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

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

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# Abstract

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

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**Background:** Clinical trials show that antimicrobial-impregnated central venous catheters reduce catheter-related bloodstream infection in adults and children receiving intensive care, but there is insufficient evidence for use in newborn babies.

**Objectives:** The objectives were (1) to determine clinical effectiveness by conducting a randomised controlled trial comparing antimicrobial-impregnated peripherally inserted central venous catheters with standard peripherally inserted central venous catheters for reducing bloodstream or cerebrospinal fluid infections (referred to as bloodstream infections); (2) to conduct an economic evaluation of the costs, cost-effectiveness and value of conducting additional research; and (3) to conduct a generalisability analysis of trial findings to neonatal care in the NHS.

**Design:** Three separate studies were undertaken, each addressing one of the three objectives. (1) This was a multicentre, open-label, pragmatic randomised controlled trial; (2) an analysis was undertaken of hospital care costs, lifetime cost-effectiveness and value of information from an NHS perspective; and (3) this was a retrospective cohort study of bloodstream infection rates in neonatal units in England.

**Setting:** The randomised controlled trial was conducted in 18 neonatal intensive care units in England.

**Participants:** Participants were babies who required a peripherally inserted central venous catheter (of 1 French gauge in size).

**Interventions:** The interventions were an antimicrobial-impregnated peripherally inserted central venous catheter (coated with rifampicin–miconazole) or a standard peripherally inserted central venous catheter, allocated randomly (1 : 1) using web randomisation.

**Main outcome measure:** Study 1 – time to first bloodstream infection, sampled between 24 hours after randomisation and 48 hours after peripherally inserted central venous catheter removal. Study 2 – cost-effectiveness of the antimicrobial-impregnated peripherally inserted central venous catheter compared with the standard peripherally inserted central venous catheters. Study 3 – risk-adjusted bloodstream rates in the trial compared with those in neonatal units in England. For study 3, the data used were as follows: (1) case report forms and linked death registrations; (2) case report forms and linked death registrations linked to administrative health records with 6-month follow-up; and (3) neonatal health records linked to infection surveillance data.

**Results:** Study 1, clinical effectiveness – 861 babies were randomised (antimicrobial-impregnated peripherally inserted central venous catheter,  $n = 430$ ; standard peripherally inserted central venous catheter,  $n = 431$ ). Bloodstream infections occurred in 46 babies (10.7%) randomised to antimicrobial-impregnated peripherally inserted central venous catheters and in 44 (10.2%) babies randomised to standard peripherally inserted central venous catheters. No difference in time to bloodstream infection was detected (hazard ratio 1.11, 95% confidence interval 0.73 to 1.67;  $p = 0.63$ ). Secondary outcomes of rifampicin resistance in positive blood/cerebrospinal fluid cultures, mortality, clinical outcomes at neonatal unit discharge and time to peripherally inserted central venous catheter removal were similar in both groups. Rifampicin resistance in positive peripherally inserted central venous catheter tip cultures was higher in the antimicrobial-impregnated peripherally inserted central venous catheter group (relative risk 3.51, 95% confidence interval 1.16 to 10.57;  $p = 0.02$ ) than in the standard peripherally inserted central venous catheter group. Adverse events were similar in both groups. Study 2, economic evaluation – the mean cost of babies' hospital care was £83,473. Antimicrobial-impregnated peripherally inserted central venous catheters were not cost-effective. Given the increased price, compared with standard peripherally inserted central venous catheters, the minimum reduction in risk of bloodstream infection for antimicrobial-impregnated peripherally inserted central venous catheters to be cost-effective was 3% and 15% for babies born at 23–27 and 28–32 weeks' gestation, respectively. Study 3, generalisability analysis – risk-adjusted bloodstream infection rates per 1000 peripherally inserted central venous catheter days were similar among babies in the trial and in all neonatal units. Of all bloodstream infections in babies receiving intensive or high-dependency care in neonatal units, 46% occurred during peripherally inserted central venous catheter days.

**Limitations:** The trial was open label as antimicrobial-impregnated and standard peripherally inserted central venous catheters are different colours. There was insufficient power to determine differences in rifampicin resistance.

**Conclusions:** No evidence of benefit or harm was found of peripherally inserted central venous catheters impregnated with rifampicin–miconazole during neonatal care. Interventions with small effects on bloodstream infections could be cost-effective over a child's life course. Findings were generalisable to neonatal units in England. Future research should focus on other types of antimicrobial impregnation of peripherally inserted central venous catheters and alternative approaches for preventing bloodstream infections in neonatal care.

**Trial registration:** Current Controlled Trials ISRCTN81931394.

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# Contents

List of tables	xiii
List of figures	xvii
List of boxes	xxi
Glossary	xxiii
List of abbreviations	xxv
Plain English summary	xxvii
Scientific summary	xxix
<b>Chapter 1</b> Introduction	<b>1</b>
Background	1
Evidence review	2
Study rationale	4
Aims and objectives	4
<i>Aims</i>	4
<i>Objectives</i>	4
<b>Chapter 2</b> Clinical effectiveness randomised controlled trial methods	<b>7</b>
Trial design	7
<i>Ethics approval and research governance</i>	7
<i>Selection of trial sites</i>	7
<i>Participants</i>	8
Recruitment procedure	9
<i>Screening</i>	9
<i>Enrolment</i>	9
<i>Randomisation, concealment and blinding</i>	9
Treatments	9
Follow-up	10
Measures	11
<i>Baseline characteristics</i>	11
<i>Adherence to treatment and the protocol</i>	11
<i>Primary outcome</i>	11
<i>Secondary outcomes</i>	11
<i>Safety outcomes</i>	12
Sample size	12
Statistical methods	12
<i>General statistical considerations</i>	12
<i>Baseline characteristics</i>	13
<i>Adherence to treatment and the protocol</i>	13
<i>Primary outcome</i>	13
<i>Secondary outcomes</i>	14
<i>Safety analyses</i>	15

## CONTENTS

Patient and public involvement	15
Trial oversight and role of funders	15
<i>Trial Management Group</i>	15
<i>Trial Steering Committee</i>	15
<i>Independent Data and Safety Monitoring Committee</i>	15
<i>Role of the funding source</i>	16
<i>Dual publication</i>	16
<b>Chapter 3 Clinical effectiveness randomised controlled trial results</b>	<b>17</b>
Recruitment	17
Interim analysis	17
Final analysis	18
<i>Baseline characteristics</i>	18
<i>Adherence to treatment and the protocol</i>	21
<i>Primary outcome</i>	22
<i>Secondary outcomes</i>	23
<i>Safety analysis</i>	26
<b>Chapter 4 Economic evaluation</b>	<b>27</b>
Introduction	27
Revised objectives	28
Cost of hospital care	28
<i>Background</i>	28
<i>Methods</i>	28
<i>Results</i>	33
Cost-effectiveness of antimicrobial-impregnated versus standard peripherally inserted central venous catheters over a lifetime	38
<i>Background</i>	38
<i>Methods</i>	38
<i>Results</i>	47
Value of information	51
<i>Methods</i>	51
<i>Results</i>	52
Summary of findings	52
<b>Chapter 5 Generalisability analysis</b>	<b>55</b>
Introduction	55
Aims and objectives	56
<i>Objectives</i>	56
Methods	56
<i>Data sources</i>	56
<i>Case definition</i>	57
<i>Identifying babies in the PREVAIL trial</i>	58
<i>Generalisability and applicability</i>	58
<i>Trends in rates of bloodstream infection in all babies admitted to neonatal intensive care units and local neonatal units</i>	59
<i>The contribution of peripherally inserted central venous catheters to total bloodstream infection</i>	60
Results	60
<i>Identifying babies in the PREVAIL trial</i>	60
<i>Generalisability and applicability</i>	60

<i>Trends in rates of bloodstream infection in all babies admitted to neonatal intensive care units and local neonatal units</i>	63
<i>The contribution of peripherally inserted central venous catheters to total bloodstream infection rates</i>	67
<b>Chapter 6 Discussion</b>	<b>69</b>
Main findings	69
<i>Clinical effectiveness randomised controlled trial</i>	69
<i>Economic analysis</i>	69
<i>Generalisability analysis</i>	69
Clinical effectiveness randomised controlled trial	70
<i>Strengths and limitations</i>	70
<i>Findings in context</i>	70
<i>Practice context</i>	71
Economic evaluation	71
<i>Strengths and limitations</i>	71
<i>Findings in context</i>	73
Generalisability analysis	74
<i>Strengths and limitations</i>	74
<i>Findings in context</i>	75
Relevance to future research	75
<b>Chapter 7 Conclusions</b>	<b>77</b>
Implications for practice	77
Recommendations for research	77
<b>Acknowledgements</b>	<b>79</b>
<b>References</b>	<b>85</b>
<b>Appendix 1</b> Additional information on clinical effectiveness methods	<b>95</b>
<b>Appendix 2</b> Additional information on clinical effectiveness results	<b>97</b>
<b>Appendix 3</b> Additional information on economic analysis: data access	<b>105</b>
<b>Appendix 4</b> Additional information on economic analysis: data	<b>109</b>
<b>Appendix 5</b> Additional information on economic analysis: data cleaning	<b>111</b>
<b>Appendix 6</b> Additional information on economic analysis: type and length of stay	<b>117</b>
<b>Appendix 7</b> Additional information on economic analysis: review and meta-analysis	<b>123</b>
<b>Appendix 8</b> Additional information on economic analysis: probability calculations	<b>127</b>
<b>Appendix 9</b> Additional information on economic analysis: costs	<b>131</b>
<b>Appendix 10</b> Additional information on economic analysis: model validation	<b>137</b>
<b>Appendix 11</b> Additional information on economic analysis: sensitivity analysis	<b>141</b>
<b>Appendix 12</b> Additional information on generalisability study: linkage methods	<b>147</b>

## CONTENTS

<b>Appendix 13</b> Additional information on generalisability study: clearly pathogenic organisms	<b>151</b>
<b>Appendix 14</b> Additional information on the generalisability study: changes over time in national infection surveillance	<b>157</b>
<b>Appendix 15</b> Additional information on the generalisability study: comparison of included and excluded PREVENTing infection using Antimicrobial-Impregnated Long lines trial babies	<b>159</b>
<b>Appendix 16</b> Additional information on the generalisability study: model-building for rate per 1000 peripherally inserted central venous catheter days	<b>161</b>
<b>Appendix 17</b> Additional information on the generalisability study: model-building for trend per 1000 peripherally inserted central venous catheter days	<b>165</b>
<b>Appendix 18</b> Additional information on the generalisability study: model-building for trend per 1000 days	<b>169</b>
<b>Appendix 19</b> Additional information on the generalisability study: model-building for rate per 100 admissions	<b>173</b>
<b>Appendix 20</b> Additional information on the generalisability study: bloodstream infection definitions	<b>177</b>
<b>Appendix 21</b> Additional information on the generalisability study: flow diagram of included PREVAIL babies	<b>179</b>
<b>Appendix 22</b> Additional information on the generalisability study: causative organisms	<b>181</b>
<b>Appendix 23</b> Additional information on the generalisability study: rates of bloodstream infection per 1000 peripherally inserted central venous catheter days	<b>183</b>
<b>Appendix 24</b> Additional information on the generalisability study: trends in bloodstream infection risk factors	<b>185</b>
<b>Appendix 25</b> Additional information on the generalisability study: flow diagrams	<b>189</b>

# List of tables

<b>TABLE 1</b> Overview of evidence on the effectiveness of miconazole- and rifampicin-impregnated or minocycline- and rifampicin-impregnated CVCs for reducing the rate of BSIs	3
<b>TABLE 2</b> Number of NICUs, LNUs and SCBUs in the NHS in England in 2017, based on data from the NNAP	8
<b>TABLE 3</b> Definitions of level of neonatal care	8
<b>TABLE 4</b> Baseline characteristics: demographics	19
<b>TABLE 5</b> Baseline characteristics: delivery characteristics	20
<b>TABLE 6</b> Baseline characteristics: neonatal care	20
<b>TABLE 7</b> Baseline characteristics: other clinical characteristics	21
<b>TABLE 8</b> The PICC insertion status and end point of follow-up	22
<b>TABLE 9</b> Results: primary outcome	23
<b>TABLE 10</b> Results: secondary outcomes relating to infection	24
<b>TABLE 11</b> Results: secondary outcome – type of organism isolated from BSI	25
<b>TABLE 12</b> Results: other clinical secondary outcomes	25
<b>TABLE 13</b> Results: secondary outcomes to detect potential biases in sampling	26
<b>TABLE 14</b> Related AEs	26
<b>TABLE 15</b> Length of stay and costs per PREVAIL baby recorded in each database within the follow-up period	35
<b>TABLE 16</b> Length of stay and cost of hospital care of the PREVAIL babies with hospitalisations recorded in the NNRD and HES APC	37
<b>TABLE 17</b> Parameters for predicting outcomes in early childhood	41
<b>TABLE 18</b> Parameters for predicting lifetime costs and health outcomes	46
<b>TABLE 19</b> Distribution of children by NDI level at 2 years of age	48
<b>TABLE 20</b> Cost-effectiveness results over the lifetime time horizon	49
<b>TABLE 21</b> Comparison of baby characteristics of babies who received S-PICCs in NICUs and LNUs according to enrolment in the PREVAIL trial during the PREVAIL trial period	61



<b>TABLE 22</b> Comparison of clinical characteristics in babies who received S-PICCs in NICUs and LNUs, according to enrolment in the PREVAIL trial during the PREVAIL trial period	<b>61</b>
<b>TABLE 23</b> The unadjusted and risk-adjusted annual percentage change in rate of BSI (clearly pathogenic organisms) during PICC days at risk per 1000 PICC days in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs from March 2010 to June 2017	<b>64</b>
<b>TABLE 24</b> The annual change in the rate of late-onset BSI (pathogens) per 1000 days of intensive and high-dependency care and per 100 admissions in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs from March 2010 to June 2017	<b>65</b>
<b>TABLE 25</b> The BSI rate and proportion of total BSIs (all organisms) per 100 admissions for babies receiving intensive or high-dependency care in NICUs and LNUs from August 2015 to June 2017	<b>67</b>
<b>TABLE 26</b> Substantial amendments to the trial protocol	<b>95</b>
<b>TABLE 27</b> Pathogen classifications	<b>96</b>
<b>TABLE 28</b> Randomisation details for each site	<b>97</b>
<b>TABLE 29</b> Screening and recruitment summary for each site	<b>98</b>
<b>TABLE 30</b> Reasons for parents not being approached	<b>98</b>
<b>TABLE 31</b> Reasons for parents declining consent	<b>99</b>
<b>TABLE 32</b> Reasons babies not randomised despite parents providing consent	<b>99</b>
<b>TABLE 33</b> Co-enrolment in other trials, split by site	<b>101</b>
<b>TABLE 34</b> Oversight committee meetings and recommendations	<b>101</b>
<b>TABLE 35</b> Sampling for outcomes and resistance testing for secondary outcomes	<b>102</b>
<b>TABLE 36</b> Protocol deviations	<b>102</b>
<b>TABLE 37</b> Number of babies experiencing a BSI in each subgroup	<b>103</b>
<b>TABLE 38</b> Rifampicin-resistant positive isolates	<b>104</b>
<b>TABLE 39</b> Number of BSIs each baby experienced	<b>104</b>
<b>TABLE 40</b> Types of treatment for retinopathy of prematurity	<b>104</b>
<b>TABLE 41</b> Correspondence between 15/16 HRG code and 16/17 HRG code	<b>115</b>
<b>TABLE 42</b> Derivation of the 'deflated' HRGs	<b>115</b>
<b>TABLE 43</b> Unit cost of HRGs relating to the stay in the neonatal and paediatric care unit	<b>116</b>

<b>TABLE 44</b> The NNRD data on PREVAIL babies: breakdown of days in the neonatal care unit by critical care HRGs, without adjustment for time outside the follow-up period	<b>117</b>
<b>TABLE 45</b> The NNRD data on PREVAIL babies: length of stay and cost per episode and per baby, with and without adjustment for time outside follow-up	<b>118</b>
<b>TABLE 46</b> The PICANet data on PREVAIL babies: breakdown of days in the paediatric intensive care unit by critical care HRG codes within the follow-up period	<b>119</b>
<b>TABLE 47</b> The HES APC data on PREVAIL babies: length of stay per spell and per baby, with and without adjustment for time outside follow-up	<b>119</b>
<b>TABLE 48</b> The HES APC data on the PREVAIL babies: costs of FCEs	<b>120</b>
<b>TABLE 49</b> The HES APC data on the PREVAIL babies: breakdown of FCEs by admission type and cost, unadjusted by the time outside the follow-up period	<b>120</b>
<b>TABLE 50</b> The HES APC data on the PREVAIL babies: length and cost of admissions unadjusted and adjusted by time outside follow-up	<b>121</b>
<b>TABLE 51</b> The HES outpatient data on the PREVAIL babies: cost per outpatient appointment	<b>121</b>
<b>TABLE 52</b> Items included in the NDI measure	<b>123</b>
<b>TABLE 53</b> Studies on the effect of infection on NDI in preterm infants	<b>124</b>
<b>TABLE 54</b> Studies on the effect of infection on the risk of death in preterm infants	<b>124</b>
<b>TABLE 55</b> Meta-analysis on the effect of infection on NDI	<b>124</b>
<b>TABLE 56</b> Meta-analysis on the effect of infection on the risk of death at 2 years of age	<b>125</b>
<b>TABLE 57</b> Probability of clinically serious BSI with S-PICCs	<b>127</b>
<b>TABLE 58</b> Probability of death over the time horizon of 6 months	<b>128</b>
<b>TABLE 59</b> Predictors of the risk of death	<b>128</b>
<b>TABLE 60</b> Number of deaths before end of follow-up, by infection status (all gestational ages)	<b>129</b>
<b>TABLE 61</b> Probability of death before the end of follow-up, without infection	<b>129</b>
<b>TABLE 62</b> Annual transition probabilities across impairment states (age 2–5 years)	<b>130</b>
<b>TABLE 63</b> Annual transition probabilities across impairment states (age 5–8 years)	<b>130</b>
<b>TABLE 64</b> Summary statistics of all hospital costs over 6 months from PICC insertion	<b>132</b>
<b>TABLE 65</b> Results of regression analysis Gaussian distribution log link	<b>133</b>

<b>TABLE 66</b> Unit cost weighted average by activity	<b>134</b>
<b>TABLE 67</b> Resource use 6–24 months	<b>135</b>
<b>TABLE 68</b> Costs 6–24 months	<b>135</b>
<b>TABLE 69</b> List of sensitivity analyses	<b>141</b>
<b>TABLE 70</b> Details of the alternative scenarios on RR of death and costs	<b>142</b>
<b>TABLE 71</b> Maximum acquisition price per AM-PICC effectiveness (gestational age: 23–27 weeks)	<b>143</b>
<b>TABLE 72</b> Maximum acquisition price per AM-PICC effectiveness (gestational age: 28–32 weeks)	<b>143</b>
<b>TABLE 73</b> Incremental net health and monetary benefit by scenario for cost-effectiveness thresholds of £13,000 and £20,000 per QALY	<b>145</b>
<b>TABLE 74</b> The rules followed in manual review	<b>148</b>
<b>TABLE 75</b> The trend pre and post system change and step change in number of BSIs reported from the interrupted time series regression of all BSIs, skin organism BSIs only and excluding skin organism BSIs	<b>158</b>
<b>TABLE 76</b> Distribution of baseline risk factors in babies with S-PICCs in the PREVAIL trial who were included in the analysis compared with those who were excluded	<b>159</b>
<b>TABLE 77</b> The IRRs and 95% CIs for risk factors from forward stepwise multilevel Poisson regression of BSI per 1000 PICC days	<b>162</b>
<b>TABLE 78</b> The IRRs and 95% CIs for risk factors from forward stepwise multilevel Poisson regression of BSI (pathogens) per 1000 PICC days per month	<b>166</b>
<b>TABLE 79</b> The IRRs and 95% CIs for risk factors from forward stepwise multilevel Poisson regression of the rate of BSI (pathogens) per 1000 days of intensive and high-dependency care per month	<b>170</b>
<b>TABLE 80</b> The IRRs and 95% CIs for risk factors from forward stepwise multilevel Poisson regression of the rate of total late-onset BSIs (pathogens) per 100 admissions per month	<b>174</b>
<b>TABLE 81</b> Definitions of BSI used in this study	<b>177</b>
<b>TABLE 82</b> The distribution of causative organisms of the first BSI during PICC days at risk per admission in the PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs during the PREVAIL trial period (August 2015 to January 2017)	<b>181</b>
<b>TABLE 83</b> Crude and risk-adjusted rates of BSI per 1000 PICC days for babies in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs during the PREVAIL trial period (August 2015 to January 2017)	<b>184</b>

# List of figures

<b>FIGURE 1</b> Flow diagram to show inter-relationship between the three components of the PREVAIL study	6
<b>FIGURE 2</b> Schematic representation of the trial procedures	10
<b>FIGURE 3</b> The CONSORT flow diagram for all trial participants	18
<b>FIGURE 4</b> Kaplan–Meier plot: time to first BSI (primary outcome)	23
<b>FIGURE 5</b> Overview of the methods used to estimate the cost of hospitalisations	29
<b>FIGURE 6</b> Model structure for predicting outcomes in early childhood	40
<b>FIGURE 7</b> Model structure for predicting lifetime costs and health outcomes	41
<b>FIGURE 8</b> Costs and health outcomes by NDI level over expected lifetime	49
<b>FIGURE 9</b> Maximum acquisition price per AM-PICC effectiveness (gestational age at birth of 23–27 weeks)	50
<b>FIGURE 10</b> Time at risk for PICC days at risk, early-onset BSI (no PICC) and late-onset BSI (no PICC)	57
<b>FIGURE 11</b> Crude and risk-adjusted rates of BSI (for all organisms) per 1000 PICC days in babies who received S-PICCs in NICUs and LNUs, according to enrolment in the PREVAIL trial during the PREVAIL trial period	63
<b>FIGURE 12</b> Risk-adjusted rate of BSI (clearly pathogenic organisms) during PICC days at risk per 1000 PICC days, by year of admission in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs	64
<b>FIGURE 13</b> Risk-adjusted rate of total late-onset BSI (pathogens) per 1000 intensive and high-dependency care days of stay, by year of admission in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs	66
<b>FIGURE 14</b> Risk-adjusted rate of late-onset BSI (pathogens) per 100 admissions, by year of admission in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs	66
<b>FIGURE 15</b> Recruitment graph	100
<b>FIGURE 16</b> Kaplan–Meier plot for babies born at < 28 weeks of gestation	103
<b>FIGURE 17</b> Kaplan–Meier plot for babies born at $\geq$ 28 weeks of gestation	103
<b>FIGURE 18</b> Preparation of the neonatal care data (received from NNRD)	111
<b>FIGURE 19</b> Preparation of the paediatric intensive care data (received from PICANet)	113

<b>FIGURE 20</b> Preparation of the HES APC data (received from NHS Digital)	<b>114</b>
<b>FIGURE 21</b> Preparation of the HES outpatient and A&E data (received from NHS Digital)	<b>114</b>
<b>FIGURE 22</b> Maximum acquisition price per AM-PICC effectiveness, gestational age: 28–32 weeks	<b>144</b>
<b>FIGURE 23</b> Univariate sensitivity analyses for gestational age subgroup 23–27 weeks at the £20,000 per QALY cost-effectiveness threshold	<b>144</b>
<b>FIGURE 24</b> Univariate sensitivity analyses for gestational age subgroup 28–32 weeks at the £20,000 per QALY cost-effectiveness threshold	<b>145</b>
<b>FIGURE 25</b> Interrupted time series for the number of BSI episodes reported to the PHE surveillance system over time for infants aged < 1 year, excluding CoNS (aqua) and only CoNS (coral)	<b>158</b>
<b>FIGURE 26</b> Flow diagram to show babies randomised to receive S-PICCs in PREVAIL who were linked to the NNRD and included in the generalisability analysis	<b>179</b>
<b>FIGURE 27</b> Crude and risk-adjusted rates of BSI (pathogens) per 1000 PICC days in babies who received S-PICCs in NICUs and LNUs according to enrolment in the PREVAIL trial during the PREVAIL trial period (August 2015 to January 2017)	<b>183</b>
<b>FIGURE 28</b> The percentage of babies admitted to NICUs and LNUs according to gestational age and year	<b>185</b>
<b>FIGURE 29</b> The mean number of days of intensive and high-dependency care per baby in NICUs and LNUs by week of gestational age at birth	<b>185</b>
<b>FIGURE 30</b> The mean number of PICC days per baby in NICUs and LNUs by week of gestational age at birth	<b>186</b>
<b>FIGURE 31</b> The mean number of central line days per baby in NICUs and LNUs by week of gestational age at birth	<b>186</b>
<b>FIGURE 32</b> The mean age at first PICC insertion in NICUs and LNUs by week of gestational age at birth	<b>187</b>
<b>FIGURE 33</b> The mean number of non-invasive ventilation days per baby in NICUs and LNUs by week of gestational age at birth	<b>187</b>
<b>FIGURE 34</b> The mean number of invasive ventilation days per baby in NICUs and LNUs by week of gestational age at birth	<b>188</b>
<b>FIGURE 35</b> The number of admissions and babies receiving S-PICCs according to NNU level and enrolment in the PREVAIL trial for the PREVAIL trial period (August 2015 to January 2017)	<b>189</b>

**FIGURE 36** The number of admissions and babies who received PICCs from March 2010 to June 2017 and who were included in the analysis of changes over time in BSI during PICC days at risk **189**

**FIGURE 37** The number of admissions and babies who received intensive or high-dependency care from March 2010 to June 2017 and who were included in the analysis of changes over time in late-onset BSI **190**



# List of boxes

<b>BOX 1</b> Main model assumptions	<b>141</b>
<b>BOX 2</b> List of clearly pathogenic organisms from surveillance data that linked to babies in the NNRD	<b>151</b>
<b>BOX 3</b> List of other organisms from surveillance data that linked to babies in the NNRD	<b>153</b>





# Glossary

**Bloodstream infection** This refers to any positive bacterial or fungal cultures from blood or cerebrospinal fluid samples. A clinically serious bloodstream infection refers to a bloodstream infection for which the baby was treated for > 72 hours with intravenous antibiotics or died during treatment.

**CATheter Infections in CHildren** A randomised controlled trial and economic evaluation comparing impregnated and standard central venous catheters in children.

**Catheter-related bloodstream infection** This refers to a bloodstream infection with isolation of the same organism from the peripherally inserted central venous catheter tip and blood or cerebrospinal fluid.



## List of abbreviations

A&E	accident and emergency	IGARD	Independent Group Advising on the Release of Data
AE	adverse event		
AIC	Akaike information criterion	IQR	interquartile range
AM-PICC	antimicrobial-impregnated peripherally inserted central venous catheter	IRR	incidence rate ratio
ANOVA	analysis of variance	LCTC	Liverpool Clinical Trials Centre
APC	Admitted Patient Care	LNU	local neonatal unit
Apgar	appearance, pulse, grimace, activity, respiration	MDI	Mental Development Index
BIC	Bayesian information criterion	NDAU	Neonatal Data Analysis Unit
BSI	bloodstream infection	NDI	neurodevelopmental impairment
CATCH	CATheter Infections in CHildren	NEC	necrotising enterocolitis
CI	confidence interval	NICE	National Institute for Health and Care Excellence
CoNS	coagulase-negative staphylococcus	NICU	neonatal intensive care unit
CONSORT	Consolidated Standards of Reporting Trials	NIHR	National Institute for Health Research
CRF	case report form	NNAP	National Neonatal Audit Programme
CSF	cerebrospinal fluid	NNRD	National Neonatal Research Database
CVC	central venous catheter	NNU	neonatal unit
EVPI	expected value of perfect information	OR	odds ratio
EVPII	expected value of partial perfect information	PDI	Psychomotor Developmental Index
FCE	finished consultant episode	PHE	Public Health England
GDPR	General Data Protection Regulation	PI	principal investigator
HES	Hospital Episode Statistics	PICANet	Paediatric Intensive Care Audit Network
HQIP	Healthcare Quality Improvement Partnership	PICC	peripherally inserted central venous catheter
HR	hazard ratio	PICU	paediatric intensive care unit
HRG	Healthcare Resource Group	PREVAIL	PREVenting infection using Antimicrobial-Impregnated Long lines
HRQoL	health-related quality of life	QALY	quality-adjusted life-year
IDSMC	Independent Data and Safety Monitoring Committee	RCT	randomised controlled trial
		RN	research nurse

## LIST OF ABBREVIATIONS

RR	relative risk	TSC	Trial Steering Committee
SAE	serious adverse event	UCL	University College London
SCBU	special care baby unit	UKNC	UK Neonatal Collaborative
SD	standard deviation	UoL	University of Liverpool
S-PICC	standard peripherally inserted central venous catheter	UoY	University of York
SGSS	Second Generation Surveillance System	VICSG	Victorian Infant Collaborative Study Group
TMG	Trial Management Group	Vol	value of information

## Plain English summary

Babies who are born too early or who are very sick require intensive care after birth and during early life. Most will have a long, narrow, plastic tube, called a catheter, inserted into a vein. The catheter is used to give babies fluids containing medicines and nutrition to keep them well and help them grow.

The catheter can remain in place for several days or weeks. But the presence of plastic tubing in the vein increases the risk of infection. This study aimed to find out whether or not catheters coated with antimicrobial medicines, called rifampicin and miconazole, could reduce the risk of infection. These medicines act by stopping germs from growing on the catheter, but do not harm the baby or interfere with other treatments.

A randomised controlled trial was carried out in 18 neonatal units in England. Whenever a baby needed a catheter, their parents were asked for consent to participate in the trial. The baby was then randomised, similar to tossing a coin, to receive either the antimicrobial catheter or a standard one. A total of 861 babies participated. We followed up all babies in the same way until after the catheter was removed to compare how often babies in each group had an infection.

It was found that antimicrobial catheters were no better or worse at preventing infection than standard catheters. Antimicrobial catheters cost more and we found no evidence of benefit; these results suggest that their use in neonatal intensive care is not justified. It was calculated that further research on ways to reduce infection may be good value for money, depending on the costs of this research. The babies who took part in this study were typical of babies in England receiving catheters, meaning that the results can be applied across the NHS. Future research should focus on catheters that contain other types of antimicrobials and alternative ways of preventing infection.



# 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 ( $\geq 2$  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.

### **Funding**

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# Chapter 1 Introduction

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## Background

In the UK, approximately 8% of all babies are born preterm, defined as delivery before 37 weeks of gestational age.<sup>2</sup> Preterm birth is associated with high rates of neonatal and childhood mortality and with high rates of long-term chronic conditions, manifesting as adverse neurodevelopment and respiratory disease.<sup>3-6</sup> Risks of these outcomes increase steeply with earlier gestational age at birth. Risks are even higher in babies who develop a bloodstream infection (BSI).<sup>7-10</sup> A BSI can be an early-onset infection (i.e. before 2 days of age), which is thought to be predominantly due to organisms transmitted from mother to baby.<sup>11,12</sup> Thereafter, a BSI is commonly caused by organisms that enter the bloodstream through skin or mucosal barriers in babies with immature immune defences, or through contamination of internal devices, such as central venous catheters (CVCs).<sup>13-15</sup> In the UK, 14% of all babies born are admitted to a neonatal unit (NNU), but this proportion is much higher for babies born preterm: all of the 1.4% of babies born before 32 weeks of gestation spend time in a NNU.<sup>16</sup> On average, 5% of all babies admitted to a NNU experience a BSI, but this proportion rises to 22% for babies born before 33 weeks of gestation and to 36% for babies born before 29 weeks of gestation.<sup>17,18</sup> Therefore, prevention of BSI, and its acute and long-term adverse outcomes, is a very high priority for neonatal care.

Central venous catheters are a common source of BSI in babies receiving neonatal care. According to two national surveillance studies,<sup>19,20</sup> 43–48% of BSIs occurring after the first 2 days of age are considered to be related to CVCs. An estimated 21% of babies admitted born at  $\geq 34$  weeks of gestation and admitted to a NNU receive a CVC, but this proportion rises to 70% for babies born before 32 weeks of gestational age [based on unpublished analysis of the National Neonatal Research Database (NNRD) (Katie Harron, University College London, 2014, personal communication)].<sup>21</sup> Peripherally inserted central venous catheters (PICCs) are frequently used in NNUs. The PICC is a very narrow tube placed through the skin and into a central vein, using a needle, which is then removed. The PICC is used to administer medicines, fluids or parenteral nutrition into a large vein near the heart. A PICC can stay in place for several weeks, avoiding the need for repeated procedures, which can be harmful and distressing for small babies.

The mechanism by which CVCs lead to BSI is through microbial colonisation. Bacteria or fungi stick to the catheter tubing inside the vein and secrete a protective biofilm protecting themselves from host defences and any circulating antimicrobial agents, and enabling sustained colonisation.<sup>22,23</sup> The organisms multiply and, in babies with immature immunity, infection spreads via the bloodstream, causing sepsis and infecting other organs, with damaging effects, particularly on the brain and lungs. The organism causing the BSI is important. Gram-positive organisms, such as Group B streptococci, and Gram-negative organisms, including *Escherichia coli*, *Klebsiella* and *Pseudomonas*, are associated with high rates of mortality and morbidity.<sup>7</sup> BSIs due to skin commensals, predominantly coagulase-negative staphylococci (CoNS), can also cause death and adverse neurodevelopmental outcomes, but the risk is lower than for clearly pathogenic organisms.<sup>17</sup> Lower risks of adverse consequences for BSIs due to skin organisms may reflect two factors. First, skin organisms are less virulent than non-skin organisms, evidenced by their status as normal commensal bacteria that colonise the skin and gut of newborn babies. Second, skin organisms frequently contaminate blood culture samples. A positive culture from blood does not, therefore, always reflect the presence of organisms circulating in the bloodstream, and rates of infection with skin organisms may be overestimated.

Bloodstream infections related to PICCs can be treated with intravenous antibiotics, and sometimes require removal of the PICC.<sup>24</sup> Systemic antibiotic treatment alters the microbial ecology of the gut, which increases the risk of necrotising enterocolitis (NEC), an inflammatory condition of gut mucosa, which affects babies born before 32 weeks of gestation.<sup>25,26</sup> Prevention of BSIs in babies who receive a PICC is, therefore, important to avoid these serious and costly consequences.

Antimicrobial impregnation of the tubing of CVCs is widely used to prevent BSIs in adult and paediatric intensive care. Use of antimicrobial-impregnated CVCs is recommended in UK<sup>27</sup> and US<sup>28</sup> national guidelines for patients at high risk of infection. No such recommendations exist, however, for newborn babies, because of the lack of antimicrobial-impregnated catheters suitable for preterm babies and the lack of evidence from adequately powered randomised trials.<sup>29,30</sup> Various forms of antimicrobial impregnation have been evaluated in 54 randomised controlled trials (RCTs) and numerous systematic reviews, including two systematic reviews combined with network meta-analyses that reported direct and indirect comparisons between types of CVCs.<sup>31,32</sup> The network meta-analyses report the most effective form of antimicrobial impregnation to be a combination of minocycline and rifampicin antimicrobials. However, the only form of impregnated PICC licensed in Europe for newborn babies, and small enough for use in preterm babies, is the Premistar™ catheter, manufactured by Vygon (UK) Ltd (Swindon, UK). The Premistar PICC is impregnated with the antifungal miconazole, in combination with the antibacterial agent rifampicin. In the next section, we summarise findings from an overview of systematic reviews of RCTs that evaluated CVCs impregnated with miconazole and rifampicin, or with minocycline and rifampicin, in any setting or age group.

## Evidence review

We searched the Cochrane Central Register of Controlled Trials, EMBASE and MEDLINE on 29 March 2018, and ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform on 3 April 2018, for studies evaluating the effectiveness of antimicrobial-impregnated CVCs compared with any other type of CVC for reducing the rate of BSIs in newborn infants, children and adults. We included systematic reviews or meta-analyses of RCTs of miconazole- and rifampicin-impregnated or minocycline- and rifampicin-impregnated CVCs published since 2008, and RCTs in children or newborn infants published since the searches conducted in the systematic reviews. We used search terms related to CVCs, antimicrobial impregnation and infection. We identified 11 RCTs of CVCs impregnated with rifampicin combined with another antimicrobial agent (two with miconazole and nine with minocycline) (Table 1).

Further details of studies and search terms are reported in the appendix to the recent trial report.<sup>1</sup> Of the two trials that compared miconazole- and rifampicin-impregnated CVCs with standard CVCs, one involved newborn infants, but was published as an abstract only.<sup>30</sup> The other was conducted in adult surgical patients.<sup>36</sup> Neither trial reported a significant difference in the rate of catheter-related BSIs. This widely used outcome may give biased catheter-related BSI results because of inhibition of laboratory culture of organisms from the CVC tip due to leaching of the antimicrobial agent from the impregnated CVC tubing onto the culture media.<sup>34</sup> Use of any BSI as an outcome, meaning any positive culture, whether catheter related or otherwise, avoids this problem.

There were nine RCTs<sup>34,37-44</sup> of minocycline- and rifampicin-impregnated CVCs. In eight of the RCTs, the comparator was standard CVCs, in the other RCT the comparator was CVCs impregnated with chlorhexidine and silver sulfadiazine. Two RCTs were conducted with children and seven with adults. All nine RCTs reported large reductions in the rates of catheter-related BSIs. The systematic review and network meta-analysis of trials in adults by Chong *et al.*<sup>32</sup> reported an estimated risk ratio for minocycline and rifampicin impregnation, compared with no impregnation, of 0.29 [95% confidence interval (CI) 0.16, 0.52]. Only one RCT, the CATHeter Infections in CHildren (CATCH) trial,<sup>34</sup> reported results for BSI from any cause: the rate of BSI was reduced by 57% (see Table 1).

TABLE 1 Overview of evidence on the effectiveness of miconazole- and rifampicin-impregnated or minocycline- and rifampicin-impregnated CVCs for reducing the rate of BSIs

Comparison	Population	Source	Review/study	Included studies	Number randomised	Outcome	Result, OR/RR/HR (95% CI)
Miconazole- and rifampicin-impregnated vs. standard CVCs	Children	Balain 2015 <sup>29</sup>	Review	No RCTs			
		Wu 2017 <sup>33</sup>	Review	No RCTs			
		Flemmer 2016 <sup>30</sup>	Study	1 RCT	86	PICC colonisation and signs of sepsis	OR 0.22 (0.02 to 2.27)
Minocycline- and rifampicin-impregnated vs. standard CVCs	Adults	Chong 2017 <sup>32</sup>	Review	1 RCT	223	Catheter-related BSI	RR 0.89 (0.02 to 45.33)
	Children	Wu 2017 <sup>33</sup>	Review	2 RCTs	1773	Catheter-related BSI	OR 0.40 (0.15 to 1.04)
		Gilbert 2016 <sup>34</sup>	Study	1 RCT	1485	BSI	HR 0.43 (0.20 to 0.96)
	Adults	Lai 2016 <sup>35</sup>	Review	4 RCTs	1335	Catheter-related BSI	RR 0.26 (0.13 to 0.49)
		Chong 2017 <sup>32</sup>	Review and network meta-analysis	7 RCTs	2724 <sup>a</sup>	Catheter-related BSI	RR 0.29 (0.16 to 0.52)

CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.

a 2724/13953 randomised in network meta-analysis indirect comparison with minocycline-rifampicin.



## Study rationale

Citing the paucity of evidence for newborn babies, a systematic review published in The Cochrane Library in 2015 recommended that a large, simple and pragmatic RCT of antimicrobial-impregnated CVCs be undertaken to guide policy and practice.<sup>29</sup> The only type of antimicrobial-impregnated CVC developed and licensed to date for use in newborn babies in the UK is the Premistar, which is impregnated with miconazole and rifampicin. Although two RCTs found no evidence of reduced catheter-related BSIs with rifampicin–miconazole impregnation, an *in vitro* experimental study reported reduced bacterial colonisation of CVCs with rifampicin–miconazole impregnation, compared with no impregnation.<sup>30,36,45</sup>

When planning the PREVenting infection using Antimicrobial-Impregnated Long lines (PREVAIL) trial, we sought support for the proposed trial from the Neonatology Clinical Studies Group of the Medicines for Children Research Network. The group emphasised the need for RCT evidence of reduced rates of BSIs in preterm babies, and of safety in relation to antibiotic resistance. Extrapolation of findings from children and adults was not sufficient for clinicians to change practice. Concerns were expressed about the additional costs of impregnated CVCs, and the fact that rates of hospital-acquired infection were declining following implementation of ‘bundles’ of practice designed to improve sterile procedures during catheter insertion and maintenance of the line.<sup>46–48</sup>

Combining the overview of published evidence and clinical opinion, it was concluded that:

- The frequency and serious long-term consequences of BSI in preterm babies could result in significant health gains and reduced health-care costs if impregnated CVCs were found to reduce rates of BSI in babies receiving neonatal intensive care.
- Evidence would be needed from a large RCT specifically in preterm newborns of the benefits, safety and cost-effectiveness of miconazole- and rifampicin-impregnated PICCs before neonatologists would be willing or able to change purchasing decisions to adopt this type of PICC in NNUs.
- Reductions over time in BSI rates due to improved infection control practices in neonatal care would need to be taken into account when applying the findings of a large RCT to practice.

## Aims and objectives

### Aims

The overall aim of the study was to determine whether or not antimicrobial-impregnated PICCs (AM-PICCs) should be adopted across the NHS for babies receiving neonatal care. We undertook three inter-related analyses to address this aim (see *Figure 1*):

1. a clinical effectiveness RCT – to determine the clinical effectiveness of AM-PICCs, compared with standard PICCs (S-PICCs), for babies receiving neonatal care
2. an economic analysis – to determine the cost-effectiveness of AM-PICCs, compared with S-PICCs, from an NHS perspective
3. a generalisability analysis – to generalise the trial results to neonatal care in the NHS in England.

### Objectives

#### Clinical effectiveness randomised controlled trial

The objectives of the RCT were to determine the clinical effectiveness of AM-PICCs compared with S-PICCs in terms of:

- time to BSI (primary outcome), and other measures of BSI (e.g. rate)
- safety, including measures of rifampicin resistance in blood, cerebrospinal fluid (CSF) and PICC cultures
- clinical outcomes, for example death before discharge, NEC, time to full enteral feeds and time to PICC removal.

The data sources were case report forms (CRFs) completed by research nurses from routine clinical records, and mortality within 6 months of randomisation based on linked death registration data.

### Economic analysis

The economic analysis was conducted to determine:

- the hospital costs of using AM-PICCs compared with S-PICCs over the 6-month follow-up of the trial
- the cost-effectiveness of AM-PICCs versus S-PICC in terms of NHS costs and quality-adjusted life-years (QALYs), combined to assess incremental net health benefit over the babies' expected lifetimes
- the value of further information from research.

The original study objectives included determining the cost to the NHS of a BSI in preterm babies and the value of implementing the cost-effective PICC type. These objectives were not addressed because we found no evidence of a reduction in BSI rates in babies randomised to AM-PICCs, compared with babies randomised to S-PICCs.

The data sources were as follows: national data from Hospital Episodes Statistics (HES) [all admissions, accident and emergency (A&E), outpatients], paediatric intensive care unit (PICU) admissions [from the Paediatric Intensive Care Audit Network (PICANet)]; and the NNRD for all care in NNUs.

### Generalisability analysis

The objectives of the generalisability analysis were as follows:

- to determine generalisability and applicability by comparing BSI risk factors, causative organisms and rates of BSI among babies in the PREVAIL trial with other babies receiving PICCs
- to determine the applicability of BSI rates in the PREVAIL trial to rates of BSI in the NHS in England by comparing trends in BSI in babies receiving PICCs in the PREVAIL trial neonatal intensive care units (NICUs), non-PREVAIL trial NICUs and local neonatal units (LNUs)
- to provide context through understanding of changes in BSI over time by evaluating trends in rates of late-onset BSI per 1000 days of intensive or high-dependency care and per 100 admissions for all babies receiving intensive or high-dependency care in NICUs and LNUs
- to determine the contribution of PICCs to the overall rate of BSI per admission.

The data source was the NNRD linked to national laboratory infection surveillance data for England.

The three components of the study are illustrated in *Figure 1*. We also considered further uses of these linked data. First, for ongoing monitoring of BSI rates following implementation of an effective intervention. Second, to link trial and linked administrative health data to school achievement data to assess long-term effects of PICC impregnation on cognitive ability measured in school achievement assessments. These uses have not been pursued, because the infection outcome in the randomised groups did not differ.

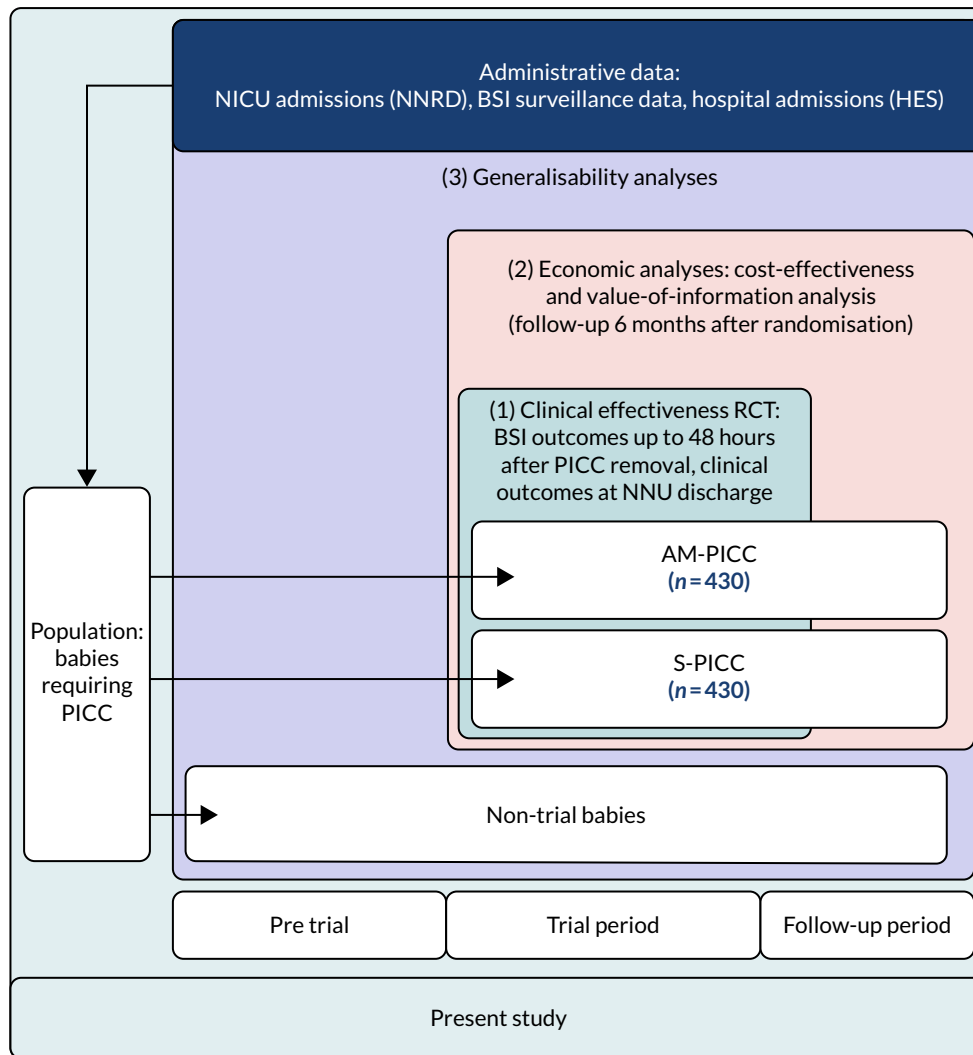


FIGURE 1 Flow diagram to show inter-relationship between the three components of the PREVAIL study.

## Chapter 2 Clinical effectiveness randomised controlled trial methods

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### Trial design

We conducted an open-label, two-arm parallel-group RCT in 18 NICUs in England. The trial was a pragmatic trial designed to determine the clinical effectiveness of AM-PICCs in the context of local practice in NICUs. Recruitment was planned over a 24-month period, starting in June 2015. An internal pilot was used to assess recruitment. The threshold for determining that recruitment was feasible was set at 130 participants being randomised after 8 months (to allow the initial sites 6 months of recruiting at full capacity). An interim analysis of the primary outcome took place half-way through the trial (when approximately half of the participants had been randomised), using Haybittle–Peto stopping rule.<sup>49</sup>

### Ethics approval and research governance

The protocol was approved by the Yorkshire and the Humber Health Research Authority (reference number 14-YH-1202). The trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and included in the International Standard Randomised Controlled Trial Number registry [<https://doi.org/10.1186/ISRCTN81931394> (accessed 22 July 2020)]. Centre-specific approval was obtained at all recruiting centres.

Full details of the amended trial protocol (version 5.0, 26 April 2017), the research ethics approval and the statistical analysis plan are available online [<http://prevailtrial.org.uk/> (accessed 22 July 2020)].

A summary of substantial protocol amendments is provided in *Appendix 1, Table 26*.

### Selection of trial sites

Recruitment took place in 18 out of 43 NICUs in England. Overall, there are 154 NNUs in England (*Table 2*), of which 43 are NICUs that provide intensive care for babies, such as invasive ventilation and organ system support (*Table 3*). Days of intensive care are supported by nurse staffing ratios of one nurse to one baby, with step-down care for high-dependency (one nurse to two babies) and special care (one nurse to four babies).<sup>51</sup> Of the 154 NNUs, 76 LNUs provide short-term intensive care and high-dependency and special care, and 35 NNUs provide special care only [i.e. special care baby units (SCBUs)]. One in 10 babies admitted to a NNU is transferred to another unit for higher or lower levels of care. Step-up transfers between NNUs within neonatal networks are used to provide centralised intensive care when needed, including neonatal surgery for a small proportion of babies. Step-down transfers are frequently used to allow babies to be cared for near to parents and to reduce pressure for beds in NICUs. Low-intensity neonatal care is also provided in transitional care wards, which are not considered here.

We invited expressions of interest from NNUs in 2015. We prioritised NICUs with the largest number of babies born before 32 weeks of gestation, using NNRD data, and those sites invited to participate through the Children's Clinical Research Network.

