Cost-effectiveness of strategies preventing late-onset infection in preterm infants

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ABSTRACT
Objective Developing a model to analyse the cost-effectiveness of interventions preventing late-onset infection (LOI) in preterm infants and applying it to the evaluation of anti-microbial impregnated peripherally inserted central catheters (AM-PICCs) compared with standard PICCs (S-PICCs). 
Design Model-based cost-effectiveness analysis, using data from the Preventing infection using Antimicrobial Impregnated Long Lines (PREVAIL) randomised controlled trial linked to routine healthcare data, supplemented with published literature. The model assumes that LOI increases the risk of neurodevelopmental impairment (NDI).
Setting Neonatal intensive care units in the UK National Health Service (NHS).
Patients Infants born ≤32 weeks gestational age, requiring a 1 French gauge PICC.
Interventions AM-PICC and S-PICC.
Main outcome measures Life expectancy, quality-adjusted life years (QALYs) and healthcare costs over the infants’ expected lifetime.
Results Severe NDI reduces life expectancy by 14.79 (95% CI 4.43 to 26.68; undiscounted) years, 10.63 (95% CI 7.74 to 14.02; discounted) QALYs and costs £19 057 (95% CI £14 197; £24 697; discounted) to the NHS. If LOI causes NDI, the maximum acquisition price of an intervention reducing LOI risk by 5% is £120. AM-PICCs increase costs (£54.85 (95% CI £25.95 to £89.95)) but have negligible impact on health outcomes (−0.01 (95% CI −0.09 to 0.04) QALYs), compared with S-PICCs. The NHS can invest up to £2.4 million in research to confirm that AM-PICCs are not cost-effective.
Conclusions The model quantifies health losses and additional healthcare costs caused by NDI and LOI during neonatal care. Given these consequences, interventions preventing LOI, even by a small extent, can be cost-effective. AM-PICCs, being less effective and more costly than S-PICCs, are not likely to be cost-effective.
Trial registration number NCT03260517.

INTRODUCTION
Preterm infants hospitalised in neonatal intensive care units (NICUs) often require a peripherally inserted central catheter to receive medicines, fluids and parenteral nutrition. 1 PICCs provide a conduit for microorganisms to enter the bloodstream and a site where microorganisms can proliferate, increasing the risk of late-onset infection (LOI). LOI has been linked to higher risk of death and permanent neurodevelopmental impairment (NDI). 2,3 Furthermore, treating LOI with antibiotics is harmful to the developing gut microbiome, 4 potentially leading to serious conditions such as necrotising enterocolitis. 5–7
Antimicrobial impregnated PICCs (AM-PICCs) have been shown to prevent LOI in adults and children but evidence is sparse in preterm infants. 8 To address this evidence gap, the PREVAIL trial (NIHR HTA 12/167/02) investigated the safety, effectiveness and cost-effectiveness of AM-PICCs versus standard non-impregnated PICCs (S-PICCs) in reducing LOI in prematurity. 9

This study reports the cost-effectiveness model to establish the long-term value of preventing LOI in preterm infants hospitalised in NICUs, and its application to estimate the cost-effectiveness of AM-PICCs versus S-PICCs. The model uses data from PREVAIL, linked to hospital use collected from the UK National Neonatal Research Database (NNRD), Hospital Episode Statistics (HES) and Paediatric Intensive Care Network (PICANet) to estimate costs, alongside evidence from the external literature on the long-term health and economic consequences of LOI.

What is already known on this topic?
- Late-onset infection (LOI) in preterm infants is associated with a higher risk of mortality and long-term neurodevelopmental impairment.
- Antibiotic treatment is onerous, expensive and risky.
- Studies in children and adults suggest that antibiotic-impregnated peripherally inserted central catheters (PICCs) are effective and cost-effective in reducing bloodstream infections.

What this study adds?
- The study presents a new decision analytic model which can be used to evaluate alternative strategies to prevent LOI.
- Antibiotic-impregnated PICCs are not cost-effective, when compared with standard PICCs, in a group of infants born ≤32 weeks gestational age.
- Strategies preventing LOI have a great potential to be cost-effective, even when minimally effective.
METHODS
A new decision analytic model was developed to simulate the lifetime costs, life expectancy and quality-adjusted life years (QALYs) of infants born ≤32 weeks gestational age (GA) who required a PICC during their NICU stay. Given the impact of GA on health outcomes, results are presented for two subgroups: GA 23–27 weeks and GA 28–32 weeks. Costs are expressed in UK pound sterling at a 2016 price base, from the perspective of the UK NHS. Future costs and QALYs are discounted at 3.5% per annum.1 The model was developed using Microsoft Excel.

