Antimicrobial-impregnated central venous catheters for preventing neonatal bloodstream infection: the PREVAIL RCT

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Scientific summary

Background

A bloodstream infection is a serious adverse outcome of using central venous catheters. Earlier gestational age at birth is associated with increasing rates of bloodstream infection and in susceptibility to serious and long-term adverse outcomes. Bloodstream infection increases the risks of death and serious morbidity, especially adverse neurodevelopment in the long term.

Evidence from clinical trials shows that antimicrobial-impregnated central venous catheters reduce catheter-related bloodstream infection in adults and children receiving intensive care. However, there is insufficient evidence to guide use of antimicrobial-impregnated central venous catheters for newborn babies receiving neonatal intensive care.

We conducted a large, pragmatic randomised controlled trial to address uncertainty about the clinical effectiveness of antimicrobial-impregnated peripherally inserted central venous catheters for reducing bloodstream infection in babies receiving neonatal care. The study had three objectives addressed in three separate studies.

Study objectives

1. A clinical effectiveness randomised controlled trial of antimicrobial-impregnated versus standard peripherally inserted central venous catheters for reducing the incidence of bloodstream or cerebrospinal fluid infections (referred to as bloodstream infections).
2. An economic evaluation to determine the costs, cost-effectiveness and value of conducting additional research.
3. A generalisability analysis of the trial findings to neonatal care in the NHS.

Clinical effectiveness randomised controlled trial

Methods

Design, trial population and intervention

We conducted a multicentre, open-label, two-arm, pragmatic randomised controlled trial. Trial participants were newborn babies, admitted to one of 18 neonatal intensive care units in England, who required the narrowest available peripherally inserted central venous catheter (1 French gauge). Randomisation was 1 : 1 to receive an antimicrobial peripherally inserted central venous catheter, impregnated with the antibiotic rifampicin and antifungal miconazole, or a standard peripherally inserted central venous catheter, manufactured by Vygon (UK) Ltd (Swindon, UK).

Randomisation and masking

Random allocation used a web-based program controlled by Liverpool Clinical Trials Centre. Randomisation sequences were computer-generated in random variable blocks of two and four, stratified by site. The intervention was not masked for clinicians because rifampicin stained the antimicrobial-impregnated peripherally inserted central venous catheter tubing brown, but all decisions about analyses were prespecified in an analysis plan developed blind to treatment allocation.
Main outcome measures
The primary outcome was the time from random allocation to the first microbiologically confirmed bloodstream or cerebrospinal fluid infection between 24 hours after randomisation and 48 hours after peripherally inserted central venous catheter removal or death. Secondary outcomes assessed rifampicin resistance in any isolate from blood, cerebrospinal fluid or peripherally inserted central venous catheter tip culture; potential biases in sampling or treatment; clinical outcomes at discharge from neonatal care; and death up to 6 months after randomisation.

Sample size and statistical analyses
To detect a constant hazard ratio of 2.078 (i.e. a proportion of babies experiencing a bloodstream infection in the standard peripherally inserted central venous catheter arm of 0.14 and in the antimicrobial-impregnated peripherally inserted central venous catheter arm of 0.07) with 90% power and a significance level of 0.05, using a two-sided log-rank test for equality of survival curves, required 816 babies and 79 events. To allow for a 5% loss to follow-up, the target was increased to 858 babies. Effectiveness analyses included all randomised participants following the intention-to-treat principle. Safety analyses excluded randomised babies who did not have a peripherally inserted central venous catheter inserted. The primary outcome was analysed using the log-rank test and Cox regression to calculate the hazard ratio.