TABLE 2 Number of NICUs, LNUs and SCBUs in the NHS in England in 2017, based on data from the NNAP<sup>16</sup>

Type of NNU	Units, n (%)	Babies admitted, <sup>a</sup> n (%)	Median annual admissions per unit (range)	Percentage of all births <sup>b</sup> (n = 676,794)
NICU [provide intensive care, high-dependency care and special care (levels 1–3)]	43 (27.9)	22,717 (42.9)	509 (200–1150)	3.4%
LNU [provide short-term intensive care, high-dependency care and special care (levels 1–2)]	76 (49.4)	24,211 (45.8)	307 (83–749)	3.6%
SCBU [provide special care only (level 1)]	35 (22.7)	5972 (11.3)	154 (46–362)	0.9%
Total	154	52,900	319 (46–1150)	7.8%

NNAP, National Neonatal Audit Programme.

a Babies are counted if admitted for at least 12 hours to receive special care, high-dependency care or intensive care. Only the first admission for each baby is counted.

b The number of live births in England was obtained from the Office for National Statistics.<sup>50</sup>

TABLE 3 Definitions of level of neonatal care

Level of care	Care received
Level 3: intensive care	Any day on which a baby receives/undergoes at least one of the following: <ul style="list-style-type: none"> <li>• Mechanical respiratory support via a tracheal tube</li> <li>• Both non-invasive ventilation AND parenteral nutrition</li> <li>• Surgery</li> </ul> Or the day of death
Level 2: high-dependency care	Any day on which a baby who does not meet the criteria for intensive care receives at least one of the following: <ul style="list-style-type: none"> <li>• Non-invasive respiratory support</li> <li>• Parenteral nutrition</li> </ul>
Level 1: special care	Any day on which a baby who does not meet the criteria for intensive or high-dependency care receives or has at least one of the following: <ul style="list-style-type: none"> <li>• Oxygen via low-flow nasal cannula</li> <li>• Feeding by nasogastric tube, jejunal tube or gastrostomy</li> <li>• Continuous physiological monitoring</li> <li>• Care of stoma</li> <li>• Presence of an intravenous cannula</li> <li>• Phototherapy</li> <li>• Special observation of physiological variables at least every 4 hours</li> </ul>

### Participants

Eligible participants were all babies who required the narrowest (1 French gauge) PICC. Only babies who had previously participated in the trial or who were known to have an allergy or hypersensitivity to rifampicin or miconazole were excluded.

The reason for insertion was not requested, but PICCs are primarily used for parenteral nutrition, particularly in preterm babies. As this was a pragmatic trial, designed to reflect routine practice, we did not restrict eligible participants to preterm babies. However, in practice, the 1-French gauge PICC is predominantly used in preterm babies born before 32 weeks of gestation, as more mature and larger babies normally require a wider-gauge PICC to infuse sufficient volumes of fluid. Preliminary, unpublished analyses using the NNRD revealed that 70% of babies in neonatal units born before 32 weeks of gestation had a PICC inserted (unpublished data, NNRD, England).

## Recruitment procedure

### Screening

The principal investigator (PI) or research nurse (RN) maintained a screening log of babies whose parents were approached about the trial, detailing reasons for declining consent or reasons for no randomisation occurring for those who did consent. They also kept a log of all babies who received a PICC [a 1-French Premicath®; Vygon (UK) Ltd], but whose parents were not approached for the trial, and why they were not approached.

### Enrolment

When a baby was likely to require a PICC (Premicath, 1 French), the clinician or RN provided written information and met with the parents to discuss participation in the trial.<sup>52</sup> Written consent was required, along with confirmation of eligibility from the PI or designated other before randomisation could occur. Twins were treated as separate individuals for consent and randomisation, if both babies required a PICC. Babies could be simultaneously enrolled in multiple studies, as agreed between chief investigators.

### Randomisation, concealment and blinding

Participants were randomised to either an AM-PICC or a S-PICC using a secure web-based randomisation programme by the PI or delegated other at each of the 18 recruitment sites. PICC insertion was scheduled to occur within 48 hours of randomisation by a designated staff member. Randomisation sequences were computer-generated by an independent statistician in random, variable blocks of two and four, stratified by site. Randomisation was controlled centrally by the Liverpool Clinical Trials Centre (LCTC), at the University of Liverpool (UoL), to ensure allocation concealment. It was impractical to mask clinicians to PICC allocation because rifampicin caused brown staining of the AM-PICC. Participant inclusion in analyses and occurrence of outcome events were determined by following an analysis plan that was specified before individuals saw unblinded data.

## Treatments

Trial participants were allocated in a ratio of 1 : 1 to receive either:

- a miconazole- and rifampicin-impregnated PICC (AM-PICC; Premistar)
- a standard (non-impregnated) PICC (S-PICC; Premicath).

Miconazole is an antifungal agent that is effective against systemic fungal infection. Rifampicin is an antibacterial agent, previously evaluated as rifampicin–minocycline CVC impregnation in adults and children. The manufacturer, Vygon (UK) Ltd, reported continuing elution from the CVC of rifampicin and miconazole over 21 days.<sup>53</sup> The AM-PICC was marketed after certification under the Conformité Européenne (CE) process in December 2012 (certificate number Z/12/02895).

The method for PICC insertion was according to clinician preference. Either a needle or a 24-gauge intravenous cannula was inserted into a peripheral vein and the PICC tubing was threaded through the stylet until the tip reached a large central vein, such as the inferior or superior vena cava. The position of the PICC was checked by a radiograph. In the case of malposition, for example in a spinal vein or the PICC tip lying within the heart, the catheter was adjusted or withdrawn. For the purposes of the trial, a PICC was deemed to have been successfully inserted if the site of line insertion was dressed in preparation for a radiograph to confirm PICC tip position, even if the result of the radiograph led to the PICC being withdrawn. If PICC insertion was unsuccessful, the clinical team attempted further

insertions using the same type of PICC as randomised until 48 hours after randomisation, at which point subsequent PICC insertion attempts were of the S-PICC regardless of the randomised allocation. Babies could not be randomised more than once.

### Follow-up

Infection outcomes (including the primary outcome) 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) (Figure 2). During this time, the RN assessed babies daily to record whether or not any blood or CSF samples were taken for clinical indications of infection (or results received), any concomitant antimicrobials or parenteral nutrition were given, the PICC was removed (and tip cultured) or any adverse events (AEs) were observed.

Follow-up for secondary clinical outcomes continued until discharge from the neonatal unit, death or 6 months after randomisation, whichever occurred first (see Figure 2). As babies matured and required less intensive care, some were transferred to a NNU nearer home that was not one of the recruitment centres. We counted date of discharge from the final NNU after all transfers. Information was captured on all deaths within 6 months of randomisation.

Data were collected on paper-based CRFs completed by centre staff authorised to do so and returned to the LCTC. Information on deaths was recorded on the CRF, if death occurred in the NNU, and/or through linked death registration records.

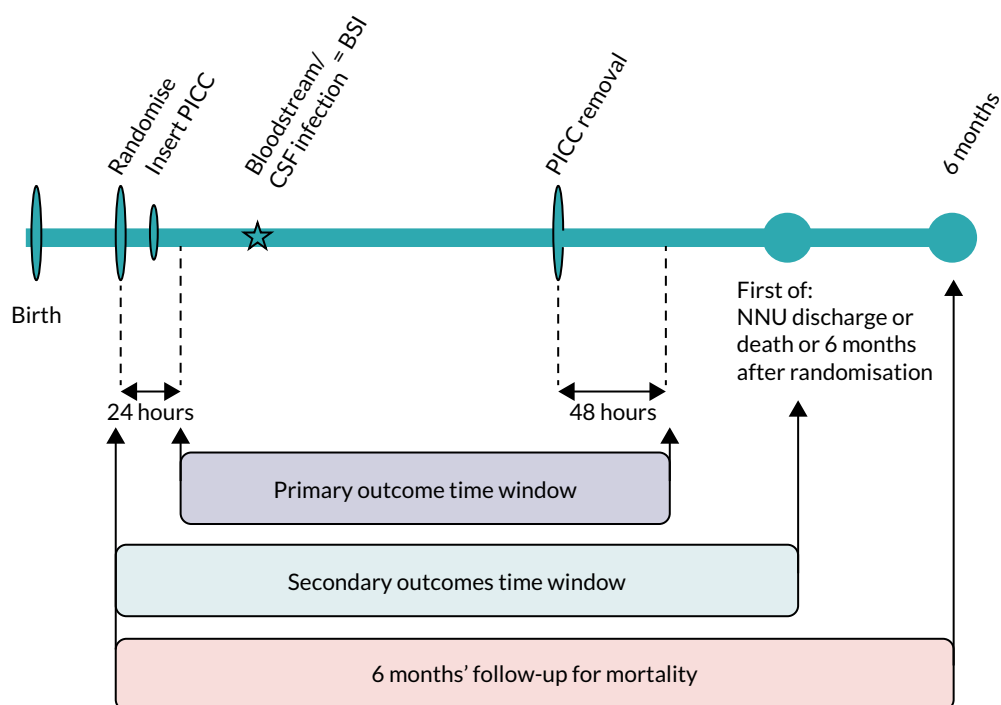


FIGURE 2 Schematic representation of the trial procedures.

## Measures

### Baseline characteristics

We recorded the following demographic and relevant clinical characteristics at randomisation.

- demographics – sex, birthweight, gestational age at birth and age at randomisation
- delivery characteristics – born in the trial hospital or transferred to the trial hospital after birth, vaginal or caesarean delivery, ruptured membranes > 24 hours before birth, maternal antenatal steroids received or not, and maternal antibiotics received within 12 hours pre delivery
- characteristics of neonatal care before randomisation – surgery in the previous 14 days, samples taken, antimicrobial medication received and the highest level of respiratory support required, all within the previous 72 hours
- other clinical characteristics – major congenital anomaly; appearance, pulse, grimace, activity, respiration (Apgar) score at 5 minutes of age; number of invasive devices in situ; and the site where the randomised PICC was successfully inserted.

### Adherence to treatment and the protocol

To measure adherence to the intervention, we recorded whether or not a PICC was inserted, and, if so, whether or not it was the allocated PICC, the reasons for removal, the length of time that the PICC was in situ, and whether or not positive samples were tested for resistance.

Protocol deviations were monitored centrally via evaluation of inclusion/exclusion criteria at trial entry and throughout the course of the trial. Some of the secondary outcomes (see the following sections) were also designed to detect potential biases in adherence to the trial protocol that might be influenced by knowledge of the type of PICC.

### Primary outcome

The primary outcome was time from randomisation to first bloodstream or CSF infection, defined as a microbiological culture of a bacteria or fungus from blood or CSF sampled for clinical reasons. We use the term BSI to refer to a positive culture from blood or CSF. We defined the primary outcome time window as the period when any positive blood or CSF cultures could be counted in the primary outcome. The time window was from 24 hours post randomisation until 48 hours after PICC removal or death (or 48 hours after randomisation if the PICC was not inserted; see *Figure 2*). We imposed a priori decision rules to avoid counting pre-existing BSI. We excluded microbial cultures that were within the time window if the same organism was isolated from blood or CSF and samples were taken < 14 days apart, or if a different organism was isolated and samples were < 24 hours apart. When there were multiple positive cultures within the primary outcome time window, each positive culture was assessed and the first one that met the definition was counted.

### Secondary outcomes

#### Secondary outcomes related to infection

These outcomes were measured during the primary outcome time window (see *Figure 2*):

- rifampicin resistance in any isolate from blood or CSF culture
- rifampicin resistance in any isolate from the PICC tip
- 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 7 March 2018, before database lock (study closure)]
- occurrence of one or more BSI
- rate of BSIs (including recurrent BSIs) per 1000 PICC days
- rate of catheter-related BSIs (defined as isolation of the same organism from the PICC tip and blood or CSF) per 1000 PICC days
- type of organism isolated from BSI meeting primary outcome criteria.



Multiple infection episodes within the time window were considered as distinct infection episodes if positive samples for each episode involved the same organism in samples taken > 14 days apart or involved different organisms in samples taken > 24 hours apart.

Rifampicin resistance was detected using ETEST® (bioMérieux, Marcy-l'Étoile, France) strips.<sup>54</sup>

### Other clinical secondary outcomes

These outcomes were captured up until neonatal discharge home, death or 6 months after randomisation, whichever occurred first (see *Figure 2*):

- 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
- NEC – Bell's stage II or III
- abnormalities on cranial ultrasound (periventricular leukomalacia or intracranial haemorrhage; worst grade of one to four used in analyses)
- treatment for retinopathy of prematurity (medical or surgical)
- time from randomisation to full milk feeds (150 ml/kg/day)
- total duration of parenteral nutrition from randomisation until discharge from neonatal care
- death –
  - before discharge home from neonatal care
  - within 6 months (26 weeks) of randomisation.

### Secondary outcomes to detect potential biases in sampling or treatment on the basis of knowledge of peripherally inserted central venous catheter allocation

- Rate of blood/CSF culture sampling per 1000 PICC days.
- Duration of antimicrobial exposure from randomisation up to 48 hours after PICC removal.
- Time from randomisation to PICC removal.

### Safety outcomes

All AEs (expected and unexpected) considered to be related to the PICC were reported until 48 hours after PICC removal.

## Sample size

The sample size calculation for the primary outcome was based on the log-rank test for equality of survival curves. We hypothesised a similar effect of rifampicin–miconazole 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.*<sup>31</sup> for catheter-related BSI [mean odds ratio (OR) 0.18 and upper 95% CI 0.34], and the results of the CATCH trial.<sup>34</sup> Using a two-sided significance level of 0.05, to detect a reduction in the proportion of babies experiencing a BSI from 14% in the standard arm, which was expected based on audit data from three participating NNUs, to 7% in the antimicrobial-impregnated arm, 79 events were required from 816 babies (408 in each arm) for 90% power. To allow for a 5% loss to follow-up, the target was inflated to 858 babies.

## Statistical methods

### General statistical considerations

The analysis and reporting of the trial were undertaken in accordance with the Consolidated Standards of Reporting Trials (CONSORT)<sup>55,56</sup> and the International Conference on Harmonisation E9 Guidelines.<sup>57</sup>

The main features of the statistical analysis plan are included in this section, with a full and detailed statistical analysis plan provided as a supplementary file<sup>58</sup> on the PREVAIL trial website.

Outcome data were analysed according to the intention-to-treat principle, which is including all randomised participants in the group to which they were allocated (regardless of whether or not the allocated PICC was inserted) and for whom the outcome was measured/observed. All statistical tests were two-sided and performed using a 5% significance level. We used 95% CIs throughout. There were no adjustments for multiple testing; rather, all secondary analyses were treated as hypothesis-generating.

All analyses were conducted with SAS<sup>®</sup> version 9.4 (SAS Institute Inc., Cary, NC, USA). Results from the primary outcome and safety analyses were validated by independent programming by another statistician from the point of raw data.

### **Baseline characteristics**

Demographics and other clinical baseline characteristics were summarised for each treatment group and overall, using descriptive statistics. No formal statistical testing was performed on these data. Descriptive statistics, including the number of observations, mean and standard deviation (SD) for continuous variables, and counts and percentages for discrete variables, were presented as appropriate.

### **Adherence to treatment and the protocol**

All protocol deviations were agreed with the co-chief investigators prior to them seeing any unblinded results. These data were summarised for each treatment group and overall, using descriptive statistics, as for the baseline data. No formal statistical testing was performed on these data.

### **Primary outcome**

The primary outcome, time to first BSI, was measured from randomisation to the first sample that met the definition of an independent episode of BSI. Participants not experiencing the primary outcome were censored at death, 48 hours after PICC removal or 48 hours after randomisation (for those with no PICC inserted). The difference between the groups was tested using the log-rank test, and the hazard ratios (HR) and associated 95% CIs obtained from the Cox proportional hazards model were presented. Kaplan–Meier curves were used to present the number of babies at risk. The number of samples taken, the number of babies with samples taken and the number of babies with a BSI within the primary outcome time window were also presented for each treatment group, overall and split by sample type.

Four sensitivity analyses of the primary outcome were prespecified to determine the robustness of the results of the primary analysis:

1. time from randomisation to first clinically serious BSI, defined as treatment with antimicrobials for  $\geq 72$  hours or death during treatment
2. time from PICC insertion to first BSI
3. time from randomisation to first BSI excluding samples obtained via arterial cannulas or CVCs
4. time from randomisation to first BSI including only clearly pathogenic organisms, as defined in *Appendix 1, Table 27*.

After seeing the results, we specified an additional analysis of the primary outcome to investigate whether or not the treatment effect varied by gestational age at birth ( $< 28$  weeks or  $\geq 28$  weeks of gestation at birth) using a Cox proportional hazards model, including an interaction between treatment and gestational age.

## Secondary outcomes

### Secondary outcomes relating to infection

The analysis of the rifampicin resistance outcomes and occurrence of one or more BSI used Fisher's exact test to compare the proportions of participants in each group for whom these outcomes (rifampicin resistance and BSI) were observed. Relative risks (RRs) were presented, along with 95% CIs. Frequency tables are also presented for the resistance outcomes, split by treatment and whether samples were Gram positive or negative, along with line listings of the resistant isolates showing the type of PICC and the organism cultured (see *Appendix 2, Table 38*).

The differences in the rate of BSI (including recurrent BSI) and rate of catheter-related BSI per 1000 PICC days during the primary outcome time window were analysed using Poisson regression. The rate ratios and associated 95% CIs were presented. For comparability with published studies, rates per 1000 PICC days between randomisation and PICC removal were also reported.

The number and proportion of BSIs by type of organism isolated were presented, but no formal statistical analysis of this outcome was performed.

### Other clinical secondary outcomes

The proportion of participants in each treatment group experiencing chronic lung disease, NEC, abnormalities on cranial ultrasound and treatment for retinopathy of prematurity were compared using Fisher's exact test. RRs were presented, along with 95% CIs. We described the type of treatment given for retinopathy of prematurity without formal statistical analysis by treatment allocation.

The time to full milk feeds was compared across the two treatment groups using the log-rank test and Cox proportional hazards models. The HRs and associated 95% CIs were presented, along with a Kaplan–Meier curve stratified by treatment. Survival times were measured from randomisation.

The duration of parenteral nutrition was compared across the two treatment groups using the Mann–Whitney *U*-test. The medians and interquartile ranges (IQRs) were presented for each group.

Death was analysed in two ways. Fisher's exact test was used to compare the proportion of deaths in each group before discharge home from neonatal care and within 6 months from randomisation (updated to include data from NHS digital). RRs were presented, along with associated 95% CIs. Time to death was analysed using the log-rank test and Cox proportional hazard models. The HR and associated 95% CIs were presented, along with a Kaplan–Meier curve stratified by treatment. Survival times were measured from randomisation.

### Secondary outcomes to detect potential biases in sampling or treatment on the basis of knowledge of peripherally inserted central venous catheter allocation

The difference in rate of blood/CSF culture sampling per 1000 PICC days (during the primary outcome time window) was analysed using Poisson regression. The rate ratio and associated 95% CIs were presented. As with the other rate outcomes, for comparability with published studies, the rate per 1000 PICC days between randomisation and PICC removal was also reported.

Time to PICC removal was compared across the two treatment groups using the log-rank test and Cox proportional hazard models. The HR and associated 95% CIs were presented, along with a Kaplan–Meier curve stratified by treatment. Survival times were measured from randomisation.

The difference between groups in the duration of antimicrobial exposure was analysed using the Mann–Whitney *U*-test. The medians and IQRs were presented for each group.

### **Safety analyses**

The statistical analysis plan specified that all babies who had a PICC inserted or who had an attempted insertion would be included in the safety analysis population. The plan specified that babies who had a PICC inserted would be analysed according to the treatment they received, and that babies for whom PICC insertion was attempted but unsuccessful would be analysed according to the allocated treatment group, as information was not recorded on the type of PICC that was used for attempted insertion. However, after seeing the trial results, it was deemed more appropriate to exclude babies in whom insertion was unsuccessful from the safety analysis population.

All AEs and serious adverse events (SAEs) reported by the clinical investigator and classified as 'possibly', 'probably' or 'almost certainly' related to the trial treatment were presented. The number (and percentage) of occurrences of each AE/SAE and of babies experiencing each AE/SAE were presented for each treatment arm. The same information was also presented split by severity. For each baby, only the maximum severity that they experienced for each type of AE was displayed. No formal statistical testing was undertaken.

### **Patient and public involvement**

We worked closely with Bliss (registered charity number 1002973) to develop the trial, provide advice to the trial team, identify suitable parent and public representatives and disseminate updates and results. Bliss was involved in the development of the study at an early stage, as one of their members was a co-applicant to the grant. A Bliss representative was a member of the Trial Management Group (TMG) and was involved in the development and review of trial documentation.

A parent of a prematurely born infant who had spent substantial time in a NICU sat on the Trial Steering Committee (TSC) and assisted with decision-making about the trial. The parent representative also aided with the review of trial documentation.

### **Trial oversight and role of funders**

#### ***Trial Management Group***

The TMG comprised the co-chief investigators, specific co-investigators (clinical and non-clinical), members of the LCTC and members of the chief investigator's team at University College London (UCL). The TMG was responsible for the month-to-month management of the trial. The TMG proposed the membership of the oversight committees [the TSC and the Independent Data and Safety Monitoring Committee (IDSMC)] to the trial funders, who then made appointments according to their constitutional requirements. Members are listed in the *Acknowledgements*.

#### ***Trial Steering Committee***

The TSC consisted of an independent chairperson, an independent expert in the field of neonatology, an independent statistician and a parent representative. One of the co-chief investigators was a non-independent member of the TSC. The TSC was the executive decision-making committee considering the recommendations of the IDSMC. Monitoring reports viewed by the TSC did not present data split by treatment group. Members are listed in the *Acknowledgements*.

#### ***Independent Data and Safety Monitoring Committee***

The IDSMC included an independent chairperson, an expert in the field of microbiology and an independent statistician. The IDSMC was responsible for reviewing and assessing recruitment and for interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC provided recommendations to the TSC concerning the continuation of the trial. Members are listed in the *Acknowledgements*.

***Role of the funding source***

The funder appointed independent members to the TSC and the IDSMC, 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.

***Dual publication***

*Chapters 1 and 2* contain information published in the 2019 report of the PREVAIL trial findings, with further details and results.<sup>1</sup> *Chapter 2* includes details reported in the PREVAIL trial protocol and statistical analysis plan, which have already been published on the PREVAIL website.<sup>58,59</sup>

# Chapter 3 Clinical effectiveness randomised controlled trial results

## Recruitment

The first participant was randomised on 12 August 2015. The internal pilot at 8 months found that actual recruitment ( $n = 229$ ) exceeded the target number ( $n = 179$ ) (see *Appendix 2, Figure 15*) and the threshold of 130 participants, which was set to demonstrate feasibility. The last participant was randomised on 11 January 2017, 4 months earlier than planned, as the recruitment target had been met (see *Appendix 2, Table 28*, for additional randomisation information for each site). Clinical follow-up of enrolled participants continued until 30 May 2017.

The CONSORT flow diagram (*Figure 3*) illustrates the pathway of participants through the trial. Parents or legal guardians of 1404 babies were approached about the trial; consent was provided for 937 (66.7%) babies, and 861 (61.3%) went on to be randomised (see *Appendix 2, Table 29*, for screening and recruitment details for all sites). The most frequently recorded reason for declining consent was that the parents did not want their baby to participate in research [195/467 (41.8%); see *Appendix 2, Table 31*]. The most frequently recorded reason for babies not being randomised despite parents providing consent was that the baby no longer required a PICC [49/76 (64.5%); see *Appendix 2, Table 32*]. There were an additional 487 babies who received a PICC (1 French gauge) at one of the participating sites during the recruitment period, but who were not approached for the trial. The most frequent reasons recorded were parents not available [163/487 (33.5%)] or missed by the clinical team [134/487 (27.5%); see *Appendix 2, Table 30*].

A total of 191 babies (22.2%) were co-enrolled in the PREVAIL trial and at least one other RCT. *Appendix 2, Table 33*, provides details on the number of babies who were co-enrolled in other trials at each of the recruiting sites.

## Interim analysis

An interim analysis was undertaken using a data snapshot taken on 22 June 2016. At this point, 523 participants were randomised. A total of 412 participants were included in the intention-to-treat analysis set (i.e. randomised and consented with sufficient data to analyse), and 411 participants were included in the safety analysis set (i.e. insertion successful or attempted).

In the AM-PICC group, 27 of the 208 participants had experienced at least one BSI (13.0%) and in the S-PICC group, 21 of the 204 participants had experienced at least one BSI (10.3%). The median time to BSI could not be calculated as the event had not been experienced by enough participants. There was no difference between the two groups (HR 1.24, 95% CI 0.70 to 2.19;  $p$ -value 0.46).

In the AM-PICC group, 24 related AEs occurred in 22 of the 206 participants (10.7%); in the S-PICC group, 22 related AEs occurred in 20 of the 205 participants (9.8%). One of the related AEs in the AM-PICC group was classified as an unexpected SAE.

The IDSMC did not raise any significant issues of trial conduct, governance or safety and was happy to recommend that the trial continue as planned.

Details of all oversight committee meetings along with recommendations are shown in *Appendix 2, Table 34*.

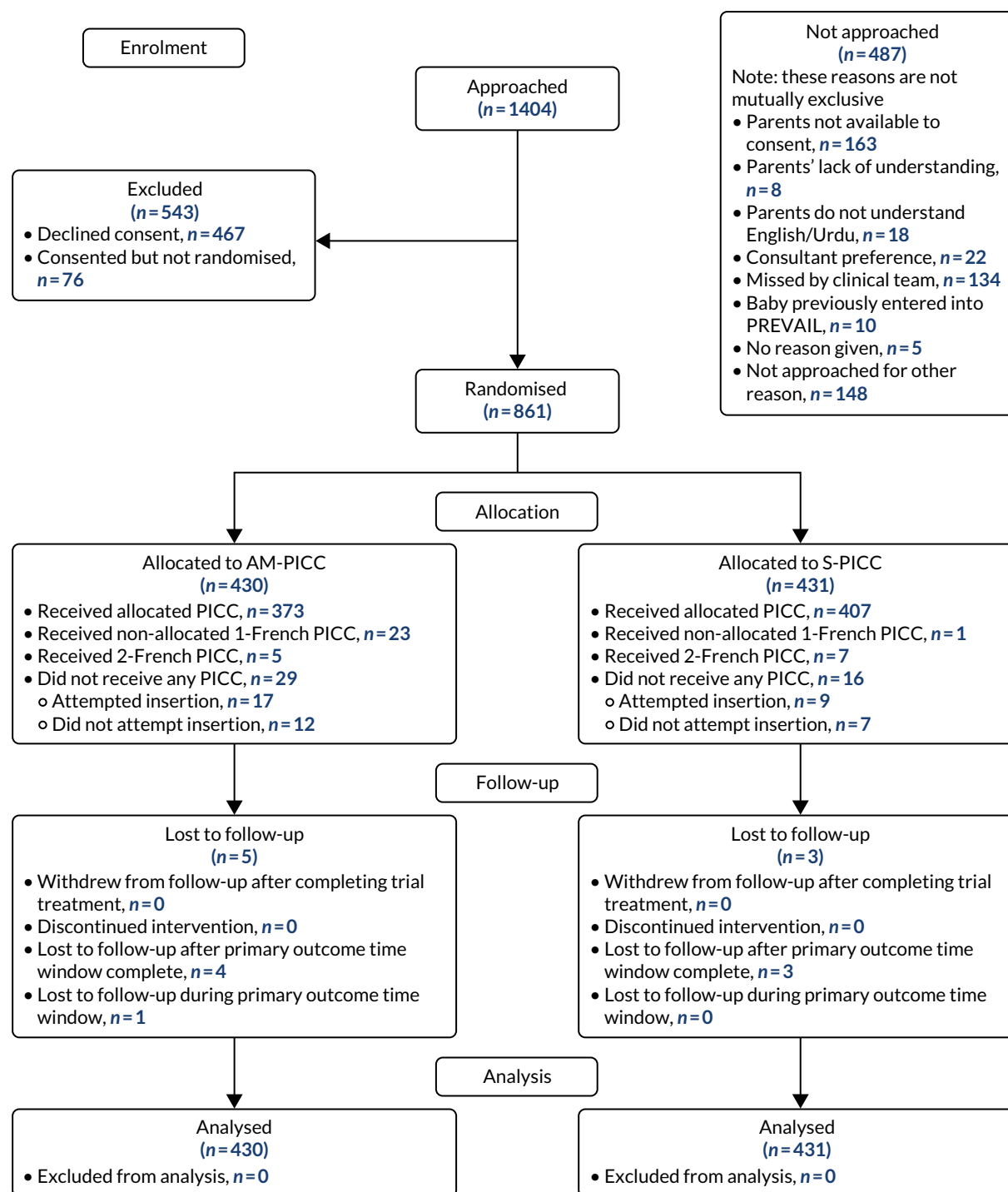


FIGURE 3 The CONSORT flow diagram for all trial participants.

## Final analysis

### Baseline characteristics

The two treatment groups were comparable in terms of baseline characteristics (Tables 4–7). Of the 861 babies who were randomised, 715 (83%) were randomised before 7 days of age and 754 (88%) were born before 32 weeks of gestation.

TABLE 4 Baseline characteristics: demographics

Baseline characteristic	Trial group	
	AM-PICC (N = 430)	S-PICC (N = 431)
<b>Sex, n (%)</b>		
Male	214 (49.8)	225 (52.2)
Female	216 (50.2)	206 (47.8)
<b>Birthweight (g)</b>		
Median (IQR)	962.5 (729–1220)	960 (770–1250)
< 750, n (%)	119 (27.7)	92 (21.3)
750–999, n (%)	110 (25.6)	140 (32.5)
1000–1249, n (%)	102 (23.7)	91 (21.2)
1250–1499, n (%)	52 (12.1)	62 (14.4)
1500–1749, n (%)	27 (6.3)	27 (6.3)
1750–1999, n (%)	8 (1.9)	7 (1.6)
≥ 2000, n (%)	12 (2.8)	12 (2.8)
<b>Gestational age at birth (weeks)</b>		
Median (IQR)	27.90 (25.78–29.94)	28.06 (26.23–30.14)
< 26, n (%)	115 (26.7)	93 (21.6)
26 or 27, n (%)	101 (23.5)	110 (25.5)
28 or 29, n (%)	103 (24.0)	102 (23.7)
30 or 31, n (%)	54 (12.6)	76 (17.6)
32 or 33, n (%)	28 (6.5)	15 (3.5)
34 or 35, n (%)	7 (1.6)	9 (2.1)
36 or 37, n (%)	5 (1.2)	3 (0.7)
≥ 38, n (%)	7 (1.6)	11 (2.6)
Missing, n (%)	10 (2.3)	12 (2.8)
< 32, n (%)	373 (86.7)	381 (88.4)
<b>Age at randomisation (days)</b>		
Median (IQR)	4.12 (2.04–5.93)	3.90 (1.90–6.12)
< 2, n (%)	106 (24.7)	113 (26.2)
2–6, n (%)	256 (59.5)	240 (55.7)
7–13, n (%)	39 (9.1)	52 (12.1)
14–20, n (%)	6 (1.4)	11 (2.6)
21–27, n (%)	3 (0.7)	5 (1.2)
≥ 28, n (%)	20 (4.7)	10 (2.3)



TABLE 5 Baseline characteristics: delivery characteristics

Baseline characteristic	Trial group, n (%)	
	AM-PICC (N = 430)	S-PICC (N = 431)
<b>Location of birth</b>		
Born in study hospital	340 (79.1)	367 (85.2)
Transferred after birth	90 (20.9)	64 (14.8)
<b>Mode of delivery</b>		
Vaginal	196 (45.6)	198 (45.9)
Caesarean	234 (54.4)	233 (54.1)
<b>Membrane rupture &gt; 24 hours before delivery</b>		
Yes	111 (25.8)	104 (24.1)
No	299 (69.5)	310 (71.9)
Missing	20 (4.7)	17 (3.9)
<b>Maternal antenatal corticosteroids</b>		
Yes	375 (87.2)	381 (88.4)
No	53 (12.3)	50 (11.6)
Missing	2 (0.5)	0 (0)
<b>Maternal antibiotics ≤ 12 hours before delivery</b>		
Yes	135 (31.4)	102 (23.7)
No	275 (64.0)	310 (71.9)
Missing	20 (4.7)	19 (4.4)

TABLE 6 Baseline characteristics: neonatal care

Baseline characteristic	Trial group, n (%)	
	AM-PICC (N = 430)	S-PICC (N = 431)
<b>Surgery before randomisation</b>		
> 6 days	2 (0.5)	3 (0.7)
≤ 6 days	15 (3.5)	10 (2.3)
No surgery	413 (96.0)	418 (97.0)
<b>Positive blood culture &lt; 72 hours prior to randomisation</b>		
Yes	29 (6.7)	19 (4.4)
No	401 (93.3)	412 (95.6)
<b>Antibiotics/antifungals &lt; 72 hours prior to randomisation<sup>a</sup></b>		
Yes	367 (85.3)	363 (84.2)
No	63 (14.7)	68 (15.8)
<b>Respiratory support &lt; 72 hours prior to randomisation</b>		
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)
a Excluding prophylaxis.		

TABLE 7 Baseline characteristics: other clinical characteristics

Baseline characteristic	Trial group, n (%)	
	AM-PICC (N = 430)	S-PICC (N = 431)
<b>Major congenital anomaly</b>		
Yes	21 (4.9)	27 (6.3)
No	408 (94.9)	404 (93.7)
Missing	1 (0.2)	0 (0.0)
<b>Apgar score at 5 minutes</b>		
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)
<b>Devices in situ at randomisation</b>		
< 4	370 (86.0)	390 (90.5)
≥ 4	60 (14.0)	41 (9.5)
<b>PICC insertion site</b>		
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)

### Adherence to treatment and the protocol

Fewer babies randomised to the AM-PICC had the randomly allocated PICC inserted [373 participants (86.7%)] than those randomised to the S-PICC group [407 participants (94.4%)] (Table 8). Approximately half of the babies who did not receive the allocated AM-PICC had no PICC inserted, and half received a different PICC.

The intention-to-treat analysis population included all 861 participants (100%) who were randomised, regardless of whether or not they received the allocated PICC. The safety population as defined in the statistical analysis plan (all participants in whom insertion was successful or attempted) included 842 of the 861 randomised participants (97.8%). The modified safety analysis (all participants in whom insertion was successful) included 816 of the 861 randomised participants (94.8%) (see Table 8 for further details on which participants were included in the safety analysis populations).

The time points for end of follow-up were similar in both groups (see Table 8). The majority of participants completed follow-up for infection outcomes (outcomes for which samples were required to be taken) 48 hours after removal of the PICC [785/861 (91.2%)] and follow-up for other outcomes at discharge home from neonatal care [768/861 (89.2%)].

The type and frequency of sampling for microbiological cultures were similar in both groups (see Appendix 2, Table 35); blood/CSF samples were taken from 198 babies in the AM-PICC group (46.0%) and from 190 babies in the S-PICC group (44.1%). The frequency of testing for rifampicin resistance

TABLE 8 The PICC insertion status and end point of follow-up

	Trial group, n (%)	
	AM-PICC (N = 430)	S-PICC (N = 431)
<b>PICC status</b>		
Allocated PICC inserted	373 (86.7) <sup>a,b</sup>	407 (94.4) <sup>c,d</sup>
Non-allocated PICC inserted	28 (6.5) <sup>c</sup>	8 (1.9) <sup>a</sup>
1 French PICC	23 (5.3) <sup>d</sup>	1 (0.2) <sup>b</sup>
2 French PICC	5 (1.2)	7 (1.6)
No PICC inserted	29 (6.7)	16 (3.7)
PICC insertion attempted	17 (4.0) <sup>a</sup>	9 (2.1) <sup>c</sup>
PICC insertion not attempted	12 (2.8)	7 (1.6)
<b>End of follow-up for infection outcomes</b>		
48 hours after PICC removal	387 (90.0)	398 (92.3)
Death with PICC in situ	13 (3.0)	18 (4.2)
48 hours after randomisation	29 (6.7)	15 (3.5)
Lost to follow-up	1 (0.2)	0 (0.0)
<b>End of follow-up for other outcomes</b>		
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)
<p>a Included in AM-PICC group in safety analysis set defined in the statistical analysis plan.  b Included in AM-PICC group in modified safety analysis set.  c Included in S-PICC group in safety analysis set defined in the statistical analysis plan.  d Included in S-PICC group in modified safety analysis set.</p>		

in blood or CSF positive cultures was slightly lower in the AM-PICC group than in the S-PICC group, but similar for PICC tips, although there were half as many positive cultures from PICC tips in the AM-PICC group [47 participants (10.9%)] as in the S-PICC group [90 participants (20.9%)].

Protocol deviations were generally similar across the two treatment groups (see *Appendix 2, Table 36*). A total of 86 participants (10.0%) had at least one major protocol deviation. The most common major deviation was not receiving the allocated PICC [81 participants (9.4%)], and the most common minor deviations were the PICC tip culture not being taken at removal [167 participants (19.4%)] and resistance testing not being done on positive cultures [135 participants (15.7%)].

### Primary outcome

A total of 46 participants in the AM-PICC group (10.7%) and 44 participants in the S-PICC group (10.2%) experienced a BSI in the primary outcome time window. The median time to BSI could not be calculated as not enough participants experienced an event. The time from randomisation until first BSI did not differ between the groups (HR 1.11, 95% CI 0.73 to 1.67) (*Table 9 and Figure 4*). 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; this was not significant ( $p = 0.62$ ).

TABLE 9 Results: primary outcome

Primary outcome	Trial group, n (%)		HR (95% CI)	p-value
	AM-PICC (N = 430)	S-PICC (N = 431)		
Time to first BSI	46 (10.7)	44 (10.2)	1.11 (0.73 to 1.67)	0.63
<b>Sensitivity analyses</b>				
Time to first clinically serious BSI	42 (9.8)	40 (9.3)	1.11 (0.72 to 1.71)	0.65
Time to first BSI (from insertion) <sup>a</sup>	45 (11.2)	44 (10.6)	1.08 (0.71 to 1.64)	0.72
Time to first BSI excluding arterial or PICC samples	45 (10.5)	43 (10.0)	1.11 (0.73 to 1.68)	0.64
Time to first BSI excluding skin organisms	16 (3.7)	9 (2.1)	1.90 (0.84 to 4.31)	0.12

a Only includes participants for whom a PICC was successfully inserted (AM-PICC: 401 babies; S-PICC: 415 babies).

**Notes**  
Events were considered only on samples taken between 24 hours after randomisation until 48 hours after removal. Median time to BSI is not reported as not enough participants experienced an event.

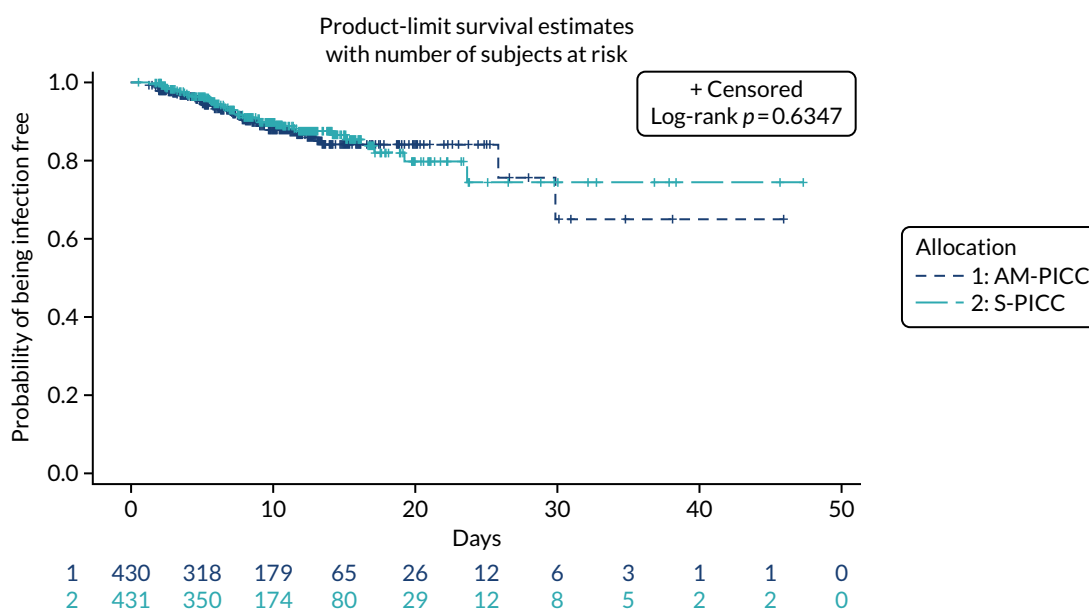


FIGURE 4 Kaplan-Meier plot: time to first BSI (primary outcome). The table under the graph presents the numbers of study participants at risk (i.e. not censored) at each time point.

The results from all four sensitivity analyses are consistent with the results from the primary analysis, indicating that the original results are robust regarding the assumptions that were made (see Table 9). The post hoc analysis that was performed to determine if there was evidence of a difference in treatment effect for babies with a gestational age of < 28 weeks compared with babies with a gestational age of  $\geq 28$  weeks found that this was not the case ( $p = 0.28$ ). Appendix 2, Figures 16 and 17 show further results from the post hoc analysis.

## Secondary outcomes

### Secondary outcomes relating to infection

The proportion of babies experiencing rifampicin resistance from PICC tip cultures was significantly higher in the AM-PICC group than in the S-PICC group, but this was not observed in blood or CSF cultures or in the combined outcome of blood or CSF or PICC tip cultures (Table 10). Resistant organisms are categorised and shown by intervention group in Appendix 2, Table 38.

TABLE 10 Results: secondary outcomes relating to infection

Secondary outcomes	Trial group		Treatment difference	p-value
	AM-PICC (N = 430)	S-PICC (N = 431)		
<b>Rifampicin resistance</b>	n (%)	n (%)	<b>RR (95% CI)</b>	
Rifampicin resistance from blood/CSF culture	4 (0.9)	7 (1.6)	0.57 (0.17 to 1.94)	0.55
Rifampicin resistance from PICC tip culture	14 (3.3)	4 (0.9)	3.51 (1.16 to 10.57)	0.02
Rifampicin resistance from blood/CSF or PICC tip culture <sup>a</sup>	18 (4.2)	10 (2.3)	1.80 (0.84 to 3.86)	0.13
Occurrence of $\geq 1$ BSI	46 (10.7)	44 (10.2)	1.05 (0.71 to 1.55)	0.82
<b>Rate of BSI per 1000 PICC days</b>			<b>Rate ratio (95% CI)</b>	
Rate of BSI	13.15	10.87	1.21 (0.78 to 1.88)	0.40
Rate of BSI (when line is in situ) <sup>b</sup>	12.57	11.21	1.12 (0.73 to 1.12)	0.60
Rate of catheter-related BSI	1.84	2.35	0.78 (0.27 to 2.25)	0.65
Rate of catheter-related BSI (when line is in situ) <sup>b</sup>	1.71	2.46	0.70 (0.25 to 1.96)	0.49
<p>a Outcome not prespecified in protocol, but requested by investigators and included in the statistical analysis plan before any unmasked data were seen.</p> <p>b Sensitivity analysis – includes only babies for whom a PICC was successfully inserted (AM-PICC: 401 babies; S-PICC: 415 babies).</p> <p><b>Note</b> Events were considered only on samples taken between 24 hours after randomisation and 48 hours after removal.</p>				

The number of participants experiencing one or more BSI during the primary outcome time window was not significantly different between the two groups (see Table 10). Details on the number of BSIs that each participant experienced are provided in Appendix 2, Table 39.

There were no significant differences in the rates of BSI or catheter-related BSI (see Table 10). Results from sensitivity analyses of the rates during the time that the PICC was in situ were consistent with the main results.

The types of organisms isolated from BSIs are shown in Table 11.

### Other clinical secondary outcomes

There were no significant differences in the proportions of participants experiencing chronic lung disease, NEC, abnormality on cranial ultrasound or treatment for retinopathy of prematurity (Table 12). Further information on the type of treatment for retinopathy of prematurity is shown in Appendix 2, Table 40.

There was no detectable difference in time to full milk feeds (the median number of days was approximately 9 in each group) or in the duration of parenteral nutrition (the median number of days was 11 in the AM-PICC group and 10 in the S-PICC group) (see Table 12).

There was no difference between the treatment groups in terms of the proportion of deaths before discharge home from neonatal care or within 6 months of randomisation, or in terms of the time to death within 6 months of randomisation (see Table 12).

TABLE 11 Results: secondary outcome – type of organism isolated from BSI

Category	Organism	Trial group, n (%)	
		AM-PICC (N = 49)	S-PICC (N = 45)
Gram-positive	CoNS	31 (63.3) <sup>a</sup>	35 (77.8) <sup>a</sup>
	<i>Enterococcus</i> spp.	3 (6.1)	1 (2.2)
	<i>Staphylococcus aureus</i>	2 (4.1)	2 (4.4)
	Haemolytic streptococcus	1 (2.0)	0 (0.0)
Gram-negative	<i>E. coli</i>	4 (8.2) <sup>a</sup>	2 (4.4)
	<i>Klebsiella</i> spp.	4 (8.2) <sup>a</sup>	1 (2.2)
	<i>Enterobacter</i> spp.	2 (4.1)	1 (2.2)
	<i>Acinetobacter</i> spp.	0 (0.0)	1 (2.2)
	<i>Moraxella osloensis</i>	0 (0.0)	1 (2.2)
Fungi	<i>Candida</i> spp.	2 (4.1) <sup>a</sup>	1 (2.2)
Total (n)		49	45

<sup>a</sup> Indicates cases in which a single baby grew multiple organisms.

**Note**

Data are n (%) of participants experiencing a BSI.

TABLE 12 Results: other clinical secondary outcomes

	Trial group		Treatment difference	p-value
	AM-PICC (N = 430)	S-PICC (N = 431)		
	n (%)	n (%)	RR (95% CI)	
Chronic lung disease	190 (44.2)	178 (41.3)	1.07 (0.92 to 1.25)	0.41
NEC: Bell's stage II or III	41 (9.5)	46 (10.7)	0.89 (0.59 to 1.32)	0.57
Abnormality on cranial ultrasound	166 (38.6)	150 (34.8)	1.11 (0.93 to 1.33)	0.26
Treatment for retinopathy of prematurity	40 (9.3)	30 (7.0)	1.34 (0.85 to 2.11)	0.21
Death before discharge	36 (8.4)	33 (7.7)	1.09 (0.70 to 1.72)	0.71
Death within 6 months of randomisation	36 (8.4)	35 (8.1)	1.03 (0.66 to 1.61)	0.90
	Median (IQR)	Median (IQR)	HR (95% CI)	
Time to death within 6 months of randomisation <sup>a</sup>	–	–	1.06 (0.67 to 1.70)	0.79
Time to full milk feeds (days)	9.51 (6.37–17.26)	9.40 (6.32–16.37)	0.99 (0.86 to 1.14)	0.85
Days of parenteral nutrition	11.00 (7.00–19.00)	10.00 (7.00–18.00)	–	0.83

<sup>a</sup> Median time to event not reported as not enough participants experienced an event.

Five deaths were captured in the CRFs that were not reported in the data provided by NHS Digital, and two deaths were reported in the data provided by NHS Digital that were not captured in the CRFs. There was also a discrepancy in the date of death for one baby; the date reported by NHS Digital was 1 day later than the date captured in the CRF.

### Secondary outcomes to detect potential biases in sampling or treatment on the basis of knowledge of peripherally inserted central venous catheter allocation

The rate of blood sampling for signs of infection was significantly higher in the AM-PICC arm than in the S-PICC arm (98/1000 PICC days vs. 80/1000 PICC days, respectively; rate ratio 1.23, 95% CI 1.05 to 1.45; *p*-value 0.01) (Table 13). There were no differences in the median time to PICC removal (8 days in both groups) or in the median duration of antimicrobial treatment (3 days in both groups) (see Table 13).

#### Safety analysis

All related AEs in participants who had a 1 French PICC successfully inserted are listed in Table 14. A total of 60 events were reported from 49 participants in the AM-PICC group (13.1%), and 50 events were reported from 45 participants in the S-PICC group (10.5%).

One SAE involving supraventricular tachycardia following PICC placement was reported in the AM-PICC arm. This event met the seriousness criterion of 'medically significant', and the local investigator felt that it was 'possibly' related to the recent insertion of the PICC. The event resolved and the PICC was not removed. This event was assessed as 'unlikely' to be related to the trial intervention by the chief investigator, but was reported to the Medicines and Healthcare products Regulatory Agency Adverse Incident Centre in line with the local investigator's assessment.

TABLE 13 Results: secondary outcomes to detect potential biases in sampling

Secondary outcome	Trial group		Treatment difference	<i>p</i> -value
	AM-PICC ( <i>n</i> = 430)	S-PICC ( <i>n</i> = 431)		
	<i>Rate per 1000 PICC days</i>	<i>Rate per 1000 PICC days</i>	<i>Rate ratio (95% CI)</i>	
Rate of blood/CSF culture sampling	97.90	79.64	1.23 (1.05 to 1.45)	0.01
Rate of blood/CSF sampling (line in situ) <sup>a</sup>	93.72	82.01	1.14 (0.98 to 1.34)	0.09
	<i>Median (IQR)</i>	<i>Median (IQR)</i>	<i>HR (95% CI)</i>	
Time to PICC removal (days)	8.20 (4.77–12.13)	7.86 (5.00–12.53)	1.03 (0.89 to 1.18)	0.73
Days of antimicrobial treatment	3.00 (2.00–6.00)	3.00 (2.00–6.00)	–	0.25

a Sensitivity analysis – includes only babies for whom a PICC was successfully inserted (AM-PICC: 401 babies; S-PICC: 415 babies).

TABLE 14 Related AEs

AE	AM-PICC group ( <i>N</i> = 374 participants)		S-PICC group ( <i>N</i> = 430 participants)	
	Events ( <i>n</i> )	Participants, <i>n</i> (%)	Events ( <i>n</i> )	Participants, <i>n</i> (%)
Any AE	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)

# Chapter 4 Economic evaluation

## Introduction

The aim of the economic evaluation was to examine the costs and health benefits of using AM-PICCs rather than S-PICCs in PREVAIL trial babies. In doing so, the economic analysis can inform decisions regarding which type of PICC should be purchased for neonatal care in the NHS, identify the areas where more research is needed and inform future research by providing estimates on the costs of having babies in the NICU.

The economic evaluation planned to include the following elements, as defined in the PREVAIL trial protocol,<sup>59</sup> section 2.3.2:

1. the hospital costs of using AM-PICCs compared with using S-PICCs over the time horizon of the trial
2. the cost-effectiveness of AM-PICCs compared with that of S-PICCs over a patient's expected lifetime, including the minimum clinical effectiveness required for AM-PICCs to be considered cost-effective
3. the value of information (VoI) to assess the benefits of potential additional research
4. the value of implementing the cost-effective PICC type
5. the hospital costs to the NHS of a BSI.

As reported in *Chapter 3*, the PREVAIL trial found that there was no difference in the risk of BSI or of clinically serious BSI between the AM-PICC and the S-PICC groups. The implication is that AM-PICCs are unlikely to be cost-effective, compared with S-PICCs, given the additional purchasing cost and that the prevention of BSI was expected to be their key benefit. Consequently, the economic analysis plan was revised to include elements 1, 2 and 3 in the preceding list, but not 4 or 5.

The objective of 1, to estimate the hospital costs of using AM-PICCs compared with using S-PICCs, was to understand whether or not the type of PICC had any impact on the costs of hospitalisations. This is henceforth referred to as the 'cost of hospital care'. Estimates of the cost of hospital care are useful to understand the resources required to improve the health of preterm babies and to inform research on the cost-effectiveness of interventions to reduce hospital length of stay or other hospital use.