Model structure
The model structure is represented in figure 1. Infants enter the model at the time of PICC insertion and are at risk of LOI. LOI increases the risk of death and NDI (but not its severity). At 2 years of age, children are assessed for the presence and severity of NDI. From age 2 onwards, the model follows the same structure as the model by Mangham et al, which estimated the costs of prematurity.12 Children transition between NDI states or die. The transitions represent improvement or deterioration in NDI status, as well as inaccuracies in the assessment, which might appear over time. After reaching age 8, children remain at risk of death but their NDI level is assumed to remain stable.

Model parameterisation
Model parameters are presented in table 1. LOI corresponds to clinically serious bloodstream infection in the PREVAIL trial (subgroup with GA ≤33 weeks), a pragmatic randomised controlled trial performed across 18 NICUs in England. Infants requiring a narrow (1 French) gauge PICC were considered eligible and once enrolled in the trial were allocated 1:1 to receive either a PICC impregnated with miconazole and rifampicin (AM-PICC) or an S-PICC. Clinically serious bloodstream infection, defined as positive blood/cerebrospinal fluid culture and ≥72 hours treatment with intravenous antibiotic, or death during treatment, was thought to be closer to the definition of LOI in the literature than PREVAIL’s primary outcome of any positive blood/cerebrospinal fluid culture.7

The probability of death at 6 months was informed by an observational study covering all NICUs in England, for a total of 7369 hospitalised infants in 2014; details in online supplementary material 1. The probability of death between 6 months and 2 years of age if infants had received S-PICC was sourced from Mangham et al,12 and based on data from the ‘91–’92 Victorian Infant Collaborative Study Cohort.14 The probability of death from age 2 was obtained from the UK lifetables 2013–15,15 to which the excess risk due to NDI was added; see online supplementary material 2.

The probability of NDI, its severity and the probability of progression between NDI levels over time was also obtained from Mangham et al; for details see online supplementary material 3. Mangham et al defined NDI as a composite outcome encompassing visual, hearing, mobility and cognitive impairment.14 Each item is assigned a level ranging from no to severe disability following standardised paediatric tests, with the most severe level of impairment recorded identifying the overall NDI for the infant.14 17 18

A pearl growing review and meta-analysis was conducted to estimate the effect of LOI on death and NDI; details in online supplementary material 4. The search started from Stoll et al,2 a US observational study linking LOI to death and NDI. Studies were selected if their definition of LOI was consistent with the PREVAIL trial, and if their definition of NDI was consistent with Mangham et al.12 Three systematic reviews were identified,20 23 from which Schlapbach et al24 and Bassler et al25 were selected. Stoll et al2 and Schlapbach et al24 were meta-analysed to inform the added risk of developing NDI at 2 years of age given LOI (1.51, 95% CI 1.33 to 1.70), while Schlapbach et al24 and Bassler et al25 were meta-analysed to inform the added risk of death between 6 months and 2 years of age, given LOI (2.74, 95% CI 1.43 to 5.24).

Costs
The cost of S-PICC and AM-PICC was provided by the manufacturer (personal communication).

Costs between PICC insertion and 6 months were calculated using routine healthcare data of the infants enrolled in the PREVAIL trial: NNID for the NICU stay, PICANet for stays in the paediatric intensive care unit, HES inpatient, A&E and outpatient data, costed with NHS
Table 1  Model parameters

