |
| Sensitivity analyses |  |  |  |  |
| *Time to first clinically serious BSI* | 42 (9.8) | 40 (9.3) | 1.11 (0.72-1.71) | 0.65 |
| *Time to first BSI (from insertion)\*\** | 45 (11.2) | 44 (10.6) | 1.08 (0.71-1.64) | 0.72 |
| *Time to first BSI excluding arterial or PICC samples* | 45 (10.5) | 43 (10.0) | 1.11 (0.73-1.68) | 0.64 |
| *Time to first BSI excluding skin organisms* | 16 (3.7) | 9 (2.1) | 1.90 (0.84-4.31) | 0.12 |
| **Secondary outcomes** | **Rate/1000 PICC days** | | **Rate ratio (95% CI)** | **p-value** |
| Rate of BSI | 13.15 | 10.87 | 1.21 (0.78-1.88) | 0.40 |
| *Rate of BSI (when line is in situ)\*\** | 12.57 | 11.21 | 1.12 (0.73-1.12) | 0.60 |
| Rate of catheter-related (CRBSI) | 1.84 | 2.35 | 0.78 (0.27-2.25) | 0.65 |
| *Rate of CRBSI (when line is in situ)\*\** | 1.71 | 2.46 | 0.70 (0.25-1.96) | 0.49 |
| Rate of blood/CSF culture sampling | 97.90 | 79.64 | **1.23 (1.05-1.45)** | **0.01** |
| *Rate of blood/CSF sampling (line in situ)\*\** | 93.72 | 82.01 | 1.14 (0.98-1.34) | 0.09 |
|  | **Number of babies**  **n (%)** | | **Relative Risk (95% CI)** | **P-value** |
| Occurrence of 1 or more BSI | 46 (10.7) | 44 (10.2) | 1.05 (0.71-1.55) | 0.82 |
| Rifampicin resistance from blood/CSF culture | 4 (0.9) | 7 (1.6) | 0.57 (0.17-1.94) | 0.55 |
| Rifampicin resistance from PICC tip culture | 14 (3.3) | 4 (0.9) | **3.51 (1.16-10.57)** | **0.02** |
| Rifampicin resistance from blood/CSF or PICC tip culture\*\*\* | 18 (4.2) | 10 (2.3) | 1.80 (0.84-3.86) | 0.13 |
| Chronic lung disease | 190 (44.2) | 178 (41.3) | 1.07 (0.92-1.25) | 0.41 |
| Necrotizing enterocolitis: Bell’s stage II or III | 41 (9.5) | 46 (10.7) | 0.89 (0.59-1.32) | 0.57 |
| Treatment for retinopathy of prematurity | 40 (9.3) | 30 (7.0) | 1.34 (0.85-2.11) | 0.21 |
| Abnormality on cranial ultrasound | 166 (38.6) | 150 (34.8) | 1.11 (0.93-1.33) | 0.26 |
| Death before discharge | 36 (8.4) | 33 (7.7) | 1.09 (0.70-1.72) | 0.71 |
| Death within 6 months of randomisation | 36 (8.4) | 35 (8.1) | 1.03 (0. 66-1. 61) | 0. 90 |
|  | **Median (IQR)** | | **Hazard Ratio (95% CI)** | **P-value** |
| 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 |
| Days of antimicrobial treatment | 3.00 (2.00-6.00) | 3.00 (2.00-6.00) | N/A | 0.25 |
| Days of parenteral nutrition | 11.00 (7.00-19.00) | 10.00 (7.00-18.00) | N/A | 0.83 |

For all outcomes that relate to samples, events are only considered on samples taken between 24 hours after randomisation and until 48 hours after removal; *Analyses in italics and indented are sensitivity analyses;* \*Median time to event not reported as not enough babies experienced the event; \*\*Only includes babies where PICC was successfully inserted (Antimicrobial: n=401; Standard: n=415); \*\*\*Outcome not pre-specified in protocol but requested by investigators and included in statistical analysis plan prior to them seeing any unblinded data

**Table 4: Adverse Events in babies with PICC inserted (Safety analysis)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Antimicrobial (n=374)** | | **Standard (n=430)** | |
| **Adverse events** | **Events**  **n** | **Babies**  **n (%)** | **Events**  **n** | **Babies**  **n (%)** |
| Any adverse event | 60 | 49 (13.1) | 50 | 45 (10.5) |
| Evidence of catheter blockage | 15 | 15 (4.0) | 15 | 15 (3.5) |
| Extravasation | 11 | 11 (2.9) | 11 | 11 (2.6) |
| Swelling/haematoma at line site | 10 | 10 (2.7) | 7 | 7 (1.6) |
| Clinically evident thrombophlebitis | 4 | 4 (1.1) | 7 | 7 (1.6) |
| Difficulty removing stylet | 8 | 8 (2.1) | 1 | 1 (0.2) |
| Catheter damage | 3 | 3 (0.8) | 4 | 4 (0.9) |

**Panel – research in context**

**Research in context**

**Evidence before this study**

Systematic reviews and subsequent searches include nine randomised controlled trials (RCTs) of CVCs impregnated with rifampicin combined with another antimicrobial agent (details in Appendix 3). Two trials compared miconazole-rifampicin impregnated vs standard CVCs. One of these involved newborn infants and was published only in abstract form. Neither trial reported a significant difference in bloodstream infection. Nine RCTs of minocycline-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 from any cause in children (details in Appendix 3). A Cochrane review in 2015 of antimicrobial impregnated CVCs in newborns concluded that, given the paucity of evidence, a large, simple and pragmatic RCT of this intervention was needed to guide policy and practice.

**Added value of this study**

The PREVAIL trial shows that use of antimicrobial (miconazole-rifampicin)-impregnated percutaneously-inserted CVCs compared with use of standard CVCs does not reduce the risk of catheter-related infection, other morbidity, or mortality in newborn infants. This is the largest trial of this intervention and the validity is enhanced by the methodological quality and power. The findings are broadly applicable to newborn infants cared for in facilities in well-resourced health services.

**Implications of the available evidence**

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

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