Results
We randomised 861 babies (antimicrobial-impregnated peripherally inserted central venous catheter group, n = 430; standard peripherally inserted central venous catheter group, n = 431) over 17 months from August 2015. Of these, 754 (87.6%) participants were born before 32 weeks of gestation. The median time to peripherally inserted central venous catheter removal was 8.20 days (interquartile range 4.77–12.13 days) in the antimicrobial-impregnated peripherally inserted central venous catheter group and 7.86 days (interquartile range 5.00–12.53 days) in the standard peripherally inserted central venous catheter group. Bloodstream infection occurred in 46 (10.7%) and 44 (10.2%) babies randomised to the antimicrobial-impregnated peripherally inserted central venous catheter and standard peripherally inserted central venous catheter groups, respectively. We did not find a difference in time to bloodstream infection (hazard ratio 1.11, 95% confidence interval 0.73 to 1.67). Rifampicin resistance in positive blood or cerebrospinal fluid cultures, mortality, clinical outcomes at neonatal unit discharge and time to peripherally inserted central venous catheter removal did not differ significantly between groups, although rifampicin resistance in positive cultures colonising peripherally inserted central venous catheter tips was higher in the antibiotic group (relative risk 3.51, 95% confidence interval 1.16 to 10.57) than in the standard group. Adverse events were similarly low in both groups.

Economic evaluation
We estimated the hospital costs and length of stay using routine health-care data. We developed a new cost-effectiveness model to predict the PREVenting infection using Antimicrobial-Impregnated Long lines (PREVAIL) trial participants' long-term, quality-adjusted life expectancy, health-care costs and the minimum reduction in the rate of bloodstream infections for antimicrobial-impregnated peripherally inserted central venous catheters to be cost-effective, and we estimated the value of future research.

Methods
We estimated the costs of hospital care over 6 months from randomisation using routine health data, costed on a 2016 price base. Data sources for PREVAIL trial participants were as follows:

- data from the PREVAIL trial
- data from the National Neonatal Research Database relating to each participant's stay in neonatal units (neonatal intensive care, local neonatal units or special care baby units)
- data from the Paediatric Intensive Care Audit Network on admissions to the paediatric intensive care unit
- Hospital Episode Statistics, containing information on all other hospital admissions, outpatient appointments, accident and emergency attendances and deaths.
We developed a decision-analytic model to evaluate the cost-effectiveness of interventions to prevent bloodstream infections from the perspective of the NHS. The model simulated the lifetime costs, life expectancy and quality-adjusted life-years of babies requiring a peripherally inserted central venous catheter during their neonatal unit stay. The model assumes that a bloodstream infection increases the risk of death and the risk of developing neurodevelopmental impairment in early childhood, leading to higher costs, worse quality of life and greater risk of death. The model was informed by the PREVAIL trial and external literature. Model results were computed as mean costs and quality-adjusted life-years over 10,000 Monte Carlo simulations. We used value-of-information methods to explore whether or not uncertainty in the model evidence and assumptions warrants additional research.

**Results**

The length of hospital stay per infant was 68.43 days (standard deviation 36.64 days) for the antimicrobial-impregnated peripherally inserted central venous catheter group and 70.60 days (standard deviation 38.94 days) for the standard peripherally inserted central venous catheter group. Most of this time was spent in the neonatal intensive care unit. The cost of hospital care per baby was £82,752.99 (standard deviation £49,738.66) in the antimicrobial-impregnated peripherally inserted central venous catheter group and £84,185.39 (standard deviation £50,602.54) in the standard peripherally inserted central venous catheter group. The largest contribution to the total cost was the neonatal intensive care unit stay and hospital care other than critical care. The type of peripherally inserted central venous catheter did not have an impact on the length of hospital stay or cost.

The model predicted that greater levels of neurodevelopmental impairment are associated with a reduction in life expectancy and quality-adjusted life-years and higher costs. For example, severe neurodevelopmental impairment reduces life expectancy by 14.79 years (95% confidence interval 4.43 to 26.68 years), reduces quality-adjusted life expectancy by 10.63 quality-adjusted life-years (95% confidence interval 7.74 to 14.02 quality-adjusted life-years) and costs of £19,060 (95% confidence interval £14,197 to £24,697) to the NHS. The difference in lifetime costs between the antimicrobial-impregnated and the standard peripherally inserted central venous catheter was £54.85 (95% confidence interval £25.95 to £89.12); in health outcomes, the difference was –0.01 quality-adjusted life-years (95% confidence interval –0.09 to 0.04 quality-adjusted life-years). Therefore, antimicrobial-impregnated peripherally inserted central venous catheters were not cost-effective. Results remained stable across a series of scenario-testing key assumptions. Given the price difference between the antimicrobial-impregnated and the standard peripherally inserted central venous catheter, the minimum reduction in the risk of bloodstream infection required for the antimicrobial-impregnated peripherally inserted central venous catheter to be cost-effective was 3% for babies born at 23–27 weeks’ gestational age, and 15% for babies born at 28–32 weeks’ gestational age. The value of additional research is £2M over a time horizon of 10 years, based largely on the effectiveness of antimicrobial-impregnated peripherally inserted central venous catheters.