| Parameter | Value GA 23–27 weeks (95% CI; distribution) | Value GA 28–32 weeks (95% CI; distribution) | Source |
|-----------|---------------------------------------------|---------------------------------------------|--------|
| Effect of AM-PICC on the probability of LOI | | | |
| Relative risk of AM-PICC vs S-PICC | 1.06 (0.70 to 1.60; lognormal) | | PREVAIL trial (subgroup of infants born ≤32 weeks GA) |
| Effect of LOI on NDI and death | | | |
| Relative risk of the effect of LOI on death at 6 months | 1 (fixed) | | Assumed that LOI has no effect on death at 6 months in the base case. |
| OR for the effect of LOI on NDI at 2 years of age | 1.51 (1.33 to 1.70; lognormal) | | Meta-analysis of Stoll et al12 and Schlabach et al28 |
| OR for the effect of LOI on death at 2 years of age | 2.74 (1.43 to 5.24; lognormal) | | Meta-analysis of Schlabach et al28 and Bassler et al29 |
| Probabilities using 5-PICC | | | |
| Probability of LOI | 0.14 (0.09 to 0.20; beta) | 0.04 (0.02 to 0.08; beta) | PREVAIL trial (subgroup of infants born ≤32 weeks GA), Santhakumar et al13 |
| Probability of death between PICC insertion and 6 months | 0.20 (0.16 to 0.23; beta) | 0.03 (0.03 to 0.04; beta) | Santhakumar et al13 |
| Probability of death between 6 months and 2 years | 0.02 (0.01 to 0.03; beta) | 0.01 (0.00 to 0.02; beta) | Mangham et al12 |
| Probability of developing NDI | 0.45 (0.42 to 0.49; dirichlet) | 0.26 (0.25 to 0.28; dirichlet) | Mangham et al12 estimated to be similar for both sepsis and non-sepsis groups. Severe NDI calculated as the complement. |
| Distribution by NDI levels, given that NDI occurred | | | |
| Mild NDI | 0.54 (0.51 to 0.58; dirichlet) | 0.73 (0.70 to 0.76; dirichlet) | Mangham et al12 |
| Moderate NDI | 0.29 (0.28 to 0.30; dirichlet) | 0.16 (0.15 to 0.17; dirichlet) | Mangham et al12 |
| Health-related quality of life (to calculate QALYs) | | | |
| No NDI | 0.96 (0.94 to 0.97; beta) | | Petrou et al28 |
| Mild NDI decrement | 0.18 (0.14 to 0.31; gamma) | | Petrou et al28 |
| Moderate NDI decrement | 0.30 (0.24 to 0.46; gamma) | | Petrou et al28 |
| Severe NDI decrement | 0.56 (0.44 to 0.77; gamma) | | Petrou et al28 |
| Costs | | | |
| Difference in cost between PICCs (AM-PICC vs S-PICC) | £53.70 | | Personal communication from the manufacturer |
| Healthcare costs between PICC insertion and 6 months | £105,873.47 (101 444.99 to 110 495.27; gamma) | £62,255.37 (54 711.87 to 70 838.93; gamma) | PREVAIL trial and linked datasets (NNRD, PICANet, NHS) |
| Healthcare costs between 6 months and 2 years | £5989.17 (5989.14 to 5994.98) | £3026.17 (3026.43 to 3028.73) | NHS Reference Cost 15/1627 derived from HES inpatient, A&E and outpatient data. |
| Annual costs between age 2 and 10 years | | | |
| No NDI | £388 (£285 to £509; gamma) | | Petrou et al28 inflated to 2016 |
| Mild NDI | £753 (£584 to £946; gamma) | | Petrou et al28 inflated to 2016 |
| Moderate NDI | £814 (£560 to £1063; gamma) | | Petrou et al28 inflated to 2016 |
| Severe NDI | £1487 (£1096 to £1943; gamma) | | Petrou et al28 inflated to 2016 |
| Annual costs after age 11 years | | | |
| No NDI | £686 (£440 to £993; gamma) | | Petrou et al28 inflated to 2016 |
| Mild NDI | £867 (£782 to £1222; gamma) | | Petrou et al28 inflated to 2016 |
| Moderate NDI | £1252 (£933 to £1624; gamma) | | Petrou et al28 inflated to 2016 |
| Severe NDI | £1796 (£1411 to £2648; gamma) | | Petrou et al28 inflated to 2016 |

GA, gestational age; HES, Hospital Episode Statistics; LOI, late-onset infection; NDI, neurodevelopmental impairment; NHS, National Health Service; NNRD, National Neonatal Research Database; PICANet, Paediatric Intensive Care Network; PICC, peripherally inserted central catheter; QALY, quality-adjusted life year.

Reference Costs 15/16.27 For details, see online supplementary material 6.

Annual costs by NDI level between 2 and 10 years of age were sourced from Mangham et al12 which reports the results from the EPICure cohort at 6 years of age.28 The annual costs by NDI level ≥11 years of age related to the same EPICure cohort, obtained from Petrou et al.29 Costs from age 2 refer to any healthcare costs, both related and unrelated to NDI.