Objective 2, to examine the cost-effectiveness of AM-PICCs compared with S-PICCs over a patient's expected lifetime, required the development of a cost-effectiveness model informed by population-specific inputs to evaluate interventions to prevent BSI. As far as was possible and relevant, the cost-effectiveness model was informed by data collected in the PREVAIL trial. The cost-effectiveness model was used to estimate the cost-effectiveness of AM-PICCs compared with S-PICCs, given the results of the trial, and to determine the minimum effect that would be required so that AM-PICCs were cost-effective given their greater acquisition cost.

The objective of 3, calculating the VoI, was to estimate the impact of parameter uncertainty on the likelihood of not choosing the most cost-effective option and the consequences in terms of health losses and additional costs. These estimates are used to calculate the expected value of further information and the magnitude of the benefits of investing in future research.<sup>60</sup>

The economic analysis planned to include objective 4, the value of implementing the cost-effective PICC type.<sup>61</sup> This analysis was not conducted because, as it is unlikely that the AM-PICC is the cost-effective technology and the type of PICC currently implemented is the S-PICC, there is no value in implementation activities.



The estimation of the hospital costs to the NHS of a BSI (objective 5) was not conducted for two reasons. First, this analysis required the use of the random allocation to one of the two PICC types as an instrument to estimate the causal effect of BSI on the costs. As the PREVAIL trial found that there was no difference in the risk of BSI between the two PICC types, the instrumental variable analysis was not feasible. Second, the process for the health economics team to receive the data suffered a considerable delay (see *Appendix 3*), which did not allow sufficient time to explore alternative statistical models.

### Revised objectives

The aim of the economic evaluation was to determine the cost-effectiveness of AM-PICCs compared with S-PICCs over a patient's lifetime. The specific objectives were to:

- estimate the cost of hospital care over the follow-up of the trial (reported in *Cost of hospital care*)
- predict the long-term costs and quality-adjusted survival of babies with AM-PICCs or S-PICCs (reported in *Cost-effectiveness of antimicrobial-impregnated versus standard peripherally inserted central venous catheters over a lifetime*)
- explore the extent to which the consequences of uncertainty indicate that there is value in additional research (reported in *Value of information*).

### Cost of hospital care

#### Background

This section estimates the cost of hospital care for babies taking part in the PREVAIL trial (hereafter termed 'PREVAIL babies') for whom routine health-care data were available and whose parents had consented for their data to be shared with the research team.

#### Methods

##### Overview

*Figure 5* summarises the methods. The PREVAIL babies may have received a variety of hospital care during the 6-month follow-up period. We sought data on hospitalisations from different data sources, which included stay in the NNU, admission to a PICU, admissions to paediatric hospital care, procedures such as surgery and diagnostic tests, outpatient appointments, and visits to the A&E department. We obtained data on the nature and intensity of hospital care in these different settings and used it to generate standardised units of cost called Healthcare Resource Groups (HRGs). We obtained the unit costs of the HRGs from NHS reference costs 2015–16,<sup>62</sup> which represent their average cost to the NHS. The cost of hospital care for each baby is the sum of the costs of the HRGs.

##### Study population

The study population comprised the PREVAIL babies for whom the parents or guardians consented to share their routine health-care data and for whom routine records were available.

##### Time horizon

The time horizon was from the randomisation date in the PREVAIL trial to 6 months' follow-up or death, whichever occurred first.

##### Data sources

##### *The PREVAIL trial data*

The PREVAIL babies' characteristics, trial group and outcomes were obtained from LCTC. The data were collected by the RNs using CRFs (forms 2, 3, 6, 7a, 7b and 10; details of the variables can be

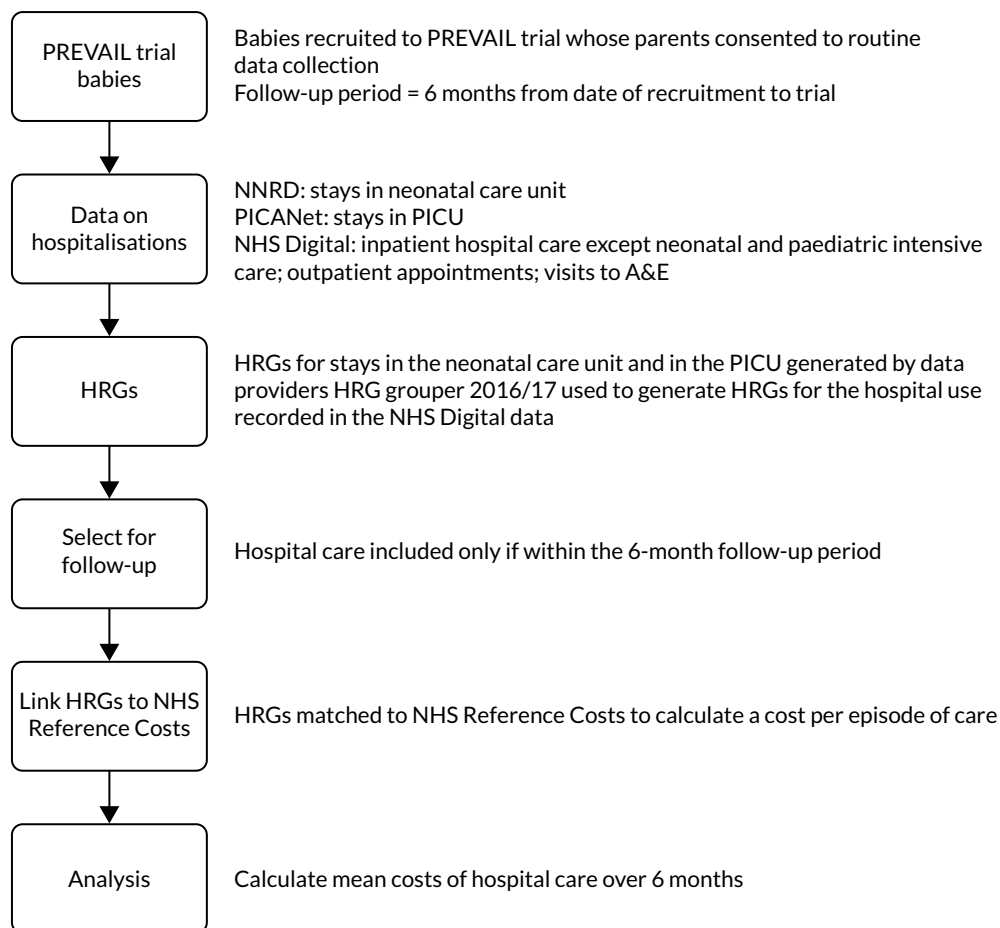


FIGURE 5 Overview of the methods used to estimate the cost of hospitalisations.

found in *Appendix 4*. The forms are available on the PREVAIL trial website.<sup>63</sup> The individual-level trial data were linked to data on hospitalisations using the trial participant study number. These data were encrypted, password protected and transferred securely to the University of York (UoY).

### Data on hospital care

Hospital care includes care in the NNU and/or PICU, procedures and diagnostic tests, outpatient appointments, and visits to the A&E. To capture the full data on hospital care, data on the PREVAIL babies were extracted from five different databases. The specific data fields obtained from each database are detailed in *Appendix 4*. The databases and respective data custodians were as follows:

- Hospital critical care during the stay in the NICU was obtained from the NNRD. The NNRD is a clinical data set (the National Neonatal Data Set) within the NHS Data Model and Dictionary Service. The NNRD compiles information entered by clinicians and nurses onto the electronic patient records of babies in the NNU. The National Neonatal Data Set is extracted quarterly from the electronic records to form the NNRD, which covers England, Wales and Scotland.<sup>64</sup> Details of all data items are searchable online.<sup>65</sup>
- Hospital critical care during any stay in the PICU was obtained from PICANet. PICANet is an audit database comprising details of care, such as need for ventilation, in PICUs in the UK and the Republic of Ireland.<sup>66</sup> PICANet has data on paediatric critical care during each day of hospitalisation in the unit.
- Information on other hospital care during hospitalisations other than the critical care in the neonatal or paediatric critical care units was obtained from the HES Admitted Patient Care (APC) database.<sup>67</sup>

- Outpatient appointments were obtained from the HES outpatient database.
- Accident and emergency attendances were obtained from the HES A&E database.
- Date of randomisation was obtained from the PREVAIL trial data, collected by the UoL.

The HES APC, outpatient and A&E databases contain details of all admissions at NHS hospitals in England. The data are collected during a patient's time at hospital and submitted to NHS Digital for processing.<sup>67</sup>

### **Data on whether or not death occurred within the 6-month follow-up**

Data on deaths occurring within the follow-up period were obtained from both the PREVAIL trial CRFs, which refer to date of death within the primary follow-up period, and from death registrations supplied to the Personal Demographics Service linked to the HES databases. LCTC received death registration data on date of death if death occurred within the 6-month follow-up (see *Chapter 2, Secondary outcomes*). These data are used to inform the decision model (see *Probability of death between peripherally inserted central venous catheter insertion and 6 months of age*).

### **Fair processing**

The parents and guardians of the PREVAIL babies were asked for their consent to use data about their babies' admissions and visits to hospital from the date of PICC insertion for a period of 6 months. For the babies whose parents gave consent, the team at LCTC sent the personal identifiers (NHS number, name, date of birth, sex and postcode) and trial identifier to PICANet (for the stays in the PICU) and NHS Digital (for all hospital stays, outpatient admissions, visits to A&E and date of death). Babies in the PREVAIL trial were linked to the NNRD using patient identifiers (NHS number, sex, date of birth and postcode) within Public Health England (PHE) for the generalisability study (see *Chapter 5*). The NNRD received de-personalised trial identifiers linked to the NNRD baby identifiers from PHE to identify PREVAIL babies for the NNRD extract for the health economics study.

Individual-level data containing the de-identified hospitalisation records and the trial identifier were transferred from NNRD, PICANet (via LCTC) and NHS Digital to the UoY. These data were password-protected, encrypted and transferred securely. The UoY transferred the data on the date of death, obtained from NHS Digital via the Personal Demographics Service, to LCTC. All data transfers were subject to data-sharing contracts between the various institutions. The privacy notice is available in the parents' section of the PREVAIL trial website [[www.prevailtrial.org.uk/parents.html](http://www.prevailtrial.org.uk/parents.html) (accessed 16 August 2020)].

### **Generating Healthcare Resource Groups from the data on hospital care**

The data on hospital care consists of information on the nature and length of the hospital stay. The first step in costing hospital care is to generate HRGs from these hospital records. HRGs are standard groupings of clinically similar treatments that use common levels of health-care resource.<sup>68</sup> They form the payment structure of hospital care, and are relevant to all hospital stays, appointments and A&E visits. The algorithm to generate the relevant HRGs, given the resources involved in the hospitalisations, is released by the National Casemix Office in partnership with NHS Digital.<sup>68</sup>

There are two types of HRGs: 'bundled' and 'unbundled'. Bundled HRGs represent the set of procedures, treatments and other interventions for a given diagnosis and case mix. Unbundled HRGs represent high-cost or specialist service elements in addition to the care recorded in the bundled HRG.<sup>68</sup> Examples of unbundled HRGs are diagnostic imaging and high-cost drugs.<sup>69</sup> Activity in critical care units are captured in the critical care HRGs, which are a type of unbundled HRG.

Given that costs can be obtained only for admissions with a HRG, the admissions with insufficient information to derive a HRG were discarded. In principle, the hospitalisation data would be of sufficient quality to derive HRGs for all admissions. In practice, however, errors in coding occur.

These errors are likely to be random and unrelated to the babies' characteristics and the admissions themselves. Therefore, we assumed that the data were missing completely at random and removed missing observations (i.e. the specific hospitalisation) from the analysis.<sup>70</sup>

### ***Healthcare Resource Groups for the neonatal care stay (in the National Neonatal Research Database)***

The neonatal care HRGs are critical care HRGs that are added to the core HRG relating to the hospitalisation. There are five neonatal critical care HRGs to represent the intensity of care over a 24-hour period, and a neonatal critical-care transport HRG, which is paid per patient journey (see *Appendix 1, Table 43*).<sup>69</sup> Therefore, each neonatal critical care HRG represents a day in the neonatal care unit or, if a transport HRG, a patient journey. Stays in the neonatal care unit can be aggregated into episodes, which, in turn, can be aggregated into an admission (or spell).

The data on the PREVAIL babies' stays in the NNU (which were received from NNRD) included two files: the 'episode file' and the 'daily file'. The 'episode file' contained the trial identifier, episode number, anonymised date of admission and anonymised date of discharge. Given that the follow-up period was restricted to 6 months after the date of randomisation, some of the episodes for which the date of discharge was outside the follow-up period did not include the record for the date of discharge. The 'daily file' contained the trial identifier, the episode number, the anonymised time stamp referring to when the day of care was recorded and the HRGs corresponding to the care on each day. The two files were processed and combined to obtain the length of stay and cost of stays in the neonatal care unit over the 6-month follow-up of the trial.

In principle, all PREVAIL babies have neonatal HRGs referring to their stay in the neonatal care unit. However, some units do not report to NNRD; hence, the data on the PREVAIL babies who had stays in these non-reporting units were not available. Furthermore, errors in entering records or in registering the details of the babies in the PREVAIL trial may result in some babies and some parts of their neonatal care not being recorded in NNRD.

### ***Critical Care Healthcare Resource Groups for the paediatric intensive care stay (in the Paediatric Intensive Care Audit Network)***

The paediatric care HRGs are critical care HRGs. Each day in the PICU is assigned to a paediatric critical care HRG. There are eight daily HRGs, in addition to a paediatric transport HRG, which is paid per patient journey.<sup>69</sup>

Similarly to the NNRD data, the PICANet data included two files. One file had information on the episodes of care, trial identifier, episode number, date of admission and date of discharge. The other file contained information on the activity in each day of care, trial identifier, episode number, daily date and HRG.

### ***Healthcare Resource Groups for hospital admissions (Hospital Episode Statistics Admitted Patient Care)***

The hospital admission comprises the entire continuous stay in a specific hospital. The admission can include one or more finished consultant episodes (FCEs). A FCE is the period of care under a given consultant. Patients can have more than one FCE at the same time. Generally, all FCEs can be assigned to one or more HRGs. Typically, the FCE includes a bundled HRG, as well as one or more unbundled HRGs for high-cost items, and critical care HRGs for stays in critical care units, such as the NNU and PICU. It is not possible to link the FCE admissions in HES APC to the neonatal care episodes in NNRD and paediatric care episodes in PICANet with certainty, because of the lack of a common identifier to link episodes of care in critical care to FCEs in HES APC.

The HES APC data on the PREVAIL babies included the information required to generate HRGs and calculate length of stay for each FCE. The HRG4+ 2016/17 Reference Costs Grouper was used to generate the HRGs at the FCE level.<sup>68</sup> These included the bundled HRG and unbundled HRGs related to high-cost items over and above critical care stays.

### **Healthcare Resource Groups for outpatient appointments**

Outpatient appointments also need to be assigned to a HRG for costing. These were generated with the HRG4+ 2016/17 Reference Costs Grouper.<sup>68</sup>

### **Healthcare Resource Groups for accident and emergency visits**

The HRG4+ 2016/17 Reference Costs Grouper was also used to assign each A&E visit to the relevant HRGs.<sup>68</sup>

The data-cleaning processes required to prepare the data for the HRG4+ 2016/17 Reference Costs Grouper are detailed in *Appendix 5*.

### **Calculating length of stay**

In the NNRD and PICANet, the length of stay (in the NNU and PICU, respectively) was calculated by subtracting the date of discharge from the date of admission for each episode of care. In HES APC, length of stay was calculated at the spell level, given that there can be more than one FCE at the same time in the same spell. When the date of admission of the subsequent episode of care or spell was earlier than the date of the discharge of the previous hospitalisation, the date of admission was changed to the previous date of discharge.

The length of stay recorded in HES APC overlaps with the length of stay in the NNUs and PICUs. This is because the days in these units are recorded in the NNRD and PICANet, respectively, in terms of the critical care HRGs, as well as in HES APC for the core hospitalisation. To calculate the cost of hospital care, however, the cost of care recorded in each database needs to be added up together, as the cost of the FCE (from HES APC) reflects only the core HRG and the unbundled HRGs, but not the critical care HRGs (which are recorded in the NNRD and PICANet).

### **Selecting hospital care that was within the trial follow-up**

The period of follow-up was from randomisation for 6 months or until death, whichever happened first. The dates of outpatient and A&E visits were examined to confirm that all referred to the period between date of randomisation and the end of the 6-month follow-up.

The FCEs, which are captured in the HES APC data set, and the episodes of critical care, which are captured in the NNRD and PICANet, span a period of time. This period of time can include days before randomisation and/or days after the end of the follow-up period.

Stays in the NNUs and PICUs have records of daily activity and of the date of admission and discharge. For each database, the records of daily activity and of dates of admission and discharge were compared for consistency. The preferred option was to use the record of daily activity to select the days of care that were within the follow-up period. If these data were inconsistent, the dates of admission and discharge were used to select the episodes of care that were within the follow-up period. The dates of admission and discharge were also used to select the FCEs in the HES APC data set that were within the follow-up period.

The length of stay and cost of FCEs or episodes of care that fell partly outside the trial follow-up were adjusted to account for the time period outside the trial follow-up. This was done to ensure that the costs referred to the same time period for all babies. For the length of stay, this was done by removing the days outside the follow-up period. The costs were rescaled by the proportion of the episode of care or FCE within the follow-up period. The proportion of the episode of care or FCE within the

follow-up period was calculated by adding 1 day to the length of stay within and outside the period of follow-up. This was to account for episodes in which the date of discharge corresponds to the date of randomisation or in which the date of admission corresponds to the date of end of follow-up.

### Costing hospital care

Data were cleaned prior to costing (see *Appendix 5*). The HRGs were matched with the relevant costs using the NHS reference costs for 2015–16.<sup>62</sup> NHS reference costs for 2015–16<sup>62</sup> were the most recent year for which costs were available when the economic work commenced. HRGs from 2016–17, which were different from 2015–16, were replaced or the costs deflated (see *Appendix 5, Tables 41 and 42*). *Appendix 5, Table 43*, reports the unit costs of the HRGs relating to the stay in the neonatal and paediatric critical care unit. The other unit costs are not reported here because of their large number, but are freely available online.<sup>62</sup>

## Analysis

### Hospital care by database

Hospital care was analysed separately by database. For each database, the number of PREVAIL babies with hospital care recorded, the length of days in hospital (or the number of attendances for outpatient and A&E), the HRGs and the cost are reported.

### Cost of hospital care

As the FCEs in HES APC cannot be uniquely linked to the episodes of care in the NNRD and PICANet, the cost of hospital care was calculated on a per-baby basis, separately, for each data set. Subsequently, the various data sets were merged to calculate the cost of hospital care in the PREVAIL trial population. The analytical sample comprised the PREVAIL babies with at least one valid record in HES APC and in the NNRD. Babies with no hospital care recorded in the PICANet, HES outpatient and HES A&E were assumed not to have used this care; hence, the cost of hospital care referring to each database was assumed to be zero. This was a complete-case analysis using the valid records in the NNRD and in the HES APC as the reference. It assumed that the likelihood of having none or incomplete information is unrelated to babies' characteristics and costs.<sup>70</sup>

## Results

### Neonatal care recorded in the National Neonatal Research Database

#### Data preparation

*Appendix 5* details the process of data preparation, including *Figure 18*. Thirteen PREVAIL babies (1.51%) were not available in the NNRD extract: six were allocated to AM-PICC and seven to S-PICC. After cleaning, the file with the episode dates (the 'episode file') contained data on 848 (98.49%) PREVAIL babies, with a total of 1568 episodes. The file with the daily care record (the 'daily file') contained data on 848 (98.49%) PREVAIL babies with 57,702 days in NNUs. The date of discharge was imputed using the latest daily care date for 147 episodes without a date of discharge; of these, three episodes of care had their date of admission corrected to the earliest date stamp for the daily care in the episode. Episodes with a date of discharge before the date of randomisation were removed and permanently deleted. The resulting file contained data on 837 PREVAIL babies, with 1388 episodes and 56,610 days in the neonatal care unit.

#### Length of stay, care activity and cost of care

The breakdown of days of care by HRG code is presented in *Appendix 6, Table 44*. This breakdown refers to the data without any adjustments for hospitalisations spanning beyond the 6-month follow-up period, because the HRGs are recorded on a daily basis.

*Appendix 6, Table 45*, shows the length of stay recorded in the NNRD and costs by episode of care, with and without adjusting for the time outside the follow-up period. Without adjusting for the time outside the follow-up period, the average length of stay per episode of care was 40 days and the average cost per episode of care was approximately £36,000. Adjusting for the time outside the follow-up period, the average length of stay per episode of care was 37 days and the average cost per episode of care was approximately £33,000.

*Table 15* shows the average length of stay and cost per baby, with adjustment for the follow-up period (see *Appendix 6, Table 45*, for the results without adjustment). The average length of stay per baby was 61 days and the average cost per baby was £54,086. This was similar for both PICC types.

## Paediatric critical care recorded in the Paediatric Intensive Care Audit Network

### **Data preparation**

*Appendix 5* details the process of data preparation, including *Figure 19*. A total of 177 PREVAIL babies were recorded in PICANet, with 184 episodes of care and 1237 days in the PICU. After removing the days of care outside the follow-up period, the PICANet files contained records on 94 (10.92%) PREVAIL babies who had 126 episodes of care and 779 days in the PICU.

### **Intensity, length of stay and cost of care within the follow-up period**

*Table 15* shows the results. For the 94 PREVAIL babies for whom PICANet recorded days in paediatric intensive care, the average length of stay, per baby, was 8 days and the average cost was approximately £14,500. This was similar for both PICC types. The breakdown by HRG code is presented in *Appendix 6, Table 46*.

## Hospital care recorded in the Hospital Episode Statistics Admitted Patient Care

### **Data preparation**

*Appendix 5* details the process of data preparation, including *Figure 20*. A total of 834 (96.86%) PREVAIL babies were recorded in HES APC, with a total of 2772 FCEs. During the data preparation process prior to generating HRGs, 58 FCEs were removed, as well as the records referring to two PREVAIL babies. The grouper was fed 2714 FCEs, relating to 832 babies. Of these, 20 FCEs were not grouped into HRGs because of data errors, eight FCEs were removed because of missing admission type, and four FCEs were removed because of lack of unit cost data. As a result, data on the hospital admission for four PREVAIL babies were removed. In total, the HES APC included 2682 FCEs relating to 828 (96.17%) PREVAIL babies.

### **Intensity, length of stay and cost of care within the follow-up period**

All of the 2682 FCEs for the 828 PREVAIL babies were within the follow-up period of 6 months. These corresponded to 2128 spells. The length of stay by spell is presented in *Appendix 6, Table 47*; it was 29 days, on average, without any adjustment for spells with days outside the follow-up period. There were 744 spells with admissions before the date of randomisation and 21 spells with discharge after the end of follow-up. The average length of stay by spell, adjusting for days outside the follow-up period, was 27 days. These spells with days outside the follow-up period corresponded to 732 FCEs that started before the randomisation date and 21 FCEs that finished after the end of the 6-month follow-up date. Therefore, the cost of these episodes that spanned outside the follow-up period were adjusted, as explained in *Selecting hospital care that was within the trial follow-up*.

The costs were calculated at the FCE level (results are shown in *Appendix 6, Table 48*). The average total cost per FCE was £8698, unadjusted, and £8129, adjusted. The number and cost per FCE by admission type is shown in *Appendix 6, Table 49*. Most of the FCEs were non-elective inpatient long stays [1798 (67.04%)], with an average cost of £12,122, followed by non-elective inpatient short stays [952 (35.50%)], with an average cost of £10,635.

TABLE 15 Length of stay and costs per PREVAIL baby recorded in each database within the follow-up period

	Total			AM-PICC			S-PICC		
	Babies, <sup>a</sup> n (%)	Mean	SD	Babies, <sup>a</sup> n (%)	Mean	SD	Babies, <sup>a</sup> n (%)	Mean	SD
<b>Hospital care recorded in the NNU recorded in NNRD<sup>a</sup></b>									
Length of stay (days)	837 (97)	61.04	35.74	420 (98)	60.70	36.31	417 (97)	61.40	35.20
Cost (£)	837 (97)	£54,086.19	£35,223.79	420 (98)	£53,959.65	£36,046.58	417 (97)	£54,213.65	£34,418.05
<b>Hospital care recorded in the paediatric unit recorded in PICANet</b>									
Length of stay (days)	94 (11)	8.29	9.56	46 (11)	8.20	10.50	48 (11)	8.38	8.67
Cost (£)	94 (11)	£14,547.84	£17,021.59	46 (11)	£14,501.07	£18,531.86	48 (11)	£14,592.66	£15,636.00
<b>Hospital care recorded in HES APC<sup>a</sup></b>									
Length of stay (days)	828 (96)	68.65	37.91	410 (95)	67.68	36.77	418 (97)	69.61	39.01
Cost (£)	828 (96)	£26,332.09	£18,190.26	410 (95)	£26,222.37	£18,055.68	418 (97)	£26,439.72	£18,342.29
<b>Outpatient appointments recorded in HES outpatient</b>									
Number of attendances	784 (91)	7.47	7.60	394 (92)	7.65	8.03	390 (90)	7.29	7.14
Cost (£)	784 (91)	£1155.97	£1009.64	394 (92)	£1166.57	£1027.54	390 (90)	£1145.27	£992.44
<b>A&amp;E visits recorded in HES A&amp;E</b>									
Number of attendances	320 (37)	1.68	1.17	163 (38)	1.72	1.19	157 (36)	1.64	1.14
Cost (£)	320 (37)	£223.41	£162.09	163 (38)	£227.34	£152.69	157 (36)	£219.34	£171.70
<p>a The number of babies is the number of PREVAIL babies recorded in each database with hospitalisations within the follow-up period of 6 months after randomisation who had sufficient data for costing (see Appendix 5, Figures 18–21, for details). The percentage refers to the proportion of PREVAIL babies compared with the analysis population of 861 babies (430 allocated to AM-PICCs and 431 allocated to S-PICCs).</p>									



Table 15 shows the length of stay and the costs per baby, after adjusting for the time outside the 6-month follow-up period (unadjusted results are presented in Appendix 6, Table 50). For the 828 PREVAIL babies for whom the hospitalisation was recorded in HES APC, the average length of stay, per baby, was 69 days and the average cost of hospital admission, adjusted for the length of stay outside the 6-month follow-up period, was £26,332 per baby. This is similar across both PICC types.

### Outpatient attendances recorded in Hospital Episode Statistics outpatient

#### Data preparation

Appendix 5 details the process of data preparation, including Figure 21. A total of 799 PREVAIL babies (92.80% of the PREVAIL trial population) were recorded in the HES outpatient data set, with a total 6425 outpatient appointments. Of these, 19 records (i.e. outpatient appointments) did not have valid data to generate a HRG. The grouper derived HRGs for 6406 appointments, which correspond to 798 PREVAIL babies. A total of 547 appointments were removed because they were flagged as either postponed or cancelled; hence, no cost was incurred. One outpatient appointment was associated with an invalid HRG, and so was deleted. As a result, 5858 outpatient appointments, referring to 784 PREVAIL babies (91.06%), were taken forward for costing.

#### Intensity, length of stay and cost of care within the follow-up period

All 5858 outpatient appointments were within the follow-up period. The average cost per outpatient appointment was £155, and was similar by PICC type (see Appendix 6, Table 51). Table 15 shows the length of stay and the costs per baby. For the 784 PREVAIL babies for whom outpatient appointments were recorded, the average number of outpatient appointments was 7.47 and the average cost per baby was £1156; both values were similar by type of PICC.

### Accident and emergency visits recorded in Hospital Episode Statistics accident and emergency

#### Data preparation

Appendix 5 details the process of data preparation, including Figure 21. A total of 352 PREVAIL babies (40.88% of PREVAIL trial population) were recorded in HES A&E, with a total of 622 A&E attendances. No observations were deleted in the preparation of the data set for the grouper. The grouper derived valid HRGs for 539 A&E attendances among 320 PREVAIL babies (37.17%).

#### Intensity, length of stay and cost of care within the follow-up period

All 539 A&E attendances, by 320 PREVAIL babies, were within the follow-up period. The average cost per A&E attendance was £132.64, which was similar across both PICC types. Of the 539 A&E attendances, 293 (54%) led to an inpatient admission and 246 (46%) did not; these values were also similar by PICC type. Table 15 shows the number of A&E attendances and A&E costs per PREVAIL baby recorded in HES A&E. For those 320 PREVAIL babies for whom A&E attendances were recorded, the average number of A&E attendances was 1.68 per baby and the average cost was £223 per baby; both values were similar by PICC type.

The number of babies is the number of PREVAIL babies recorded in each database with hospitalisations within the follow-up period of 6 months after randomisation, which had sufficient data for costing (see Appendix 5, Figures 18–21, for details). The percentage refers to the proportion of PREVAIL babies compared with the analysis population of 861 babies (AM-PICC,  $n = 430$ ; S-PICC,  $n = 431$ ).

The length of stay and the costs of the hospital care in the NNU recorded in the NNRD and the hospital care recorded in HES APC were adjusted by the proportion of time outside the trial follow-up window.

## Cost of hospital care

To calculate the total cost of hospital care, the files with the cost per baby from each data set were merged into one single file. Of the 861 PREVAIL babies, 33 babies had records of hospital use in the NNRD, but not in HES APC, and 24 babies had record of hospital use in HES APC, but not in the NNRD. The analytical sample comprised the PREVAIL babies with data on the cost of hospital care both in HES APC and in the NNRD. The analytical sample comprises 804 PREVAIL babies with data on the cost of hospital care in HES APC and NNRD.

Table 16 summarises the costs of hospital care in the analytical sample. The average costs were similar by PICC type. The average total cost per baby was £83,473. Most of the costs were incurred in the NNU (£54,047; 64.75% of the total cost of hospital care), followed by hospital care other than intensive care (£26,617; 31.89% of the total cost of hospital care). The cost was similar by PICC type. Some of the costs per database are different between Tables 15 and 16. This is because Table 15 shows the average costs per baby with an admission recorded in each database. For example, 94 babies were recorded in the PICANet database, with an average cost each of £14,458 due to their PICU stay. Conversely, Table 16 shows the average costs per baby in the analytical sample. For example, the average cost of a PICU admission is £1641 over the 6 months' follow-up for all of the 804 PREVAIL babies who comprise the analytical sample, based on a mean of 0.93 days in PICU per baby.

## Deaths during the 6-month follow-up period

The HES data sets included date of death according to the Personal Demographics Service. Within the follow-up period of 6 months from date of randomisation, 66 deaths were recorded. The PREVAIL trial CRFs recorded whether death had occurred in the neonatal care unit. The CRFs recorded 69 deaths. Five deaths were recorded in the CRFs that were not recorded in the Personal Demographics Service records (which were linked to HES), and two deaths were recorded in the Personal Demographics Service records but not in the CRFs. In total, 71 deaths occurred. These data are used to inform the economic model (see *Probability of death between peripherally inserted central venous catheter insertion and 6 months of age*).

TABLE 16 Length of stay and cost of hospital care of the PREVAIL babies with hospitalisations recorded in the NNRD and in HES APC

Type of hospital care	Total (n = 804)		AM-PICC group (n = 400)		S-PICC group (n = 404)	
	Mean	SD	Mean	SD	Mean	SD
<b>Length of stay (days)</b>						
NICU (recorded in NNRD)	66.53	36.52	66.05	36.80	67.01	36.27
PICU (recorded in PICANet)	0.93	4.19	0.90	4.37	0.97	4.00
In total for all hospital admissions (recorded in HES APC)	69.52	37.81	68.43	36.64	70.60	38.94
Number of outpatient attendances (recorded in HES outpatient)	7.03	7.70	7.22	8.16	6.85	7.23
Number of A&E attendances (recorded in HES A&E)	0.64	1.09	0.68	1.13	0.60	1.03
<b>Costs</b>						
NICU	£54,047.15	£34,834.76	£53,526.62	£35,110.30	£54,562.53	£34,595.59
PICU	£1641.37	£7417.34	£1590.98	£7718.18	£1691.25	£7116.19
Other inpatient hospital care	£26,616.92	£18,268.35	£26,447.75	£18,152.15	£26,784.41	£18,403.65
Outpatient appointments	£1082.63	£1027.28	£1098.27	£1056.66	£1067.15	£998.42
A&E appointments	£84.68	£146.73	£89.36	£147.89	£80.05	£145.61
Total cost	£83,472.75	£50,148.48	£82,752.99	£49,738.66	£84,185.39	£50,602.54

## Cost-effectiveness of antimicrobial-impregnated versus standard peripherally inserted central venous catheters over a lifetime

### Background

The primary objective of the cost-effectiveness analysis was to estimate the long-term costs and health benefits of using AM-PICCs, compared with using S-PICCs, in babies in the NICU. The PREVAIL trial provided data on the risk of BSI, the AM-PICC effectiveness and the hospital costs over 6 months of babies who received AM-PICCs, compared with babies who received S-PICCs. To estimate the costs and health benefits of using an AM-PICC or a S-PICC over a baby's lifetime, information was needed on the long-term consequences of using each PICC. This information was obtained from the published literature and synthesised in a de novo cost-effectiveness model. This section reports the methods used to develop the cost-effectiveness model and the results of the cost-effectiveness analysis.

The model was developed to evaluate the cost-effectiveness of any intervention for the prevention of infection in neonates in the NNU. For the purposes of the cost-effectiveness model, infection is an umbrella term that includes, not only BSI and clinically serious BSI, as defined in the PREVAIL trial, but also sepsis (indicating BSI with clinical signs of tissue damage). The key assumption of the model was that infection increases the risk of death and of developing neurodevelopmental impairment (NDI) in early childhood. NDI is associated with lower life expectancy, worse health-related quality of life (HRQoL) and higher costs to the NHS.<sup>71</sup> Consequently, babies who had a BSI during their stay in the NNU are expected to experience worse health outcomes and higher costs because of the long-term consequences of infection. Therefore, interventions reducing the risk of infection may be cost-effective, depending on the magnitude of risk reduction and costs.

### Methods

#### Overview

The cost-effectiveness model simulated the costs, life expectancy and QALYs of preterm babies who required a PICC during their stay in the neonatal care unit. Costs were expressed in Great British pounds at a 2016 price base, from the perspective of the NHS. Future costs and QALYs were discounted at 3.5% per annum.<sup>72</sup> The time horizon was the babies' predicted lifetime from birth. The model was built in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA).

#### Population and subgroups

Gestational age is strongly associated with long-term costs and health outcomes.<sup>71</sup> Therefore, the target population was considered in terms of subgroups defined by gestational age. The gestational age cut-off points were based on Mangham *et al.*,<sup>71</sup> defined as extremely preterm babies (< 28 weeks), very preterm babies (28–32 weeks) and preterm (33–37 weeks). Given that only 12% of the PREVAIL babies were born at  $\geq 33$  weeks' gestation, and the advice by clinical collaborators that the babies who need a PICC of 1 French gauge are unlikely to be representative of the population of babies born at 33–37 weeks, the target population for the cost-effectiveness analysis was restricted to babies born at  $\leq 32$  weeks' gestation.

#### Model conceptualisation

##### *Consequences of infection in preterm neonates*

A 2016 study on the clinical effectiveness and cost-effectiveness of AM-PICCs in children reviewed the existing cost-effectiveness studies and found no published reports on the effectiveness in preterm babies.<sup>73</sup> Therefore, a systematic review on cost-effectiveness models in interventions that reduce the risk of BSI in preterm babies was not conducted.

The association between infection in preterm neonates and increased risk of NDI and death is supported by various observational studies.<sup>10,74-77</sup> Published meta-analyses<sup>78-80</sup> estimated that infection (specifically sepsis) significantly increases the risk of post-discharge death (RR 2.05, 95% CI 1.28 to 3.28)<sup>80</sup> and NDI, which manifests in early childhood (various definitions pooled, OR 2.09, 95% CI 1.65 to 2.65).<sup>78-80</sup> NDI may develop into physical and mental impairment in childhood, adolescence and adulthood, leading to a reduction in HRQoL and life expectancy, and a greater need for health and social care.<sup>9,10,81,82</sup>

The long-term outcomes of sepsis have been the subject of various studies, as have the consequences of infection, which is defined as an event requiring the use of antibiotics for at least 3–5 days.<sup>10,78-80</sup> No studies were found that used the same definition of BSI as used in the PREVAIL trial. The PREVAIL trial did collect data on clinically serious BSIs; a clinically serious BSI was defined as a BSI for which a baby is treated for > 72 hours with intravenous antibiotic, or dies during treatment (see section 4.1 of the trial protocol<sup>59</sup>). Consequently, clinically serious BSI was taken as the key intermediate outcome for the cost-effectiveness model, rather than BSI. In practice, however, there was little difference between the incidence of BSI and clinically serious BSI in the PREVAIL trial (see *Chapter 2, Primary outcome*). Hence, for consistency with the rest of the report, the term BSI is used throughout, although it refers to clinically serious BSI in this chapter.

### **Model design**

The cost-effectiveness model simulated long-term outcomes in preterm babies by assuming that the occurrence of a BSI during the stay in the NNU increases the risk of developing NDI and increases the risk of death at 2 years of age. The model assumed that having a BSI during the stay in the NNU has no direct consequences after 2 years of age. After 2 years of age, the model was driven by the NDI state that children experience at 2 years of age, which can improve or deteriorate and is associated with an increased risk of death compared with the general population.

In the cost-effectiveness model, NDI was defined as a composite outcome encompassing different types of impairment, namely visual, hearing, mobility and cognitive.<sup>83</sup> Each item is assigned a level ranging from no impairment to severe impairment, following standardised paediatric assessment tests; the most serious level of impairment recorded defines the overall NDI classification for an infant. This classification was previously used and validated as part of the Victorian Infant Collaborative Study Group (VICSG)<sup>83-85</sup> and in the UK economic analysis by Mangham *et al.*<sup>71</sup>

A summary of the main model assumptions is available in *Appendix 11, Box 1*.

### **Model structure**

#### ***Predicting outcomes in early childhood***

The model included a short- and a long-term component. The short-term component was a decision tree. Babies enter the model at the time of PICC insertion. The model estimated the proportion of children alive at 2 years of age, and their distribution by level of NDI (none, mild, moderate or severe) (*Figure 6*). PICC type (AM-PICC or S-PICC) determines the probability of BSI and costs, as observed in the PREVAIL trial. BSI is assumed to increase the probabilities of death and of experiencing NDI.

#### ***Predicting lifetime costs and health outcomes beyond 2 years of age***

The long-term component of the model simulated the lifetime health outcomes and costs given the children's NDI levels. It assumed that previous BSI does not influence longer-term lifetime costs and health outcomes. The model was a Markov model,<sup>86</sup> based on the model depicting the costs of prematurity by Mangham *et al.*<sup>71</sup> Children enter the model at 2 years of age in one of the NDI states, according to the proportion of babies computed by the decision tree (*Figure 7*). At each cycle, children can transition between NDI states or die. The transitions represent the improvement or deterioration in the neurodevelopmental state of the child, as well as inaccuracies in the assessment, which might become apparent over time. After reaching 8 years of age, children were assumed to no longer

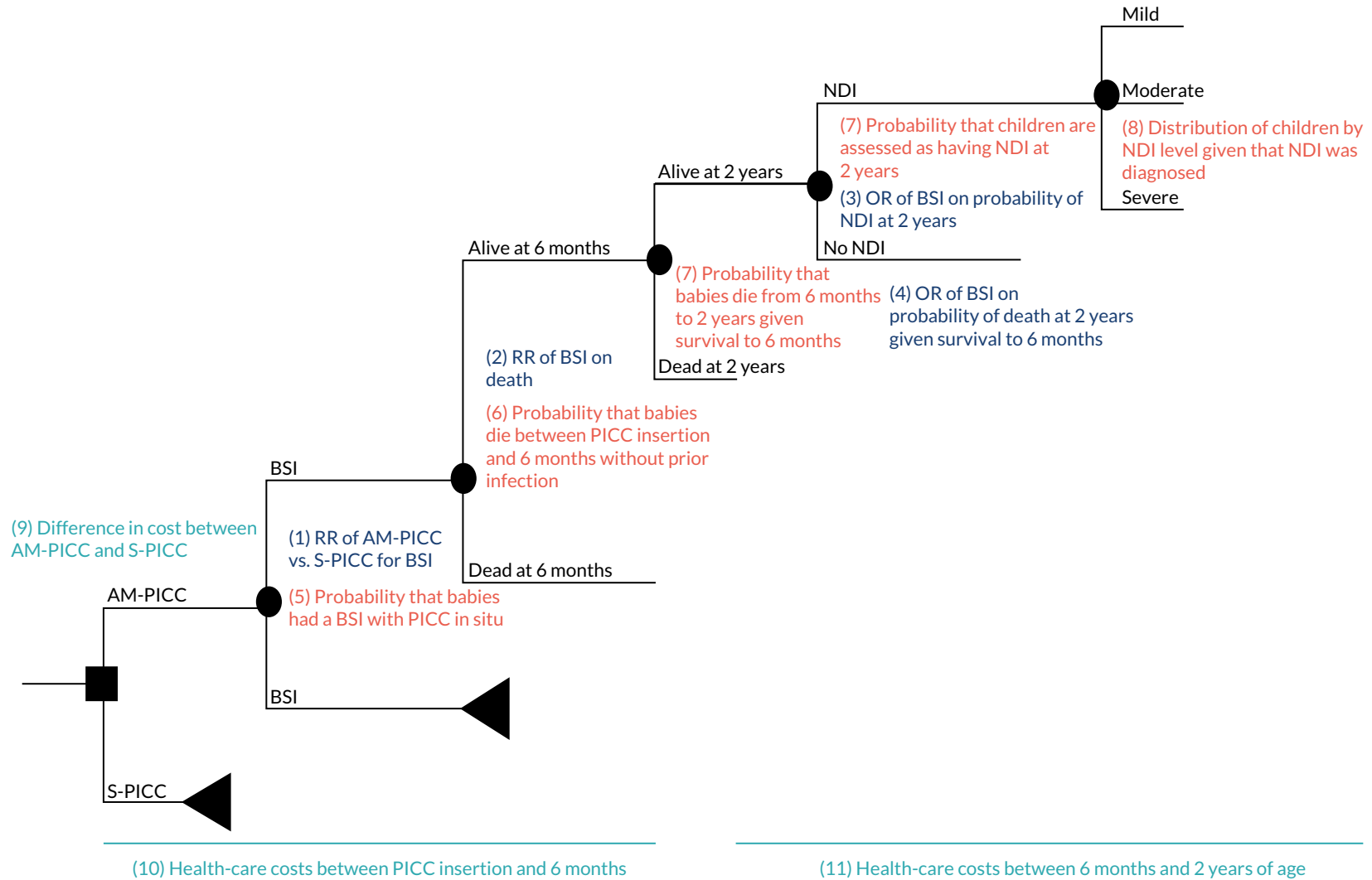


FIGURE 6 Model structure for predicting outcomes in early childhood. The square denotes the decision: use either an AM-PICC or a S-PICC. The circle denotes a probability (or chance) node. The triangle denotes when the structure is the same in both arms. The diagram details the parameter inputs; their numbers correspond to the numbers in Table 17.

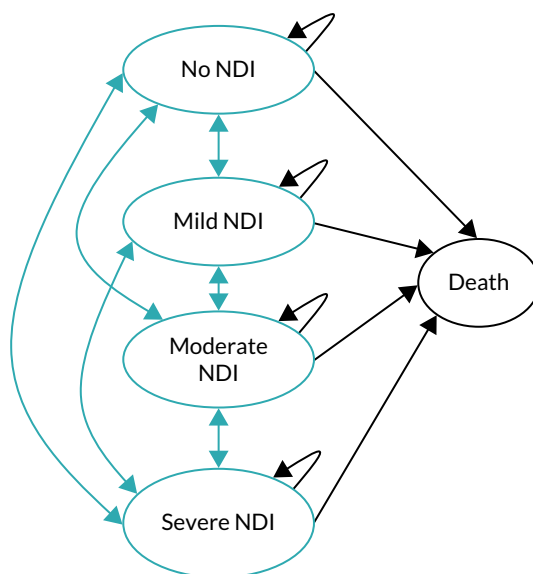


FIGURE 7 Model structure for predicting lifetime costs and health outcomes. The arrows depict the possible transitions between model states in each cycle.

transition between NDI states; therefore, the only transition after age 8 years is to the absorbing death state. The risk of death depends on both age and NDI state.

### Model inputs for predicting outcomes in early childhood

Table 17 presents the short-term model parameters used to predict the outcomes at 2 years of age. Each parameter is shown in Table 17 and discussed in detail in the following text. The base case refers to the primary analysis.

#### **Effect of antimicrobial-impregnated peripherally inserted central venous catheter in preventing bloodstream infection**

The effect of AM-PICC in preventing BSI was obtained from the PREVAIL trial: RR 1.06 (95% CI 0.70 to 1.60). As discussed earlier, it refers to the RR of clinically serious BSI, as defined in the PREVAIL trial. It refers to the full trial population because gestational age was not expected to be a treatment effect modifier.

TABLE 17 Parameters for predicting outcomes in early childhood

Parameter	Value (95% CI); distribution	Source
<b>Effect of AM-PICC on the probability of a BSI occurring</b>		
(1) RR of AM-PICC vs. S-PICC on BSI; same for both gestational age subgroups	1.06 (0.70 to 1.60); log-normal	PREVAIL trial: calculated from the number of babies who had a clinically serious BSI in the PREVAIL trial
<b>Effect of BSI on NDI and death</b>		
(2) RR of the effect of BSI on death at 6 months; same for both gestational age subgroups	Base case: 1 (fixed)	Assumed that BSI has no causal effect on death at 6 months
(3) OR of BSI on NDI index at 2 years of age; same for both gestational age subgroups	1.51 (1.33 to 1.70); log-normal	Meta-analysis of Stoll <i>et al.</i> <sup>10</sup> and Schlapbach <i>et al.</i> <sup>74</sup>
(4) OR of BSI on probability of death at 2 years of age; same for both gestational age subgroups	2.74 (1.43 to 5.24); log-normal	Meta-analysis of Schlapbach <i>et al.</i> <sup>74</sup> and Bassler <i>et al.</i> <sup>76</sup>

continued

TABLE 17 Parameters for predicting outcomes in early childhood (continued)

Parameter	Value (95% CI); distribution	Source
<b>Baseline probabilities</b>		
(5) Probability of having a BSI with S-PICC		
Gestational age $\leq$ 27 weeks	0.14 (0.09 to 0.20); beta	PREVAIL trial: proportion of babies who had a BSI who were allocated to S-PICC, by gestational age. For consistency with the costs, the probabilities refer to the subpopulation with gestational age of $\leq$ 32 weeks for whom costs of hospital care could be calculated
Gestational age $\geq$ 28 weeks	0.04 (0.02 to 0.08); beta	
(6) Probability of death between PICC insertion and 6-months if BSI had not occurred		
Gestational age $\leq$ 27 weeks	0.20 (0.16 to 0.23); beta	<ul style="list-style-type: none"> <li>• Santhakumaran <i>et al.</i><sup>87</sup> for gestational age 23–27 and 28–32 weeks on survival to discharge</li> <li>• PREVAIL trial for the probability of BSI and the RR of BSI on death</li> </ul>
Gestational age $\geq$ 28 weeks	0.03 (0.03 to 0.04); beta	
(7) Probability that children who did not have a BSI during PICC use die between 6 months and 2 years		
Gestational age $\leq$ 27 weeks	0.02 (0.01 to 0.03); beta	Mangham <i>et al.</i> <sup>71</sup>
Gestational age $\geq$ 28 weeks	0.01 (0.00 to 0.02); beta	
(7) Probability that children aged 2 years who did not have a BSI during PICC use are diagnosed with NDI		
Gestational age $\leq$ 27 weeks	0.45 (0.42 to 0.49); Dirichlet	Mangham <i>et al.</i> <sup>71</sup>
Gestational age $\geq$ 28 weeks	0.26 (0.25 to 0.28); Dirichlet	
(8) Distribution by NDI levels, given that NDI was diagnosed (independent of previous BSI during PICC use)		
Mild NDI		
Gestational age $\leq$ 27 weeks	0.54 (0.51 to 0.58); Dirichlet	<ul style="list-style-type: none"> <li>• Mangham <i>et al.</i><sup>71</sup> assumed to be similar for both infection and non-infection groups</li> <li>• Severe NDI is the remaining proportion, so that the total sums to 1</li> </ul>
Gestational age $\geq$ 28 weeks	0.73 (0.70 to 0.76); Dirichlet	
Moderate NDI		
Gestational age $\leq$ 27 weeks	0.29 (0.28 to 0.30); Dirichlet	
Gestational age $\geq$ 28 weeks	0.16 (0.15 to 0.17); Dirichlet	
<b>Costs</b>		
(9) Difference in cost between AM-PICC and S-PICC	£53.70	Vygon (UK) Ltd, 2015, personal communication
(10) Health-care costs between PICC insertion and 6 months		
Base case		
Gestational age 23–27 weeks	£105,873.47 (£101,444.99 to £110,495.27); gamma	PREVAIL trial: generalised linear model with Gaussian distribution and log-link; explanatory variable is gestational age group. Estimated in the subpopulation with gestational age of $\leq$ 32 weeks for whom costs of hospital care could be calculated
Gestational age 28–32 weeks	£62,255.37 (£54,711.87 to £70,838.93); gamma	
(11) Health-care costs between 6 months and 2 years		
Gestational age 23–27 weeks	£5989.17 (£5989.14 to £5994.98)	<ul style="list-style-type: none"> <li>• NHS Reference Costs 2015 to 2016<sup>62</sup></li> <li>• Inpatient admission, outpatient and A&amp;E visit from an unpublished study about variation in neonatal and paediatric admission (Katie Harron, personal communication)</li> </ul>
Gestational age 28–32 weeks	£3026.17 (£3024.21 to £3028.73)	

### **Long-term consequences of bloodstream infection**

Systematic reviews of the association between BSI during the NNU stay and NDI were used to identify studies using a similar NDI measure as the study by Mangham *et al.*,<sup>71</sup> the source of the transition probabilities between NDI levels for the Markov model. In Mangham *et al.*,<sup>71</sup> NDI was defined as an impairment affecting one of four functional dimensions: motor ability (including cerebral palsy), visual ability, hearing ability or development delay and cognitive ability, based on Doyle *et al.*<sup>83</sup> (see *Appendix 7, Table 52*, for details). Therefore, only studies that reported the association between infection during the neonatal stay and impairment including all the aforementioned four dimensions were selected and meta-analysed (see *Appendix 7, Table 53*, for details).<sup>86</sup>

### **Effect of clinically serious bloodstream infection on the risk of neurodevelopmental impairment**

Two studies were identified: Stoll *et al.*<sup>10</sup> and Schlapbach *et al.*<sup>74</sup> Stoll *et al.*<sup>10</sup> is a retrospective study describing the outcomes at 18–22 months of age of 6093 babies in a US registry of very low-birthweight infants born between 1993 and 2001 weighing 401–1000 g at birth. Stoll *et al.*<sup>10</sup> report an adjusted OR for infection on NDI of 1.50 (95% CI 1.20 to 1.70). Schlapbach *et al.*<sup>74</sup> report a prospective cohort study in Switzerland of 541 babies born between 2000 and 2007 at 24–27 weeks' gestational age; the OR for sepsis on NDI is 1.69 (95% CI 0.96 to 2.98). The base case uses the meta-analysed OR using Stoll *et al.*<sup>10</sup> and Schlapbach *et al.*<sup>74</sup> at 1.51 (95% CI 1.33 to 1.70; fixed effects; see *Appendix 7, Table 55*). Both estimates used the ORs, adjusted for differences in observed characteristics using multivariate logistic regression.