**Generalisability analysis**

We evaluated the generalisability of results from the PREVAIL trial to other babies who received peripherally inserted central venous catheters in neonatal intensive care units. Peripherally inserted central venous catheters are used in neonatal intensive care units and in local neonatal units; therefore, we evaluated the applicability of the results of the PREVAIL trial to babies who receive peripherally inserted central venous catheters in local neonatal units. We compared risk factors, bloodstream infection rates and changes in bloodstream infection rates over time, adjusting for risk factors. We calculated what proportion of bloodstream infections in neonatal units could be attributed to peripherally inserted central venous catheters. These findings could help in targeting strategies to prevent bloodstream infections occurring in neonatal units.
Methods
We obtained clinical data from the National Neonatal Research Database for babies receiving intensive and high-dependency care in 112 of 124 neonatal intensive care units and local neonatal units in England from March 2010 to June 2017. We defined bloodstream infection as a link to a positive blood or cerebrospinal fluid culture recorded in the national infection surveillance data set.

We determined the generalisability and applicability of results of the PREVAIL trial to babies who received peripherally inserted central venous catheters in neonatal intensive care units and local neonatal units during the PREVAIL trial period (August 2015 to January 2017).

First, we compared the prevalence of baby characteristics, all causative organisms of bloodstream infection, and crude and risk-adjusted rates of bloodstream infection per 1000 peripherally inserted central venous catheter days in babies who received the standard peripherally inserted central venous catheter in the PREVAIL trial with those of other babies who received peripherally inserted central venous catheters in neonatal intensive care units (those in the PREVAIL trial neonatal intensive care units who were not enrolled in the PREVAIL trial, and those who received peripherally inserted central venous catheters in non-PREVAIL trial neonatal intensive care units during the PREVAIL trial recruitment period) and local neonatal units.

Second, we compared trends in bloodstream infection rates in PREVAIL trial neonatal intensive care units, other neonatal intensive care units and local neonatal units, using multilevel Poisson regression, restricted to clearly pathogenic organisms to avoid spurious trends caused by increased reporting of skin commensals.

Third, to inform targeting of preventative strategies, we evaluated trends in rates of late-onset bloodstream infection per 1000 days of intensive or high-dependency care and per 100 admissions.

Fourth, we determined the contribution of peripherally inserted central venous catheters to the overall rate of bloodstream infection per admission by calculating the proportions of total bloodstream infection that occur (1) as early onset without peripherally inserted central venous catheter before 2 days of age; (2) during peripherally inserted central venous catheter days at risk, defined as 1 day after insertion to 2 days after PICC removal; and (3) as late onset without peripherally inserted central venous catheter days (≥ 2 days after birth).

Results
We found no differences at the 5% level between PREVAIL trial babies and other babies receiving peripherally inserted central venous catheters in neonatal intensive care units and local neonatal units in the distribution of causative organisms isolated from bloodstream infection, or in crude and adjusted rates of any bloodstream infection per 1000 peripherally inserted central venous catheter days.

We found stable rates over time in the bloodstream infection rate per 1000 peripherally inserted central venous catheter days (for clearly pathogenic organisms) in PREVAIL trial neonatal intensive care units from 2010 to 2017. The rate of late-onset bloodstream infection (i.e. bloodstream infection in babies older than 2 days of age, with or without a peripherally inserted central venous catheter) per 1000 days of intensive and high-dependency care decreased in local neonatal units and the percentage of admissions with at least one late-onset bloodstream infection declined in PREVAIL trial neonatal intensive care units and local neonatal units from March 2010 to June 2017.