Health-related quality of life

Health-related quality of life by NDI level was obtained from Petrou et al.28 which collected Health Utilities Index (HUI) Mark 3 at 11 years of age from parents of infants in the EPICure cohort. The HUI scores are applied throughout lifetime, and no additional decrement has been added to consider additional comorbidities due to, for example, age, given the lack of published estimates for people with NDI.

Analytical methods

Simulation methods were used to generate mean costs, life years and QALYs.30 The model estimated outcomes and costs given different levels of NDI at age 2, conditional on whether LOI occurred during the NICU stay, and by PICC type. The utility of the model in establishing which intervention is cost-effective was illustrated by the comparison between AM-PICC and S-PICC. The cost-effective intervention is the one which achieves the most health benefits given its costs and the cost-effectiveness threshold of £20 000/QALY,11 a benchmark of the maximum...
acceptable added cost per QALY gained commonly used for the UK NHS. The robustness of the results was assessed by varying the parameter values over the 95% CI and with scenario analysis. For details, see online supplementary material 8. The model was validated using the Advishe checklist, see online supplementary material 9.

Exploring the value of further research
The model can calculate the health benefits of knowing which is the cost-effective intervention with absolute certainty (ie, with perfect information), the ‘expected value of perfect information’ (EVPI). Using the cost-effectiveness threshold as the monetary value of 1 QALY, the health benefits can be converted to monetary units. This represents the most that the UK NHS should invest in future research to inform a policy decision. The EVPI was calculated considering the uncertainty around all parameters informing the model and for each individual parameter. It is presented for the preterm infant population in England over 10 years, assuming that this is the population who would benefit from any future research. The calculations were conducted using the online SAVI simulator.

RESULTS
Long-term value of preventing NDI
Figure 2 shows the outcomes by NDI level over the infants’ expected lifetime. The model predicts that, as the NDI level worsens, life expectancy and QALYs reduce, while costs increase. The long-term value of preventing NDI can be computed as the difference between the predicted QALYs and costs with and without impairment. As an example, the difference in costs and health outcomes between mild and no NDI is £3690 lower costs and 2.16 additional QALYs. If a QALY is valued at £20 000/QALY, the maximum price that could would still make such a new hypothetical intervention cost-effective, assuming that 1 QALY is valued at £20 000. For instance, at GA 23–27 weeks, for every 5% reduction in relative risk of LOI cases (eg, from 0.95 to 0.90), the maximum price increases by £120. Because the risk of LOI is lower in infants with older GAs (28–32 weeks), the maximum acquisition price increases only by £20. A new hypothetical intervention reducing 20% of LOI (relative risk 0.8) could cost up to £479 and £79 and still be cost-effective in the subgroups of infants born at 23–27 and 28–32 weeks GA, respectively.

Cost-effectiveness of an intervention to prevent LOI: AM-PICC versus S-PICC
The model can be used to analyse the cost-effectiveness of any intervention to prevent LOI in preterm infants during their stay in the NICU. To illustrate, table 2 shows the results of the cost-effectiveness analysis comparing AM-PICC with S-PICC. As expected given the results of the PREVAIL trial, AM-PICC is not cost-effective.

Sensitivity analysis
The results were robust to all sensitivity analyses and scenarios apart from varying the effect of AM-PICC in preventing LOI, and, to a smaller extent, the effect of LOI on the risk of death. For details, see online supplementary material 8.

Table 2  Cost-effectiveness results

| Cost-effectiveness results | Gestational age (weeks) | 23–27 | 28–32 |
|----------------------------|-------------------------|-------|-------|
| AM-PICC                    |                         |       |       |
| Total costs (95% CI)       | £127 183 (120 983 to 133 919) | £83 588 (77 048 to 90 839) |
| Total QALYs (95% CI)       | 16.48 (15.41 to 17.59)   | 21.46 (20.67 to 22.17)  |
| S-PICC                     |                         |       |       |
| Total costs (95% CI)       | £127 128 (120 936 to 133 866) | £83 533 (76 994 to 90 784) |
| Total QALYs (95% CI)       | 16.49 (15.44 to 17.60)   | 21.46 (20.67 to 22.17)  |
| AM-PICC vs S-PICC           |                         |       |       |
| Cost difference (95% CI)   | £35 (26 to 88)           | £35 (48 to 64)            |
| QALY difference (95% CI)   | −0.01 (−0.09 to 0.04)    | 0.00 (−0.01 to 0.01)      |
| Incremental net health benefit at £20 000/QALY | −0.01 (−0.09 to 0.04) | −0.01 (−0.02 to 0.00) |