**Effect of clinically serious bloodstream infection on the risk of death at 6 months of age** As discussed in *Deaths during the 6-month follow-up period*, 71 deaths were recorded in the PREVAIL trial population, according to the PREVAIL trial CRFs and NHS Digital's Personal Demographics Service. However, some of these deaths occurred in babies who were born at  $\geq 33$  weeks' gestation, who are outside the scope of the economic model. In the modelled population of babies born at  $\leq 32$  weeks' gestation, 63 deaths occurred among 735 babies (8.57%). There was no clear evidence that BSI (specifically, clinically serious BSI as defined in the PREVAIL trial) increased the risk of death, controlling for gestational age (see *Appendix 7*). Furthermore, we found no evidence in the literature that BSI increased the risk of death at 6 months of age. Therefore, the model assumes that BSI does not increase the risk of death at 6 months and the assumption is tested in the sensitivity analysis.

### **Effect of bloodstream infection on the risk of death at 2 years of age given survival to 6 months**

Two studies were identified (see *Appendix 7, Table 54*): Schlapbach *et al.*,<sup>74</sup> which also provided the link to NDI, and Bassler *et al.*<sup>76</sup> Stoll *et al.*<sup>10</sup> did not examine the probability of death. Schlapbach *et al.*<sup>74</sup> report that the OR for infection on death before 2 years of age (conditional on survival past 36+<sup>0/7</sup> weeks) is 5.38 (95% CI 0.55 to 52.07). The study by Bassler *et al.*<sup>76</sup> is a Canadian prospective cohort study in 944 babies born between 1996 and 1998 weighing 500–999 g at birth who participated in a Trial of Indomethacin Prophylaxis in Preterms.<sup>88</sup> The OR for infection on death before 18 months of age, conditional on survival to 36 weeks, was 2.57 (95% CI 1.31 to 5.07).<sup>76</sup> Schlapbach *et al.*<sup>74</sup> and Bassler *et al.*<sup>76</sup> do not report these ORs. Instead, the ORs were calculated for the present study using the count data reported in these studies.<sup>74,76</sup> The base case uses the meta-analysed OR using Schlapbach *et al.*<sup>74</sup> and Bassler *et al.*<sup>76</sup> This OR is 2.74 (95% CI 1.43 to 5.24; fixed effects; see *Appendix 7, Table 56*).

### **Probability of bloodstream infection with standard peripherally inserted central venous catheter**

The probability of BSI with a S-PICC was obtained directly from the PREVAIL trial data: 0.14 (95% CI 0.09 to 0.20) and 0.04 (95% CI 0.02 to 0.08) for babies with gestational age at birth of 23–27 weeks and 28–32 weeks, respectively (see *Appendix 8, Table 57*).

### **Probability of death between peripherally inserted central venous catheter insertion and 6 months of age**

The probability of death between PICC insertion and 6 months of age for babies with gestational age of 23–27 and 28–32 weeks was obtained from Santhakumaran *et al.*,<sup>87</sup> which reports the outcomes



from the English NNRD for the years 2008–14. The PREVAIL trial data were not used owing to the small sample size for each gestational age subgroup (see *Appendix 8, Tables 58 and 59*). The probability of death without prior BSI was calculated as 0.20 (95% CI 0.16 to 0.23) and 0.03 (95% CI 0.03 to 0.04) for babies with gestational age at birth of 23–27 and 28–32 weeks, respectively (see *Appendix 8, Tables 60 and 61*, for details).

### **Probability of death between 6 months and 2 years of age**

The probability of death between 6 months and 2 years of age, without prior BSI, was based on Mangham *et al.*<sup>71</sup> 0.02 (95% CI 0.01 to 0.03) and 0.01 (95% CI 0.00 to 0.02) for babies with gestational age at birth of 23–27 and 28–32 weeks, respectively. Mangham *et al.*<sup>71</sup> estimated the probability of death for children born preterm between hospital discharge and 2 years of age using individual-level data from three cohort studies: the first EPICure cohort from the UK and Ireland in 1995,<sup>89,90</sup> the 1991–2 VICSG cohort in Australia<sup>83</sup> and the Oxford Record Linkage Study from 1990 to 1993.<sup>91–93</sup> Hospital discharge in the Mangham *et al.*<sup>71</sup> study was assumed to occur at 6 months for the purposes of our model, and refers to a mixed population with and without prior BSI.

### **Probability that children suffered neurodevelopmental impairment who had not suffered prior bloodstream infection**

Evidence is available suggesting that NDI can occur even without prior BSI being diagnosed.<sup>10</sup> The occurrence of BSI increases the risk of impairment over and above this baseline level associated with prematurity per se. Three alternative sources for the probability that NDI occurred were identified.<sup>10,71,74</sup> Stoll *et al.*<sup>10</sup> and Schlapbach *et al.*<sup>74</sup> report the probability of NDI separately for babies with and babies without prior BSI.<sup>13,94</sup> Mangham *et al.*<sup>71</sup> report the probability of NDI occurring, the distribution over NDI level and the probability of progression of NDI by gestational age for a mixed population (with and without BSI).<sup>71</sup> Although Mangham *et al.*<sup>71</sup> refers to the probability of NDI occurring for a mixed population, it was preferred because it provides the probabilities by gestational age subgroup. Hence, the probability of NDI without prior BSI in the model is 0.45 (95% CI 0.42 to 0.49) and 0.26 (95% CI 0.25 to 0.28) for babies with gestational age at birth of 23–27 and 28–32 weeks, respectively.

### **Distribution of neurodevelopmental impairment by severity level**

In the absence of evidence to the contrary, BSI during the neonatal stay was assumed not to change the probability of having a mild, moderate or severe NDI, given that some level of NDI has occurred. NDI encompasses four different outcomes, as defined by Doyle *et al.*<sup>83</sup> cerebral palsy (classified according to Kitchen *et al.*<sup>95</sup>), blindness (visual acuity of < 20/200 in the better eye), deafness (hearing loss requiring amplification) and developmental delay (Mental Developmental Index, of the Bayley Scales of Infant Development, score of < -1 SD relative to the control group mean). The scale classifies each of these outcomes on a scale: no, mild, moderate or severe NDI. Doyle *et al.*<sup>83</sup> use the worst recorded severity across the four outcomes as the reference to define the overall level of impairment in an infant. The same scale was subsequently adopted by the Mangham *et al.*<sup>71</sup> study and, as a result, translates in the current model when babies are assumed to be assigned a level of impairment following a neurological assessment. The proportion of babies at each NDI level, given that NDI was diagnosed, was 0.54 (95% CI 0.51 to 0.58) and 0.29 (95% CI 0.28 to 0.30) for mild and moderate NDI, respectively, for babies with gestational age at birth of 23–27 weeks, and 0.73 (95% CI 0.70 to 0.76) and 0.16 (95% CI 0.15 to 0.17) for mild and moderate NDI for babies with gestational age at birth of 28–32 weeks.

### **Costs between peripherally inserted central venous catheter insertion and 2 years of age**

**Additional cost of antimicrobial-impregnated versus standard peripherally inserted central venous catheters** The cost of S-PICCs and AM-PICCs was provided by their manufacturer [Vygon (UK) Ltd]; each AM-PICC is £53.70 more costly than a S-PICC [Vygon (UK) Ltd, personal communication].

**Costs between peripherally inserted central venous catheter insertion and 6 months** The costs between PICC insertion and 6 months were estimated from the PREVAIL trial data linked to the NNRD; PICANet; and HES APC, outpatient and A&E (see *Cost of hospital care*). Costs were estimated using a generalised linear model with a Gaussian distribution and log link, controlling for gestational age at birth, survival and BSI status across different specifications (details can be found in *Appendix 9, Tables 64 and 65*). Base-case estimates amounted to £105,873.47 (95% CI £101,444.99 to £110,495.27) and £62,255.37 (95% CI £54,711.87 to £70,838.93) for gestational age at birth of 23–27 weeks and 28–32 weeks, respectively.

**Costs between 6 months and 2 years of age** The costs between 6 months and 2 years of age were based on the hospital admissions of babies aged between 6 months and 2 years by gestational age and valued with 2016 NHS reference costs.<sup>69</sup> Estimated costs amounted to £5989.17 (95% CI £5983.44 to £5994.98) for babies born between 23 and 27 weeks of gestation and to £3026.43 (95% CI £3024.21 to £3028.73) for babies born between 28 and 32 weeks of gestation (see *Appendix 9, Table 68*). Details are in *Appendix 9, Tables 66–68*.

### Model inputs for predicting outcomes beyond 2 years

The parameter inputs for the long-term component of the model include the transition probabilities between NDI states or death, and the respective costs and utilities. Each parameter is shown in *Table 18* and discussed in detail in the following text.

### Transitions between neurodevelopmental impairment states or death

**Patients aged 2–8 years** The 1-year transition probabilities were computed from the counts of babies at each level of NDI from the 1991–2 cohort of the VICSG observed at 2, 5 and 8 years of age in Mangham *et al.*<sup>71</sup> (see *Appendix 8, Tables 62 and 63*).<sup>71</sup>

**Patients aged  $\geq 8$  years** The transitions between NDI states stop once a child reach 8 years of age, which corresponds to the last time point for the transition probabilities from Mangham *et al.*<sup>71</sup> As far as we are aware, no data are available on progression beyond this age. This assumption of no progression beyond 8 years of age was confirmed with the PREVAIL trial clinical team. From this age onwards, the cohort in the model is subject only to the probability of death, which depends on their NDI level.

**Probability of death by neurodevelopmental impairment level from age 18 onwards** The probability of death was obtained from the UK lifetables 2013–15,<sup>99</sup> to which the excess risk due to NDI is added. The additional risk of death by NDI level was obtained from Reid *et al.*<sup>98</sup>

The study by Reid *et al.*<sup>98</sup> was a prospective population-based study including 3507 individuals with cerebral palsy related to factors in the antenatal, perinatal or neonatal period born in the state of Victoria (Australia) between 1970 and 2004, and identified from the Victorian Cerebral Palsy Register. It assesses the impact of clinical variables, including motor, visual, hearing and intellectual impairment, on mortality. The classification system is similar between this study and the VICSG one, allowing for the extrapolation of the adjusted HRs from the Reid *et al.*<sup>98</sup> study to the current model. Each impairment level from the Doyle *et al.*<sup>83</sup> study can include up to four health outcomes with different level of severity: blindness, deafness, developmental delay and cerebral palsy. For the purpose of this study, we matched each of these outcomes to the covariates used in the Cox regression model performed by Reid *et al.*,<sup>98</sup> with levels of the categorical covariates corresponding to different level of impairment. For each level of impairment (no, mild, moderate, severe), the largest HR across the health outcomes was then taken as representative of the overall impairment level, and used to adjust the baseline probability of death by NDI level.

TABLE 18 Parameters for predicting lifetime costs and health outcomes

Parameter	Value (95% CI); distribution	Source
<b>HRQoL values (utilities)</b>		
HRQoL value with no NDI	0.96 (0.94 to 0.97); beta	Baseline HRQoL from Petrou <i>et al.</i> <sup>96</sup> It also corresponds to the utility value for non-impaired babies as their decrement was set at 0 (fixed)
Reduction in HRQoL due to mild NDI	0.18 (0.14 to 0.31); gamma	Petrou <i>et al.</i> <sup>96</sup> HRQoL decrement: 0.179 (SE 0.042)
Reduction in HRQoL due to moderate NDI	0.30 (0.24 to 0.46); gamma	Petrou <i>et al.</i> <sup>96</sup> HRQoL decrement: 0.298 (SE 0.055)
Reduction in HRQoL due to severe NDI	0.56 (0.44 to 0.77); gamma	Petrou <i>et al.</i> <sup>96</sup> HRQoL decrement: 0.558 (SE 0.084)
<b>Annual costs between ages 2 and 10 years</b>		
No NDI	£388 (£285 to £509); gamma	Petrou <i>et al.</i> <sup>97</sup> inflated to 2016 prices
Mild NDI	£753 (£584 to £946); gamma	Petrou <i>et al.</i> <sup>97</sup> inflated to 2016 prices
Moderate NDI	£814 (£560 to £1063); gamma	Petrou <i>et al.</i> <sup>97</sup> inflated to 2016 prices
Severe NDI	£1487 (£1096 to £1943); gamma	Petrou <i>et al.</i> <sup>97</sup> inflated to 2016 prices
<b>Annual costs from age 11 years</b>		
No NDI	£686 (£440 to £993); gamma	Petrou <i>et al.</i> <sup>96</sup> inflated to 2016 prices
Mild NDI	£987 (£782 to £1222); gamma	Petrou <i>et al.</i> <sup>96</sup> inflated to 2016 prices
Moderate NDI	£1252 (£933 to £1624); gamma	Petrou <i>et al.</i> <sup>96</sup> inflated to 2016 prices
Severe NDI	£1976 (£1411 to £2648); gamma	Petrou <i>et al.</i> <sup>96</sup> inflated to 2016 prices
<b>HRs for mortality for all gestational age subgroups</b>		
Type of motor impairment: moderate	1.51 (0.71 to 3.24); log-normal	Reid <i>et al.</i> <sup>98</sup> – baseline: mild impairment
Type of motor impairment: severe	6.21 (3.28 to 11.77); log-normal	Reid <i>et al.</i> <sup>98</sup> – baseline: mild impairment
Type of cognitive impairment: mild/moderate	1.11 (0.62 to 1.97); log-normal	Reid <i>et al.</i> <sup>98</sup> – baseline: no impairment
Type of cognitive impairment: severe/profound	3.01 (1.74 to 5.22); log-normal	Reid <i>et al.</i> <sup>98</sup> – baseline: no impairment
Vision impairment: blind	0.94 (0.58 to 1.53); log-normal	Reid <i>et al.</i> <sup>98</sup> – baseline: not blind
Hearing impairment: deaf	2.61 (1.44 to 4.74); log-normal	Reid <i>et al.</i> <sup>98</sup> – baseline: not deaf
SE, standard error.		

### Costs and health-related quality of life

**Patients aged 2–10 years** Annual costs by NDI level between ages 2 and 10 years were sourced from Mangham *et al.*<sup>71</sup> which reports resource use and HRQoL by NDI level collected for the first EPICure study at 6 years of age using a questionnaire completed by the parent(s).<sup>100,101</sup>

**Patients aged ≥ 11 years** Annual costs between 11 and 18 years of age and HRQoL by NDI level were obtained from Petrou *et al.*<sup>96</sup> who estimated costs and HRQoL at 11 years of age of the children in the first EPICure cohort using a questionnaire filled in by the parent(s) and related it to a NDI classification similar to the one in our model.

Annual costs and HRQoL values after the age of 18 years were assumed to be the same as those used in the model for children aged between 11 and 18 years. These parameters have a minimal impact in the model because of discounting.

## Analytical methods

### Base case

The model was probabilistic in that the base-case results are computed as the mean costs and QALYs over 10,000 Monte Carlo simulations.<sup>86</sup> Cost-effectiveness was evaluated at two cost-effectiveness thresholds: the cost-effectiveness threshold of the National Institute for Health and Care Excellence (NICE)<sup>102</sup> at £20,000 per QALY and the empirical estimate of the opportunity cost to the NHS of bearing additional costs, at £13,000 per QALY. Results are presented in terms of incremental net health benefit, calculated as the difference in expected QALYs between the AM-PICC and S-PICC groups and the difference in costs, expressed in terms of QALYs using the NICE cost-effectiveness threshold and the empirical estimate of the opportunity cost to the NHS.<sup>102,103</sup>

Cost-effectiveness acceptability curves are presented, which represent the probability that AM-PICCs are cost-effective for each gestational age subgroup over the range of cost-effectiveness thresholds from null to £30,000 per QALY. The probability that AM-PICCs are cost-effective was calculated as the proportion of simulations in which the AM-PICC has the highest net benefit (i.e. it is the cost-effective option).

### Sensitivity analysis

A bivariate sensitivity analysis on the effect of the AM-PICC and its additional cost compared with the S-PICC was conducted to determine the maximum acquisition price of AM-PICCs for a given reduction in the risk of BSI. This analysis can help inform future decisions on whether or not to commission more costly interventions that may reduce the risk of BSI.

A univariate sensitivity analysis was conducted to identify which parameters have the greatest impact on the results in addition to the direct effect and cost of AM-PICCs versus S-PICCs. For this, all parameters predicting the outcomes in early childhood were varied across the extremes of their 95% CIs.

Scenario sensitivity analyses were conducted to understand the impact of the key assumptions (see *Appendix 11, Table 69*). This includes assuming that BSI has no effect on the risk of NDI or of death, stopping backward transitions from the severe NDI state, employing 3-year transition probabilities, allowing for transitions between NDI states until 18 years of age, applying the age and sex decrement on HRQoL and removing the increased risk of death by NDI level.<sup>104</sup> Additional scenarios regarding the effect of BSI on death and costs before 6 months were also implemented (see *Appendix 11, Table 70*). One scenario used linked data from the PREVAIL trial to calculate an unadjusted RR of BSI on death before 6 months (2.51, 95% CI 1.44 to 4.38); see *Appendix 8, Application to the Model*. Two scenarios were tested to consider the possibility that BSI and death before 6 months of age have an impact on the hospital cost over 6 months.

### Model validation

Model acceptability and face validity were ascertained during a series of meetings with members of the PREVAIL team. The model underwent quality control to ensure internal consistency and external validity following the recommendations of Vemer *et al.*<sup>105</sup> This is described in *Appendix 10*.

## Results

### Predicting outcomes in early childhood

*Table 19* shows the distribution of children at 2 years of age by NDI level and gestational age group, according to S-PICC or AM-PICC allocation. The outcomes are similar between PICC types, although

TABLE 19 Distribution of children by NDI level at 2 years of age

Intervention	NDI at 2 years of age	Gestational age (weeks), mean over the probabilistic simulations (%) (95% CI)	
		23–27	28–32
S-PICC	No	41.43 (38.36 to 44.79)	70.41 (68.71 to 72.06)
	Mild	19.80 (18.80 to 21.03)	18.63 (18.08 to 19.16)
	Moderate	10.56 (9.28 to 11.79)	4.16 (3.59 to 4.75)
	Severe	6.14 (4.75 to 7.50)	2.80 (2.29 to 3.34)
	Dead	22.07 (18.08 to 25.39)	3.99 (3.33 to 5.10)
	Total	100%	100%
AM-PICC	No	41.32 (38.19 to 44.76)	70.38 (68.64 to 72.04)
	Mild	19.85 (18.80 to 21.14)	18.65 (18.09 to 19.19)
	Moderate	10.58 (9.29 to 11.81)	4.16 (3.60 to 4.76)
	Severe	6.15 (4.77 to 7.52)	2.81 (2.30 to 3.35)
	Dead	22.10 (18.12 to 25.42)	4.00 (3.34 to 5.11)
	Total	100%	100%

there is a small disadvantage for AM-PICCs given their marginally higher risk of developing BSI, which is not statistically significant.

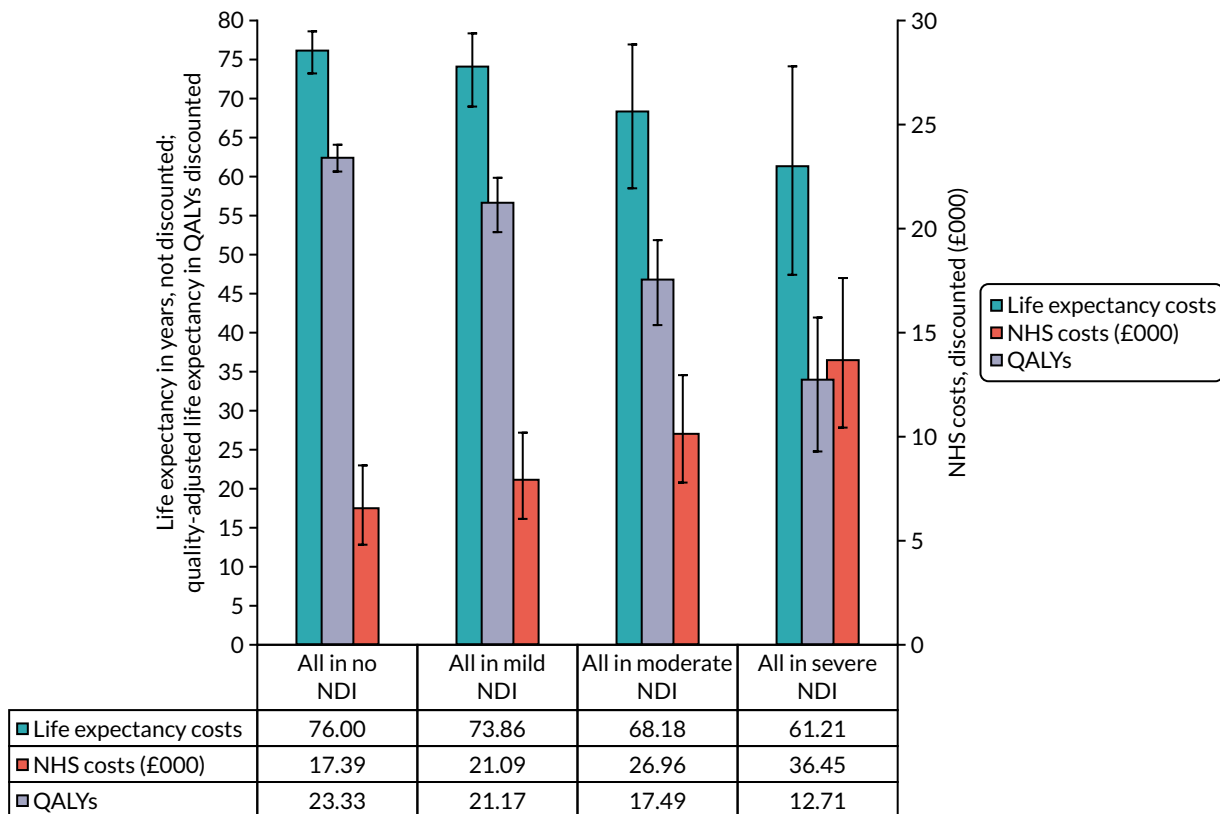
### Predicting lifetime costs and health outcomes

Figure 8 shows the outcomes by NDI level over the children's expected lifetime. The model predicts that children who are assessed as having no NDI at 2 years of age live to 76 years, on average (95% CI 73 to 78 years). As the NDI level increases, life expectancy reduces. Children who are assessed as having a severe NDI at 2 years of age are predicted to live to 61 years (95% CI 47 to 74 years).

The differences in costs and health outcomes between mild NDI and no impairment are £3690 lower costs and 2.16 additional QALYs. This means that if one child has mild NDI, then, on average, and compared with having no NDI, the child loses 2.16 QALYs over their lifetime and costs an additional £3690 to the NHS. If a QALY is valued at £20,000 by the NHS, avoiding mild NDI in one child warrants £46,890 (2.16 QALYs × £20,000 + £3690) in investment by the NHS.

### Cost-effectiveness of antimicrobial-impregnated versus standard peripherally inserted central venous catheters

Table 20 shows the cost-effectiveness results. The AM-PICC is not cost-effective when compared with the S-PICC; rather, the S-PICC dominates at both gestational ages (23–27 and 28–32 weeks). The AM-PICC increases costs by a small extent, to £54.85 (95% CI £25.95 to £89.12) for babies born at 23–27 weeks of gestation and to £54.81 (95% CI £48.21 to £64.28) for those born at 28–32 weeks of gestation. The AM-PICC also reduces health outcomes by a small extent, at -0.01 (95% CI -0.09 to 0.04) and 0.00 (95% CI -0.01 to 0.01), for babies born at 23–27 and 28–32 weeks of gestation, respectively. The cost-effectiveness of an AM-PICC versus a S-PICC can be synthesised in terms of its incremental net benefit, given the cost-effectiveness threshold.<sup>103</sup> At a cost-effectiveness threshold of £13,000 per QALY, the incremental net benefit of AM-PICCs versus S-PICCs is -0.01 QALYS (95% CI -0.09 to 0.04 QALYS) and -0.01 QALYS (95% CI -0.02 to 0.00 QALYS) for babies with gestational age at birth of 23–27 and 28–32 weeks, respectively. This means that using the AM-PICC has a small, non-significant detrimental effect on health outcomes, given its direct impact on babies' health outcomes and its indirect impact on the health-care system as a result of its additional costs.



**FIGURE 8** Costs and health outcomes by NDI level over expected lifetime. The NHS costs and the lifetime QALYs accrued in the future are discounted at 3.5% in line with current guidelines. The life expectancy from PICC insertion is not discounted. The vertical lines indicate the 95% CIs. Adapted from Grosso *et al.*<sup>106</sup> © Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY. Published by BMJ. This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: <https://creativecommons.org/licenses/by/4.0/>. Minor formatting changes have been made.

**TABLE 20** Cost-effectiveness results over the lifetime time horizon

Cost-effectiveness results	Gestational age at birth (weeks), mean (95% CI)	
	23-27	28-32
<b>AM-PICC</b>		
Total costs (£)	127,182.65 (120,983.15 to 133,919.12)	83,588.20 (77,048.17 to 90,839.31)
Total health outcomes (QALYs)	16.48 (15.41 to 17.59)	21.46 (20.67 to 22.17)
<b>S-PICC</b>		
Total costs (£)	127,127.79 (120,935.61 to 133,866.31)	83,533.39 (76,993.85 to 90,784.10)
Total health outcomes (QALYs)	16.49 (15.44 to 17.60)	21.46 (20.67 to 22.17)
<b>AM-PICC vs. S-PICC</b>		
Difference in costs (£)	54.85 (25.95 to 89.12)	54.81 (48.21 to 64.28)
Difference in health outcomes (QALYs)	-0.01 (-0.09 to 0.04)	0.00 (-0.01 to 0.01)
Incremental net health benefit at £13,000 per QALY [probability that AM-PICC is cost-effective]	-0.01 (-0.09 to 0.04) [0.32]	-0.01 (-0.02 to 0.00) [0.09]
Incremental net health benefit at £20,000 per QALY [probability that AM-PICC is cost-effective]	-0.01 (-0.09 to 0.04) [0.34]	-0.00 (-0.02 to 0.00) [0.15]

For babies born at 23–27 weeks' gestation, the probability that the AM-PICC is cost-effective is  $< 0.40$ , irrespective of the cost-effectiveness threshold; for babies born at 28–32 weeks' gestation, it remains  $< 0.20$  as the cost-effectiveness threshold asymptotes to £30,000 per QALY. The probability of cost-effectiveness reflects the uncertainty in the parameter estimates, particularly the large CI around the RR of AM-PICCs versus S-PICCs in preventing infection.

### Sensitivity analysis

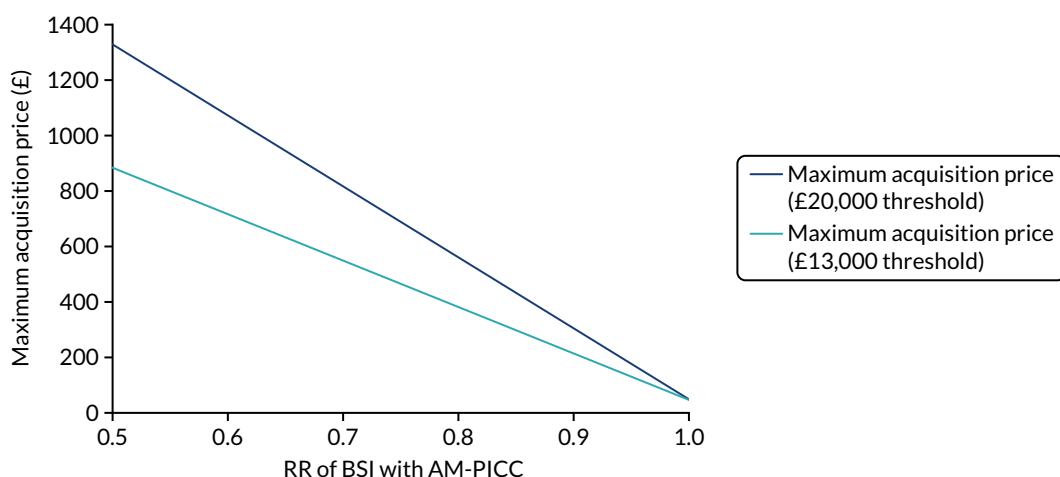
The sensitivity analysis results are presented in detail in *Appendix 11*. The key results are discussed in this section.

#### **Bivariate sensitivity analysis: effectiveness and price**

At the current price, the minimum level of effectiveness at which the AM-PICC is cost-effective, at a cost-effectiveness threshold of £20,000 per QALY, is a relative reduction of 3% in the risk of BSI for babies with gestational age at birth of 23–27 weeks, that is a maximum RR of 0.97. For babies with gestational age at birth of 28–32 weeks, the minimum reduction is of 15%, that is a maximum RR of 0.85. At the cost-effectiveness threshold of £13,000 per QALY, the minimum relative reduction is 4% and 20% for babies with gestational age at birth of 23–27 and 28–32 weeks, respectively (*Figure 9*).

The maximum acquisition price would increase if the effectiveness increased. For example, if the AM-PICC reduced 5% of BSI cases (RR 0.95), the maximum acquisition price at a cost-effectiveness threshold of £20,000 per QALY would be £165, if used solely in babies born at 23–27 weeks' gestation, or £65 in babies born at 28–32 weeks' gestation. At a cost-effectiveness threshold of £13,000 per QALY, and for the same effectiveness, the maximum price would be £120 and £55 if used solely in the gestational age groups 23–27 and 28–32 weeks, respectively. At the prices currently charged for the AM-PICC, and at a cost-effectiveness threshold of £20,000 per QALY, the AM-PICC would have to reduce 2% and 15% of cases to be cost-effective for babies born at 23–27 and 28–32 weeks' gestation, respectively. At a cost-effectiveness threshold of £13,000 per QALY, the AM-PICC would have to reduce at least 3% and 20% of cases to be cost-effective for babies born at 23–27 and 28–32 weeks' gestation, respectively.

Complete results of this sensitivity analysis are presented in *Appendix 11, Tables 71 and 72*.



**FIGURE 9** Maximum acquisition price per AM-PICC effectiveness (gestational age at birth of 23–27 weeks). Reproduced from Grosso *et al.*<sup>106</sup> © Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY. Published by BMJ. This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: <https://creativecommons.org/licenses/by/4.0/>. Minor formatting changes have been made.

### **Univariate sensitivity analysis**

For both gestational age groups considered, the key cost-effectiveness driver was the RR of the AM-PICC in preventing BSI (see *Appendix 11, Figures 23 and 24*).

### **Scenario analysis**

The AM-PICC was found to be not cost-effective (i.e. negative incremental net benefit), irrespective of the scenario implemented (see *Appendix 11, Table 73*). In most scenarios, the incremental net benefit was similar to the base case. Large decreases in incremental net benefit were observed in the scenarios assuming that BSI increased the risk of death, and, to a smaller extent, in the scenarios assuming different hospital costs depending on whether or not death and BSI had occurred. This happens because the PREVAIL trial indicates that the AM-PICC results in a slightly higher number of BSIs (as per *Table 17*). In scenarios in which BSI increases the risk of death, the costs are lower because children who die do not incur subsequent hospital costs. However, there is a large loss of QALYs, owing to the increased proportion of babies who die in infancy. In these scenarios, the AM-PICC appears to be more detrimental to babies than in the base-case assumption of no direct effect of BSI on death at 6 months.

## **Value of information**

The Vol analysis aims to estimate the health losses, in QALYs, associated with decision uncertainty about which is the most cost-effective PICC type, whether or not future research is worthwhile, and which parameters should be prioritised for research.

The analysis of the value of implementing the cost-effective PICC type (originally planned as objective 4; see *Introduction*) was not carried out, as the S-PICC was found to be the cost-effective option. Given that the S-PICC is currently in use in the NHS, its value of implementation is, by definition, null.<sup>61</sup>

## **Methods**

### **Expected value of perfect information for the population**

The Vol analysis quantifies the consequences of making the wrong decision (using AM-PICCs or S-PICCs) in terms of the health losses if the wrong intervention is deemed cost-effective, and the investment required to resolve this uncertainty.<sup>107</sup> The expected cost of uncertainty is defined as the expected value of perfect information (EVPI), conceived as the difference between the incremental net benefit if every uncertainty was resolved, and the actual incremental net benefit under current uncertainty.<sup>107</sup> A necessary condition for conducting further research is that the cost of research does not exceed the EVPI. The EVPI is computed with the online Sheffield Accelerated Value of Information (SAVI) tool.<sup>108</sup> The analysis is run for a time horizon of 10 years in the population of preterm babies who require a PICC of 1 French.

### **Expected value of partial perfect information for the population**

An approach similar to EVPI can be employed to determine which model parameters are the most important drivers of uncertainty, which are those for which resolving uncertainty would provide the greatest benefit in terms of making the 'right' decision. Expected value of partial perfect information (EVPPI) is defined as the difference in net benefits under perfect and current information, but where the uncertainty is resolved for one (or more) parameters at a time only, and averaging across all possible values for the others.<sup>86</sup> As above, EVPPI provides a measure of the maximum amount a funder should be willing to pay for conducting further research related to a specific parameter (or group of parameters).



### Patient population

Based on the analysis of the full NNRD by a member of the PREVAIL trial team, 2212 infants with gestational age of 23–27 weeks and 3888 infants with gestational age of 28–32 weeks were estimated to require a PICC each year. Therefore, the population EVPI is presented as a weighted average of the individual EVPI for the two gestational age subgroups considered, using the number of infants requiring a PICC as the weight for each group.

### Time horizon

The EVPI and EVPPI are calculated over a time horizon of 10 years, assuming a constant incident population. The value related to future incident populations was discounted to present values at 3.5% per annum.<sup>72</sup>

## Results

### Expected value of perfect information

The EVPI for the annual population of preterm babies who require a PICC is £274,126, or 13.71 QALYs, at the cost-effectiveness threshold of £20,000 per QALY gained. Over 10 years, the EVPI is £2,359,587.27, or 117.98 QALYs. At a cost-effectiveness threshold of £13,000 per QALY, the EVPI is £156,902.00, or 12.07 QALYs, per year, or £1,350,564.85, or 67.53 QALYs, over 10 years.

### Expected value of partial perfect information

The main component of the EVPI is the RR parameter; its EVPPI is 99% of the EVPI of the decision. At the cost-effectiveness threshold of £20,000 per QALY, the yearly EVPPI amounts to £268,430.00 (or 13.42 QALYs); over 10 years, it amounts to £2,310,564.28 (115.53 QALYs). At the cost-effectiveness threshold of £13,000 per QALY, the EVPPI on the RR parameter is £151,490.00 (11.65 QALYs) per year, and amounts to £1,303,974.33 (100.31 QALYs) over 10 years.

## Summary of findings

Babies born preterm show a high level of resource use over the first 6 months of life, mainly driven by the length of their stays in NICUs and hospital inpatient care (about 70 days on average). This translates to an average total cost per infant of ≈£84,000, of which ≈£54,000 relates to neonatal care and ≈£27,000 relates to costs due to other hospital care during the hospitalisations. The costs of paediatric intensive care, outpatient care and A&E appointments are much lower in comparison. There is no evidence that the type of PICC has any impact on the intensity of hospital care, as measured by the HRGs, or on the length of hospitalisation over the 6-month follow-up. This is consistent with the results of the PREVAIL trial, in that the type of PICC had no effect on either the primary or the secondary outcomes.

Based on information from the trial and on a review of the external literature, a decision-analytic model was built to determine the cost-effectiveness of AM-PICCs compared with S-PICCs, over a baby's lifetime. The key assumption of the model was that BSI is associated with an increase in the risk of death and of developing NDI. Under this assumption, an intervention preventing BSI can reduce total NHS costs and result in an increase in life expectancy and associated HRQoL, via a reduction in both death and NDI cases.

Findings from the PREVAIL trial suggest that the AM-PICC increases costs and does not improve quality-adjusted survival over the babies' lifetimes. Therefore, the AM-PICC is not cost-effective. Results are robust with respect to the key model assumptions, as tested through a series of scenarios and sensitivity analyses, which further highlight the pivotal role of PICC effectiveness in driving the model results. At current prices, it would be enough to reduce the probability of BSI by 3% to make the AM-PICC a cost-effective intervention for babies born at 23–27 weeks' gestational age.

The Vol analysis suggests that, for the population of preterm babies in England and Wales eligible to receiving the 1-French PICC under evaluation, the EVPPI on the RR is £2,310,564.28 over a time horizon of 10 years. This does not represent the value of a RCT concerning the RR for this parameter; instead, it represents the value of knowing this RR with perfect certainty, which may not be possible with further research. This said, the EVPPI suggests that it is worthwhile to invest in additional research on this parameter, which was the primary outcome of the PREVAIL trial.



# Chapter 5 Generalisability analysis

## Introduction

The PREVAIL trial recruited 861 babies, over 17 months, from 18 NICUs out of a total of 43 NICUs in England. However, if AM-PICCs were effective and adopted, they would be used in all babies who receive the smallest PICC in neonatal care. This is because hospitals are likely to make a policy decision about which PICCs to use and bulk purchase the same type of PICC for all babies who need one. To make this purchasing decision, clinicians need to decide whether or not the results from the trial are generalisable and applicable, and, if so, what is the absolute risk difference given that the baseline risk of BSI may vary between babies and over time. Generalisability refers to whether or not the babies in the PREVAIL trial were similar to the population from which they were drawn, that is, babies in participating NICUs. Applicability refers to whether or not the relative effect can be applied to all babies who receive PICCs in NNUs in England, that is, babies in LNUs in addition to babies in NICUs.

Results from the PREVAIL trial may not be generalisable to other babies in NICUs or applicable to babies in LNUs for several reasons. First, babies in the PREVAIL trial may be treated differently from other babies receiving PICCs in NICUs or LNUs because of trial participation; therefore, they may have a different risk of BSI. Second, there could be differences in characteristics between participating and non-participating babies (e.g. if babies in the PREVAIL trial have lower gestational ages) that were also related to the effectiveness of the AM-PICC (e.g. if the AM-PICC was more effective in babies of a younger gestational age). In this example, we would not be able to extend the results from the trial to other babies in NICUs and LNUs. Third, if BSI risk factors and, hence, the baseline rate of BSI in babies in the PREVAIL trial differed from other babies receiving PICCs in NICUs and LNUs, the absolute benefit (or risk difference) would be different.

We sought the following evidence to indicate whether or not the relative effect of AM-PICCs was likely to differ between subgroups. First, in post hoc analyses of the PREVAIL trial, the effect of AM-PICCs did not differ between babies with a gestational age of < 28 weeks and babies with a gestational age of  $\geq 28$  weeks (see *Chapter 3, Primary outcome*). Second, we compared risk factors for BSI and causative organisms in PREVAIL babies randomised to receive S-PICCs with those of other babies with PICCs in NICUs. The proposed mechanism for CVCs leading to BSI is microbial colonisation of the CVC surface spreading to the bloodstream. Certain organisms are more sensitive to the antimicrobials used to impregnate the AM-PICC, for example CoNS is more susceptible to rifampicin-miconazole impregnation than Enterobacteriaceae.<sup>94</sup> Therefore, differences in the distribution of pathogens between PREVAIL and other babies could result in different effects of AM-PICCs than those seen in the PREVAIL trial.

To determine whether or not the baseline rate of BSI differed in babies in the PREVAIL trial compared with other babies receiving PICCs in NICUs and LNUs, we compared crude and risk-adjusted rates during the PREVAIL trial recruitment period. Differences between these groups could reflect selection to the trial based on unmeasured characteristics or different management of PREVAIL babies, resulting in higher or lower rates of BSI in PREVAIL babies than in other babies in participating NICUs. For example, despite the PREVAIL trial protocol requiring blood samples only when clinically necessary, samples may have been taken more often in PREVAIL babies. This could result in detection of asymptomatic BSI or contaminated blood samples that would otherwise not be detected in practice. Conversely, staff may have followed hygiene protocols more closely for babies enrolled in the PREVAIL trial and, therefore, the risk of BSI could be lower.

We also examined trends in BSI over time. Rates of BSI may have declined since the start of the trial because of improved infection control practices.<sup>12,48</sup> Improvements in CVC care may reduce BSI associated with PICCs, but have less effect on BSI due to other causes. To inform targeting of BSI interventions, we determined the contribution of BSI during PICC use to the overall rate of BSI during intensive or high-dependency care in NICUs and LNUs.

## Aims and objectives

We aimed to determine whether or not rates of BSI in PREVAIL trial participants were generalisable and applicable to all babies receiving PICCs in NICUs and LNUs in the NHS in England.

### Objectives

- To determine the generalisability and applicability of the trial results by comparing BSI risk factors, causative organisms and BSI rates among babies in the PREVAIL trial with those of other babies receiving PICCs.
- To determine the applicability of BSI rates in the PREVAIL trial to rates of BSI in the NHS in England by comparing trends in the rates of BSI in babies receiving PICCs in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs.
- To provide context through understanding of changes in BSI over time by evaluating trends in rates of BSI per 1000 days of intensive or high-dependency care and per 100 admissions for all babies receiving intensive or high-dependency care in NICUs and LNUs.
- To determine the contribution of PICCs to the overall rate of BSI per admission during intensive and high-dependency care.

The generalisability study originally aimed to predict the number of BSIs prevented and the reduction in cost to the NHS if AM-PICCs were adopted and used in place of S-PICCs. This was not feasible, because the PREVAIL trial detected no difference in the risk of BSI between AM-PICCs and S-PICCs, and, based on these results, AM-PICCs are unlikely to be adopted. A further reason is that the cost of BSI could not be calculated in the health economics study (see *Chapter 4*).

## Methods

### Data sources

There is no single data source to study risk-adjusted rates of BSI in NNUs in England. The NNRD provides clinical data on babies in NICUs. Historically, data on BSI in the NNRD was poorly completed, but entry of data on BSI is improving: 74 NNUs reported entering data on all positive cultures in 2017, compared with 25 in 2016.<sup>16,109,110</sup> PHE operate a national infection surveillance system, known as the Second Generation Surveillance System. We linked these two data sources to create a linked data set of babies in all available NICUs and LNUs (112/124) in England. A combination of deterministic and probabilistic linkage methods were used to link babies recorded in the NNRD to records of BSI reported to the national infection surveillance system during their NNU admission.<sup>111</sup> The linkage process is described in *Appendix 12*. In brief, deterministic links, based on an exact match on NHS number, were used as reference standards to calculate match weights in probabilistic linkage, based on agreement on postcode prefix, postcode suffix, date of birth, laboratory/hospital and sex.<sup>112</sup> Match weights were summed across each comparison pair and the frequency of the summed weights were examined to determine an upper and lower threshold. Pairs with weights above the upper threshold were classified as links, pairs with weights below the threshold were classified as non-links and pairs between the two thresholds were manually reviewed (using rules presented in *Appendix 12, Table 74*). Links identified in deterministic and probabilistic linkage were combined to produce a NNRD data set enhanced with BSI from the national infection surveillance.

Three NICUs [3/49 (6%)] and nine LNUs [9/78 (12%)] were excluded from our NNRD data. The number of NNUs changed over time: there were 49 NICUs during the generalisability study period (2010–17), but only 43 during the PREVAIL trial. Two NICUs and eight LNUs were excluded because we did not receive responses to our requests for consent to linkage of their data. One NICU and one LNU were excluded because of poor reporting of BSI in the surveillance data. A further three NICUs and six LNUs had reporting gaps in the BSI surveillance data; we excluded months when reporting was poor, but included periods with good reporting. We did not include any SCBUs and we restricted our analyses of the linked data to babies receiving intensive or high-dependency care, as PICCs are not routinely used in special care. Three LNUs became SCBUs during the trial period; they were removed when they became SCBUs. We obtained data from the NNRD in two extractions, (1) March 2010 to December 2015 and (2) January 2016 to June 2017, which resulted in missing data for babies admitted in the first extract but discharged in the second extract. More than 5% of baby days between September 2015 and December 2015 were missing a discharge date, probably due to missing records in 2016. We therefore excluded admissions during the 6 months between September 2015 and February 2016. We excluded all babies who were missing a discharge date as we were unable to correctly calculate time at risk.

### Case definition

We defined BSI as a link to a record of positive blood or CSF culture reported to the national infection surveillance system. Multiple cultures of the same organism from the same baby within 14 days were classified as one episode. We use five terms to describe BSI depending on time at risk (Figure 10; see also Appendix 20, Table 81):

1. BSI during PICC days at risk, which included BSI cultured in samples taken between 1 day after PICC insertion and 2 days after PICC removal.
2. Early-onset BSI (no PICC), defined as BSI in babies aged < 2 days. If a baby had a PICC inserted on the day of birth and a BSI on the following day, the BSI would be classified as during PICC days at risk, not as early onset.
3. Late-onset BSI describes BSI from samples taken between 2 days of age and 2 days after discharge from the NICU or LNU, given that the BSI is not during PICC days at risk.
4. Total late-onset BSI included BSIs that were either during PICC days at risk or late onset.
5. Total BSI included all BSI occurring between birth and 2 days after discharge from the NICU or LNU.

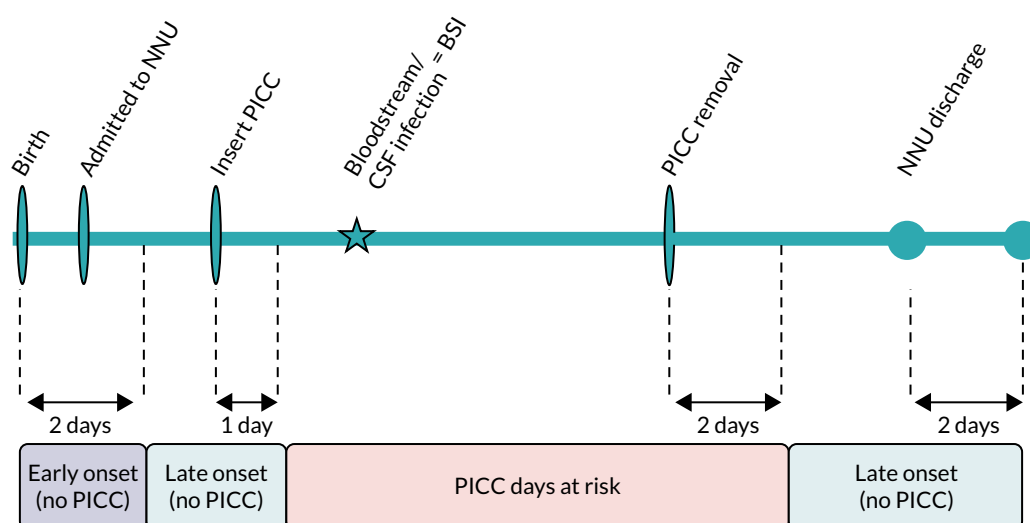


FIGURE 10 Time at risk for PICC days at risk, early-onset BSI (no PICC) and late-onset BSI (no PICC).

Our definition of PICC days at risk (see *Figure 10* and *Appendix 20, Table 81*) differed slightly from the definition used in the trial (see *Figure 2*), as we used linked infection surveillance data (not BSI recorded on CRFs in the trial) to ensure comparability between PREVAIL babies and other groups. Surveillance data do not record the exact time of blood or CSF culture sampling, and the NNRD records whether or not a PICC was present each day, but not the time of insertion. Therefore, we used 1 or 2 days, rather than 24 or 48 hours, to define the interval for samples related to the PICC: 1 day after PICC insertion to 2 days after PICC removal (as recorded in the NNRD).

We categorised all organisms recorded in the surveillance data as 'clearly pathogenic' or 'other' with the guidance of a microbiologist (JG). We used the term 'clearly pathogenic organisms' to indicate that a BSI would be diagnosed without the requirement of repeat samples or clinical signs. A full list of clearly pathogenic and other organisms is given in *Appendix 13, Boxes 2 and 3*. We restricted trend analyses to clearly pathogenic organisms because of a change in the surveillance system in 2014 that resulted in a sharp increase in the reporting of organisms with uncertain clinical significance (e.g. skin commensals) (see *Appendix 14, Table 75* and *Figure 25*).

### **Identifying babies in the PREVAIL trial**

We linked babies who were randomised to receive S-PICCs in the PREVAIL trial to the NNRD. We used deterministic linkage on NHS number or postcode, sex and date of birth. We excluded babies randomised to receive AM-PICCs in the PREVAIL trial and any babies who had no daily records of intensive or high-dependency care, were present only in months excluded because of missing NNRD days between 2015 and 2016, were present only in months excluded because of poor BSI reporting, had missing discharge dates, or had no record of receiving a PICC. We compared the distribution of baseline baby characteristics [gestation, admission to surgical NICU, sex and small for gestational age (birthweight in the < 10th centile for gestation)] using the chi-squared test to determine whether or not there was a significant difference ( $p < 0.05$ ) between included and excluded PREVAIL babies.

### **Generalisability and applicability**

To determine the generalisability of results of the PREVAIL trial to other babies in NICUs, we compared babies admitted to NICUs who were randomised to receive S-PICCs in the PREVAIL trial with babies who received S-PICCs in the PREVAIL trial NICUs who were not enrolled in the trial, and those in non-PREVAIL trial NICUs, during the recruitment period. Approximately 10% of babies were admitted to more than one NICU or LNU. We evaluated admissions to NNUs, rather than evaluating babies, to ensure that BSI, PICC days and other clinical factors were attributed to the correct NICU or LNU. To determine applicability, we extended the comparison of PREVAIL babies to babies receiving S-PICCs in LNUs during the recruitment period. We compared the prevalence of baby and clinical characteristics, causative organisms and the rate of BSI per 1000 PICC days during the PREVAIL trial recruitment period (August 2015 to January 2017). We used the start and end date specific to each participating NICU, as these dates varied between units. For non-PREVAIL trial NICUs and LNUs, we included the total recruitment period. We also compared trends in rates of BSI per 1000 PICC days from March 2010 to June 2017.

### **Comparing clinical characteristics in PREVAIL and non-PREVAIL babies**

We compared the prevalence of clinical characteristics in the following babies: those receiving S-PICCs who were enrolled in the PREVAIL trial, those who were in a PREVAIL trial NICU but not enrolled in the PREVAIL trial, those who were in a non-PREVAIL trial NICU and those who were in a LNU. The characteristics we included were gestational age at birth (in weeks), sex, small for gestational age, age (in days) at first PICC insertion, PICC days per admission, invasive ventilation days per admission, non-invasive ventilation days per admission and whether or not the NICU provided surgery. We tested for a significant difference ( $p < 0.05$ ) in the distribution of the characteristics between babies not enrolled in PREVAIL trial NICUs, babies in non-PREVAIL trial NICUs or LNUs and PREVAIL babies, using the chi-squared test.