Of all bloodstream infections during neonatal intensive or high dependency care in neonatal units, 18% were early-onset bloodstream infections, 46% occurred on days when a peripherally inserted central venous catheter was inserted, and 35% were late-onset bloodstream infections when there was no peripherally inserted central venous catheter. For babies born before 32 weeks of gestation,
the proportions were 8%, 55% and 37% for early-onset bloodstream infections, bloodstream infections during peripherally inserted central venous catheter days and late-onset bloodstream infections when there was no peripherally inserted central venous catheter, respectively, and 42%, 26% and 32%, respectively, for babies born at \( \geq \) 32 weeks of gestation.

Conclusions

Main findings
We found no evidence of benefit or harm of the use of the miconazole- and rifampicin-impregnated peripherally inserted central venous catheter during neonatal care. Interventions with a small effect on bloodstream infection could be cost-effective over the life course. Trial findings are generalisable to neonatal care in England.

Implications for practice

- We found no evidence to support the use of antimicrobial-impregnated peripherally inserted central venous catheters in neonatal intensive care. The antimicrobial-impregnated peripherally inserted central venous catheter was not more effective than the standard peripherally inserted central venous catheter, but was more costly; hence, it was not cost-effective.
- Rifampicin resistance in bloodstream infection or peripherally inserted central venous catheter tips was not significantly increased in the antimicrobial-impregnated peripherally inserted central venous catheter group compared with the standard peripherally inserted central venous catheter group, but organisms isolated just from the peripherally inserted central venous catheter tip were more likely to be rifampicin resistant. As rifampicin is not routinely used in UK neonatal care, this is likely to be of limited clinical relevance in the UK setting.
- We found that preventing bloodstream infection in preterm babies can result in better health outcomes over the babies’ lifetimes, with potential savings in terms of health service costs, by avoiding serious outcomes of bloodstream infection, principally neurodevelopmental impairment and death (as suggested by prior epidemiological studies).
- Findings from the PREVAIL trial are generalisable to neonatal intensive care in the NHS in England. Rates of bloodstream infection per peripherally inserted central venous catheter days at risk in the PREVAIL trial were similar to the rates across neonatal care in England, before and after adjusting for birth characteristics and intensity of care. Similar organisms were cultured from babies in the PREVAIL trial and babies not in the PREVAIL trial.
- Rates of bloodstream infection (excluding skin organisms) per 1000 peripherally inserted central venous catheter days in neonatal intensive or high-dependency care remained stable in neonatal intensive care units and local neonatal units from 2010 to 2017. The percentage of admissions with at least one late-onset bloodstream infection (defined as during peripherally inserted central venous catheter insertion or > 2 days after birth) declined in local neonatal units and neonatal intensive care units that participated in the PREVAIL trial.
- A bloodstream infection that occurs while peripherally inserted central venous catheters are in situ contributes to less than half of all bloodstream infection during neonatal intensive and high-dependency care. Preventative strategies for reducing hospital-acquired bloodstream infections in neonatal care may want to focus on other sources of infection in addition to central venous catheters.

Recommendations for research

- Low-cost interventions that reduce bloodstream infection in preterm babies by a small amount would be likely to be cost-effective over the child’s life course, based on the assumption of reduced risk of neurodevelopmental impairment and death. Investment in further research to develop other types of antimicrobial peripherally inserted central venous catheter impregnation or alternative approaches for preventing infection in neonatal care would, therefore, be worthwhile.
The finding of no evidence of benefit associated with the rifampicin- and miconazole-impregnated peripherally inserted central venous catheter contrasts with substantial reductions in rates of bloodstream infection or catheter-related bloodstream infection reported in previous trials in children and adults randomised to rifampicin- and minocycline-impregnated central venous catheters, compared with standard central venous catheters. We recommend further research to develop and evaluate the rifampicin- and minocycline-impregnated peripherally inserted central venous catheter for use in preterm babies.

Further research is needed to strengthen the evidence on the causal link between bloodstream infection and neurodevelopmental impairment and death, and on methods to reflect the uncertainty in these causal links in cost-effectiveness modelling.

Patient-level linked data combining electronic clinical records from neonatal care, Hospital Episode Statistics and infection surveillance data should be made routinely available for research and infection surveillance in England.

Further research is required to understand which practices contribute to changes (or lack of change) in rates of bloodstream infection over time in neonatal care.

**Trial registration**

The trial is registered as ISRCTN81931394.

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This report

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