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Value of further research
For the population of preterm babies, over a period of 10 years, the EVPI was £2.4 million. The model input driving the EVPI is the relative risk of LOI. This means that, if the UK NHS were to invest in more research to make sure that S-PICCs are the best policy, this research should be on another trial on the effectiveness of S-PICCs versus AM-PICCs. Depending on the cost and the design of a new trial, and given that such a trial would not determine the relative risk with absolute certainty, further research on the comparison of AM-PICC with S-PICC may not be good value for money.

DISCUSSION
Summary of findings
A new decision analytic model was developed to predict the quality-adjusted life expectancy and lifetime NHS costs of infants using AM-PICC or S-PICC. Based on existing literature, the model assumes that LOI negatively affects health outcomes. Under this assumption, a strategy to prevent LOI is valuable as it can lead to an increase in life expectancy, health-related quality of life and a reduction in costs. AM-PICCs, however, being more costly and with no evidence of benefits over S-PICCs, are not cost-effective. Whether more research on the effectiveness of AM-PICC versus S-PICC is cost-effective depends on the cost and the design of future trials.

Strengths
This study represents the first attempt at estimating the cost-effectiveness of AM-PICCs in the NICU setting. Available studies on impregnated PICCs considered older populations and different antimicrobials agents, precluding meaningful comparisons. The model synthesises relevant information on the costs and consequences of LOI. It is flexible so that it can be used to evaluate the cost-effectiveness of any other intervention to prevent LOI during a NICU stay, informing various policy decisions, that is, whether new interventions should be adopted and how much to invest in future research.

Limitations
The causal effect of LOI on death and hospital costs could not be estimated given the small number of deaths. Consequently, the model base-case assumes that infants incur the same costs irrespective of LOI or survival status, and that LOI does not increase the risk of death at 6 months. These assumptions were tested in a scenario analysis, and in the comparison between AM-PICC and S-PICC, they had no impact on the results. If LOI is linked with higher costs and higher risk of death during the NICU stay, its prevention can be linked to greater health and economic benefit than those estimated above.

The model assumes that LOI increases the risk of death and NDI at 2 years of age, based on publications identified from a non-systematic citation search. Despite the nature of the searches, three systematic reviews were identified, and carers, which were not accounted for here.

The model structure constrains the impact of preventing LOI to reducing the risk of NDI and death at 2 years of age. Some studies suggest that the impact of LOI on NDI is mediated via necrotising enterocolitis. Given that no studies were identified that disentangled the direct effect of LOI on NDI from the indirect effect via antibiotic treatment, necrotising enterocolitis was not modelled explicitly.

This study takes the perspective of the NHS for costs and benefits following the National Institute for Health and Care Excellence guidance to evaluate interventions funded by the NHS.

This covers hospital costs and costs of community healthcare. It was not possible to include the latter over the time period from PICC insertion to 2 years of age due to a lack of comprehensive routine healthcare databases which compile such data. Costs falling on other sectors, such as social care and education, are likely to be relevant, but fall outside the NHS perspective. The study considers the impact of LOI on the infants’ length and health-related quality of life only. Health outcomes experienced by infants and children may have spill over effects to their family and carers, which were not accounted for here.

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Contributors
AG, RINdeF and LB conceptualised the model with valuable input from SJO and RG. CD, CIF and KLH provided valuable assistance in obtaining access to the data. AG and RINdeF performed the main analysis with support from LB. All authors provided input in the interpretation of the study results. AG led the drafting of the manuscript with support from RINdeF and LB. All authors contributed to the editing of the manuscript. All authors read and approved the final manuscript.

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Disclaimer
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England, the Welsh Government and, with some individual projects, other devolved administrations and crown dependencies. www.hqip.org.uk/national-programmes. This research was informed by data collected by NHS Digital (former Health and Social Care Information Centre). Copyright 2015–2018, the Health and Social Care Information Centre. Re-used with the permission of the Health and Social Care Information Centre. All rights reserved.

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