### **Comparing causative organisms in PREVAIL and non-PREVAIL trial neonatal intensive care units and local neonatal units**

We compared the distribution of causative organisms in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs. In these analyses, we grouped together all babies admitted to NICUs who were participating in the PREVAIL trial, whether or not they were enrolled in the trial, to avoid small cell counts that could be disclosive. We used the chi-squared test to determine whether or not there was a significant difference ( $p < 0.05$ ) in the distribution of organisms in non-PREVAIL trial NICUs or LNUs, in comparison to PREVAIL trial NICUs.

### **Comparing rates of bloodstream infection during the PREVAIL trial in PREVAIL and non-PREVAIL babies**

We calculated BSI rates per 1000 PICC days for BSI during PICC days at risk during the PREVAIL period separately for all BSI and BSI caused by clearly pathogenic organisms (listed in *Appendix 13, Box 2*). We calculated risk-adjusted rates of BSI using forward stepwise multilevel Poisson regression to decide which baby characteristics (gestational age at birth in weeks, small for gestational age, age in days at first PICC insertion, invasive ventilation days per admission, non-invasive ventilation days per admission, and whether or not the NICU provided surgery) were significant risk factors for BSI. We considered the risk factor significant if the 95% CI did not include 1. NNU was included as a random effect to account for clustering of admissions in NNUs.

### **Changes over time in bloodstream infection rates in PREVAIL and non-PREVAIL trial neonatal intensive care units and local neonatal units**

To determine trends from March 2010 to June 2017, we calculated the rates of BSI per 1000 PICC days per month of admission for BSI caused by clearly pathogenic organisms during PICC days at risk. We used forward stepwise regression to decide which covariates (as mentioned previously) were significant in the trend analysis, as significant risk factors may differ from the model restricted to the PREVAIL trial period. We included an interaction between NNU group (PREVAIL trial NICU, non-PREVAIL trial NICU and LNU) and month to allow for different trends in BSI rate between the groups. Trends were modelled per admission month, but results are presented per year to aid interpretation.

### ***Trends in rates of bloodstream infection in all babies admitted to neonatal intensive care units and local neonatal units***

To contextualise the trial, we extended the analyses to include all babies who received intensive and high-dependency care in NICUs and LNUs, regardless of whether they received a PICC. First, we examined how BSI risk factors had changed from 2010 to 2017 for all babies who received high-dependency or intensive care in LNUs and NICUs. Second, we evaluated trends in total late-onset BSI per 1000 days of intensive and high-dependency care days and per 100 admissions.

### **Changes over time in bloodstream infection risk factors**

We examined how risk factors have changed over time in babies receiving intensive or high-dependency care in NICUs and LNUs from 2010 to 2017 by plotting the proportion of babies admitted to NICUs and LNUs according to gestational age at birth, grouped as:  $< 26$ ,  $26$  to  $< 28$ ,  $28$  to  $< 32$ ,  $32$  to  $< 37$ , and  $\geq 37$  weeks. We plotted the mean number of days of stay, PICC days, central line days, non-invasive ventilation days, invasive ventilation days, and age in days at first PICC insertion by gestational age in weeks in 2010 and 2017. We used two-way analysis of variance (ANOVA) to determine whether or not the mean of each risk factor was significantly different ( $p < 0.05$ ) by week of gestation in 2010 compared with 2017.

### **Changes over time in total late-onset bloodstream infection**

We evaluated the change over time in rates of total late-onset BSI per 1000 intensive and high-dependency care days and per 100 admissions. In the model per 100 admissions, we included only the first BSI per admission to evaluate whether or not the number of admissions in which a baby develops a BSI has changed over time. We modelled late-onset BSI rates by month of admission restricted to



clearly pathogenic organisms. For each model, we used forward stepwise multilevel Poisson regression to identify significant risk factors. We included an interaction between NNU group (PREVAIL trial NICU, non-PREVAIL trial NICU and LNU) and month to allow for different trends in BSI rate between the groups.

### ***The contribution of peripherally inserted central venous catheters to total bloodstream infection***

We calculated the proportion of total BSI that was early onset (no PICC), during PICC days at risk or late onset (no PICC). We included BSI caused by all organisms for the period of August 2015 to June 2017. We excluded the period before the start of the PREVAIL trial to give an up-to-date snapshot of recent BSI and to ensure that results were not affected by the change in surveillance methodology in 2014. To determine the contribution of PICCs to the overall rate of BSI per admission, we first calculated the BSI rate per admission for early-onset BSI (no PICC), BSI during PICC days at risk and late-onset BSI (no PICC), for all babies admitted to NICU or LNUs and stratified by gestation at birth (< 32 or ≥ 32 weeks).

## **Results**

### ***Identifying babies in the PREVAIL trial***

We identified 423 babies in the NNRD out of the 431 babies recorded as randomised to receive the S-PICC in the PREVAIL trial CRFs. All babies randomised to receive the AM-PICC in the PREVAIL trial were excluded from the generalisability analyses using linked data from the NNRD. We included 269 out of 423 (64%) babies randomised to S-PICCs (see *Appendix 21, Figure 26*). The reasons for excluding 154 babies were as follows: present only in months excluded because of missing days between 2015 and 2016 ( $n = 97$ ), present only in months excluded because of poor BSI reporting ( $n = 24$ ), missing discharge dates ( $n = 2$ ) and no recording of PICCs ( $n = 31$ ). Only 16 babies randomised to S-PICCs were recorded as not receiving a PICC in the PREVAIL trial CRFs. Therefore, 15 of the 31 babies with no PICC recorded in the NNRD (4% of the total of 423 babies) had a PICC recorded in the trial CRFs but not in the NNRD. There were no significant differences in the distributions of gestation, small for gestational age or sex between the 269 babies with S-PICCs included in our analysis and the 154 excluded PREVAIL babies for whom we had baseline data available (see *Appendix 15, Table 76*). Excluded babies were significantly less likely to be in surgical NICUs. Eighteen NICUs participated in the PREVAIL trial; however, only 16 were included in our analysis, as one NICU did not consent to linkage of its data and one was excluded because the corresponding laboratory was a poor reporter during the PREVAIL trial period.

### ***Generalisability and applicability***

Peripherally inserted central venous catheters were used for at least 1 day in 8443 admissions involving 8206 babies receiving intensive and high-dependency care during the PREVAIL trial period (August 2015 to January 2017) (see *Appendix 25, Figure 35*).

### **Comparing baby and clinical characteristics in PREVAIL and non-PREVAIL babies**

Comparing babies in the PREVAIL trial with babies in the same NICUs who were not enrolled in the PREVAIL trial and with babies in other NICUs, more of the PREVAIL babies were born before 32 weeks of gestation, received invasive ventilation and were admitted to a surgical unit (*Tables 21 and 22*). Admissions to NICUs not in the PREVAIL trial had an earlier median age at first PICC insertion than PREVAIL babies. Use and duration of non-invasive ventilation were significantly higher in NICUs not participating in the PREVAIL trial and in LNUs than among PREVAIL babies (see *Table 22*). Babies enrolled in the PREVAIL trial were more likely to be born before 32 weeks of gestation, to be older when a PICC was inserted, to retain the PICC for longer, to be small for gestational age and to have more days of ventilation than babies in LNUs (see *Tables 21 and 22*).

TABLE 21 Comparison of baby characteristics of babies who received S-PICCs in NICUs and LNUs according to enrolment in the PREVAIL trial during the PREVAIL trial period

Characteristic	NICUs (n = 16) participating in the PREVAIL trial		NICUs (n = 28) and LNUs (n = 68) not participating in the PREVAIL trial	
	Admissions in the PREVAIL trial	Admissions not in the PREVAIL trial	Admissions to NICU	Admissions to LNU
Total babies (n)	269	1608	3745	2358
Total admissions (n)	325	1522	4051	2460
Total PICC days (n)	3809	18,115	49,902	17,187
Gestation (weeks)				
< 26, n (%)	73 (22)	235 (15)	776 (19)	40 (2)
26 to < 28, n (%)	91 (28)	195 (12)	804 (20)	253 (10)
28 to < 32, n (%)	136 (42)	488 (30)	1320 (33)	1374 (56)
32 to < 37, n (%)	17 (5)	378 (24)	614 (15)	610 (25)
≥ 37, n (%)	8 (2)	312 (19)	536 (13)	183 (7)
p-value (chi-squared test) <sup>a</sup>		< 0.001	< 0.001	< 0.001
Small for gestational age, n (%)	62 (19)	251 (16)	640 (16)	358 (15)
p-value (chi-squared test) <sup>a</sup>		0.245	0.278	0.032
Male sex, n (%)	170 (52)	920 (57)	2203 (55)	1361 (55)
p-value (chi-squared test) <sup>a</sup>		0.094	0.423	0.283
Surgical NICU, n (%)	144 (44)	1037 (65)	2056 (51)	N/A
p-value (chi-squared test) <sup>a</sup>		< 0.001	0.025	
N/A, not applicable.				
a Chi-squared test comparing distribution of risk factors in each group with babies enrolled in the PREVAIL trial.				
<b>Note</b>				
Period for NICUs that participated in the PREVAIL trial depends on NICU start and end date of recruitment. Period for other NICUs and LNUs is August 2015 to January 2017 (whole PREVAIL trial recruitment period).				

TABLE 22 Comparison of clinical characteristics in babies who received S-PICCs in NICUs and LNUs, according to enrolment in the PREVAIL trial during the PREVAIL trial period

Characteristic	NICUs (n = 16) participating in the PREVAIL trial		NICUs (n = 28) and LNUs (n = 68) not participating in the PREVAIL trial	
	Babies in PREVAIL trial	Babies not in PREVAIL trial	NICU	LNU
<b>Age at first PICC (days)</b>				
0, n (%)	19 (6)	115 (7)	398 (10)	171 (7)
1–2, n (%)	56 (17)	410 (26)	1144 (28)	857 (34)
3–5, n (%)	104 (32)	482 (30)	1249 (31)	773 (31)
6–11, n (%)	77 (24)	318 (20)	707 (17)	385 (16)
≥ 12, n (%)	69 (21)	283 (18)	553 (14)	274 (11)
Median (IQR)	5 (3–9)	4 (2–7)	3 (1–7)	3 (2–6)
p-value (chi-squared test) <sup>a</sup>		0.013	< 0.001	< 0.001
continued				

TABLE 22 Comparison of clinical characteristics in babies who received S-PICCs in NICUs and LNUs, according to enrolment in the PREVAIL trial during the PREVAIL trial period (continued)

Characteristic	NICUs (n = 16) participating in the PREVAIL trial		NICUs (n = 28) and LNUs (n = 68) not participating in the PREVAIL trial	
	Babies in PREVAIL trial	Babies not in PREVAIL trial	NICU	LNU
<b>PICC days per admission</b>				
1–4, n (%)	72 (22)	461 (29)	905 (22)	863 (35)
5 or 6, n (%)	59 (18)	199 (12)	571 (14)	497 (20)
7 or 8, n (%)	37 (11)	217 (14)	575 (14)	445 (18)
9–12, n (%)	59 (18)	281 (17)	786 (19)	409 (17)
≥ 13, n (%)	98 (30)	450 (28)	1214 (30)	246 (10)
Median (IQR)	8 (5–15)	8 (4–14)	8 (5–14)	6 (4–9)
p-value (chi-squared test) <sup>a</sup>		0.015	0.249	< 0.001
<b>Invasive ventilation days per admission</b>				
0	75 (23)	456 (28)	1045 (26)	1368 (56)
1–4, n (%)	107 (33)	523 (33)	1428 (35)	904 (37)
5–8, n (%)	37 (11)	229 (14)	520 (13)	129 (5)
9–12, n (%)	23 (7)	116 (7)	282 (7)	30 (1)
≥ 13, n (%)	83 (26)	284 (18)	776 (19)	29 (1)
Median (IQR)	3 (1–14)	3 (0–8)	3 (0–9)	0 (0–2)
p-value (chi-squared test) <sup>a</sup>		0.010	0.089	< 0.001
<b>Non-invasive ventilation days per admission</b>				
0, n (%)	54 (17)	528 (33)	878 (22)	520 (21)
1 to 5, n (%)	59 (18)	397 (25)	1034 (26)	783 (32)
6 to 15, n (%)	63 (19)	267 (17)	783 (19)	622 (25)
16 to 49, n (%)	107 (33)	320 (20)	1035 (26)	466 (19)
≥ 50, n (%)	42 (13)	96 (6)	321 (8)	69 (3)
Median (IQR)	14 (3–34)	3 (0–16)	6 (1–24)	5 (1–13)
p-value (chi-squared test) <sup>a</sup>		< 0.001	< 0.001	< 0.001
a Chi-squared test comparing distribution of risk factors in each group to babies enrolled in the PREVAIL trial.				
<b>Note</b>				
Period for NICUs that participated in the PREVAIL trial depends on NICU start and end date of recruitment. Period for other NICUs and LNUs is August 2015 to January 2017 (whole PREVAIL trial recruitment period).				

### Comparing causative organisms in PREVAIL and non-PREVAIL trial neonatal intensive care units and local neonatal units

We found no differences in the distribution of organisms between PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs (see Appendix 22, Table 82). CoNS was the most prevalent organism in all NICUs and LNUs.

### Comparing rates of bloodstream infection during the PREVAIL trial in PREVAIL and non-PREVAIL babies

Crude and risk-adjusted rates of BSI per 1000 PICC days were similar in PREVAIL babies compared with non-PREVAIL babies in the PREVAIL trial NICUs and babies in non-PREVAIL trial NICUs (Figure 11) (see Appendix 23, Table 83 and Figure 27). BSI rates were lower in LNUs; however, the difference between babies in LNUs and babies enrolled in the PREVAIL trial was not significant. The risk factors included in the risk-adjusted model were gestational age at birth, age at first PICC, and days of invasive and non-invasive ventilation. Full details of model-building are presented in Appendix 16, Table 77.

### Changes over time in bloodstream infection rates in PREVAIL and non-PREVAIL trial neonatal intensive care units and local neonatal units

From March 2010 to June 2017, there were 55,058 admissions involving 47,669 babies who received PICCs (see Appendix 25, Figure 36). There was no significant change in the risk-adjusted rates of BSI per 1000 PICC days in PREVAIL trial NICUs, non-PREVAIL trial NICUs or LNUs (Table 23 and Figure 12). The trend in non-PREVAIL trial NICUs was not significantly different at the 5% level from the trend in PREVAIL trial NICUs or LNUs. The selected model adjusted for gestational age at birth and days of invasive and non-invasive ventilation (see Appendix 17, Table 78).

### Trends in rates of bloodstream infection in all babies admitted to neonatal intensive care units and local neonatal units

#### Changes over time in bloodstream infection risk factors

Risk factors for BSI changed from 2010 to 2017 in babies who received intensive or high-dependency care in NICUs and LNUs. First, the proportion of babies born at term or later ( $\geq 37$  weeks' gestation) increased over time (see Appendix 24, Figure 28). The proportion of babies born at 32 to  $< 37$  weeks and at  $< 26$  weeks of gestation remained fairly stable, but the proportion born at 28 to  $< 32$  weeks and at 26 to  $< 28$  weeks of gestation declined. Second, patterns of care between NICUs and LNUs changed. Extremely preterm babies ( $< 28$  weeks' gestation) had longer stays in LNUs (see Appendix 24, Figure 29), but fewer PICC and central line days in LNUs in 2017 than in 2010. By contrast, babies in

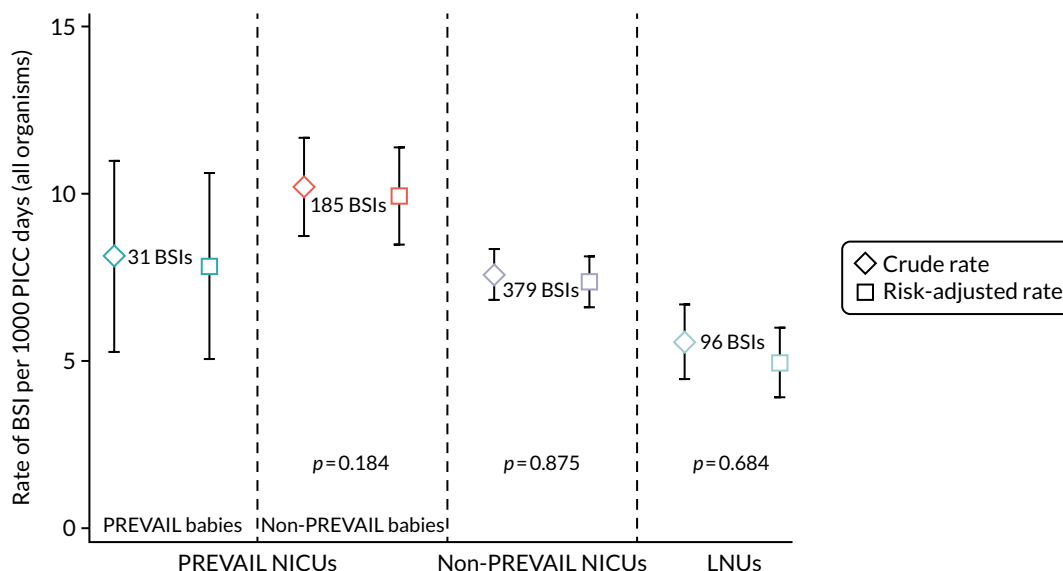


FIGURE 11 Crude and risk-adjusted rates of BSI (for all organisms) per 1000 PICC days in babies who received S-PICCs in NICUs and LNUs, according to enrolment in the PREVAIL trial during the PREVAIL trial period. Adjusted for gestational age at birth, age at first PICC, and days of invasive and non-invasive ventilation. *p*-value for effect of group (PREVAIL babies in NICU, babies in non-PREVAIL trial NICUs, babies in LNUs) on BSI rate in comparison to babies in the PREVAIL trial. Period for NICUs that participated in the PREVAIL trial depends on NICU start and end date of recruitment; period for other NICUs and LNUs is August 2015 to January 2017 (whole PREVAIL trial recruitment period).

TABLE 23 The unadjusted and risk-adjusted annual percentage change in rate of BSI (clearly pathogenic organisms) during PICC days at risk per 1000 PICC days in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs from March 2010 to June 2017

Clearly pathogenic BSI per 1000 PICC days	PREVAIL trial NICUs (n = 16)	Non-PREVAIL trial NICUs (n = 28)	LNUs (n = 68)
Babies (n)	14,667	21,267	15,594
Admissions (n)	15,927	23,537	14,892
Number of PICC days	195,360	296,824	121,750
Number of BSIs	495	736	211
<b>Unadjusted</b>			
BSI rate (95% CI)	2.53 (2.31 to 2.76)	2.48 (2.30 to 2.66)	1.73 (1.50 to 1.97)
Annual percentage change (95% CI)	2.33% (-1.98% to 6.82%)	2.14% (-1.32% to 5.72%)	-5.14% (-11.10% to 1.22%)
p-value <sup>a</sup>		0.972	0.093
<b>Risk-adjusted<sup>b</sup></b>			
BSI rate (95% CI)	2.50 (2.28 to 2.72)	2.44 (2.26 to 2.62)	1.64 (1.41 to 1.87)
Annual percentage change (95% CI)	2.73% (-1.62% to 7.27%)	2.63% (-0.86% to 6.25%)	-2.19% (-8.37% to 4.40%)
p-value <sup>a</sup>		0.969	0.202

a p-value comparing trend with that of PREVAIL trial NICUs.

b Adjusted for gestational age at birth and days of invasive and non-invasive ventilation.

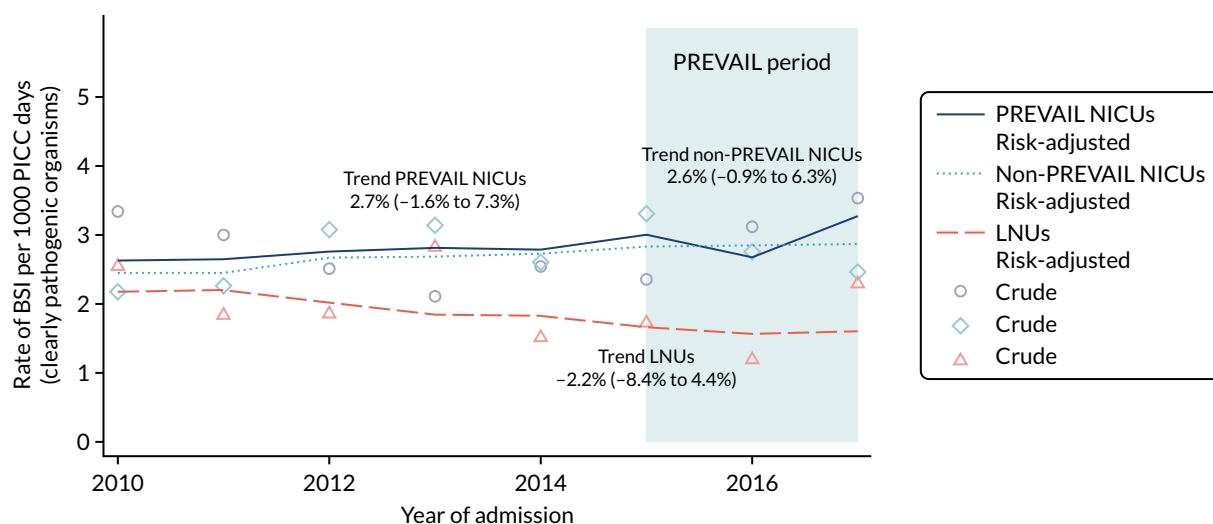


FIGURE 12 Risk-adjusted rate of BSI (clearly pathogenic organisms) during PICC days at risk per 1000 PICC days, by year of admission in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs. Adjusted for gestational age at birth and days of invasive and non-invasive ventilation. Shading denotes the period of enrolment in the PREVAIL trial.

NICUs had more PICC days in 2017 than in 2010 (see Appendix 24, Figures 30 and 31). In both LNUs and NICUs, babies born at  $\geq 32$  weeks of gestation had fewer PICC and central line days in 2017 than in 2010. Across all gestational ages, PICCs were first inserted at a younger age in 2017 than in 2010 (see Appendix 24, Figure 32). Third, extremely preterm babies in LNUs had more days with non-invasive ventilation and fewer days with invasive ventilation in 2017 than in 2010 (see Appendix 24, Figures 33 and 34).

### Changes over time in total late-onset bloodstream infection

From March 2010 to June 2017, there were 161,117 admissions (see *Appendix 25, Figure 37*) who were at least 2 days old or had a PICC inserted on their day of birth; 2.4% (3798) of these admissions had at least one total late-onset BSI caused by clearly pathogenic organisms. The overall rate was 2.3 (4170/1,849,611) per 1000 days of intensive and high-dependency care.

Risk-adjusted rates of total late-onset BSI (clearly pathogenic organisms) per 1000 days of intensive and high-dependency care remained stable in PREVAIL and non-PREVAIL trial NICUs, but decreased in LNUs (*Table 24 and Figure 13*). These rates were adjusted for gestational age at birth and days of invasive and non-invasive ventilation (see *Appendix 18, Table 79*). Risk-adjusted, total late-onset BSI

**TABLE 24** The annual change in the rate of late-onset BSI (pathogens) per 1000 days of intensive and high-dependency care and per 100 admissions in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs from March 2010 to June 2017

Total late-onset BSI	PREVAIL trial NICUs (n = 16)	Non-PREVAIL trial NICUs (n = 28)	LNUs (n = 68)
Babies (n)	37,497	53,967	58,320
Admissions (n)	40,787	58,845	61,485
Number of days	558,303	813,776	477,532
Number of BSIs	1329	1791	1050
Number of admissions with BSI	1190	1612	996
<b>Total late-onset BSI per 1000 intensive and high-dependency care days</b>			
<i>Unadjusted</i>			
BSI rate (95% CI)	2.38 (2.25 to 2.51)	2.20 (2.10 to 2.30)	2.20 (2.07 to 2.33)
Annual percentage change (95% CI)	-1.87% (-4.46% to 0.80%)	1.68% (-0.58% to 3.99%)	-4.44% (-7.21% to -1.59%)
p-value <sup>a</sup>		0.036	0.233
<i>Risk-adjusted<sup>b</sup></i>			
BSI rate (95% CI)	2.30 (2.18 to 2.43)	2.18 (2.08 to 2.28)	2.11 (1.98 to 2.24)
Annual percentage change (95% CI)	-1.40% (-4.01% to 1.29%)	2.20% (-0.07% to 4.52%)	-2.91% (-5.73% to 0.00%)
p-value <sup>a</sup>		0.035	0.342
<b>Total late-onset BSI per 100 admissions<sup>c</sup></b>			
<i>Unadjusted</i>			
Total late-onset BSI per 100 admissions (95% CI)	2.92 (2.75 to 3.08)	2.74 (2.61 to 2.87)	1.62 (1.52 to 1.72)
Annual percentage change (95% CI)	-4.84% (-7.48% to -2.12%)	-0.60% (-2.90% to 1.75%)	-7.12% (-9.88% to -4.28%)
p-value <sup>a</sup>		0.015	0.565
<i>Risk-adjusted<sup>b</sup></i>			
Total late-onset BSI per 100 admissions (95% CI)	2.83 (2.67 to 2.99)	2.66 (2.53 to 2.79)	1.56 (1.46 to 1.65)
Annual percentage change (95% CI)	-2.86% (-5.57% to -0.08%)	1.44% (-0.93% to 3.86%)	-3.28% (-6.16% to -0.32%)
p-value <sup>a</sup>		0.015	0.774

a p-value comparing trend with that of PREVAIL trial NICUs.

b Adjusted for gestational age at birth and for days of invasive and non-invasive ventilation.

c Only one BSI counted per admission.

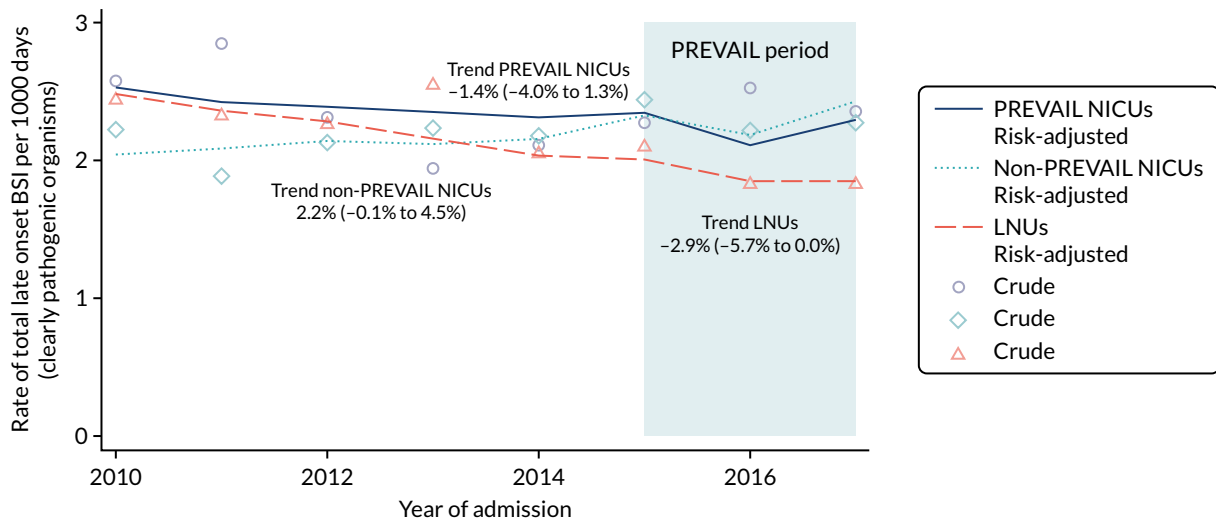


FIGURE 13 Risk-adjusted rate of total late-onset BSI (pathogens) per 1000 intensive and high-dependency care days of stay, by year of admission in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs. Rates are adjusted for gestational age at birth and for days of invasive and non-invasive ventilation.

rates per 100 admissions (clearly pathogenic organisms) declined significantly in PREVAIL trial NICUs and LNUs (Table 24 and Figure 14). These rates were adjusted for gestation and for days of invasive and non-invasive ventilation (see Appendix 19, Table 80).

Rates of total late-onset BSI per 100 admissions were lower in LNUs than in NICUs, whereas rates of total late-onset BSI per 1000 days of intensive and high-dependency care were similar. This discrepancy shows that the denominator has an important effect on rates and on trends. In this example, Table 24 shows a similar number of admissions in LNUs and non-PREVAIL trial NICUs, but LNU admissions were shorter, with fewer days of intensive and high-dependency care (477,532 in LNUs, compared with 813,776 in NICUs) (see Table 24).

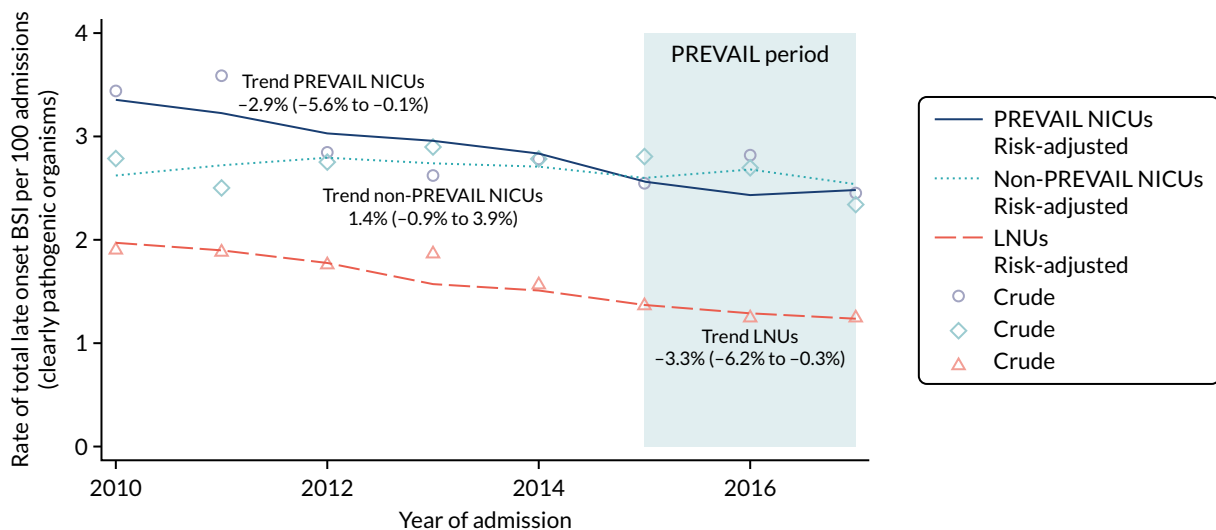


FIGURE 14 Risk-adjusted rate of late-onset BSI (pathogens) per 100 admissions, by year of admission in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs. Rates are adjusted for gestational age at birth and for days of invasive and non-invasive ventilation; only the first BSI per admission was included.

### **The contribution of peripherally inserted central venous catheters to total bloodstream infection rates**

There was a total of 2476 BSIs in 40,008 admissions receiving intensive and high-dependency care in NICUs and LNUs during the PREVAIL trial recruitment and follow-up period (August 2015 to June 2017): 18% (456) were early onset (no PICC), 46% (1143) were late onset during PICC days at risk, and the remaining 35% (877) were late onset (no PICC) (Table 25). Early-onset BSI was the most frequent type of BSI in babies born at  $\geq 32$  weeks' gestation, whereas BSI during PICC days at risk was most frequent in babies born before 32 weeks' gestation.

**TABLE 25** The BSI rate and proportion of total BSIs (all organisms) per 100 admissions for babies receiving intensive or high-dependency care in NICUs and LNUs from August 2015 to June 2017

<b>Admissions</b>	<b>Early onset (no PICC, &lt; 2 days of age)</b>	<b>During PICC days at risk</b>	<b>Late onset (no PICC, <math>\geq 2</math> days of age)</b>	<b>Total (late plus early onset)</b>
<b>All admissions</b>				
Number of admissions	31,107	12,291	26,969	40,008
Number of BSIs (% of total BSIs)	456 (18)	1143 (46)	877 (35)	2476 (100)
BSI rate per 100 admissions (95% CI)	1.5 (1.3 to 1.6)	9.3 (8.8 to 9.8)	3.3 (3.0 to 3.5)	6.2 (6.0 to 6.4)
<b>Admissions born before 32 weeks' gestation</b>				
Number of admissions	8891	8373	11,145	13,237
Number of BSIs (% of total BSIs)	130 (8)	939 (55)	631 (37)	776 (100)
BSI rate per 100 admissions (95% CI)	1.5 (1.2 to 1.7)	11.2 (10.5 to 11.9)	5.7 (5.2 to 6.1)	12.8 (12.3 to 13.4)
<b>Admissions born at 32 weeks' gestation or later</b>				
Number of admissions	22,161	3918	15,824	26,771
Number of BSIs (% of total BSI)	326 (42)	204 (26)	246 (32)	776 (100)
BSI rate per 100 admissions (95% CI)	1.5 (1.3 to 1.6)	5.2 (4.5 to 5.9)	1.6 (1.4 to 1.7)	2.9 (2.7 to 3.1)
<b>Notes</b>				
Admissions who were counted in early onset received intensive or high-dependency care before 2 days of age. Admissions who were counted in PICC days at risk received a PICC. Admissions counted in late onset received intensive or high-dependency care at $\geq 2$ days of age.				





## Chapter 6 Discussion

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### Main findings

#### *Clinical effectiveness randomised controlled trial*

We found no evidence of benefit or harm from rifampicin- and miconazole-impregnated PICCs in babies receiving intensive or high-dependency neonatal care. The 95% CI for the primary outcome excluded a 27% reduction or 67% increase in the time to BSI associated with using an AM-PICC, compared with using a S-PICC. Sensitivity analyses did not change these results. We found no differences in mortality at 6 months, or in clinical outcomes recorded at discharge home from the NNU.

#### *Economic analysis*

Preterm babies in the PREVAIL trial had an average hospital cost of approximately £84,000 over 6 months, mostly related to critical care in the neonatal care unit. The economic model predicted that preventing BSI is both beneficial, as it generates QALY gains, and cost-saving. As AM-PICCs were found in the PREVAIL trial not to prevent BSIs, the model found that AM-PICCs are not cost-effective. At the current price, AM-PICCs would be cost-effective if they achieved a RR reduction of 3% in BSI rate for babies born at < 28 weeks of gestation, or a reduction of 15% for babies born at ≥ 28 weeks of gestation. The largest driver of uncertainty on the costs and health outcomes is whether or not there is any differential effect between AM-PICCs and S-PICCs in preventing BSIs.

#### *Generalisability analysis*

The trial findings were generalisable to babies in NICUs in England. This was based on the fact that there were no differences between babies enrolled in the PREVAIL trial and other babies receiving PICCs in NICUs. We found no differences at the 5% level in the distribution of causative organisms isolated from BSI, or in crude and adjusted rates of any BSI per 1000 PICC days. In addition, post hoc trial analyses found no evidence for an interaction between the primary outcome (HR for time to first BSI) and birth before 28 weeks of gestation compared with birth at ≥ 28 weeks of gestation, suggesting that the relative effect observed in the trial could be generalised to babies receiving PICCs, despite varying gestational ages at birth.

We found stable trends in rates over time in BSI per 1000 PICC days (for clearly pathogenic organisms) in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs from 2010 to 2017. The rate of late-onset BSI (for clearly pathogenic organisms) per 100 admissions declined from March 2010 to June 2017 in LNUs and PREVAIL trial NICUs.

Overall, late-onset BSI during PICC days at risk accounted for 46% of BSIs during days of stay for babies admitted to NICUs or LNUs who received intensive or high-dependency care. Corresponding proportions for babies born before and after 32 weeks of gestation were 55% and 26%, respectively. These findings demonstrate that the time when a PICC is present is a high-risk period for BSI; they do not demonstrate that PICCs are necessarily a cause of BSI.

## Clinical effectiveness randomised controlled trial

### *Strengths and limitations*

The trial was adequately powered to detect a halving of the BSI risk and included a representative sample of babies receiving PICCs. The trial provides important new evidence for preterm infants born before 32 weeks of gestation, a group at high risk of infection, with frequent use of PICCs, but for whom trial evidence has been lacking.<sup>29,30</sup> The pragmatic design reflected routine practice, as we had no additional sampling, and used a primary outcome that is routinely used to guide antibiotic treatment in neonatal care.

A further strength was the implementation of the trial. Central web-based randomisation ensured allocation concealment and balanced treatment allocation. We achieved near complete follow-up and assessment for the primary outcome, adhered to a prespecified statistical analysis plan for intention-to-treat analyses and halted recruitment once the sample size was achieved. 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 sample size and statistical analysis methods were based on the proportional hazards assumption, which was reasonably upheld.

One limitation was that the intervention 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 further limitation was the lack of power to detect significant differences in rifampicin-resistant organisms isolated from blood or CSF cultures. The small 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 trial arms, but was significantly increased in positive tip cultures from AM-PICCs. Selection of rifampicin-resistant Gram-positive bacteria during treatment, when rifampicin is used as the sole antibacterial agent, is well recognised.<sup>113</sup> Testing for resistant organisms was considered by the investigators, the TSC and the IDSMC, but the resistance results were not monitored as the risk of AEs arising was viewed as being low because 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.

### *Findings in context*

The finding that rifampicin- and miconazole-impregnation did not reduce BSI is consistent with other studies (see *Table 1*).<sup>1,30,36,37</sup> In contrast, RCTs of the effectiveness of minocycline- and rifampicin-impregnated CVCs versus standard CVCs have reported substantial reductions in catheter-related BSIs and, in one trial in PICUs, any BSI.<sup>33,34,114</sup> First, these apparent differences in the effectiveness of rifampicin-miconazole and minocycline-rifampicin impregnation may reflect true differences in antibacterial effects. Miconazole is used to prevent invasive fungal infection in preterm babies, but has the disadvantage that rifampicin is then the sole antibacterial agent when 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 meticillin-resistant strains.<sup>113,115</sup>

Second, it is possible that, although minocycline-rifampicin is the most effective type of antimicrobial impregnation in systematic reviews,<sup>32,35</sup> this type of impregnation might not effectively reduce overall rates of BSI or sepsis.<sup>116</sup> Trials in adults show beneficial effects of antimicrobial impregnation for catheter-related BSI, but few trials measure the effect on any BSI. Catheter-related infection requires the same isolates from blood and CVC tip and could be biased because of inhibition of positive tip cultures by leaching of antimicrobial from the tip during plating-out for culture. Only the large CATCH

trial used any clinically indicated BSI as the primary outcome and found a 57% reduction in time to infection (see *Table 1*)<sup>34,38</sup> Third, the reductions in infection rates in NNUs associated with improved catheter asepsis practices and shorter duration of PICC use may have narrowed the potential for further benefits from antimicrobial impregnation.<sup>47</sup> It is also possible that PICCs are not an independent risk factor for infection in sick preterm babies because of the babies' high susceptibility to infection from multiple sources, including numerous invasive procedures and devices, gut permeability and immune immaturity.<sup>117</sup>

### **Practice context**

Since 2012, the Premistar PICC has been the only AM-PICC available for preterm babies in Europe. Its use has been reported in Germany and Italy,<sup>30</sup> but use in the UK was limited to the PREVAIL trial. We are not aware of adoption of the AM-PICC by any UK NNUs outside the context of the trial.

## **Economic evaluation**

### **Strengths and limitations**

The aim of the economic evaluation was to inform the decision of whether or not the NHS should purchase AM-PICCs rather than S-PICCs for preterm babies in NNUs. The specific objectives were to estimate the hospital costs of the PREVAIL babies over the time horizon of the trial, to determine the cost-effectiveness of AM-PICCs against S-PICCs and the minimum effectiveness of an AM-PICC required to make it cost-effective, and to assess the value of future research.

The use of routine health-care data to estimate the hospital costs of the PREVAIL babies was a strength of the economic evaluation. The economic evaluation secured access to the routine databases that record admissions to NNUs and to PICUs, hospitalisations involving procedures, outpatient appointments and visits to the A&E department. Accessing data from all these routine databases ensured that the estimation of hospital costs was as thorough as possible. It maximised the accuracy of the data on hospital use by avoiding recall bias and by having access to data on the resources involved with each hospitalisation. Furthermore, using routine health-care data precluded asking the parents and guardians to fill in lengthy questionnaires on the number and duration of hospitalisations at a time of personal distress.

A key strength of the economic evaluation was the development of a new decision-analytic model to predict the quality-adjusted life expectancy and NHS costs of using AM-PICCs or S-PICCs over the babies' expected lifetimes. The model synthesised the most up-to-date estimates of costs and outcomes of BSI in infants in the neonatal care unit, informed by data from the PREVAIL trial linked to routine health-care databases, and from the published literature. The model also considered the different risks associated with gestational age.<sup>118</sup> Although the model was developed to compare PICC types, it can be used to evaluate any interventions to prevent BSI in babies by estimating the minimal reduction in the risk of BSI that is required so that an intervention could be considered cost-effective, and the relationship between minimal risk reduction and maximum price difference.

A further strength is the use of the economic model to estimate the Vol from future research. Specifically, the Vol analysis quantified the magnitude of the health losses following a wrong adoption decision due to parameter uncertainty, the maximum bound of investment that should be warranted to resolve this uncertainty and the key uncertain parameters for which resolving uncertainty will provide the greatest reduction in the risk of making suboptimal decisions.

There were several limitations to the economic analysis. First, it was not possible to estimate the causal effect of BSI and death on hospital costs over 6 months from PICC insertion, and the causal effect of BSI on the risk of death at 6 months. This was because of the lack of difference between PICC groups (precluding an instrumental variable approach), limited number of events and time

constraints (given that the routine health-care data were received 3 months before the project's deadline). Consequently, the model base case assumes that babies incur the same costs irrespective of BSI or survival status, and assumes that BSI does not cause death at 6 months (although it includes an increased risk of death due to BSI at 2 years). As a consequence, the benefits of preventing BSI may be underestimated.

Second, the model assumes that BSI increases the risk of death and NDI at 2 years of age. The evidence of this causal link was based on the published literature, which, given the enormity of the potential evidence base, was identified from a citation search rather than from a systematic review, which would have been outside the scope and timeline of the project. As a consequence, there is a risk of having omitted some studies in the final evidence review and meta-analysis. Nonetheless, the starting point for the citation search (the so-called 'pearls') was informed by the PREVAIL trial clinical team, and great care was taken in matching the outcomes identified in the literature review with those collected in the trial. Moreover, the citation search identified three systematic reviews and one umbrella review, published between 2013 and 2016,<sup>78-80,119</sup> thereby providing some reassurance that most, if not all, of the relevant studies were included. The literature on the link of BSI to death and NDI is necessarily observational, and scarce. If this link is not causal, or if it is smaller in magnitude, the value of preventing BSI may have been overestimated. Therefore, the minimum risk reduction for interventions, such as an AM-PICC, to be cost-effective may have been underestimated. This structural uncertainty was explored in the scenario analysis, but was not considered in the VoI framework. This means that the value of future research in the effectiveness of interventions to prevent BSI may have been overestimated, compared with the value of future research on the causes of NDI and death in early years.

Third, the model structure constrains the impact of preventing BSI in increasing the risk of NDI and death at 2 years of age. There are some studies suggesting that antibiotics, given to treat infection, increase the risk of NEC, which would, in turn, increase the risk of NDI.<sup>25,26,120</sup> However, no studies were identified that enable the direct effect of BSI on NDI to be disentangled from the indirect effect via antibiotic treatment; hence, the model structure excludes NEC. If NEC was confirmed to play a role in the pathway leading to NDI over and above the direct effect of BSI, and if BSI causes NEC, preventing BSI may be more cost-effective than this study suggests. Conversely, if NEC is on the causal pathway for NDI and death at 2 years, but it is unrelated to BSI, preventing BSI will be less cost-effective.

A fourth limitation was restriction to the perspective of NHS hospitals for costs during the 6-month follow-up period. Ideally, the model would include all the costs falling on the NHS, including not only hospital costs, but also costs of community health care. This was not possible because there are no routine health-care databases that compile the use of community health-care services. Furthermore, at project conception, it was deemed excessively burdensome to ask parents for details of their use of community health-care services. Nevertheless, the lack of data on community health-care costs is unlikely to have a large impact on the results, given the high costs related to hospitalisations. Costs falling on other sectors, such as social care and education, are likely to be relevant. However, their inclusion would represent a departure from the NHS perspective and would require the consideration of how to account for costs falling on different sectors.<sup>121</sup>

Fifth, the model was also restricted to health benefits for the child, by considering the impact of BSI on death and NDI, and its consequences on the babies' length of life and HRQoL. Children's health may have spillover effects on their parents.<sup>122,123</sup> Therefore, avoiding BSI may have beneficial consequences to parents' HRQoL. If this is the case, the benefits in terms of QALYs for parent and child of preventing BSI may have been underestimated and the magnitude of the necessary risk reduction for interventions to be cost-effective may have been overestimated.

A sixth limitation relates to the measure of NDI, which was retained from the previous model of Mangham *et al.*<sup>71</sup> It is relatively crude and might have been superseded by more recent advances in paediatrics. As far as model results are concerned, most babies are classified as having no impairment at 2 years of age. However, less evident cognitive or motor deficits might become apparent at school age, even in this group, causing additional burden in terms of both health-related and education costs, and QALYs lost. Again, if this is the case, the model will underestimate the benefits from preventing these additional minor deficits related to the occurrence of BSI, which, if accounted for, would further increase the cost-effectiveness of interventions to prevent it.

Using routine health-care data to estimate hospital costs had some limitations. Given that linkage of the PREVAIL babies' data was conducted by the data providers, there was limited information on the reasons for missing data. Furthermore, as the costing of hospital care is based on HRGs, hospitalisations with insufficient data to derive a HRG were discarded. Nonetheless, complete data were retrieved for most PREVAIL babies. Moreover, any missing data are likely to be related to errors in data entry at the hospital level, which are unlikely to be related to the babies' characteristics and their hospital care, and hence can be assumed to be missing completely at random. Another limitation was the inconsistencies in the dates in some records, which were needed to calculate the hospital length of stay. However, for the estimation of hospital costs, the dates of hospitalisations are used only to select the hospital care within the trial follow-up period of 6 months. Therefore, the approach taken to analyse the dates is unlikely to have a large impact on the results.

### Findings in context

We found no published economic analyses that compared PICC impregnation in newborn babies. Previous cost-effectiveness studies for impregnated PICCs were in older populations and used different antimicrobials for impregnation, precluding meaningful comparisons.<sup>124–127</sup>

A previous study<sup>71</sup> estimated the health outcomes and costs of care of preterm babies, but it did not assess the cost-effectiveness of interventions to improve outcomes of preterm babies. The results of Mangham *et al.*<sup>71</sup> are similar to the results of the present study under the standard care (S-PICC) policy, even though some of the model inputs are different. Mangham *et al.*<sup>71</sup> predicted that at 18 years of age 36% of babies born at gestational age 23–27 weeks (66% of babies born at gestational age 28–32 weeks) would have no NDI, 10% born at gestational age 23–27 weeks (17% born at gestational age 28–32 weeks) would have mild NDI, 5% born at gestational age 23–27 weeks (6% born at gestational age 28–32 weeks) would have moderate NDI and 4% born at gestational age 23–27 weeks (4% born at gestational age 28–32 weeks) would have severe NDI. In the present study, the model predicted that, under the current policy of using S-PICCs, 45% of babies born at gestational age 23–27 weeks (67% of babies born at gestational age 28–32 weeks) would have no NDI, 17% born at gestational age 23–27 weeks (20% born at gestational age 28–32 weeks) would have mild NDI, 9% born at gestational age 23–27 weeks (6% born at gestational age 28–32 weeks) would have moderate NDI and 7% born at gestational age 23–27 weeks (3% born at gestational age 28–32 weeks) would have severe NDI. For babies born at < 28 weeks' gestation, the Mangham *et al.*<sup>71</sup> model estimates the total average cost per survivor to 18 years at £136,790 (95% CI £50,222 to £261,873), compared with an average lifetime cost per baby (using S-PICCs) predicted in our model of £126,168 (95% CI £120,133 to £132,655).

Results from the economic analysis show that the RR of BSI is the main contributor to overall parameter and decision uncertainty. If BSI in infancy increases the risk of NDI and death, as suggested by observational studies and included in the model, interventions that prevent such BSI offer a large potential for cost-effectiveness, even if their efficacy is small.<sup>10,74,78</sup> Therefore, future applied research should focus on the evaluation of the effectiveness of interventions to prevent BSIs. However, the increase in risk of NDI and death reported by observational studies may not be a true reflection

of the effect of BSI. It is possible that there is some residual confounding, in that babies who have poorer health are more likely to suffer a BSI, as well as being more likely to have NDI or die. If this is the case, the association between BSI and NDI/death may be overestimated, thereby leading the cost-effectiveness model to overestimate the benefits of preventing BSI in the long term. For these reasons, more research is needed on the effect of BSI on long-term health outcomes.

Reflecting the structural uncertainty on the link between BSI, NDI and death is a key challenge. The methodological literature is unclear about how to reflect structural uncertainty from observational studies, although some approaches have been proposed in the past.<sup>128</sup> Further research is warranted to develop adequate methods that are able to incorporate and assess potential biases due to the inclusion of observational evidence, both directly (i.e. in the model structure) and indirectly (i.e. in the evidence synthesis process). In this respect, clinical research could help inform future models, for example via longitudinal studies following preterm babies over time. These would record various types of data, including linkage to hospitalisation, community and primary care data for health outcomes, and measures relevant to health captured in non-health data, for example cognitive function measured through school achievement trajectories, so that causal estimates of the impact of infection could be estimated.

## Generalisability analysis

### *Strengths and limitations*

A key strength of our study is the national coverage of 92% of NICUs and LNUs across the NHS in England over 7 years; this minimised referral biases, provided a large enough sample to evaluate subgroups and used routinely submitted laboratory reports, thereby minimising clinician response bias. Our data on BSI are laboratory confirmed and we have data on the organism cultured and dates from both infection surveillance and clinical records, which enables us to tailor specific definitions of BSI.

Limitations include a lack of precise timing of culture sampling (day rather than hour), no consent to use data from 12 units, and lack of full data for 162 PREVAIL trial participants. Furthermore, the presence of a PICC was not recorded in 6% of PREVAIL babies known to have a PICC from trial CRFs. It is unlikely that these errors are limited to PREVAIL babies; hence, some PREVAIL and non-PREVAIL babies were misclassified as not having a PICC.

A further limitation is linkage error, which can have an important impact on trend analyses. In our study, linkage error arises predominantly from missed links, and, to a lesser extent, from false links due to incorrect or missing identifiers. In the linked data, the BSI rate in PREVAIL babies randomised to receive a S-PICC was 8.1 per 1000 PICC days, compared with 10.6 in the PREVAIL trial, highlighting the underestimation of our results. This is probably a result of missed links due to incomplete identifiers or under-reporting to the infection surveillance system. The quality and completeness of identifiers improved in both data sets (NNRD and infection surveillance) over time. This improvement could have led to a spurious increase in BSI rates. Therefore, we need to be cautious in interpreting the stable, increasing and declining BSI rates. Further research is needed to understand the case mix, practice and service factors affecting changing rates of BSI over time, taking into account all periods at risk throughout neonatal care. Stable rates in NICUs may reflect a combination of better infection control, allowing use of PICCs in more high-risk periods. For example, when PICCs are used for shorter durations, it is likely that the PICCs are used during higher-risk periods, such as during stabilisation after birth. We would expect rates of BSI per 1000 PICC days to be higher during shorter, but higher-risk, periods, even though overall BSI risk during NNU stay would decrease. Similarly, replacement of umbilical venous catheters with PICCs may decrease BSI rates if all catheter days were counted. However, the rate of BSI per 1000 PICC days would increase because BSIs that were previously counted during umbilical venous catheter days would be counted while a PICC is in situ.

### Findings in context

The total rate of BSI (clearly pathogenic organisms) of 2.4 per 100 admissions was slightly higher than the rate of 1.8 per 100 admissions reported in a retrospective cohort study of 34 NICUs and LNUs in the UK from 2005 to 2014.<sup>12</sup> This may reflect the more stringent definition used in the study of 34 NICUs that required a prescription of at least 5 days of antibiotics, or the reliance on voluntary reporting by clinicians to the study. In addition, we excluded babies who received special care from our study, who would have fewer infections. Excluding special care made the data more comparable between NNUs, and over time, as babies are kept in special care for varying lengths of time; however, this excluded 11.5% of total late-onset BSIs in all NNUs. Our finding of a declining trend in total BSIs per 100 admissions in PREVAIL trial NICUs and LNUs is similar to trends reported in the study of 34 UK NICUs and LNUs.<sup>12</sup>

Before-and-after studies have reported reductions in rates of BSI per 1000 PICC days following the introduction of care bundles.<sup>47,48</sup> However, this was not seen in our study. This may be due to the improved ascertainment of BSI over time masking true trends. Alternatively, our study represents all centres across England, where rates may differ from those voluntarily participating in a study. In our study, a mix of decreasing and increasing rates in different NNUs may have resulted in a stable average rate. Furthermore, the BSI rates may have only temporarily decreased, thereby not affecting the long-term trends.

### Relevance to future research

Had the trial found one type of PICC to be more effective, the RR could have been applied to rates of BSI per 1000 PICC days at risk in non-participating NICUs and LNUs to estimate the expected risk difference. Our methods for linking NNRD, infection surveillance, and trial data can be used for future trials in contexts of changing infection rates to assess generalisability and applicability. Linkage should be continued to monitor the impact on BSI of infection control, changes in service configuration and practice and to target high-risk groups for infection.





## Chapter 7 Conclusions

We found no evidence of benefit or harm of rifampicin- and miconazole-impregnated PICCs during neonatal care. Interventions with a small effect on BSI could be cost-effective over the life course. Our trial findings are generalisable to neonatal care in England.

### Implications for practice

- There is no evidence that PICC impregnation with miconazole and rifampicin is more effective than S-PICCs, and it is more costly; hence, it is not cost-effective. These findings indicate that AM-PICCs should, therefore, not be adopted in neonatal care.
- Rifampicin resistance in organisms cultured from blood, CSF or PICC tips was not significantly increased in the AM-PICC compared with the S-PICC group, but organisms isolated from only the PICC tip were more likely to be rifampicin resistant. As rifampicin is not routinely used in UK neonatal care, this is probably of limited clinical relevance in the UK setting.
- The economic model shows that, if there is a causal link between BSI and adverse long-term health outcomes, then interventions that achieve small reductions in the risk of BSI are potentially cost-effective.
- Findings from the PREVAIL trial are generalisable to neonatal intensive care in the NHS in England.
- Application of RRs from PICC interventions to predict absolute rate reductions in the future, or locally, need to be based on risk-adjusted rates of BSI per 1000 PICC days.
- Bloodstream infections that occur during PICC days at risk contribute to nearly half (46%) of total BSIs during neonatal intensive and high-dependency care. Preventative strategies for reducing the risk of BSI in newborn babies should focus on all aspects of care before, during and after the period of PICC use.

### Recommendations for research

1. One in 10 babies in the PREVAIL trial had a BSI, and some may suffer serious lifelong NDI or lung disease as a result. Low-cost interventions that reduce the risk of BSI in preterm babies, even by a small amount, would be likely to be cost-effective over a child's life course, based on the assumption of reduced risk of NDI and death. Investment in further research to develop other types of antimicrobial PICC impregnation or alternative approaches for preventing infection in neonatal care would, therefore, be worthwhile.
2. Our finding of no evidence of benefit associated with rifampicin- and miconazole-impregnated PICCs contrasts with substantial reductions in rates of BSI or catheter-related BSI reported in previous trials in children and adults randomised to rifampicin- and minocycline-impregnated CVCs, compared with standard CVCs. We recommend that further research be undertaken to develop and evaluate rifampicin- and minocycline-impregnated PICCs for use in preterm babies.
3. We recommend that further research be carried out to strengthen evidence on the causal link between BSI and NDI and death, and on methods to reflect the uncertainty in these causal links in cost-effectiveness models.
4. Record-level linked data combining electronic clinical records from neonatal care, HES and infection surveillance data should be made routinely available for research and infection surveillance in England.
5. Further research is required to understand which practices contribute to changes (or lack of changes) in rates of BSI over time in neonatal care.



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## Clinical effectiveness randomised controlled trial

### *Participants*

We would like to thank the 861 babies who participated in the PREVAIL trial, along with their parents and families, for their invaluable contribution to this research.

### *Trial sites*

We are grateful to the PIs and RN teams at each trial site who recruited participants and supported them and their families throughout the trial (in order of number of patients recruited): Bradford Royal Infirmary (Sam J Oddie and Rachel Wane); Leicester Royal Infirmary (Marie Hubbard and Rosalind Astles); Birmingham Women's Hospital (Andrew Ewer and Rachel Jackson); St Mary's Hospital, Manchester (Ranganath Ranganna and Nicola Booth); Liverpool Women's Hospital (Kiran Yajamanyam and Karen Harvey); Homerton University Hospital (Narendra Aladangady and Asha Mathew); The Jessop Wing, Sheffield (Elizabeth Pilling and Pauline Bayliss); Royal Oldham Hospital (Natasha Maddock and Louise Woodhead); The Royal London Hospital (Ajay Sinha and MaySze Chang); Royal Preston Hospital (Sandeep Dharmaraj and Claire Lodge); Queen's Medical Centre, Nottingham (Jon Dorling and Helen Navarra); John Radcliffe Hospital (Charles Roehr and Sheula Barlow); Royal Bolton Hospital (Mahesh Yadav and Claire Abbott); Leeds General Infirmary (Kathryn Johnson); Nottingham City Hospital (Dushyant Batra and Yvonne Hooton); St Michael's Hospital, Bristol (Pamela Cairns and Jennifer Chapman); Queen's Hospital, Romford (Bal Krishnan Sharma and Helen Smith); and Newham General Hospital (Imdad Ali and Ivone Lancoma-Malcolm). We thank the 53 hospital trusts across the UK that agreed to act as continuing care sites for the trial and assisted with collection of important follow-up data when participants were transferred away from their recruiting site.

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### *Trial Steering Committee*

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### *Independent Data and Safety Monitoring Committee*

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### Other

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### Administrative health records acknowledgements and disclaimers

#### *Clinical effectiveness randomised controlled trial*

The use of HES data was approved by the Health and Social Care Information Centre (now known as NHS Digital) for the purpose of this study (DARS-NIC-73974-POL1Z-v0.9). HES data © 2018, reused with the permission of the Health and Social Care Information Centre. All rights reserved.

#### *Economic analysis*

Electronic patient data recorded at participating NNUs that collectively form the UK Neonatal Collaborative (UKNC) are transmitted to the NDAU to form the NNRD. Laura Bojke, Rita Faria and Alessandro Grosso had full access to all the data in the study and take full responsibility for the integrity of the data and accuracy of the data economic analysis. We are grateful to all the families that agreed to the inclusion of their baby's data in the NNRD, the health professionals who recorded data and the NDAU team.

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This research was informed by data collected by NHS Digital (formerly the Health and Social Care Information Centre), © 2015–18, the Health and Social Care Information Centre. Re-used with the permission of the Health and Social Care Information Centre. All rights reserved.

#### *Generalisability analysis*

Electronic patient data recorded at participating NNUs that collectively form the UKNC are transmitted to the NDAU to form the NNRD. Ruth Gilbert, Katie Harron and Caroline Fraser had full access to all the data in the study and take full responsibility for the integrity of the data and accuracy of the data analysis. We are grateful to all the families that agreed to the inclusion of their baby's data in the NNRD,

the health professionals who recorded data, and Professor Neena Modi and the team at the NDAU. National infection surveillance data from the Second Generation Surveillance System was provided by PHE.

## Contributions of authors

**Ruth Gilbert** (<https://orcid.org/0000-0001-9347-2709>) (Co-Chief Investigator and Professor of Clinical Epidemiology) developed the study protocol and funding application in collaboration with co-investigators. She oversaw the delivery of the study, assisted with development of the statistical analysis plan and oversaw clinical interpretation of the study data. She led the preparation of the final report (drafting, reviewing and editing) and was co-chairperson of the TMG.

**Michaela Brown** (<https://orcid.org/0000-0002-7772-271X>) (Senior Statistician) developed the study protocol and funding application in collaboration with co-investigators, proposed data capture and statistical analysis methods, approved the statistical analysis plan, and oversaw trial monitoring activities and the final statistical analysis. She contributed to the final report (drafting, reviewing and editing) and was a member of the TMG.

**Rita Faria** (<https://orcid.org/0000-0003-3410-1435>) (Lead Health Economist) contributed to the study protocol and funding application, led the development of the economic analysis plan, led the applications to access the routine health-care data, led the costing analysis of hospital care, oversaw and collaborated in the model-based economic evaluation, led the interpretation of the economic analysis results, contributed to the preparation of the final report (drafting, reviewing and editing) and was a member of the TMG.

**Caroline Fraser** (<https://orcid.org/0000-0001-7260-7053>) (Research Assistant, Epidemiology) contributed to the development of the generalisability study protocol, conducted the generalisability study analysis, contributed to interpretation of the generalisability study results, contributed to the preparation of the final report (drafting, reviewing and editing), and was a member of the TMG.

**Chloe Donohue** (<https://orcid.org/0000-0001-6379-8214>) (Trial Co-ordinator) contributed to protocol development and all aspects of governance and study delivery, and led on preparation of progress reports throughout the study. She contributed to the final report (drafting and reviewing) and was a member of the TMG.

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**Alessandro Grosso** (<https://orcid.org/0000-0001-7211-438X>) (Health Economist) contributed to the development of the economic analysis plan, contributed to the costing analysis of hospital care, conducted the model-based economic evaluation and contributed to the interpretation of the economic analysis results and to the preparation of the final report (drafting, reviewing and editing).

**Ajay K Sinha** (<https://orcid.org/0000-0001-5201-7718>) (Neonatal Consultant) contributed to protocol development and clinical interpretation of the study data. He contributed to the preparation of the final report (reviewing) and was a member of the TMG.

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**William McGuire** (<https://orcid.org/0000-0002-3561-514X>) (Professor of Child Health) contributed to the development of the study protocol and funding application and interpretation of the study data. He contributed to the preparation of the final report (reviewing) and was a member of the TMG.

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**Sam J Oddie** (<https://orcid.org/0000-0001-8701-4912>) (Co-Chief Investigator and Consultant Neonatologist) developed the study protocol and funding application in collaboration with co-investigators. He oversaw the delivery of the study, assisted with development of the statistical analysis plan and oversaw clinical interpretation of the study data. He contributed to the preparation of the final report (drafting, reviewing and editing) and was co-chairperson of the TMG.

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Gilbert R, Brown M, Rainford N, Donohue C, Fraser C, Sinha A, *et al.* Antimicrobial-impregnated central venous catheters for prevention of neonatal bloodstream infection (PREVAIL): an open-label, parallel-group, pragmatic, randomised controlled trial. *Lancet Child Adolesc Health* 2019;**3**:381–90.

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Grosso A, Faria R, Bojke L, Donohue C, Fraser C, Harron K, *et al.* The cost-effectiveness of strategies preventing late-onset infection in preterm infants. *Arch Dis Child* 2020;**105**:452–7.

## Data-sharing statement

All data requests should be submitted to LCTC at UoL for review.

## Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: <https://understandingpatientdata.org.uk/data-citation>.





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# Appendix 1 Additional information on clinical effectiveness methods

TABLE 26 Substantial amendments to the trial protocol

Protocol version	Key amendments
2.0 (5 May 2015)	<ul style="list-style-type: none"> <li>• Definition of BSI specified as 'BSI per 1000 PICC days'</li> <li>• Use of miconazole-resistance testing removed</li> <li>• Rate of CSF culture sampling removed from secondary outcomes</li> <li>• Requirement for treatment for retinopathy of prematurity before discharge removed from secondary outcomes</li> <li>• Primary end point (time to BSI) amended to include any positive bacterial or fungal blood/CSF culture</li> <li>• Time frame for collection of secondary end points specified as until 48 hours post PICC removal</li> <li>• Internal pilot to assess recruitment feasibility included</li> <li>• Additional details to support transfers away from the recruiting site included</li> <li>• Randomisation procedure for twins added</li> <li>• Statement regarding willingness to consider co-enrolment with other studies added</li> <li>• Further information relating to data collection procedures for health economics analysis added</li> </ul>
3.0 (12 October 2015)	<ul style="list-style-type: none"> <li>• Requirement for protocol to be signed by lead statistician added</li> <li>• 'Breast milk intake' amended to 'milk intake'</li> <li>• Definition of successful PICC placement added</li> <li>• Minor clarifications added to the AE reporting procedure</li> <li>• Additional details regarding circumstances under which fathers of participants can/cannot provide consent added</li> </ul>
4.0 (19 August 2016)	<ul style="list-style-type: none"> <li>• Co-enrolment log to capture details of whether or not any participants were also recruited into other RCTs added</li> <li>• Clarification regarding eligibility confirmation added</li> <li>• Clarification regarding informed consent added</li> </ul>
5.0 (26 April 2017)	<ul style="list-style-type: none"> <li>• Time to death added as a secondary outcome</li> <li>• Minor clarifications added to the AE reporting procedure</li> </ul>

TABLE 27 Pathogen classifications

Organism	Pathogen group
<b>Gram positive</b>	
CoNS	Potential pathogen or likely contaminant
<i>Staphylococcus aureus</i>	Clearly pathogenic organism
Group B streptococci	Clearly pathogenic organism
<i>Streptococcus pneumoniae</i>	Clearly pathogenic organism
Streptococcus (other)	Potential pathogen or likely contaminant
<i>Enterococcus</i> spp.	Clearly pathogenic organism
<i>Micrococcus</i> sp.	Potential pathogen or likely contaminant
<i>Bacillus</i> sp.	Clearly pathogenic organism
Diphtheroids	Potential pathogen or likely contaminant
<i>Propionibacterium acnes</i>	Potential pathogen or likely contaminant
<i>Listeria monocytogenes</i>	Clearly pathogenic organism
Other Gram positive	Individual isolates reviewed
<b>Gram negative</b>	
<i>Pseudomonas</i> sp.	Clearly pathogenic organism
<i>Klebsiella</i> spp.	Clearly pathogenic organism
<i>Enterobacter</i> spp.	Clearly pathogenic organism
<i>Acinetobacter</i> spp.	Clearly pathogenic organism
<i>E. coli</i>	Clearly pathogenic organism
<i>Enterococcus</i> spp.	Clearly pathogenic organism
<i>Serratia</i> sp.	Clearly pathogenic organism
Coliform	Clearly pathogenic organism
<i>Citrobacter</i> sp.	Clearly pathogenic organism
<i>Burkholderia</i> sp.	Clearly pathogenic organism
<i>Haemophilus</i> sp.	Clearly pathogenic organism
Other Gram negative	Individual isolates reviewed
<b>Fungi</b>	
<i>Candida albicans</i>	Clearly pathogenic organism
Non- <i>candida albicans</i> species	Clearly pathogenic organism
<i>Candida</i> (other)	Clearly pathogenic organism
Other fungi	Clearly pathogenic organism
Other fungal organism	Clearly pathogenic organism

## Appendix 2 Additional information on clinical effectiveness results

TABLE 28 Randomisation details for each site

Centre code	Date of site opening	Date of site closure	Planned total recruitment (n)	Date of first randomisation	Date of last randomisation	Number randomised (n)
00075	10 August 2015	9 January 2017	40	24 August 2015	6 January 2017	99
00031	11 August 2015	12 January 2017	57	12 August 2015	11 January 2017	92
00472	1 September 2015	9 January 2017	59	2 September 2015	25 November 2016	52
00308	7 September 2015	9 January 2017	63	9 September 2015	12 December 2016	65
00039	7 September 2015	9 January 2017	34	18 September 2015	28 November 2016	31
00213	8 September 2015	9 January 2017	36	13 September 2015	10 December 2016	40
00134	18 September 2015	9 January 2017	36	26 June 2015	6 December 2016	47
18937	23 September 2015	8 December 2016	40	3 October 2015	4 December 2016	50
00292	2 October 2015	9 January 2017	71	2 October 2015	6 December 2016	57
00228	12 October 2015	9 January 2017	61	23 October 2015	9 December 2016	58
18912	10 November 2015	8 December 2016	26	27 November 2015	12 November 2016	23
18938	11 November 2015	9 January 2017	27	15 November 2015	7 December 2016	44
00234	1 December 2015	9 December 2016	41	4 December 2015	23 November 2016	24
00169	3 December 2015	9 January 2017	33	11 January 2016	29 October 2016	37
20019	4 December 2015	8 December 2016	73	4 December 2015	5 December 2016	35
18854	4 January 2016	4 November 2016	33	4 January 2016	13 June 2016	8
00235	20 January 2016	9 January 2017	59	22 January 2016	11 December 2016	60
00227	8 February 2016	13 December 2016	69	18 February 2016	30 November 2016	39
Total			858			861

TABLE 29 Screening and recruitment summary for each site

Centre code	Number of babies' parents		Number (%) of babies' parents consented	Number (%) of babies randomised
	Approached for consent	Not approached for consent		
00075	127	3	104 (81.9)	99 (95.2)
00031	132	38	105 (79.5)	92 (87.6)
00472	125	32	65 (52.0)	52 (80.0)
00308	104	46	69 (66.3)	65 (94.2)
00039	54	14	31 (57.4)	31 (100.0)
00213	54	16	40 (74.1)	40 (100.0)
00134	68	20	47 (69.1)	47 (100.0)
18937	72	19	50 (69.4)	50 (100.0)
00292	88	31	61 (69.3)	57 (93.4)
00228	117	87	81 (69.2)	58 (71.6)
18912	71	10	24 (33.8)	23 (95.8)
18938	65	9	48 (73.8)	44 (91.7)
00234	86	39	31 (36.0)	24 (77.4)
00169	40	20	37 (92.5)	37 (100.0)
20019	43	8	36 (83.7)	35 (97.2)
18854	16	2	8 (50.0)	8 (100.0)
00235	89	8	60 (67.4)	60 (100.0)
00227	53	85	40 (75.5)	39 (97.5)
Total	1404	487	937 (66.7)	861 (91.9)

TABLE 30 Reasons for parents not being approached

Reason	Number (%) of babies (N = 487)
Parents not available to consent	163 (33.5)
Parents' lack of understanding	8 (1.6)
Parents do not understand English/Urdu	18 (3.7)
Consultant preference	22 (4.5)
Missed by clinical team	134 (27.5)
Baby previously entered into the PREVAIL trial	10 (2.1)
No reason given	5 (1.0)
Other reason	148 (30.4)

**Note**  
Reasons are not mutually exclusive.

TABLE 31 Reasons for parents declining consent

Reason	Number (%) of babies (N = 467)
No reason provided	67 (14.3)
Parent does not want to take part in research	195 (41.8)
Parent does not wish baby to be randomly assigned to treatment	9 (1.9)
Parent does not wish baby to have AM-PICC	18 (3.9)
Other reason	180 (38.5)
<b>Note</b> Reasons are not mutually exclusive.	

TABLE 32 Reasons babies not randomised despite parents providing consent

Reason	Number (%) of babies (N = 76)
Baby requires different size PICC	8 (10.5)
Baby no longer requires a PICC	49 (64.5)
Baby died	6 (7.9)
Trial-trained staff not available	1 (1.3)
Unable to access randomisation system	0 (0.0)
PICC (Premicath 1 French) not available	0 (0.0)
Other reason	13 (17.1)
<b>Note</b> Reasons are not mutually exclusive.	



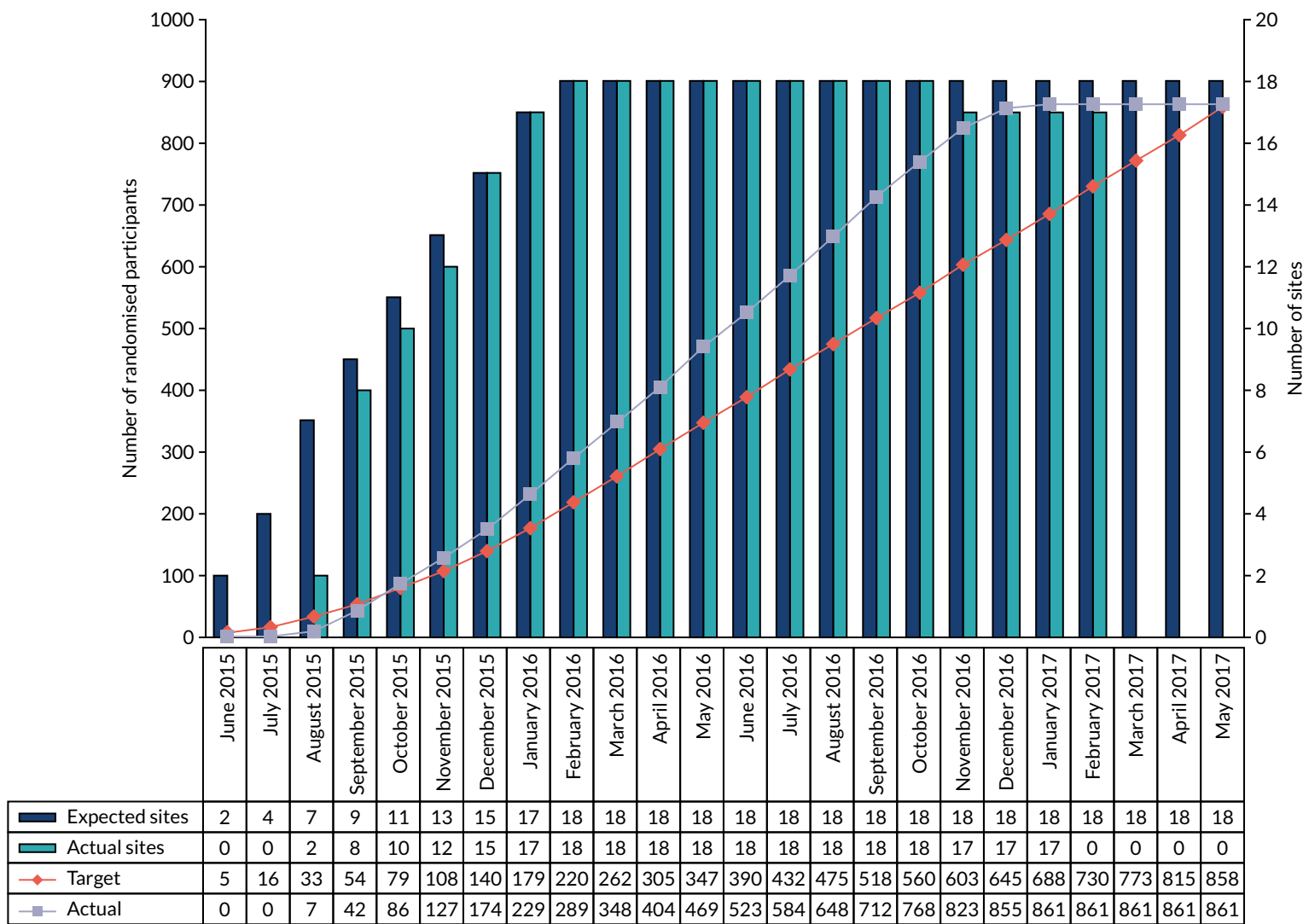


FIGURE 15 Recruitment graph.

TABLE 33 Co-enrolment in other trials, split by site

Site	Total participants randomised (n)	Participants co-enrolled in other trials, n (%)				
		ELFIN <sup>129</sup>	Baby OSCAR <sup>130</sup>	NAPPA <sup>131</sup>	Other	Total
Birmingham Women's Hospital	65	22 (33.8)	5 (7.7)	0 (0.0)	5 (7.7)	32 (49.2)
Bradford Royal Infirmary	99	80 (80.8)	0 (0.0)	0 (0.0)	0 (0.0)	80 (80.8)
Homerton Hospital	57	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
John Radcliffe Hospital, Oxford	39	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leeds General Infirmary	35	11 (31.4)	0 (0.0)	0 (0.0)	0 (0.0)	11 (31.4)
Leicester Royal Infirmary	91 <sup>a</sup>	38 (41.8)	0 (0.0)	0 (0.0)	0 (0.0)	38 (41.8)
Liverpool Women's Hospital	58	0 (0.0)	0 (0.0)	1 (1.7)	4 (6.9)	5 (8.6)
Newham General Hospital	8	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nottingham City Hospital	31	7 (22.6)	0 (0.0)	0 (0.0)	0 (0.0)	7 (22.6)
Queen's Hospital Romford	23	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Queen's Medical Centre, Nottingham	40	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Royal Bolton Hospital	37	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)	1 (2.7)
Royal Oldham Hospital	50	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	2 (4.0)
Royal Preston Hospital	44	9 (20.5)	0 (0.0)	0 (0.0)	0 (0.0)	9 (20.5)
St Mary's Hospital, Manchester	60	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.0)	3 (5.0)
St Michael's Hospital, Bristol	24	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
The Jessop Wing, Sheffield	52	3 (5.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.8)
The Royal London Hospital	47	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total (n)	860 <sup>a</sup>	170	5	1	15	191

Baby OSCAR, Outcome after Selective early treatment for Closure of patent ductus ARteriosus in preterm babies; ELFIN, Enteral LactoFerrin In Neonates; NAPPA, Neonatal And Paediatric Pharmacokinetics of Antimicrobials study.  
<sup>a</sup> Missing information for one baby.

TABLE 34 Oversight committee meetings and recommendations

Oversight committee	Meeting dates	Recommendations
IDSMC	29 April 2015 (joint with TSC)	
	12 May 2016	Trial to be continued
	July 2016 (via e-mail)	Trial to be continued
TSC	29 April 2015 (joint with IDSMC)	
	31 May 2016	Trial to be continued
	9 August 2016	Trial to be closed to recruitment when target is met, with no need to continue recruitment until planned closure date

TABLE 35 Sampling for outcomes and resistance testing for secondary outcomes

	AM-PICC (N = 430)		S-PICC (N = 431)	
	n	n (%)	n	n (%)
<b>Culture samples taken<sup>a</sup></b>				
Blood or CSF	379	198 (46.0)	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)
<b>Rifampicin resistance tested in positive cultures<sup>b</sup></b>				
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)
a 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 AM-PICCs or S-PICCs.				
b Data are total babies with a positive culture (n) and babies with at least one positive culture tested [n (%)] as a proportion of the total number of babies with a positive culture.				

TABLE 36 Protocol deviations

Protocol deviation	AM-PICC (n = 430 participants), n (%)	S-PICC (n = 431 participants), n (%)
Any protocol deviation	171 (39.8)	175 (40.6)
At least one major deviation	61 (14.2)	25 (5.8)
Baby did not receive allocated 1-French Premicath	57 (13.3)	24 (5.6)
Blood/CSF samples either not sent for culture, lost, damaged or not analysed	3 (0.7)	1 (0.2)
Baby was withdrawn from trial prior to completing clinical follow-up	1 (0.2)	0 (0.0)
Parent/legal representative of the baby did not give informed written consent for the trial	0 (0.0)	0 (0.0)
Baby was previously entered into this trial	0 (0.0)	0 (0.0)
Baby had a known allergy or hypersensitivity to rifampicin or miconazole	0 (0.0)	0 (0.0)
Date and time of PICC removal were not recorded	0 (0.0)	0 (0.0)
At least one minor deviation	132 (30.7)	155 (36.0)
PICC tip culture not taken at removal	72 (16.7)	95 (22.0)
Resistance testing not performed on positive culture	69 (16.0)	66 (15.3)
Baby has PICC inserted > 48 hours after randomisation	8 (1.9)	5 (1.2)
Baby was withdrawn from trial follow-up prematurely	4 (0.9)	3 (0.7)

TABLE 37 Number of babies experiencing a BSI in each subgroup

Subgroup	AM-PICC (N = 46 participants experiencing a BSI) (n)	S-PICC (N = 44 participants experiencing a BSI) (n)
Gestational age of < 28 weeks	33	35
Gestational age of ≥ 28 weeks	12	8
Gestational age missing	1	1

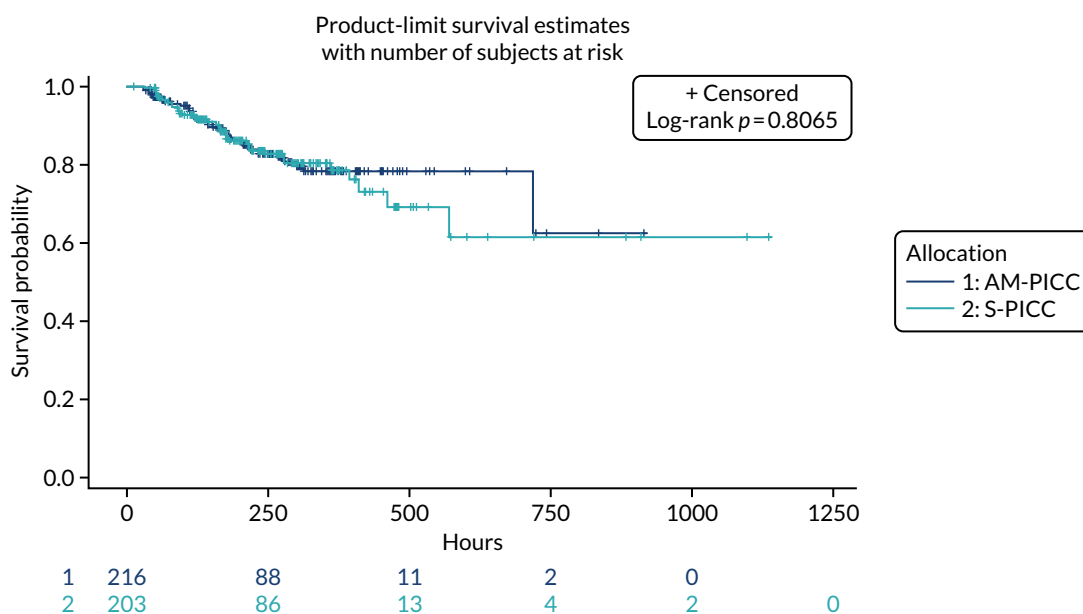


FIGURE 16 Kaplan-Meier plot for babies born at &lt; 28 weeks of gestation. Values under the graph represent the number of participants remaining at risk at each time point: group 1, AM-PICC; group 2, S-PICC.

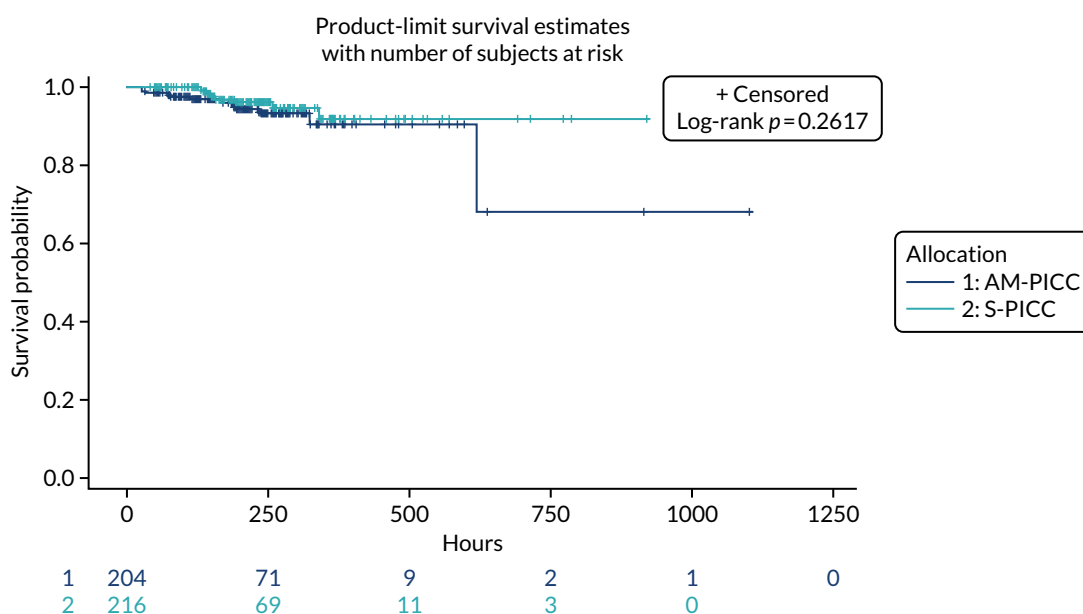


FIGURE 17 Kaplan-Meier plot for babies born at ≥ 28 weeks of gestation. Values under the graph represent the number of participants remaining at risk at each time point: group 1, AM-PICC; group 2, S-PICC.

TABLE 38 Rifampicin-resistant positive isolates

Sample type	Resistant organism	Participants, <sup>a</sup> n (%)	
		AM-PICC	S-PICC
Blood/CSF culture	<i>Enterococcus</i> spp.	3 (75.0)	2 (22.2) <sup>b</sup>
	<i>Klebsiella</i> spp.	1 (25.0)	2 (22.2) <sup>c</sup>
	<i>E. coli</i>	0 (0.0)	2 (22.2) <sup>b</sup>
	<i>Acinetobacter</i> spp.	0 (0.0)	1 (11.1)
	CoNS	0 (0.0)	1 (11.1)
	<i>Enterobacter</i> spp.	0 (0.0)	1 (11.1) <sup>b</sup>
	Total (n)	4	9
PICC tip culture	CoNS	10 (71.4)	2 (40.0) <sup>b</sup>
	<i>Candida albicans</i>	0 (0.0)	1 (20.0) <sup>b</sup>
	<i>Corynebacterium tuberculostearicum</i>	1 (7.1)	0 (0.0)
	Enterobacteriaceae	1 (7.1)	0 (0.0)
	<i>Enterobacter</i> spp.	0 (0.0)	1 (20.0) <sup>b</sup>
	<i>Enterococcus</i> spp.	0 (0.0)	1 (20.0)
	<i>Klebsiella</i> spp.	1 (7.1)	0 (0.0)
	<i>Raoultella ornithinolytica</i>	1 (7.1)	0 (0.0)
	Total (n)	14	5

a Data are n (%) of participants with a resistant organism.

b Numbers indicate when a single baby had multiple resistant organisms.

c A single baby had two samples that grew the same resistant organism.

TABLE 39 Number of BSIs each baby experienced

Number of BSIs per baby	Participants, n (%)	
	AM-PICC (N = 430)	S-PICC (N = 431)
0	384 (89.3)	387 (89.8)
1	43 (10.0)	43 (10.0)
2	3 (0.7)	1 (0.2)

TABLE 40 Types of treatment for retinopathy of prematurity

Type of treatment	Participants, n (%)	
	AM-PICC (N = 430)	S-PICC (N = 431)
Laser	38 (8.8)	28 (6.5)
Cryotherapy	0 (0.0)	0 (0.0)
Injection	4 (0.9)	2 (0.5)
Missing	0 (0.0)	1 (0.2)

**Note**

Some babies received more than one type of treatment, and so appear in the table more than once.

# Appendix 3 Additional information on economic analysis: data access

## Overview

### Data sources

The economic analysis conducted by the team at the UoY for the PREVAIL project required routinely collected health-care data from NHS Digital, PICANet and NDAU, as well as data collected in the clinical trial by the UoL. The team at UCL developed the algorithm to select the babies enrolled in the PREVAIL trial who were recorded in the NNRD held by NDAU.

### Data flows

The data flow was as follows: the UoL sent the patient identifiers to NHS Digital, PICANet, NDAU and UCL. NHS Digital selected the cohort using the identifiers and sent the administrative data identified with trial identifier to the UoY; the process was similar with PICANet, but the data were sent to the UoL, then the UoY. The UoY generated a database with the NHS Digital data on date of death and sent it to UoL. UCL linked the PREVAIL trial cohort to NNRD as part of the PREVAIL trial generalisability analysis and sent Badger identifiers (IDs) (a pseudonymised identifier) for PREVAIL babies to NDAU; NDAU used the Badger IDs to select the cohort and sent the data to the UoY. UoL sent the PREVAIL trial data to the UoY.

### Data transfer

The UoY submitted the data-sharing applications to NHS Digital, PICANet and NDAU on 21 November 2016. The UoY received the NHS Digital data on hospitalisations on 24 May 2018, and the NHS Digital data on date of death on 27 September 2018, the PICANet data on the 9 May 2018 and the NDAU data on 24 August 2018. The UoY initiated the process to develop the data-sharing agreement between the UoY and the UoL on 3 May 2018. The UoY received the data on the 16 August 2018.

## NHS Digital

### Preparing the data-sharing application

The UoY submitted the data-sharing application to NHS Digital on 21 November 2016.

### Revising the data-sharing application

NHS Digital had a number of queries with the application, which had to be addressed before formal submission to the Independent Group Advising on the Release of Data (IGARD). These issues were related to ensuring that the project had informed consent for sharing of date of death; ensuring that the trial participants had access to information about how their data were being used; processes for withdrawal from the data-sharing process; explaining the rationale for the project in lay terms; and detailing the benefits to the NHS, outputs and target dates of conducting the research. This took place between November 2016 and September 2017.

### Meeting the security requirements

The data-sharing application for NHS Digital required answering various information technology queries from the NHS Digital by the UoY and the UoL. This took place between May and July 2017.

### Submission to the Independent Group Advising on the Release of Data

The data-sharing application was submitted to the IGARD on 11 September 2017.

***Update to the framework contract***

The IGARD approved the application on 20 September 2017. At this point, it emerged that the UoY and UoL had not yet signed up to the the Data Sharing Framework Contract version 2. This meant that the data-sharing agreement could not be issued until the two institutions signed up to it, which took place in October.

***Signing the data-sharing agreement***

In December 2017, the UoY contracts' office concluded that UCL and UoL had to sign the hard copies of the data-sharing agreement so that UoY could sign it electronically. UCL signed it on 2 January 2018 and UoL on 5 February 2018. The data-sharing agreement was executed on 27 February 2018.

***Transfer of hospitalisation data***

The data were received at the UoY on 24 May 2018.

***Date of death missing***

On 6 June 2018, the UoY contacted NHS Digital to enquire about the data on date of death, which were missing from the data sets, but were included in the data-sharing agreement. On 27 September 2018, NHS Digital confirmed that the data were ready for transfer.

***Transfer of date of death data***

The data were received at Centre for Health Economics on 27 September 2018.

***Transfer of the date of death to University of Liverpool***

On 24 October 2018, the UoL confirmed that it still required the date of death data; the data were transferred by the UoY on the same day.

**Paediatric Intensive Care Audit Network*****Data-sharing application to the Paediatric Intensive Care Audit Network***

The UoY submitted the data-sharing application to PICANet on 21 November 2016. PICANet replied on 22 November, explaining that data-sharing applications were now processed via HQIP, which required another data-sharing application and agreement forms.

***Data-sharing application to the Healthcare Quality Improvement Partnership***

The UoY developed the data-sharing application and agreement between 29 November 2016 and 2 March 2018.

***Approval from the Healthcare Quality Improvement Partnership***

The UoY submitted the data-sharing application and agreement to HQIP on 14 March 2017. HQIP approved the application on 16 June 2017. PICANet signed the agreement on 16 June, and HQIP signed on 19 July 2017.

***Data transfer***

The UoL transferred PREVAIL trial identifiers to PICANet on 5 March 2018. The UoY received the data on 9 May 2018.

**Neonatal Data Analysis Unit*****Data-sharing application***

The UoY submitted the data-sharing application to NDAU on 21 November 2016. NDAU approved the data-sharing application on 5 May 2017.

### ***Data-sharing contract***

The UoY contacted NDAU for the data-sharing contract on 29 June 2017. The data-sharing contract was signed on 10 January 2018.

### ***Data-sharing agreement***

On 7 March 2018, NDAU requested a data-sharing agreement in addition to the contract. The UoY signed the data-sharing agreement on 19 March 2018.

### ***New data-sharing agreement***

On 23 May 2018, NDAU informed the UoY that, given that the General Data Protection Regulation (GDPR)<sup>132</sup> had already come into force, it required a new data-sharing agreement that was GDPR compliant. On 26 June 2018, NDAU concluded that, rather than a new data-sharing agreement, an amendment to the original contract, which had been signed on 10 January 2018, was needed. The addendum to the original contract was executed on 24 August 2018.

### ***Privacy notice***

University College London, as the study sponsor, is required to approve the privacy notice. The UoY sent the privacy notice to UCL for approval on 10 July 2018. It was approved on 13 August 2018.

### ***Data transfer***

The UoY received the data on 24 August 2018.

## **The PREVenting infection using Antimicrobial-Impregnated Long lines trial data**

### ***Developing the data-sharing agreement***

It came to light in early May 2018 that the UoY needed to have an agreement in place with the UoL to receive the PREVAIL trial data, given that the project was contracted separately between UCL and each of the partner organisations. The UoY initiated the data-sharing agreement between the UoY and the UoL on 3 May 2018.

### ***Sign-off by University of Liverpool***

The UoL signed off the agreement on 4 July 2018.

### ***Sign-off by sponsor***

University College London was contacted on 7 July 2018 to sign off the data-sharing agreement and privacy notice (see *Privacy notice*). UCL commented on the data-sharing agreement on 1 August 2018.

### ***Execution of contract between all parties***

On 16 August 2018, the contract was fully executed.

### ***Data transfer***

The UoY received the PREVAIL trial data on 16 August 2018.





## Appendix 4 Additional information on economic analysis: data

### **Hospital Episode Statistics Admitted Patient Care data on the PREVenting infection using Antimicrobial-Impregnated Long lines trial babies from NHS Digital**

Admitted Patient Care data included trial identifier; HES identifier (anonymised); provider code; provider type; patient's sex, month and year of birth; age at admission; dates of admission and discharge; method of admission and discharge; source of admission and discharge destination; dates that the episode started and finished, its duration, and whether or not it finished within the HES data year; episode key; the episode order within the spell and the episode type; indicator of the duration, start and end of the spell; main specialty under which the consultant was contracted and the specialty under which the consultant was working; patient classification; number of bed-days within the HES data year; primary and secondary diagnosis; trust-derived HRG value and its version number; neonatal level of care; procedures codes and dates; post-operative duration; and date of death according to the Personal Demographics Service. The HES APC data do not include information on the stays in intensive care units.

### **Hospital Episode Statistics outpatient data on the PREVenting infection using Antimicrobial-Impregnated Long lines trial babies from NHS Digital**

The outpatient care data included trial identifier, record identifier, patient's sex, date of the appointment, whether or not the patient attended the appointment, whether it is a first attendance or follow-up, trust-derived HRG value and its version number, main specialty under which the consultant was contracted and the specialty under which the consultant was working, procedure codes, and date of death according to the Personal Demographics Service.

### **Hospital Episode Statistics accident and emergency data on the PREVenting infection using Antimicrobial-Impregnated Long lines trial babies from NHS Digital**

The A&E data included trial identifier, record identifier, age at the time of the A&E visit and at the time of arrival, A&E patient group, date of A&E visit, code of the dominant procedure, trust-derived HRG value and version number, record identifier of the APC episode that the A&E visit was linked to, tests and investigations, and treatment code.

### **Paediatric intensive care data on the PREVenting infection using Antimicrobial-Impregnated Long lines trial babies from the Paediatric Intensive Care Audit Network**

The paediatric intensive care data included trial identifier, record identifier, dates of admission and discharge, admission type, discharge destination, critical care activity, and HRG code and description.

## **Neonatal care data on the PREventing infection using Antimicrobial-Impregnated Long lines trial babies from the National Neonatal Research Database**

The neonatal intensive care data included trial identifier, record identifier, date and time of birth, date and time of admission, date and time of discharge, HRG code, person accompanying baby (if transported), critical care episode identifier, critical care activity and diagnoses, NHS code of hospital receiving the baby, NHS code of the hospital baby was admitted from, detail of exact location of hospital baby was admitted from, reason for admission, destination on discharge, reason for discharge, type of ward baby is discharged to and NHS code of hospital the baby is transferred to.

## **PREventing infection using Antimicrobial-Impregnated Long lines trial data**

The PREVAIL trial data included type of allocated PICC; screening number; randomisation number; date of randomisation; time of randomisation; person performing the randomisation; sex; date of birth; time of birth; birthweight; final agreed estimated date of delivery; inborn status; date and time of admission to a NNU; mode of delivery; membrane rupture status; Apgar score; heart rate in beats per minute (bpm) (> 100 bpm at 5 minutes of age); presence of major congenital anomalies and type; use of antenatal corticosteroids; use of antibiotics within the 12 hours prior to delivery; presence of surgical procedure in the 14 days prior to randomisation (and date, if present); presence of samples taken for culture at any period within 72 hours prior to randomisation; antimicrobial use (antibiotics, enteral antifungal) at any period within 72 hours prior to randomisation; respiratory support (and highest level of support) at any period within 72 hours prior to randomisation; presence and type of devices in situ at randomisation; PICC placement details (whether or not a PICC was inserted and the reason for non-insertion, gauge type and justification, insertion site, whether or not allocation respected randomisation, date and time of insertion); date, time, and reason for PICC removal; whether or not the PICC tip was sent for culture and, if not, the reason why it was not sent; baby status (whether discharged, transferred or dead) with date and time; reason for death (PICC use or baby's underlying conditions); cause of death as per death certificate; date of post-randomisation assessment; in the case of transfer to other hospital, the details of the receiving hospital; PICC line status at transfer; full milk feeds status and date baby first reached full milk feeds; stays in wards other than NNU in admitting hospital; transfers for surgery during NNU stay at admitting hospital; NEC status and date of diagnosis; clinical outcomes in admitting hospital; total duration (in days) of parenteral nutrition in admitting hospital; date of withdrawal (if happened); person who made the withdrawal decision; and reason for withdrawal.

## Appendix 5 Additional information on economic analysis: data cleaning

### Cleaning of National Neonatal Research Database data

Figure 18 summarises the data preparation. The file with the episode dates (the 'episode file') contained data on 848 (98.49%) PREVAIL babies and 1575 episodes of care. Seven episodes were duplicates; for five of these, it was uncertain if these referred to PREVAIL babies. All seven duplicate episodes were permanently deleted. This left 1568 unique episodes about 848 PREVAIL babies.

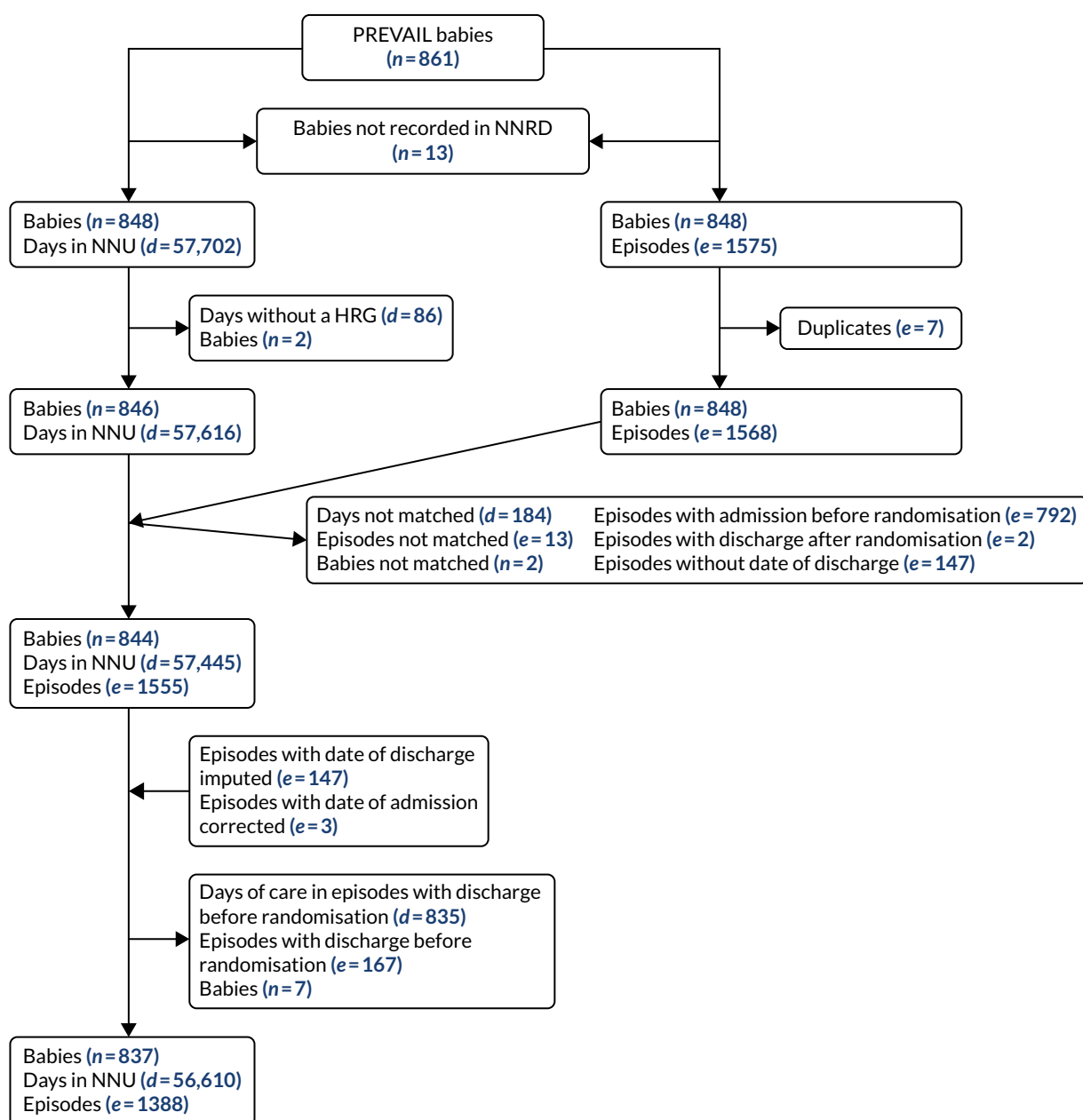


FIGURE 18 Preparation of the neonatal care data (received from NNRD).

The file with the daily care record (the 'daily file') contained data on 848 (98.49%) PREVAIL babies with 57,702 records; each record represents a day in the neonatal care unit. Of these, 86 records were removed because no HRG was recorded. As a result, records were lost for two PREVAIL babies. According to the anonymised time stamp, 5948 days were outside the follow-up of the trial in the database. If these records were removed, the records on 22 babies would also be removed. Given that the anonymised time stamp records the date and time when the record was made, and not necessarily when the activity took place, the 'episode file' was preferred to select the records within the follow-up period.

The subsequent step of data preparation was to merge the two cleaned files: the 'episode file' with records of 848 babies with a total of 1568 episodes of care with the 'daily file' with records of 846 babies with a total of 57,658 days in the NICU. After merging, 213 days of care, 13 episodes and records on two babies could not be matched. The resulting file contained data on 844 PREVAIL babies, with 1555 episodes and 57,445 days in the neonatal care unit.

Of the 1555 episodes of care, 147 episodes did not have a discharge date. This date was imputed with the date stamp of the last day of care recorded in the episode of care. In 3 (of the 147) episodes with date of discharge imputed, the date of admission was after the date stamp of the last day of care. In these episodes, the date of admission was corrected to the earliest date stamp for the daily care in the episode.

The next step was removing the 167 episodes (and 835 days of care) with a date of discharge before the date of randomisation; this corresponded to the full data on seven PREVAIL babies. These data were permanently deleted. As a result, the data on the NICU stays on the PREVAIL babies consisted of the data on 837 PREVAIL babies, with 1388 episodes of care and 56,610 days in the unit.

## Cleaning of Paediatric Intensive Care Audit Network data

*Figure 19* summarises the data preparation. The file with the episode dates contained data on 177 (20.56%) PREVAIL babies and 184 episodes of care. The discharge date of three episodes was before the date of randomisation, including of two babies for whom it consisted of all the information in the file. These were removed from the data set. The admission date of 55 episodes was after the end of follow-up, including information on 21 babies for whom it consisted of all the information in the file. As a result, the data set on the episodes of care contained data on 177 babies, with a total of 184 episodes.

The file with the HRGs contained data on 177 PREVAIL babies with 1237 days in the paediatric care unit. No inconsistencies were identified with the date of daily activity; hence, this information was used to select the days of care within the follow-up period. All days of care were assigned to a valid HRG. Thirteen days had an activity date before the randomisation date and 445 days had an activity date after the end of follow-up; these were removed. All daily records were matched to the file with the episode dates. In total, 94 (10.92%) PREVAIL babies had 126 episodes of care and 779 days in the paediatric care unit.

## Cleaning of Hospital Episode Statistics data

### *Cleaning prior to deriving Healthcare Resource Groups*

As discussed in *Chapter 4, Costing hospital care*, hospital care was costed based on the HRGs. The HES data sets, that is HES APC, HES outpatient and HRS A&E, did not include the costing HRGs. Therefore, the hospital care recorded in the HES data sets was passed through the HRG grouper software to derive them.

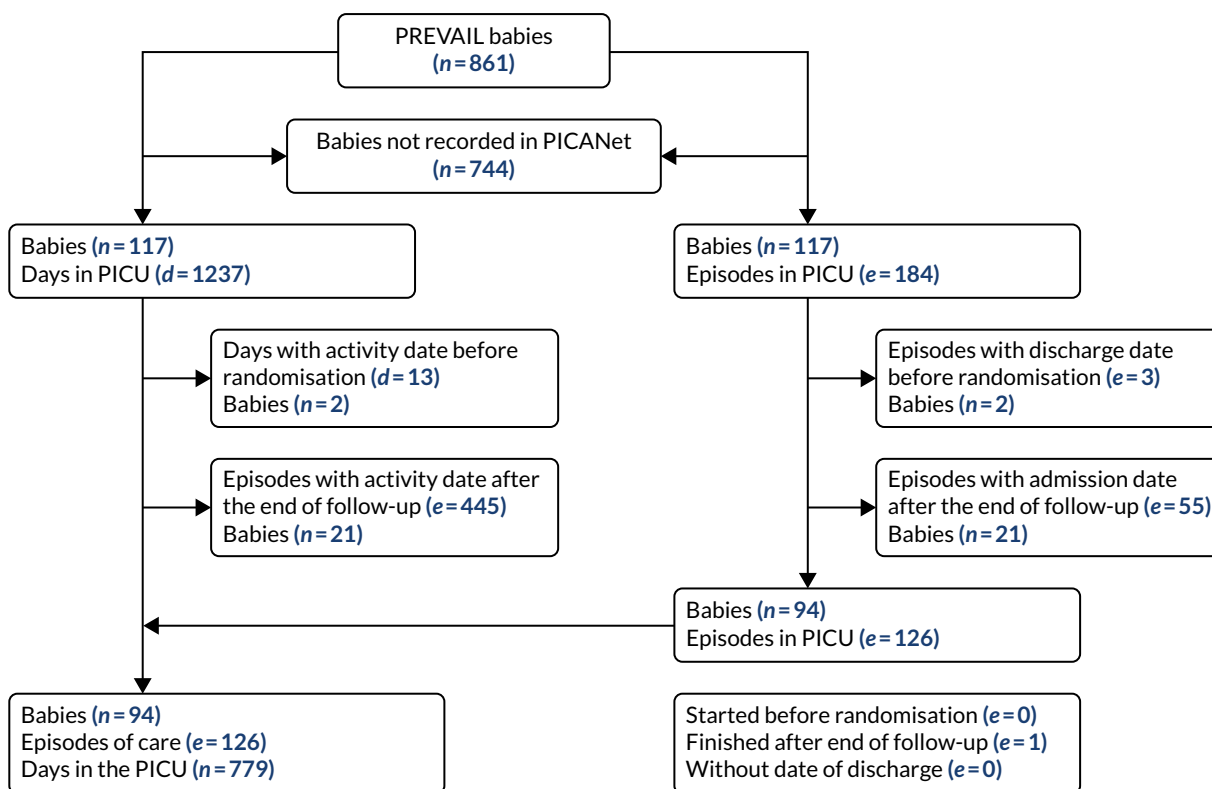


FIGURE 19 Preparation of the paediatric intensive care data (received from PICANet).

Before being passed through the grouper software, the HES data sets were cleaned to ensure both internal consistency and to fulfil the grouper software requirements. It was essential to ensure that dates were chronologically sound (e.g. episode start happening before episode end, admission date happening before discharge date, admission date happening before or on episode start date), that poorly coded observations (e.g. record identifier, episode duration, episode end date missing) and duplicates (in particular, episodes sharing the same identifier) were dropped, and that diagnosis and procedure codes included only alphanumeric characters. Episodes sharing the same episode order identifier as at least one other episode in the same spell, but showing an unspecified diagnosis code ('R69X6'), needed to be dropped. The grouper does not distinguish these particular episodes from the other correct episodes in the same spell and will not generate a HRG for any episode of that spell. Therefore, the data set was first sorted using trial identifier, NHS provider code and relevant dates, and then episodes showing a primary diagnosis code of 'R69X6', and sharing the same NHS provider code and episode order identifier of the immediately adjacent episode (above or below) in the data set, were dropped.

### Cleaning prior to costing

The data sets required additional cleaning before costing the HRG. Figures 20 and 21 summarise the process.

First, it was necessary to create an indicator variable for the type of episode (elective vs. non-elective, long vs. short stay) so that the appropriate unit cost would be attached to its respective HRG. Episodes for which there was not enough information to declare the episode type were dropped from the data set.

Some of the HRG codes were different between the 2016/17<sup>134</sup> and the 2015/16 reference costs.<sup>62</sup> Therefore, the 'new' codes were replaced with their older counterpart before attaching the reference cost table to the HRG codes (Table 41).

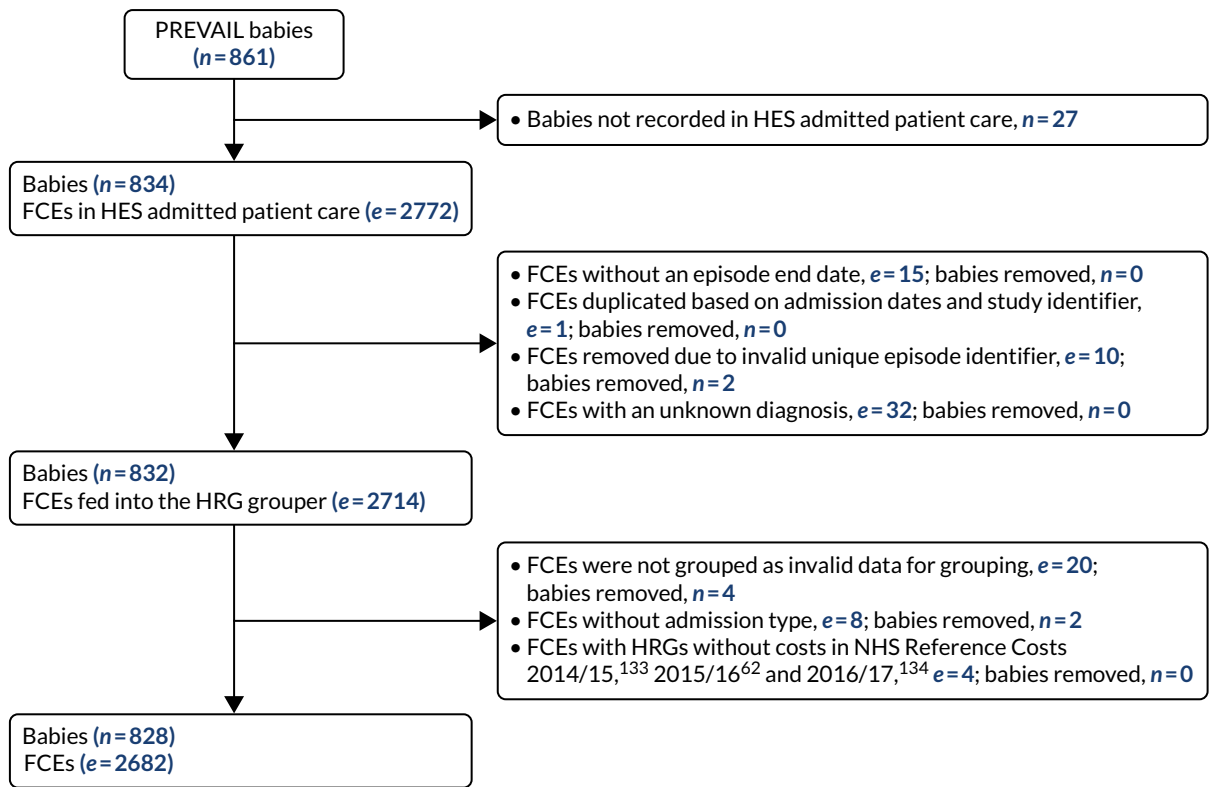


FIGURE 20 Preparation of the HES APC data (received from NHS Digital).

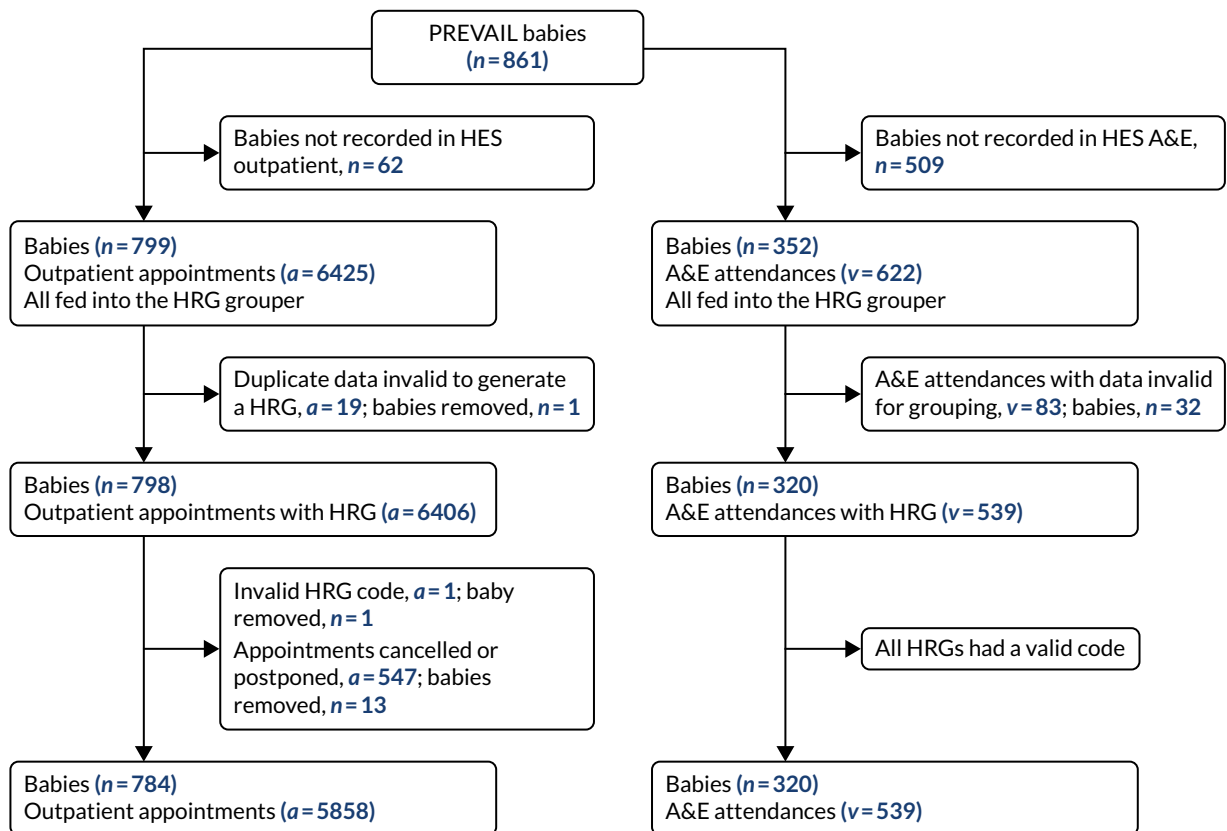


FIGURE 21 Preparation of the HES outpatient and A&E data (received from NHS Digital).

TABLE 41 Correspondence between 15/16 HRG code and 16/17 HRG code

Data set	2015/16 HRG code	2016/17 HRG code
APC	FE02E	FZ24G
APC	FE23B	FZ62B
APC	FF03B	FZ82D
APC	FF04H	FZ83F
APC	FF23E	FZ68L
APC	FF35D	FZ78D
APC	FF40C	FZ21B
APC	FF51J	FZ12U
APC	FF52D	FZ27D
APC	FF60D	FZ87G
APC	FF62F	FZ18F
APC	FF63B	FZ19B
Outpatient	FZ78D	FF35D

A small number of HRG codes were introduced in 2016/17 and did not have a corresponding code in the previous year's schedule. They were therefore deflated to 2015/16 prices using the Hospital and Community Health Service index (Table 42).<sup>135</sup>

Two pieces of information were required to correctly identify the HRG for the A&E data set: the type of department and whether or not patients were admitted for subsequent investigations (Reference Cost Guidance, section 7<sup>69</sup>). It was assumed that all babies were admitted to a 'Type 01' structure, representing hospital emergency departments.

In case an A&E admission was linked to a subsequent inpatient admission, the A&E data set presents the unique APC episode identifier. Therefore, a non-missing APC episode identifier was taken as the signal that that A&E admission led to a subsequent inpatient admission, in order to fulfil the second criteria for the correct unit cost identification.

TABLE 42 Derivation of the 'deflated' HRGs

Data set	HRG	HCHS index [1987/88 = 100 (i.e. 1987/88 taken as base year)]		Unit cost (£)	
		2016/17	2015/16	2016/17	2015/16
APC - outpatient	RD97Z	302.3	297.0	18.71	18.38
Outpatient	JB71B	302.3	297.0	26.13	25.67



## Unit costs

TABLE 43 Unit cost of HRGs relating to the stay in the neonatal and paediatric care unit<sup>62</sup>

HRG	Description	National average cost (£)
<b>Neonatal intensive care</b>		
XA01Z	Neonatal critical care, intensive care	1218
XA02Z	Neonatal critical care, high-dependency	872
XA03Z	Neonatal critical care, special care, without external carer	560
XA04Z	Neonatal critical care, special care, with external carer	384
XA05Z	Neonatal critical care, normal care	437
XA06Z	Neonatal critical care, transportation	990
<b>Paediatric intensive care</b>		
XB01Z	Paediatric critical care, advanced critical care 5	5440
XB02Z	Paediatric critical care, advanced critical care 4	3748
XB03Z	Paediatric critical care, advanced critical care 3	2538
XB04Z	Paediatric critical care, advanced critical care 2	2151
XB05Z	Paediatric critical care, advanced critical care 1	1899
XB06Z	Paediatric critical care, intermediate critical care	1448
XB07Z	Paediatric critical care, basic critical care	1173
XB08Z	Paediatric critical care, transportation	2966
XB09Z	Paediatric critical care, enhanced care	870

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## Appendix 6 Additional information on economic analysis: type and length of stay

TABLE 44 The NNRD data on PREVAIL babies: breakdown of days in the neonatal care unit by critical care HRGs, without adjustment for time outside the follow-up period

HRG code	HRG description	Total days in the neonatal care unit		Days by babies allocated to AM-PICC		Days by babies allocated to S-PICC	
		n	%	n	%	n	%
XA01Z	Neonatal critical care, intensive care	17,781	31.41	9125	32.13	8656	30.69
XA02Z	Neonatal critical care, high dependency	19,107	33.75	9524	33.53	9583	33.98
XA03Z	Neonatal critical care, special care, without external carer	18,827	33.26	9296	32.73	9531	33.79
XA04Z	Neonatal critical care, special care, with external carer	594	1.05	283	1.00	311	1.10
XA05Z	Neonatal critical care, normal care	299	0.53	174	0.61	125	0.44
Total		56,608	100	28,402	100	28,206	100
XA06Z <sup>a</sup>	Neonatal critical care, transportation	662	Not applicable	361	Not applicable	301	Not applicable

a Transport HRGs are presented separately because some admissions have both a care HRG and a transport HRG. Transport HRGs refer to the transfers of babies between units, and their unit cost is per patient journey.

TABLE 45 The NNRD data on PREVAIL babies: length of stay and cost per episode and per baby, with and without adjustment for time outside follow-up

Quantity	Total			AM-PICC			S-PICC		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
<b>Per episode</b>									
Length of stay (days) per episode in NICU without adjustment for follow-up	1388	40.19	32.32	697	40.22	33.76	691	40.16	30.82
Length of stay (days) per episode in NICU adjusting for follow-up	1388	36.81	30.25	697	36.57	30.92	691	37.05	29.57
Cost per episode in NICU without adjustment for follow-up	1388	£35,933.59	£30,101.02	697	£36,107.66	£31,930.00	691	£35,758.01	£28,158.19
Cost per episode in NICU without adjustment for follow-up	1388	£32,615.38	£27,698.45	697	£32,515.14	£28,712.61	691	£32,716.48	£26,656.86
<b>Per baby</b>									
Length of stay (days) per baby in NICU without adjustment for follow-up	837	66.65	37.38	420	66.75	38.55	417	66.54	36.21
Length of stay (days) per baby in NICU adjusting for follow-up	837	61.04	35.74	420	60.70	36.31	417	61.40	35.20
Cost per baby in NICU without adjustment for follow-up	837	£59,588.79	£37,409.92	420	£59,921.52	£38,893.53	417	£59,253.68	£35,897.37
Cost per baby in NICU without adjustment for follow-up	837	£54,086.19	£35,223.79	420	£53,959.65	£36,046.58	417	£54,213.65	£34,418.05

TABLE 46 The PICANet data on PREVAIL babies: breakdown of days in the paediatric intensive care unit by critical care HRG codes within the follow-up period

HRG code	HRG description	Total days in the paediatric intensive care unit		Days by babies allocated to AM-PICC		Days by babies allocated to S-PICC	
		n	%	n	%	n	%
XB04Z	Paediatric critical care, advanced critical care 2	124	15.92	70	18.57	54	13.43
XB05Z	Paediatric critical care, advanced critical care 1	361	46.34	162	42.97	199	49.50
XB06Z	Paediatric critical care, intermediate critical care	137	17.59	76	20.16	61	15.17
Total		779	100.00	377	100.00	402	100.00

**Note**

Only the top three HRG codes are shown to ensure suppression of small numbers, in line with the HES analysis guide.<sup>136</sup>

TABLE 47 The HES APC data on PREVAIL babies: length of stay per spell and per baby, with and without adjustment for time outside follow-up

Quantity	Total			AM-PICC			S-PICC		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
<b>Per spell</b>									
Length of stay (days) per spell in HES APC without adjustment for follow-up	2128	28.95	34.15	1080	27.96	33.84	1048	29.96	34.45
Length of stay (days) per spell in HES APC adjusting for follow-up	2128	26.71	31.54	1080	25.69	30.97	1048	27.77	32.09
<b>Per baby</b>									
Length of stay (days) per baby in HES APC without adjustment for follow-up	828	74.39	41.19	410	73.66	40.71	418	75.11	41.69
Length of stay (days) per baby in HES APC adjusting for follow-up	828	68.65	37.91	410	67.68	36.77	418	69.61	39.01

TABLE 48 The HES APC data on the PREVAIL babies: costs of FCEs

Results	Total FCEs in PREVAIL babies			FCEs for babies allocated to AM-PICCs			FCEs for babies allocated to S-PICCs		
	FCEs (n)	Mean cost (£)	SD (£)	FCEs (n)	Mean cost (£)	SD (£)	FCEs (n)	Mean cost (£)	SD (£)
<i>Unadjusted for time outside follow-up</i>									
FCE core cost unadjusted	2682	8592.90	10,581.59	1332	8561.49	10,687.94	1350	8623.88	10,479.47
FCE unbundled cost unadjusted	2682	105.40	415.90	1332	95.18	378.00	1350	115.49	450.09
FCE total cost unadjusted	2682	8698.30	10,582.63	1332	8656.68	10,695.50	1350	8739.37	10,473.87
<i>Adjusted for time outside follow-up</i>									
FCE core cost adjusted	2682	8030.28	9962.54	1332	7981.18	9970.79	1350	8078.71	9957.86
FCE unbundled cost adjusted	2682	99.10	405.48	1332	90.27	368.81	1350	107.80	438.64
FCE total cost adjusted	2682	8129.37	9964.73	1332	8071.45	9981.07	1350	8186.52	9951.95

TABLE 49 The HES APC data on the PREVAIL babies: breakdown of FCEs by admission type and cost, unadjusted by the time outside the follow-up period

Admission type	Statistic	Cost of episode (core HRG)	Cost of unbundled HRG	Total episode cost
Day case	Number of FCEs	Suppressed as a result of small numbers		
	Mean (£)	Suppressed as a result of small numbers		
	SD (£)	Suppressed as a result of small numbers		
Elective inpatient	Number of FCEs	952	952	952
	Mean (£)	12,753.70	47.21	12,800.91
	SD (£)	10,639.15	191.24	10,635.31
Non-elective inpatient long stay	Number of FCEs	643	643	643
	Mean (£)	880.56	121.99	1002.55
	SD (£)	889.51	581.24	1057.61
Non-elective inpatient short stay	Number of FCEs	1798	1798	1798
	Mean (£)	12,023.43	99.16	12,122.59
	SD (£)	10,811.21	357.77	10,816.73
Other long admission	Number of FCEs	175	175	175
	Mean (£)	4723.34	49.20	4772.55
	SD (£)	11,578.98	179.26	11,568.97
Other short admission	Number of FCEs	66	66	66
	Mean (£)	533.92	262.86	796.78
	SD (£)	285.78	368.10	396.96
Total	Number of FCEs	2682	2682	2682
	Mean (£)	8592.90	105.40	8698.30
	SD (£)	10,581.59	415.90	10,582.63

TABLE 50 The HES APC data on the PREVAIL babies: length and cost of admissions unadjusted and adjusted by time outside follow-up

Quantity	Total			AM-PICC			S-PICC		
	Babies (n)	Mean	SD	Babies (n)	Mean	SD	Babies (n)	Mean	SD
Length of stay per baby unadjusted for time outside follow-up (days)	828	74.39	41.19	410	73.66	40.71	418	75.11	41.69
Length of stay per baby adjusted for time outside follow-up (days)	828	68.65	37.91	410	67.68	36.77	418	69.61	39.01
Total cost per baby unadjusted for time outside follow-up (£)	828	£28,174.93	£19,850.20	410	£28,123.64	£20,099.41	418	£28,225.24	£19,626.65
Total cost per baby adjusted for time outside follow-up (£)	828	£26,332.09	£18,190.26	410	£26,222.37	£18,055.68	418	£26,439.72	£18,342.29

TABLE 51 The HES outpatient data on the PREVAIL babies: cost per outpatient appointment

Results	Total appointments by PREVAIL babies			Appointments by babies allocated to AM-PICCs			Appointments by babies allocated to S-PICCs		
	Number of appointments	Mean cost (£)	SD (£)	Number of appointments	Mean cost (£)	SD (£)	Number of appointments	Mean cost (£)	SD (£)
Cost of HRG core	5858	150.29	62.59	3014	148.99	63.80	2844	151.67	61.25
Cost of unbundled HRG	5858	4.42	46.33	3014	3.50	38.41	2844	5.38	53.45
Total cost per attendance	5858	154.71	78.88	3014	152.50	75.00	2844	157.05	82.75



# Appendix 7 Additional information on economic analysis: review and meta-analysis

## Effect of infection on health outcomes

### Methods

#### Pearl-growing review

A 'pearl-growing' review was conducted to identify evidence to inform the additional effect of BSI on health outcomes such as death and NDI.<sup>137</sup> Briefly, this technique requires a series of key papers to be identified at the start (the 'pearls'); from these key references, it is possible to look both forward (through the papers' citations) and backwards (through their own references). These steps are repeated using the additional papers identified, until a comprehensive evidence base on the topic is gathered and no new publications are found. This particular technique was chosen because a full systematic review was outside the scope and timeline of this report.

Advice from the PREVAIL trial clinical team suggested that the key paper in the area is Stoll *et al.*<sup>10</sup> This study was used as the starting point for finding studies on the effect of infection on NDI and death. Systematic reviews were preferred.

Studies were included if their definition of infection matched the one used in the trial for clinically serious BSI, and if the definition of NDI could be matched with the one used by Mangham *et al.*<sup>71</sup> The choice of clinically serious BSI was because literature on the consequences of infection typically uses the term sepsis or defines infection as an event requiring the use of antibiotics for at least 3–5 days.<sup>10,78–80</sup> Matching on the definition of NDI used by Mangham *et al.*<sup>71</sup> was to allow the use of Mangham *et al.*'s<sup>71</sup> transition probabilities to simulate the progression of impairment over time.

#### Definition of infection

The definition of infection follows the one of 'clinically serious BSI' as defined in the PREVAIL trial protocol,<sup>59</sup> section 4.1. A BSI case is defined as clinically serious if a baby is treated for at least 72 hours with intravenous antibiotic or dies during treatment.

#### Definition of neurodevelopmental impairment

The definition of NDI was taken from Mangham *et al.*,<sup>71</sup> whose source, Doyle *et al.*,<sup>83</sup> considered the 1991–92 cohort of the Victorian Infant Collaborative Study, covering births of 23–27 weeks' gestational age in the Australian state of Victoria. Outcomes assessed at 2 years of age included cerebral palsy, blindness, deafness and developmental delay (*Table 52*).

TABLE 52 Items included in the NDI measure

Outcome assessed	Method of assessment
Cerebral palsy	Criteria for diagnosis and severity assessment present in Kitchen <i>et al.</i> <sup>95</sup>
Blindness	Visual acuity of < 20/200 in the BSE
Deafness	Hearing loss requiring amplification
Developmental delay	Assessed using the Bayley Scales MDI. Impairment defined as DQ of < -1 SD computed relative to the mean (SD) for the respective controls on MDI

DQ, development quotient; MDI, Mental Developmental Index.

#### Note

Outcomes assessed at 2 years of age (Doyle *et al.*<sup>83</sup>) – VICSG 1991–92.



## Included studies

Three systematic reviews<sup>78-80</sup> and an umbrella review<sup>119</sup> were found on the effects of infection on health outcomes. Data from the eligible studies were re-extracted and finally synthesised. The final selection of studies for the effect of infection on NDI included Stoll *et al.*<sup>10</sup> and Schlapbach *et al.*,<sup>74</sup> whose definition of NDI matched the one used by Doyle *et al.*<sup>83</sup> and Mangham *et al.*<sup>71</sup> (Table 53).

The review on the effect of infection on the risk of death produced two studies<sup>74,76</sup> (Table 54).

## Meta-analysis results

The selected studies were meta-analysed following standard inverse variance estimator techniques.<sup>86</sup> Tables 55 and 56 show the results.

TABLE 53 Studies on the effect of infection on NDI in preterm infants

Characteristics of the studies	Composite outcome: NDI	
	Schlapbach <i>et al.</i> <sup>74</sup>	Stoll <i>et al.</i> <sup>10</sup>
Assessment period	18-24 months	18-22 months
Definition of infection	Positive culture and $\geq 5$ days of antibiotic therapy	Positive culture and $\geq 5$ days of antibiotic therapy
Cerebral palsy	Presence of cerebral palsy	Presence of cerebral palsy
Visual impairment	Bilateral blindness	Bilateral blindness
Hearing impairment	Severe hearing loss requiring auditory amplification	Bilateral hearing impairment
MDI score	< 70	< 70
PDI score	< 70	< 70

MDI, Mental Developmental Index; PDI, Psychomotor Developmental Index.

TABLE 54 Studies on the effect of infection on the risk of death in preterm infants

	Schlapbach <i>et al.</i> <sup>74</sup>	Bassler <i>et al.</i> <sup>76</sup>
Assessment period	18-24 months	18 months
Definition of Infection	Positive culture and $\geq 5$ days of antibiotic therapy	Positive culture

TABLE 55 Meta-analysis on the effect of infection on NDI

Element	OR	95% CI
<b>Studies</b>		
Schlapbach <i>et al.</i> <sup>74</sup>	1.69	0.96 to 2.98
Stoll <i>et al.</i> <sup>10</sup>	1.50	1.20 to 1.70
<b>Results</b>		
Fixed- and random-effect estimator	1.53	1.36 to 1.73

TABLE 56 Meta-analysis on the effect of infection on the risk of death at 2 years of age

Element	OR	95% CI
<b>Studies</b>		
Schlapbach <i>et al.</i> <sup>74</sup>	5.38	0.55 to 52.08
Bassler <i>et al.</i> <sup>76</sup>	2.58	1.31 to 5.07
<b>Results</b>		
Fixed- and random-effect estimator	2.74	1.43 to 5.24



## Appendix 8 Additional information on economic analysis: probability calculations

### Probability of death at 6 months

The objective of this analysis was to obtain the probability of death from PICC insertion to 6 months' follow-up in babies who did not have a clinically serious BSI, to inform the decision model.

#### Methods

##### Population and subgroups

The PREVAIL trial enrolled a mixed population of preterm babies. Of relevance to the model were babies who were born at a gestational age of  $\leq 27$  weeks and babies who were born at 28–32 weeks of gestation. This analysis uses only the data on the PREVAIL trial babies in these subgroups: 381 PREVAIL babies born at gestational age of  $\leq 27$  weeks and 354 PREVAIL babies who were born at 28–32 weeks of gestation.

##### Analysis

The analysis was initially descriptive on:

- The number of babies who had a clinically serious BSI with S-PICCs by gestational age subgroup, which represents the probability of infection with a S-PICC in the model.
- The number of babies who died over the time horizon of 6 months, taking death as recorded either in the PREVAIL trial CRFs or in the HES records via the Patient Demographics Service, by gestational age subgroup. This represents the probability of death irrespective of the type of PICC and irrespective of prior clinically serious infection.

In a second stage, a regression analysis was conducted on the probability of death given gestational age subgroup and prior clinically serious infection. The regression analysis explored the impact of using generalised linear models with binomial family or Poisson family and log link.

##### Results

Tables 57 and 58 show the results of the descriptive analysis. The probability of having a clinically serious BSI with a S-PICC was 14.52% (95% CI 9.79% to 20.41%) in the younger gestational age subgroup and was 3.80% (95% CI 1.54% to 7.68%) in the older gestational age subgroup. The probability of death over the time horizon of 6 months is shown in Table 58.

TABLE 57 Probability of clinically serious BSI with S-PICCs

Statistics	Gestational age	
	$\leq 27$ weeks	28–32 weeks
Number of babies who had infection and received a S-PICC	26	7
Number of babies who received a S-PICC	184	182
Proportion	0.14	0.04
Standard error	0.03	0.01
95% CI	0.09 to 0.20	0.02 to 0.08

TABLE 58 Probability of death over the time horizon of 6 months

Statistics	Gestational age	
	≤ 27 weeks	28–32 weeks
Number of babies who died	52	11
Number of babies	381	354
Proportion	0.14	0.03
Standard error	0.02	0.01
95% CI	0.10 to 0.18	0.02 to 0.05

Table 59 shows the results of the regression analysis of the probability of death given gestational age and prior clinically serious BSI. The best-fitting regression is the regression including both explanatory variables. It suggests that having a clinically serious BSI is associated with 78.4% greater risk of death (RR 1.784), and that being born at a gestational age of 28–32 weeks is associated with an 85.5% lower risk of death (RR 0.245).

It is not clear whether this is a correlation or a causal association. There may be other factors that increase the risk of clinically serious BSI and increase the risk of death, for example other health problems that the babies may have been born with. Without controlling for these other factors, it is not possible to ascertain whether or not preventing clinically serious BSI reduces the risk of death to the extent that the regression analysis suggests. Given the small number of deaths, the regression analysis is constrained in the number of variables that can be included.

## Application to the model

### Method

The following equations explain the methodology.

$$P(\text{death all}) = P(\text{death}|\text{infection}) \times P(\text{infection}) + P(\text{death}|\text{no infection}) \times [1 - P(\text{infection})]. \quad (1)$$

TABLE 59 Predictors of the risk of death

Explanatory variables	Controlling on only clinically serious BSI		Controlling on only gestational age category		Controlling for both clinically serious BSI and gestational age category	
	Risk ratio	SE	Risk ratio	SE	Risk ratio	SE
Clinically serious BSI	2.51**	0.71	–	–	1.85*	0.54
Gestational age category	–	–	0.23***	0.07	0.25***	0.08
Constant	0.08***	0.01	0.14***	0.02	0.12***	0.02
<i>n</i>	735				735	
AIC	0.5793931		0.5519772		0.5606888	
BIC	-4415.851		-4436.002		-4550.999	

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .

AIC, Akaike information criterion; BIC, Bayesian information criterion; SE, standard error.

$$P(\text{death all}) = RR(\text{infection on death}) \times P(\text{death|no infection}) \times P(\text{infection}) + P(\text{death|no infection}) \times [1 - P(\text{infection})]. \quad (2)$$

$$P(\text{death all}) = P(\text{death|no infection}) \times RR(\text{infection on death}) \times P(\text{infection}) + [1 - P(\text{infection})]. \quad (3)$$

$$P(\text{death|no infection}) = \frac{P(\text{death all})}{RR(\text{infection on death}) \times P(\text{infection}) + [1 - P(\text{infection})]}. \quad (4)$$

$P(\text{death all})$  is the probability of death in the mixed population of people with and without a clinically serious BSI.  $P(\text{death|infection})$  is the probability of death given a prior clinically serious BSI and  $P(\text{death|no infection})$  is the probability of death given no prior clinically serious BSI.

$P(\text{infection})$  is the probability of a clinically serious BSI occurring.

$RR(\text{infection on death})$  is the ratio between the probability of death with and death without a clinically serious BSI.

### Data inputs

Table 60 shows the distribution of babies based on their survival status at 6 months, conditional on prior infection.

Based on the data from Table 60, it was possible to compute the RR for clinically serious BSI on death before the end of follow-up (RR 2.51, 95% CI 1.44 to 4.38). As the number of events is limited, it was not feasible to compute a gestational age-specific RR by splitting the overall sample. Therefore, the RR calculated using the whole PREVAIL sample was applied to all gestational age groups.

$P(\text{death all})$  was obtained as 1 minus the probability of surviving to discharge extracted from Santhakumaran *et al.*,<sup>87</sup> and  $P(\text{Infection})$  corresponds to the probability of experiencing a clinically serious BSI, as resulted from the PREVAIL trial data. See points (6) and (5), respectively, in Table 17.

### Results

The results of Table 61 are used as the baseline probability of death before the end of trial follow-up in the model. The RR of death given clinically serious BSI is then applied to the baseline probability to obtain the probability of death given infection. As detailed in Chapter 4, it was not possible to obtain

TABLE 60 Number of deaths before end of follow-up, by infection status (all gestational ages)

Occurrence of clinically serious BSI	Death before end of follow-up (n)		
	No	Yes	Total
No	616	50	666
Yes	56	13	69
Total	672	63	735

TABLE 61 Probability of death before the end of follow-up, without infection

Gestational age (weeks)	$P(\text{death no infection})$ (95% CI)
23–27	0.20 (0.16 to 0.24)
28–32	0.034 (0.030 to 0.036)

strong evidence about the existence and the size of this effect, neither from the PREVAIL trial nor from the available literature. Therefore, the base case assumes that a clinically serious BSI does not increase the risk of death at 6 months (i.e. a RR of 1 was assumed), whereas a scenario considers the application of the RR computed from the PREVAIL data, as detailed in *Table 60*.

### Transitions between neurodevelopmental impairment states or death

Mangham *et al.*<sup>71</sup> report the counts of changes in impairment status for the babies belonging to the VICSG<sup>84</sup> 1991–92 cohort, which includes all babies born at 23–27 weeks' gestational age from the state of Victoria in Australia. The impairment levels are classified according to the definition adopted by Doyle *et al.*<sup>83</sup>

The counts reported in Mangham *et al.*<sup>71</sup> are used to compute 3-year transition probabilities for the period covering ages 2–5 and 5–8 years, respectively. After the age of 8 years, transition across impairment states are assumed to stop; hence, babies either remain in their current impairment level or will transition to the absorbing death model state. The 3-year probabilities are then converted to annual transition probabilities using standard formulas as reported in Briggs *et al.*,<sup>86</sup> and are reproduced in *Tables 62* and *63*. The counts reported in Mangham *et al.*<sup>71</sup> are supplemented by the average probability of death between the ages of 2 and 5 years, 5 and 8 years and 8 and 18 years extracted from the *National Life Tables, UK: 2013–2015*.<sup>99</sup>

TABLE 62 Annual transition probabilities across impairment states (age 2–5 years)

NDI	NDI					Total
	No	Mild	Moderate	Severe	Dead	
No	0.91	0.08	0.01	0.00	0.00	1.00
Mild	0.17	0.75	0.07	0.01	0.00	1.00
Moderate	0.03	0.12	0.80	0.05	0.00	1.00
Severe	0.00	0.04	0.04	0.91	0.00	1.00

TABLE 63 Annual transition probabilities across impairment states (age 5–8 years)

NDI	NDI					Total
	No	Mild	Moderate	Severe	Dead	
No	0.96	0.04	0.00	0.00	0.00	1.00
Mild	0.14	0.82	0.04	0.00	0.00	1.00
Moderate	0.01	0.08	0.83	0.07	0.00	1.00
Severe	0.00	0.02	0.06	0.92	0.00	1.00

## Appendix 9 Additional information on economic analysis: costs

### Costs over 6 months from peripherally inserted central venous catheter insertion

The objective of this analysis was to estimate the mean, standard error and appropriate distribution of the costs over 6 months from PICC insertion, to inform the cost-effectiveness model.

#### Methods

This analysis used the costs of the PREVAIL trial babies, which were calculated as reported in Chapter 4, *Costs of hospital care*.

#### Population and subgroups

As these estimates aimed to inform the decision model, the analysis was conducted in the populations with a gestational age of  $\leq 27$  weeks and with gestational age of 28–32 weeks who had sufficient records in the NNRD and in HES APC data. The analytical sample comprises 381 babies with gestational age of  $\leq 27$  weeks and 354 babies with gestational age of 28–32 weeks.

#### Choice of explanatory variables

Five explanatory variables were explored: gestational age subgroup ( $\leq 27$  weeks or 28–32 weeks), PICC type (AM-PICC or S-PICC), occurrence of clinically significant BSI and death at 6 months. Death at 6 months was obtained from the PREVAIL trial CRFs and from the routine health-care records (see Chapter 4, *Deaths during the 6-month follow-up period*). No other explanatory variables were explored, given that the structure of the cost-effectiveness model for the 6 months from PICC insertion differentiates babies only by these variables.

#### Description of the costs

The costs in the entire analysis sample and by the various exploratory variables were described in terms of their summary statistics. Their distributions were plotted to understand if the costs followed a normal distribution.

#### Estimation

Costs were regressed on the various exploratory variables using generalised linear models, namely with identity distribution and Gaussian link (which is equivalent to linear regression) and identity distribution and log link.

#### Results

##### Descriptive statistics

Table 64 presents the costs of hospital care in the sample of PREVAIL babies with gestational ages of  $\leq 27$  weeks and 28–32 weeks, who are those considered in the economic model, by gestational age subgroup, type of PICC, whether or not a clinically serious BSI occurred during the primary follow-up period and by whether or not death occurred during the 6-month follow-up.

- The cost of hospital care is lower for babies in the older gestational age group (£62,491 vs. £106,240).
- The cost of hospital care is similar, irrespective of the PICC type, at approximately £85,000.
- The cost of hospital care is higher for babies who had a clinically serious BSI (£105,468 vs. £83,066).
- The cost of hospital care is lower for the babies who died during the 6-month follow-up period (£53,415 vs. £88,146).



TABLE 64 Summary statistics of all hospital costs over 6 months from PICC insertion

Costs	Number of babies	Mean costs (£)	SE (£)	Number of babies	Mean costs (£)	SE (£)	Number of babies	Mean costs (£)	SE (£)
	<b>Total</b>			<b>Gestational age: ≤ 27 weeks</b>			<b>Gestational age: 28–32 weeks</b>		
Cost of hospital care	735	85,169.36	1848.49	381	106,240.27	2784.30	354	62,491.35	1720.23
	<b>Total</b>			<b>AM-PICC</b>			<b>S-PICC</b>		
Cost of hospital care	735	85,169.36	1848.49	366	86,045.40	2640.83	369	84,300.44	2590.38
	<b>Total</b>			<b>No clinically significant BSI</b>			<b>Clinically significant BSI</b>		
Cost of hospital care	735	85,169.36	1848.49	666	83,066.31	1889.95	69	105,468.37	7002.05
	<b>Total</b>			<b>Alive at 6 months</b>			<b>Death during 6-month follow-up</b>		
Cost of hospital care	735	85,169.36	1848.49	672	88,146.31	1856.02	63	53,415.21	7515.19

SE, standard error.

## Regression analysis

### Model selection

The best-fitting regression to predict costs was the generalised linear model with Gamma distribution and log link according to plot of deviance residuals and normal plot. The best-fitting regression according to the Park test was the Gaussian distribution and log link. The results for both regressions were very similar. Hence, the Gaussian distribution and log link, which produces coefficients that are easier to interpret, was the preferred estimation model.

### Results

Table 65 shows the results of four regression equations with various combinations of the candidate explanatory variables: gestational age, clinically significant BSI and death at 6 months. Gestational age is used in all regression equations because it corresponds to the definition of the subgroups. The coefficient on gestational age is similar across the four regression models. It suggests that babies born at 28–32 weeks of gestation have 53–59% lower costs than babies born at younger gestational ages.

The association between clinically significant BSI and costs is uncertain. The coefficient is positive, which indicates higher costs in babies who experienced a clinically significant BSI, but not statistically significant. Regression 4, which includes only gestational age as the explanatory variable, has the poorest fit (indicated by the higher Akaike information criterion and Bayesian information criterion). Furthermore, this regression equation does not control for whether or not a clinically significant BSI occurred or for babies' characteristics that may increase their risk of death, and also increase their costs. Hence, it is unclear if this association is confounded.

The regressions suggest that there is a negative association between whether or not death occurred and costs. This association is statistically significant and stable to the inclusion of clinically significant BSI as an explanatory variable. The association between death and costs may be related with the shorter length of stay of babies who died than those babies who were alive at 6 months. However, the association may be confounded by length of stay and by their characteristics. For example, the babies who died may have been in too poor health to allow for surgical procedures, thereby reducing their costs. Under this scenario, an intervention that prevents their death does not necessarily result in an increase in costs if the babies still do not receive the surgical procedures.

TABLE 65 Results of regression analysis Gaussian distribution log link

Specification of the regression	Regression			
	1	2	3	4
Gestational age (= 1 if 28–32 weeks) (SE)	-0.580*** (0.0419)	-0.520*** (0.0445)	-0.594*** (0.0417)	-0.531*** (0.0441)
Clinically significant BSI (= 1 if occurred) (SE)	0.144** (0.0508)	0.100 (0.0551)		
Death at 6 months (= 1 if occurred) (SE)	-0.726*** (0.104)		-0.714*** (0.104)	
Constant (SE)	11.63*** (0.0221)	11.56*** (0.0236)	11.65*** (0.0205)	11.57*** (0.0218)
N	735	735	735	735
AIC	17,753.6	17,840.8	17,758.8	17,841.9
BIC	17,772.0	17,854.6	17,772.6	17,851.1

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .

AIC, Akaike information criterion; BIC, Bayesian information criterion; SE, standard error.

### Discussion

The base-case cost-effectiveness model assumes that the costs incurred by babies over 6 months from PICC insertion are the same irrespective of the occurrence of a clinically significant BSI or death. The costs will depend only on their gestational age. The implication is that a reduction in the probability of clinically significant BSI or in the probability of death has no effect on the costs. This is a conservative assumption.

Two scenarios are tested. One scenario assumes that babies who die have lower costs, as suggested by regression equation 3 (see *Table 65*). The implication is that interventions that reduce the probability of death result in an increase in costs over 6 months. The other scenario assumes that babies who die have lower costs and that babies who have clinically significant BSI have higher costs, as suggested by regression equation 1 (see *Table 65*). The implication is that interventions that reduce the probability of a clinically significant BSI occurring result in a decrease in costs over 6 months.

### Costs between 6 months and 2 years of age

Costs between 6 months and 2 years of age were computed using two sources of information: NHS Reference Costs 2015–16,<sup>62</sup> and resource use from an unpublished study about variation in neonatal and paediatric admissions (Katie Harron, personal communication).

### Methods

Information from the NHS reference costs was used to compute average costs weighted by level of activity. This results in an estimate of average costs of inpatient care (for elective and non-elective), average outpatient visit cost, and average A&E attendance cost (*Table 66*).

Unpublished results provided information on the number of babies accessing these services, by gestational age groups 23–27 weeks and 28–32 weeks, and their resource use in terms of hospital admission and type (planned vs. unplanned), A&E and outpatient attendances. This was used to compute the number of hospital admissions by type, and visits per baby. Data about the proportion of planned and unplanned admissions were used as weight when averaging the cost of elective and non-elective hospital admission. Average costs were then multiplied by the relevant resource use and summed across type of care to obtain total cost per baby.

TABLE 66 Unit cost weighted average by activity

Type of hospital use	Average cost (£)
Elective inpatient	2790.72
Non-elective long stay	2516.04
Paediatric outpatient	196.50
A&E	161.60

## Results

TABLE 67 Resource use 6–24 months

Gestational age at birth (weeks)	Admissions (%)		Number, per baby		
	Planned	Unplanned	Episodes	A&E visits	Outpatient attendances
33–36	23	77	0.43	1.08	1.55
28–32	24	76	0.74	1.34	4.61
23–27	28	72	1.32	2.01	11.47

TABLE 68 Costs 6–24 months

Gestational age at birth (weeks)	Cost (95% CI) (£)
23–27	5989.17 (5983.44 to 5994.98)
28–32	3026.43 (3024.21 to 3028.73)



# Appendix 10 Additional information on economic analysis: model validation

## Part A: validation of the conceptual model

### *A1: Have experts been asked to judge the appropriateness of the conceptual model?*

Yes. The experts were Ruth Gilbert, Sam J Oddie and Ajay K Sinha. They were chosen because they were co-applicants in the project and are epidemiologists (RG) or clinicians (SJO, AKS) with extensive experience in this clinical area. The experts found the conceptual model to be generally appropriate, and noted the uncertainty in the link between clinically significant BSI, NEC and NDI. There was some debate about whether or not clinically significant BSI should be assumed to have a causal effect on the risk of death at 6 months, given the limited data in the PREVAIL trial.

### *A2: Has this model been compared with other conceptual models found in the literature or clinical textbook?*

Partly. The model on predicting outcomes in early childhood was informed by the Stoll *et al.*<sup>10</sup> study on the effect of infection in early infancy on neurodevelopmental outcomes. However, no other cost-effectiveness model on infection in preterm neonates was found for comparison. The model on predicting lifetime costs and health outcomes beyond 2 years of age was informed by the model by Mangham *et al.*<sup>71</sup>

## Part B: input data validation

### *B1: Have experts been asked to judge the appropriateness of the input data?*

Yes, the same experts as in A1 reviewed the input data. The experts agreed that the appropriate data were used.

### *B2: When input parameters are based on regression models, have statistical tests been performed?*

Partly; the costs from PICC insertion to 6 months were obtained from the linked data (see *Appendix 9*). The model type was chosen on the basis of the distribution of the costs, Park test and the plot of deviance residuals versus normal plot. Four model specifications were tested. The most conservative for the cost-effectiveness of interventions to prevent infections was selected for the base case, but the impact of alternative specifications was tested in a sensitivity analysis to the cost-effectiveness model.

## Part C: validation of the computerised model

### *C1: Has the computerised model been examined by modelling experts?*

Yes, the cost-effectiveness model was examined by Rita Faria. Rita Faria is not an independent expert, as she supervised the development of the cost-effectiveness model and collaborated in all economic analyses. The cost-effectiveness model is valid.

**C2: Has the model been run for specific, extreme sets of parameter values in order to detect any coding errors?**

Yes. The tests included:

- Tree –
  - Baseline risk of infection = 0. If the baseline risk of infection is set to 0, we expect both PICC groups to give identical results, as there will be no difference in the rate of death and NDI at 2 years.
  - RR of infection set to 0: AM-PICC becomes cost-effective.
  - RR of infection, OR of infection on death (6 months), OR of infection on death (2 years) and OR of infection on NDI (2 years) set to 1. AM-PICCs and S-PICCs are identical. There is only a difference of £53.70 in costs, which is the additional cost of an AM-PICC.
- Markov model –
  - Utilities = 1, disutilities = 0. Setting all utilities to 1 means that QALYs accrued in a cycle (without half-cycle correction) should be equal to the number of people alive in a state (i.e. QALYs = life expectancy). Alternatively, that the sum of the QALYs accrued in a cycle and the cumulative number of deaths should always sum to 1. This is indeed the case in our model.
  - Probability of death = 0. Setting UK lifetable value to 0. We expect cycle number of deaths and cumulative number of deaths to remain at 0, with everyone dying in the last cycle. This is indeed the case.
  - No transitions to other states. As transitions are stopped, then babies should not move from the initial distribution.
  - 50% no NDI, 50% mild NDI. Results from this test are expected to be identical to the average of having 100% of babies in 'no NDI' and 100% of babies in 'mild NDI'.
  - Setting all HRs to 1 – the mortality rate is identical for all severity levels.

Any errors identified were corrected.

**C3: Have patients been tracked through the model to determine whether or not its logic is correct?**

Yes, the patients were tracked through the model at ages 5, 8 and 18 years. The model logic is correct.

**C4: Have individual submodules of the computerised model been tested?**

No.

**Part D: operational validation****D1: Have experts been asked to judge the appropriateness of the model outcomes?**

Yes; Ruth Gilbert, Sam J Oddie and Ajay K Sinha found the results to have face validity.

**D2: Have the model outcomes been compared with the outcomes of other models that address similar problems?**

Yes. The results were compared with those reported by Mangham *et al.*,<sup>71</sup> using the same input parameters. The results were very similar.

**D3: Have the model outcomes been compared with the outcomes obtained when using alternative input data?**

No, as no alternative input data were identified.

*D4: Have the model outcomes been compared with empirical data?*

No.

## **Part E: other validation techniques**

*E1: Have any other validation techniques been performed?*

No.





# Appendix 11 Additional information on economic analysis: sensitivity analysis

## BOX 1 Main model assumptions

- The occurrence of infection increases the risk of developing NDI or of dying by 2 years of age.
- The occurrence of infection has the same effect on the risk of NDI and death for all gestational age subgroups.
- The occurrence of infection does not increase the risk of death by 6 months of age.
- The effectiveness of AM-PICCs is the same for all gestational age subgroups.
- The distribution of infants across levels of NDI at 2 years of age is the same for the two PICCs, irrespective of previous infection.
- Infants are attributed the same costs between birth and 6 months of age, and between 6 months and 2 years of age, irrespective of the occurrence of infection or death.
- After age 2 years, long-term costs and health outcomes are influenced only by a child's NDI level at 2 years of age.
- Children experience improvements or deteriorations in their NDI state only up to the age of 8 years. After age 8 years, they can transition to the absorbing 'death' state only.

TABLE 69 List of sensitivity analyses

Sensitivity analysis	Justification
<b>Effect of infection on NDI and death</b>	
Reduce the effect of infection on either death at 2 years or NDI to null effect (OR 1)	To take into account possible bias in the observational nature of the evidence regarding the impact of infection
Assume impact of infection on death at 6 months equals the RR from PREVAIL trial data of 2.62 (95% CI 1.52 to 4.51)	To take into account information about the impact of infection coming from the PREVAIL trial follow-up
<b>Baseline probabilities</b>	
Transitions up to 18 years of age	To test the sensitivity of results to the extrapolation of transition probability data beyond childhood
Stop backward transitions for babies with severe NDI	To take into account the clinical implausibility of improvement in severe babies' classification over time
Use 3-year transition probabilities instead of yearly ones	To take into account the actual assessment point in the references' sources and the likelihood of movement between disability states
<b>Costs</b>	
Differentiate costs between PICC insertion and 6 months by survival and infection status	To take into account additional evidence coming from the regression analysis of costs (see <i>Appendix 9</i> )
<b>Parameters to predict long-term outcomes and costs</b>	
Increase/decrease costs after 18 years of age	To take into account the possible changes in costs after 18 years, which were not taken into account in the base case
Apply HRQoL age and sex decrements from Ara and Brazier <sup>104</sup>	To take into account the impact of age and sex on utility values
Assume NDI level does not increase the risk of death after 2 years of age	To take into account the impact of assuming that NDI has an additional impact on mortality according to its level

TABLE 70 Details of the alternative scenarios on RR of death and costs

Parameter	Value (95% CI; distribution)	Source
<b>Effect of infection on NDI and death</b>		
RR of the association of clinically serious BSI on death at 6 months; same for both gestational age subgroups	<ul style="list-style-type: none"> <li>• Base case: 1 (fixed)</li> <li>• Scenario: 2.62 (1.52 to 4.51; log-normal)</li> </ul>	<ul style="list-style-type: none"> <li>• Assumed that clinically serious BSI has no causal effect on death at 6 months</li> <li>• PREVAIL trial</li> </ul>
<b>Costs</b>		
<i>Health-care costs between PICC insertion and 6 months</i>		
	<b>Base case</b>	<b>PREVAIL trial</b>
Gestational age: 23–27 weeks	£105,873 (£101,444.99 to £110,485.27; gamma)	<ul style="list-style-type: none"> <li>• Generalised linear model with Gaussian distribution and log-link; explanatory variable is gestational age group</li> <li>• See <i>Appendix 9</i> for more details</li> </ul>
Gestational age: 28–32 weeks	£62,255.37 (£54,711.87 to £70,838.93; gamma)	
	<b>Scenario 1</b>	<b>Scenario 1 adjusts for gestational age subgroup and whether or not the baby survived to 6 months</b>
Gestational age: 23–27 weeks	<ul style="list-style-type: none"> <li>• Alive: £114,691.36 (£110,174.42 to £119,393.50; gamma)</li> <li>• Dead: £56,162.24 (£44,001.54 to £71,683.80; gamma)</li> </ul>	
Gestational age: 28–32 weeks	<ul style="list-style-type: none"> <li>• Alive: £63,322.75 (£56,054.96 to £71,532.85; gamma)</li> <li>• Dead: £31,007.98 (£22,387.28 to £42,948.29; gamma)</li> </ul>	
	<b>Scenario 2</b>	<b>Scenario 2 adjusts for gestational age group, whether or not the baby survived to 6 months and whether or not the baby had a clinically significant BSI</b>
Gestational age: 23–27 weeks	<ul style="list-style-type: none"> <li>• Alive/no BSI: £112,420.32 (£107,654.68 to £117,396.93; gamma)</li> <li>• Alive/BSI: £129,832.44 (£112,545.85 to £149,774.18; gamma)</li> <li>• Dead/no BSI: £54,393.50 (£42,482.35 to £69,644.29; gamma)</li> <li>• Dead/BSI: £62,818.19 (£44,412.49 to £88,851.70; gamma)</li> </ul>	
Gestational age: 28–32 weeks	<ul style="list-style-type: none"> <li>• Alive/no BSI: £62,943.95 (£55,523.41 to £71,356.23; gamma)</li> <li>• Alive/BSI: £72,692.97 (£58,046.05 to £91,035.79; gamma)</li> <li>• Dead/no BSI: £31,454.83 (£21,910.47 to £42,331.21; gamma)</li> <li>• Dead/BSI: £35,171.80 (£22,905.95 to £54,005.87; gamma)</li> </ul>	

TABLE 71 Maximum acquisition price per AM-PICC effectiveness (gestational age: 23–27 weeks)

RR of infection with AM-PICC vs. S-PICC	Cost-effectiveness (£) at	
	£20,000/QALY	£13,000/QALY
0.5	1245.00	830.00
0.55	1125.00	750.00
0.6	1005.00	670.00
0.65	885.00	595.00
0.7	765.00	515.00
0.75	645.00	435.00
0.8	525.00	360.00
0.85	405.00	280.00
0.9	285.00	200.00
0.95	165.00	120.00
0.96	140.00	105.00
0.97	115.00	90.00
0.98	90.00	75.00
0.99	65.00	60.00
1	46.00	46.00

TABLE 72 Maximum acquisition price per AM-PICC effectiveness (gestational age: 28–32 weeks)

RR of infection with AM-PICC vs S-PICC	Cost-effectiveness (£) at	
	£20,000/QALY	£13,000/QALY
0.5	250.00	180.00
0.55	230.00	170.00
0.6	210.00	155.00
0.65	190.00	140.00
0.7	170.00	125.00
0.75	150.00	110.00
0.8	125.00	100.00
0.85	105.00	85.00
0.9	85.00	70.00
0.95	65.00	55.00
0.96	60.00	55.00
0.97	55.00	50.00
0.98	50.00	50.00
0.99	46.00	46.00
1	46.00	46.00

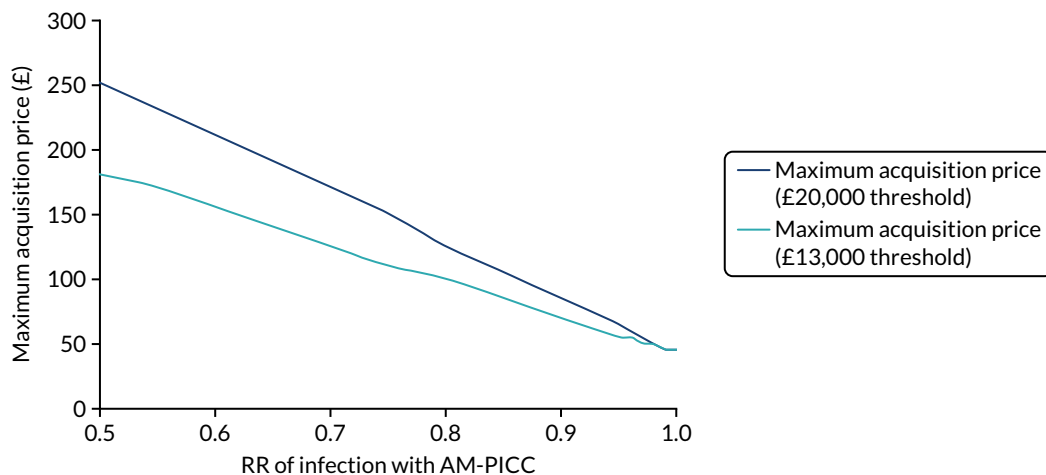


FIGURE 22 Maximum acquisition price per AM-PICC effectiveness, gestational age: 28–32 weeks.

Figures 23 and 24 represent the incremental change of net monetary benefit, with respect to its mean value, over the 95% CI for the model parameters.

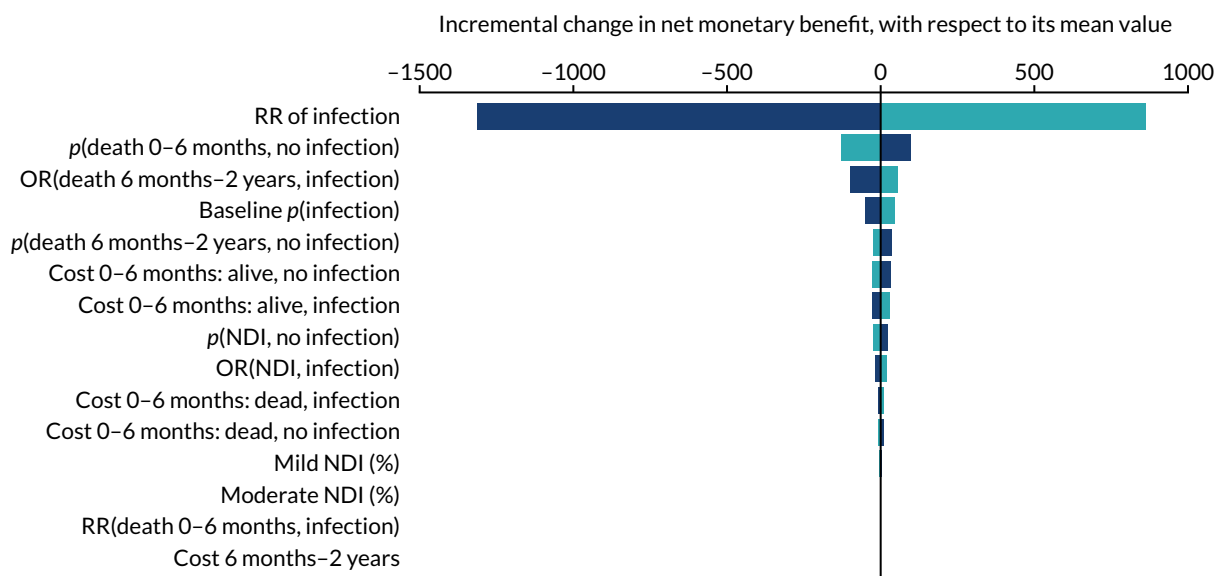


FIGURE 23 Univariate sensitivity analyses for gestational age subgroup 23–27 weeks at the £20,000 per QALY cost-effectiveness threshold. Adapted from Grosso *et al.*<sup>106</sup> © Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY. Published by BMJ. This is an open access article distributed in accordance with the Creative Commons Attribution 4.0 Unported (CC BY 4.0) license, which permits others to copy, redistribute, remix, transform and build upon this work for any purpose, provided the original work is properly cited, a link to the licence is given, and indication of whether changes were made. See: <https://creativecommons.org/licenses/by/4.0/>. Minor formatting changes have been made.

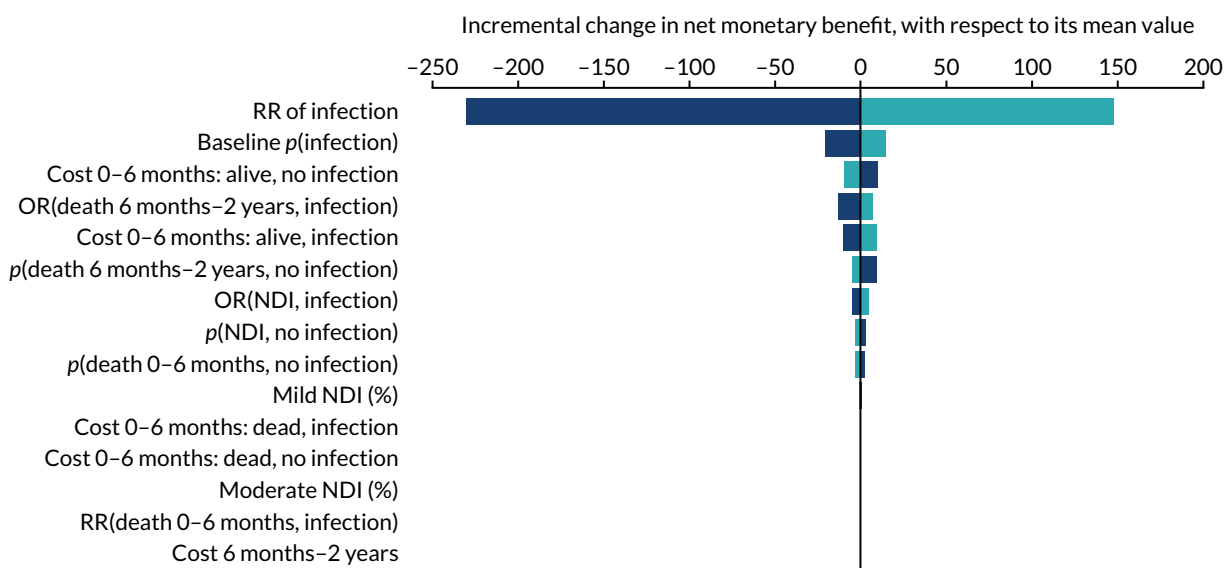


FIGURE 24 Univariate sensitivity analyses for gestational age subgroup 28-32 weeks at the £20,000 per QALY cost-effectiveness threshold.

TABLE 73 Incremental net health and monetary benefit by scenario for cost-effectiveness thresholds of £13,000 and £20,000 per QALY

Sensitivity analysis	Incremental net monetary benefit (£)			
	At £13,000 per QALY		At £20,000 per QALY	
	Gestational age: 23-27 weeks	Gestational age: 28-32 weeks	Gestational age: 23-27 weeks	Gestational age: 28-32 weeks
Base case	-145.07	-69.75	-193.63	-77.98
No effect of infection on NDI	-101.25	-59.70	-128.97	-63.16
No effect of infection on death between 6 months and 2 years	-98.83	-63.85	-120.29	-68.67
Apply RR on death from PREVAIL trial	-728.45	-99.40	-1,127.72	-124.98
Apply transition probabilities up to 18 years of age	-134.82	-67.12	-187.20	-74.10
Stop backward transitions for babies with severe NDI	-150.80	-70.98	-202.04	-79.80
Differentiate costs between PICC insertion and 6 months of age by survival and gestational age	-134.11	-69.03	-182.65	-77.26
Differentiate costs between PICC insertion and 6 months by survival, gestational age and infection status	-259.43	-90.26	-307.97	-98.49
Use 3-year transition probabilities	-123.08	-64.44	-161.17	-70.14
Double costs after 18 years of age	-145.27	-70.06	-193.83	-78.29
Apply HRQoL age and sex decrement	-147.55	-70.10	-197.43	-78.53
Assume NDI does not increase the risk of death after the age of 2 years	-143.83	-69.43	-191.46	-77.43



## Appendix 12 Additional information on generalisability study: linkage methods

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We used deterministic and probabilistic linkage to link babies in the NNRD to BSI records from national infection surveillance. We first performed deterministic linkage using the NHS number. However, not all babies had a complete NHS number; therefore, we also used probabilistic methods. In both deterministic and probabilistic linkage, links were restricted to those with a sample date from the surveillance data between 7 days before admission and 14 days after discharge from the NNU. Further restrictions to BSI dates were applied depending on the definition of BSI being used (e.g. during PICC time at risk/early onset/late onset). Each BSI could be linked to only one baby; however one baby could be linked to multiple BSI records. Therefore, linkage was one to many.

### Deterministic linkage

We first used deterministic linkage to link babies in the NNRD with BSI records in the surveillance data. Records were linked if the same NHS number was recorded in each data set. The NHS number is a unique 10-digit identifier assigned at birth. NHS number matches were manually reviewed to ensure that they represented true matches. NHS number links were then used as the training data set for probabilistic linkage.

### Probabilistic linkage

For records that were not linked on NHS number, we used probabilistic linkage based on the remaining common identifiers in each data set. The available identifiers were date of birth, postcode prefix, postcode suffix, sex and hospital/laboratory. In probabilistic linkage, match weights are created that represent the likelihood that two records belong to the same subject, according to the similarity of a set of identifiers.<sup>138</sup> We first used 'blocking' to restrict the comparisons to records that agreed on at least one of date of birth, postcode prefix or postcode suffix.<sup>139</sup> This ensured that we compared only records that had a chance of being a match; otherwise, records could, at most, agree on hospital and sex, which would not be sufficient to identify a link.

Next, we used the deterministic links as the reference standard for true matches to calculate probabilistic match weights.<sup>112</sup> Match weights were calculated as  $\log_2\left(\frac{m - \text{probability}}{u - \text{probability}}\right)$ . We estimated the probability that records were a true match, given identifiers were in agreement, disagreement or missing in either data set (*m*-probabilities). We estimated the probability that records were not a match (i.e. disagreed on NHS number), given identifier agreement, disagreement or missing in either data set (*u*-probabilities).

Match weights were totalled across identifiers to produce an overall weight ('summed weight') for each comparison pair, based on the pattern of agreement of identifiers that represents the likelihood that each pair is a match. A plot of the log frequency of the weights was examined to determine an upper and lower threshold, above which all pairs are classified as links and below which all pairs are classified as non-links. The agreement patterns of the weights close to the thresholds were examined and a second wider set of thresholds was selected to reduce potential missed matches and false matches.



Comparison pairs with a match weight between these two thresholds were reviewed manually by one author (CF) following a set of rules agreed by all authors (Table 74). To aid decision-making, any clinical records indicating BSI in the NNRD were checked as evidence that the baby had an infection. When date of birth was in disagreement, the difference between the dates was examined. When postcode prefix or suffix disagreed, the number of letters that matched was recorded (e.g. RG1 and RK1 would be 2, RG1 and NG2 would be 1).

TABLE 74 The rules followed in manual review

Agreement on identifiers <sup>a</sup> (1 = agree, 0 = disagree, x = missing)							
Prefix	Suffix	DOB	Sex	Hospital	Condition		Allocate
Any					BSI links to any baby with a match weight above the upper threshold		Non-link
1	1	1	0	1	BSI does not link to a different baby above the upper threshold		Link
1	0	1	1	1	BSI does not link to a different baby with a higher summed weight		Link
1	0	x	1	1	BSI does not link to a different baby with a higher summed weight and baby has a clinical record of BSI with the same sample date		Link
1	0	x	1	1	BSI does not link to a different baby with a higher summed weight, DOB is recorded in one of the two data sets (missing in other) and age (in data set with complete DOB) is < 28 days		Link
1	1	0	x	1	BSI does not link to a different baby with a higher summed weight and DOB disagrees, but is within 7 days		Link
1	x	0	1	1	BSI does not link to a different baby with a higher summed weight and DOB disagrees, but is same month and year, and age at BSI in surveillance data is < 28 days		Link
x	x	1	1	1	BSI does not link to a different baby with a higher summed weight and age at BSI in surveillance data is < 28 days		Link
x	x	1	1	1	BSI does not link to a different baby with a higher summed weight and age at BSI in surveillance data is ≥ 28 days old		Missing
x	x	1	x	x	Any given BSI does not link to another baby		Missing
x	x	1	x	0	Any given BSI does not link to another baby		Missing
x	x	1	0	x	Any given BSI does not link to another baby		Missing
x	x	1	0	0	Any given BSI does not link to another baby		Missing
x	x	1	0	1	Any given BSI does not link to another baby		Missing
0	x	1	x	0	Any given BSI does not link to another baby		Missing
0	x	1	0	x	Any given BSI does not link to another baby		Missing
0	x	1	1	x	Any given BSI does not link to another baby		Missing
x	x	1	1	x	Any given BSI does not link to another baby		Missing
x	x	1	1	0	Any given BSI does not link to another baby		Missing

DOB, date of birth.

<sup>a</sup> The agreement on identifiers represents how much identifiers agreed for each comparison pair, where 1 indicates agreement on a given identifier, 0 indicates disagreement, and x indicates that the identifier was missing in one or both data sets.

Following probabilistic linkage, we further inspected unlinked records in the NNRD for babies aged < 28 days with a clinical record of BSI in the NNRD, as we believed that these records should link to a BSI. For these babies, we searched the surveillance data for any BSI reported to the corresponding laboratory in the same month and reviewed the potential links. However, few additional links were identified, suggesting under-reporting of BSI to the surveillance system, or reporting from unexpected laboratories.

## Multiple births

We used the same match weights and rules for manual review of records for babies from multiple births as for singletons, but manually reviewed the records separately, as babies born on the same day to the same mother share most of their identifiers. On the few occasions when it was not possible to determine which baby a BSI should match to, we randomly allocated the BSI to one of the babies to avoid duplicates. Multiple births were identified in the NNRD using the foetus number, birth order, date of birth and mother's NHS number.



## Appendix 13 Additional information on generalisability study: clearly pathogenic organisms

BOX 2 List of clearly pathogenic organisms from surveillance data that linked to babies in the NNRD

- *E. coli*.
- *Streptococcus* Group B stem.
- *Candida albicans* (stellatoidea).
- *Staphylococcus aureus*.
- *Enterobacter cloacae*.
- *Enterococcus faecalis*.
- *Candida parapsilosis*.
- *Streptococcus pneumoniae*.
- *Klebsiella pneumoniae*.
- *Pseudomonas aeruginosa*.
- *Serratia marcescens*.
- *Haemophilus influenzae*.
- *Enterobacter* other named.
- *Streptococcus intermedius* group.
- *Enterococcus faecium*.
- Coliform.
- *Candida* other named.
- *Klebsiella oxytoca*.
- *Streptococcus* Group D stem.
- *Candida dubliniensis*.
- *Enterobacter aerogenes*.
- *Acinetobacter baumannii*.
- *Streptococcus* Group A stem.
- *Clostridium butyricum*.
- *Enterococcus* sp.
- *Morganella morganii*.
- *Bacteroides* sp.
- *Listeria monocytogenes*.
- *Citrobacter diversus* (*Citrobacter koseri*).
- *Citrobacter freundii*.
- *Proteus mirabilis*.
- *Gardnerella vaginalis*.
- *Candida* sp.
- *Streptococcus* Group C stem.
- *Candida glabrata*.
- *Klebsiella* sp.
- *Enterobacter amnigenus*.
- *Hansenula* sp.
- *Citrobacter farmeri*.
- *Streptococcus* Group G stem.
- *Cedecea lapagei*.

BOX 2 List of clearly pathogenic organisms from surveillance data that linked to babies in the NNRD (*continued*)

- *Pantoea* sp.
- *Clostridium perfringens*.
- *Candida guilliermondii*.
- *Enterobacter* sp.
- *Enterobacter kobei*.
- *Enterococcus durans*.
- *Streptococcus milleri* group.
- *Candida lusitaniae*.
- *Enterococcus hirae*.
- *Pasteurella* sp.
- *Enterococcus gallinarum*.
- *Serratia odorifera*.
- *Enterobacter cloacae* complex.
- *Citrobacter* other named.
- *Enterobacter gergoviae*.
- *Klebsiella ornitholytica*.
- *Serratia* sp.
- *Enterobacter asburiae*.
- *Enterobacter agglomerans*.
- *Citrobacter* sp.
- *Rhodotorula rubra*.
- *Candida tropicalis*.
- *Klebsiella* other named.
- *Coccidioides* sp.
- *Neisseria meningitidis*.
- *Bacteroides fragilis*.
- *Serratia liquefaciens*.
- *Citrobacter amalonaticus*.
- *Providencia alcalifaciens*.
- *Leclercia adecarboxylata*.
- *Aspergillus* sp.
- *Enterobacter sakazakii*.
- *Kluyvera* sp.
- *Pantoea septica*.
- *Candida fabianii*.
- *Klebsiella aerogenes*.
- *Enterococcus casseliflavus*.
- *Escherichia vulneris*.
- *Listeria* sp.

## BOX 3 List of other organisms from surveillance data that linked to babies in the NNRD

- *Bacillus* sp.
- CoNS.
- *Staphylococcus* other named.
- *Acinetobacter* sp.
- *Staphylococcus* sp.
- *Streptococcus* alpha and non-haemolytic.
- *Pseudomonas paucimobilis*.
- *Actinomyces cardiffensis*.
- *Micrococcus* sp.
- *Diphtheroids*.
- *Phialophora* other named.
- *Brevibacterium* other named.
- *Acinetobacter junii*.
- *Corynebacterium minutissimum*.
- *Streptococcus intermedius* group.
- *Roseomonas mucosa*.
- *Corynebacterium* sp.
- *Bacillus cereus*.
- *Actinomyces odontolyticus*.
- *Acinetobacter* other named.
- *Paenibacillus* sp.
- *Acinetobacter lwoffii*.
- *Corynebacterium striatum*.
- *Micrococcus luteus (sarcina)*.
- *Streptococcus* other named.
- *Microbacterium* sp.
- *Ochrobactrum anthropi*.
- *Pseudomonas fluorescens*.
- *Neisseria* sp.
- *Rothia* sp.
- *Actinomyces* other named.
- *Ruminococcus gnavus*.
- *Lactobacillus paracasei*.
- *Lactobacillus* sp.
- *Staphylococcus vitulinus*.
- *Stenotrophomonas* sp.
- *Comamonas testosteroni*.
- *Aerococcus* sp.
- *Bacillus* other named.
- *Gemella haemolysans*.
- *Neisseria flavescens*.
- *Streptococcus gordonii*.
- *Moraxella* sp.
- *Pseudomonas* sp.
- *Rhizobium radiobacter*.
- *Corynebacterium aurimucosum*.
- *Staphylococcus pettenkoferi*.
- *Actinomyces viscosus*.
- *Brevundimonas* sp.

## BOX 3 List of other organisms from surveillance data that linked to babies in the NNRD (continued)

- *Neisseria sicca*.
- *Roseomonas* sp.
- *Kocuria* sp.
- *Stephanoascus ciferrii*.
- *Microbacterium aurum*.
- *Paracoccus yeeii*.
- *Stomatococcus mucilaginosus*.
- *Propionibacterium freudenreichii*.
- *Acinetobacter calcoaceticus (anitratu)*.
- *Burkholderia cepacia*.
- *Neisseria* other named.
- *Bifidobacterium breve*.
- *Moraxella osloensis*.
- *Lactobacillus* other named.
- *Collinsella aerofaciens*.
- *Parabacteroides distasonis*.
- *Streptococcus* sp.
- *Brevibacterium* sp.
- *Actinomyces naeslundii*.
- *Haemophilus* sp.
- *Corynebacterium pseudodiphtheriticum*.
- *Hansenula* sp.
- *Rothia dentocariosia*.
- *Micrococcus lylae*.
- *Streptococcus vestibularis*.
- *Stenotrophomonas maltophilia*.
- *Chryseobacterium meningosepticum*.
- *Corynebacterium* other named.
- *Brevibacterium casei*.
- *Streptococcus alactolyticus*.
- *Haemophilus parainfluenzae*.
- *Roseomonas gilardii*.
- *Moraxella catarrhalis*.
- *Massilia timonae*.
- *Corynebacterium jeikeium (JK)*.
- *Corynebacterium amycolatum*.
- *Aerococcus viridans*.
- *Arcanobacterium haemolyticum*.
- *Achromobacter xylosoxidans*.
- *Pseudomonas stutzeri*.
- *Leuconostoc* sp.
- *Brevundimonas vesicularis*.
- *Globicatella sanguis*.
- *Granulicatella adiacens*.
- *Aerococcus* other named.
- *Eikenella corrodens*.
- *Haematobacter* sp.
- *Rhodococcus* other named.
- *Abiotrophia defectiva*.

BOX 3 List of other organisms from surveillance data that linked to babies in the NNRD (*continued*)

- *Paracoccus* sp.
- *Acinetobacter johnsonii*.
- *Burkholderia gladioli*.
- *Acinetobacter parvus*.
- *Delftia acidovorans*.
- *Lactococcus lactis*.
- *Kocuria rhizophila*.
- *Streptococcus pseudoporcinus*.
- *Pseudomonas luteola*.
- *Streptococcus infantarius* ssp. nov.
- *Gemella morbillorum*.
- *Micrococcus* other named.
- *Kocuria kristinae*.
- *Pseudomonas* other named.
- *Neisseria subflava*.
- *Neisseria perflava*.
- *Propionibacterium acnes*.
- *Chryseobacterium* sp.
- *Aggregatibacter (haemophilus) segnis*.
- *Pseudomonas oleovorans*.
- *Pseudoclavibacter* sp.





## Appendix 14 Additional information on the generalisability study: changes over time in national infection surveillance

In England, data on BSIs and other infections are collected through a voluntary surveillance system operated by PHE.<sup>140</sup> The current voluntary surveillance system, known as the Second Generation Surveillance System (SGSS), was introduced in 2014 to replace LabBase2, which operated from 2002 to 2014. When LabBase2 ended, data were migrated to SGSS.

In both LabBase2 and SGSS, laboratories are required to provide information on clinically significant BSIs only. PHE do not produce guidance on what is considered clinically significant; therefore, the type of BSI submitted varies by laboratory, depending on decision-making of individual staff or on local procedures. BSIs caused by selected notifiable organisms, for example *Streptococcus pneumoniae*, were on a fast-track list in LabBase2 and automatically sent to PHE, but BSIs caused by all other organisms required authorisation. In contrast, in SGSS, data on all BSIs are automatically uploaded unless a laboratory requests the ability to manually review a BSI caused by a given organism. It is reported anecdotally that many laboratories upload data on all BSIs to SGSS without any review of clinical significance, to reduce burden on staff. This has resulted in SGSS capturing data on BSIs that would not have been reported to LabBase2, such as positive cultures of skin organisms that have uncertain clinical significance, for example CoNS.

To understand how case ascertainment changed following the system change, we examined the total number of BSIs in the surveillance data over time for all BSIs, for BSIs caused by skin organisms and for BSIs caused by potential pathogens. We used interrupted time series Poisson regression of monthly BSI rates for all BSIs, BSIs caused by skin organisms and BSIs caused by potential pathogens for infants aged < 1 year to quantify the change in the number of BSIs reported to the infection surveillance system.<sup>141</sup> SGSS was first implemented in March 2014 and adoption of SGSS was gradual, owing to the large number of laboratories and their different operating systems; therefore, we examined the time before introduction (January 2010 to March 2014) and after most laboratories were reporting to SGSS (December 2015 to July 2017).

The equation used for interrupted time series regression is given in *Equation 5*, the interrupted time series Poisson model, where  $Y_t$  represents the number of BSIs at time  $t$ ,  $T$  represents the months since January 2001,  $X_t$  represents a dummy variable for either pre (0) or post (1) the introduction of SGSS.  $\beta_0$  represents the baseline level in January 2010,  $\beta_1$  is the pre-system change trend,  $\beta_2$  is the step change following the introduction of the new system and  $\beta_3$  is the trend change following the introduction of SGSS:

$$Y_t = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 T X_t \quad (5)$$

Following the introduction of SGSS, there was an increase in the number of infections reported. The largest increase was seen in BSIs caused by skin organisms, which almost doubled [incidence rate ratio (IRR) 1.96, 95% CI 1.78 to 2.15]. The number of BSIs caused by all organisms increased by 47% (IRR 1.47, 95% CI 1.39 to 1.56) and potential pathogens increased by 20% (IRR 1.20, 95% CI 1.11 to 1.30) (*Table 75*). The number of BSIs reported to the infection surveillance system was decreasing by 4% for BSIs caused by potential pathogens before the introduction of SGSS (IRR 0.96, 95% CI 0.95 to 0.98), and the decline continued after the introduction of SGSS (IRR 0.89, 95% CI 0.85 to 0.94). However, the number of BSIs reported to the infection surveillance system was stable for BSIs caused by skin organisms before and after the system change.

TABLE 75 The trend pre and post system change and step change in number of BSIs reported from the interrupted time series regression of all BSIs, skin organism BSIs only and excluding skin organism BSIs

Component of time series	Monthly rate ratio (95% CI)		
	Skin organisms	Potential pathogens	All BSIs
Trend pre system change per year	0.98 (0.96 to 1.00)	0.96 (0.95 to 0.98)	0.97 (0.96 to 0.98)
Step change in number of BSIs reported	1.96 (1.78 to 2.15)	1.20 (1.11 to 1.30)	1.47 (1.39 to 1.56)
Trend post system change per year	1.04 (0.99 to 1.10)	0.89 (0.85 to 0.94)	0.97 (0.94 to 1.01)

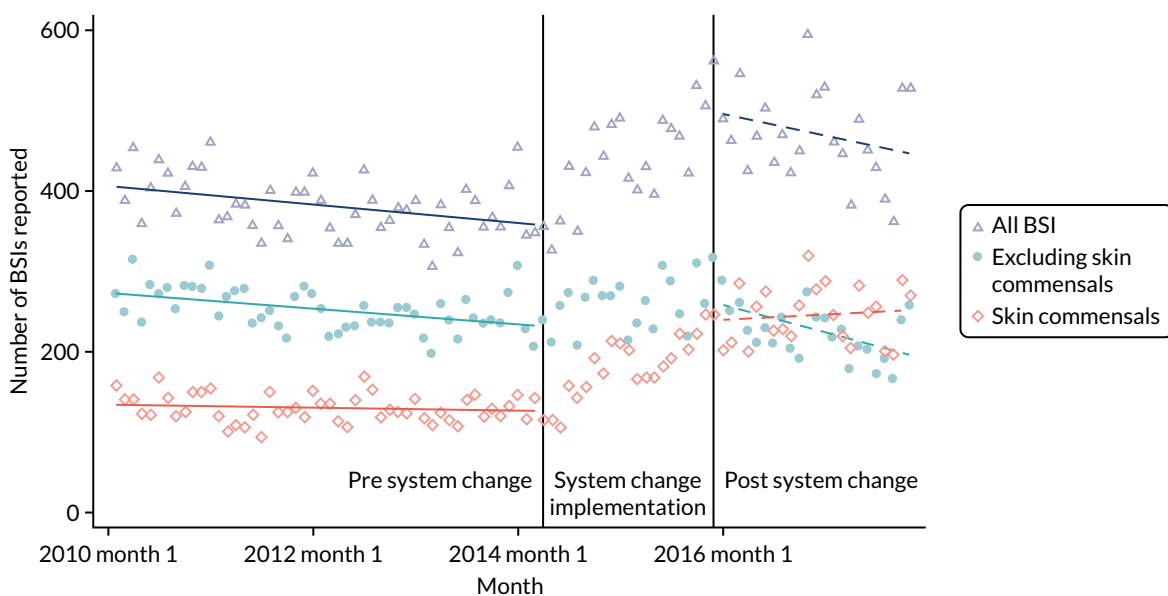


FIGURE 25 Interrupted time series for the number of BSI episodes reported to the PHE surveillance system over time for infants aged < 1 year, excluding CoNS (aqua) and only CoNS (coral).

## Appendix 15 Additional information on the generalisability study: comparison of included and excluded PREVENTing infection using Antimicrobial-Impregnated Long lines trial babies

TABLE 76 Distribution of baseline risk factors in babies with S-PICCs in the PREVAIL trial who were included in the analysis compared with those who were excluded

Risk factors	Babies in the PREVAIL trial		p-value from chi-squared test
	Included in full analysis	Excluded from full analyses	
Total babies (n)	269	154	
Gestational age (weeks), n (%)			
< 26	59 (22)	38 (25)	0.882
26–28	75 (28)	36 (24)	
28–32	114 (42)	67 (44)	
32–37	15 (6)	9 (6)	
≥ 37	6 (2)	4 (3)	
Small for gestational age, n (%)	49 (18)	25 (16)	0.606
Male sex, n (%)	141 (52)	80 (52)	0.926
Babies in NICU that provides surgery, n (%)	144 (54)	48 (31)	< 0.001



## **Appendix 16** Additional information on the generalisability study: model-building for rate per 1000 peripherally inserted central venous catheter days

TABLE 77 The IRRs and 95% CIs for risk factors from forward stepwise multilevel Poisson regression of BSI per 1000 PICC days

	Model, IRR (95% CI)						
	1	2	3	4	5	6	7 <sup>a</sup>
Group							
PREVAIL babies	1.00	1.00	1.00	1.00	1.00	1.00	1.00
NP babies in PREVAIL NICUs	1.29 (0.66 to 2.54)	1.55 (0.78 to 3.06)	1.60 (0.81 to 3.17)	1.60 (0.81 to 3.17)	1.59 (0.80 to 3.16)	1.58 (0.80 to 3.14)	1.53 (0.77 to 3.03)
NP NICUs	1.14 (0.57 to 2.26)	1.16 (0.58 to 2.31)	1.20 (0.59 to 2.41)	1.20 (0.60 to 2.42)	1.20 (0.60 to 2.42)	1.20 (0.60 to 2.43)	1.18 (0.59 to 2.37)
LNUs	0.58 (0.27 to 1.24)	0.87 (0.40 to 1.89)	0.93 (0.42 to 2.03)	0.93 (0.43 to 2.04)	0.96 (0.42 to 2.15)	1.42 (0.64 to 3.17)	1.43 (0.64 to 3.20)
NNU variance	0.13 (0.04 to 0.40)	0.13 (0.04 to 0.40)	0.15 (0.06 to 0.43)	0.15 (0.05 to 0.43)	0.82 (0.50 to 1.34)	0.15 (0.05 to 0.45)	0.14 (0.05 to 0.42)
Gestational age (weeks)							
< 26		1.00	1.00	1.00	1.00	1.00	1.00
26–28		0.52 (0.37 to 0.74) <sup>b</sup>	0.53 (0.38 to 0.75) <sup>b</sup>	0.53 (0.38 to 0.75) <sup>b</sup>	0.53 (0.38 to 0.75) <sup>b</sup>	0.62 (0.43 to 0.88) <sup>b</sup>	0.66 (0.46 to 0.94) <sup>b</sup>
28–32		0.40 (0.28 to 0.55) <sup>b</sup>	0.42 (0.30 to 0.58) <sup>b</sup>	0.41 (0.30 to 0.58) <sup>b</sup>	0.42 (0.30 to 0.58) <sup>b</sup>	0.64 (0.44 to 0.93) <sup>b</sup>	0.63 (0.42 to 0.94) <sup>b</sup>
32–37		0.27 (0.17 to 0.43) <sup>b</sup>	0.28 (0.17 to 0.45) <sup>b</sup>	0.28 (0.17 to 0.45) <sup>b</sup>	0.28 (0.17 to 0.45) <sup>b</sup>	0.45 (0.27 to 0.75) <sup>b</sup>	0.36 (0.21 to 0.62) <sup>b</sup>
≥ 37		0.32 (0.18 to 0.56) <sup>b</sup>	0.33 (0.18 to 0.58) <sup>b</sup>	0.32 (0.18 to 0.58) <sup>b</sup>	0.32 (0.18 to 0.57) <sup>b</sup>	0.52 (0.29 to 0.95) <sup>b</sup>	0.40 (0.21 to 0.74) <sup>b</sup>
Age (months) at first PICC insertion							
0			1.00	1.00	1.00	1.00	1.00
1–2			0.50 (0.31 to 0.79) <sup>b</sup>	0.50 (0.31 to 0.79) <sup>b</sup>	0.50 (0.31 to 0.79) <sup>b</sup>	0.49 (0.31 to 0.78) <sup>b</sup>	0.49 (0.31 to 0.79) <sup>b</sup>
3–5			0.62 (0.40 to 0.96) <sup>b</sup>	0.62 (0.40 to 0.96) <sup>b</sup>	0.62 (0.40 to 0.96) <sup>b</sup>	0.59 (0.38 to 0.92) <sup>b</sup>	0.60 (0.39 to 0.94) <sup>b</sup>
6–8			0.81 (0.50 to 1.33)	0.82 (0.50 to 1.34)	0.82 (0.50 to 1.34)	0.74 (0.45 to 1.21)	0.72 (0.44 to 1.19)
9–11			0.85 (0.44 to 1.64)	0.85 (0.44 to 1.66)	0.85 (0.44 to 1.65)	0.74 (0.38 to 1.44)	0.73 (0.37 to 1.41)
12–29			0.75 (0.43 to 1.30)	0.75 (0.43 to 1.30)	0.75 (0.43 to 1.30)	0.66 (0.38 to 1.15)	0.65 (0.38 to 1.14)
≥ 30			0.91 (0.54 to 1.55)	0.91 (0.53 to 1.55)	0.91 (0.53 to 1.55)	0.92 (0.54 to 1.57)	0.90 (0.53 to 1.54)

Model, IRR (95% CI)							
	1	2	3	4	5	6	7 <sup>a</sup>
Small for gestational age				1.03 (0.73 to 1.45)			
Surgery					1.05 (0.72 to 1.54)		
Days of invasive ventilation							
0						1.00	1.00
1						0.79 (0.34 to 1.88)	0.89 (0.38 to 2.12)
2-4						1.68 (0.95 to 2.98)	1.88 (1.05 to 3.34) <sup>b</sup>
5-6						2.58 (1.35 to 4.94) <sup>b</sup>	3.07 (1.59 to 5.93) <sup>b</sup>
7-8						4.82 (2.57 to 9.02) <sup>b</sup>	5.64 (2.99 to 10.65) <sup>b</sup>
9-12						2.86 (1.51 to 5.41) <sup>b</sup>	3.54 (1.85 to 6.76) <sup>b</sup>
13-21						4.23 (2.38 to 7.52) <sup>b</sup>	5.11 (2.85 to 9.18) <sup>b</sup>
≥ 22						3.06 (1.72 to 5.47) <sup>b</sup>	3.73 (2.07 to 6.74) <sup>b</sup>
Days of non-invasive ventilation							
0							1.00
1							0.47 (0.21 to 1.05)
2-5							0.63 (0.39 to 1.03)
6-9							0.96 (0.59 to 1.54)
10-15							0.52 (0.30 to 0.90) <sup>b</sup>
16-49							0.48 (0.33 to 0.72) <sup>b</sup>
≥ 50							0.46 (0.29 to 0.71) <sup>b</sup>

NP, non-PREVAIL.

a Selected model.

b Significant (CIs do not cross 0).





## **Appendix 17** Additional information on the generalisability study: model-building for trend per 1000 peripherally inserted central venous catheter days

TABLE 78 The IRRs and 95% CIs for risk factors from forward stepwise multilevel Poisson regression of BSI (pathogens) per 1000 PICC days per month

	Model, IRR (95% CI)						
	1	2	3	4	5	6	7 <sup>a</sup>
Trend							
PREVAIL NICUs	1.002 (0.998 to 1.006)	1.002 (0.999 to 1.006)	1.002 (0.999 to 1.006)	1.002 (0.999 to 1.006)	1.002 (0.999 to 1.006)	1.002 (0.999 to 1.006)	1.002 (0.999 to 1.006)
Non-PREVAIL NICUs	1.002 (0.999 to 1.005)	1.002 (0.999 to 1.005)	1.002 (0.999 to 1.005)	1.002 (0.999 to 1.005)	1.002 (0.999 to 1.005)	1.002 (0.999 to 1.005)	1.002 (0.999 to 1.005)
LNUs	0.996 (0.990 to 1.001)	0.996 (0.991 to 1.002)	0.996 (0.991 to 1.002)	0.997 (0.991 to 1.002)	0.996 (0.991 to 1.002)	0.998 (0.993 to 1.003)	0.998 (0.993 to 1.004)
Group							
PREVAIL NICUs	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Non-PREVAIL NICUs	1.05 (0.05 to 20.85)	1.15 (0.06 to 22.87)	1.14 (0.06 to 22.67)	1.26 (0.06 to 25.03)	1.15 (0.06 to 22.89)	1.02 (0.05 to 20.49)	0.94 (0.05 to 18.89)
LNUs	35.92 (0.55 to 2 to 348.57)	34.63 (0.53 to 2 to 273.80)	36.55 (0.55 to 2 to 409.53)	34.60 (0.53 to 2 to 264.16)	34.31 (0.52 to 2 to 256.43)	16.57 (0.25 to 1 to 100.00)	15.40 (0.23 to 1 to 023.51)
NNU variance	0.24 (0.14 to 0.39)	0.21 (0.12 to 0.34)	0.21 (0.13 to 0.34)	0.19 (0.11 to 0.31)	0.21 (0.12 to 0.34)	0.21 (0.13 to 0.35)	0.22 (0.13 to 0.36)
Gestational age (weeks)							
< 26		1.00	1.00	1.00	1.00	1.00	1.00
26–28		0.54 (0.47 to 0.63) <sup>b</sup>	0.55 (0.48 to 0.64) <sup>b</sup>	0.54 (0.47 to 0.62) <sup>b</sup>	0.54 (0.47 to 0.63) <sup>b</sup>	0.63 (0.54 to 0.73) <sup>b</sup>	0.66 (0.56 to 0.76) <sup>b</sup>
28–32		0.40 (0.35 to 0.46) <sup>b</sup>	0.42 (0.36 to 0.48) <sup>b</sup>	0.40 (0.35 to 0.46) <sup>b</sup>	0.40 (0.35 to 0.46) <sup>b</sup>	0.59 (0.51 to 0.70) <sup>b</sup>	0.58 (0.49 to 0.68) <sup>b</sup>
32–37		0.32 (0.27 to 0.39) <sup>b</sup>	0.33 (0.28 to 0.40) <sup>b</sup>	0.32 (0.26 to 0.38) <sup>b</sup>	0.32 (0.27 to 0.39) <sup>b</sup>	0.52 (0.42 to 0.64) <sup>b</sup>	0.44 (0.36 to 0.55) <sup>b</sup>
≥ 37		0.26 (0.20 to 0.33) <sup>b</sup>	0.26 (0.20 to 0.34) <sup>b</sup>	0.25 (0.20 to 0.33) <sup>b</sup>	0.26 (0.20 to 0.33) <sup>b</sup>	0.39 (0.30 to 0.51) <sup>b</sup>	0.32 (0.24 to 0.42) <sup>b</sup>

	Model, IRR (95% CI)						
	1	2	3	4	5	6	7 <sup>a</sup>
Age (months) at first PICC insertion							
0			1.00				
1-2			0.88 (0.71 to 1.10)				
3-5			0.91 (0.73 to 1.14)				
6-8			1.11 (0.88 to 1.39)				
9-11			1.16 (0.87 to 1.54)				
12-29			0.98 (0.74 to 1.28)				
≥ 30			0.93 (0.71 to 1.22)				
Small for gestational age				1.10 (0.96 to 1.26)			
Surgery					0.98 (0.72 to 1.32)		
Days of invasive ventilation							
0						1.00	1.00
1						1.15 (0.86 to 1.53)	1.22 (0.91 to 1.63)
2-4						1.50 (1.20 to 1.87) <sup>b</sup>	1.60 (1.28 to 2.00) <sup>b</sup>
5-6						2.27 (1.75 to 2.93) <sup>b</sup>	2.46 (1.90 to 3.20) <sup>b</sup>
7-8						2.62 (1.99 to 3.44) <sup>b</sup>	2.89 (2.19 to 3.80) <sup>b</sup>
9-12						3.02 (2.37 to 3.85) <sup>b</sup>	3.32 (2.60 to 4.25) <sup>b</sup>
13-21						2.74 (2.16 to 3.48) <sup>b</sup>	3.03 (2.38 to 3.86) <sup>b</sup>
≥ 22						2.73 (2.17 to 3.43) <sup>b</sup>	3.08 (2.44 to 3.89) <sup>b</sup>
Days of non-invasive ventilation							
0							1.00
1							0.85 (0.65 to 1.11)
2-5							0.86 (0.71 to 1.06)
6-9							0.79 (0.63 to 0.99) <sup>b</sup>
10-15							0.78 (0.63 to 0.97) <sup>b</sup>
16-49							0.68 (0.57 to 0.80) <sup>b</sup>
≥ 50							0.61 (0.49 to 0.74) <sup>b</sup>

a Selected model.

b Significant (CIs do not cross 0).



## **Appendix 18** Additional information on the generalisability study: model-building for trend per 1000 days

**TABLE 79** The IRRs and 95% CIs for risk factors from forward stepwise multilevel Poisson regression of the rate of BSI (pathogens) per 1000 days of intensive and high-dependency care per month

	Model, IRR (95% CI)						
	1	2	3	4	5	6	7 <sup>a</sup>
Trend							
PREVAIL NICUs	0.998 (0.996 to 1.001)	0.998 (0.996 to 1.000)	0.998 (0.996 to 1.000)	0.998 (0.996 to 1.000)	0.998 (0.996 to 1.001)	0.999 (0.997 to 1.001)	0.999 (0.997 to 1.001)
Non-PREVAIL NICUs	1.001 (1.000 to 1.003)	1.001 (0.999 to 1.003)	1.001 (0.999 to 1.003)	1.001 (0.999 to 1.003)	1.001 (0.999 to 1.003)	1.002 (1.000 to 1.003)	1.002 (1.000 to 1.004)
LNUs	0.996 (0.994 to 0.999) <sup>b</sup>	0.996 (0.994 to 0.999) <sup>b</sup>	0.996 (0.994 to 0.999) <sup>b</sup>	0.996 (0.994 to 0.999) <sup>b</sup>	0.997 (0.994 to 0.999) <sup>b</sup>	0.998 (0.995 to < 1.000) <sup>b</sup>	0.998 (0.995 to < 1.000) <sup>b</sup>
Group							
PREVAIL NICUs	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Non-PREVAIL NICUs	0.13 (0.02 to 0.88)	0.12 (0.02 to 0.79)	0.14 (0.02 to 0.94)	0.14 (0.02 to 0.94)	0.14 (0.02 to 0.92)	0.15 (0.02 to 1.03)	0.13 (0.02 to 0.87)
LNUs	3.70 (0.43 to 31.65)	3.83 (0.45 to 32.78)	3.84 (0.45 to 32.79)	3.78 (0.44 to 32.31)	2.90 (0.34 to 24.83)	2.86 (0.33 to 24.48)	2.84 (0.33 to 24.36)
NNU variance	0.13 (0.09 to 0.19)	0.13 (0.09 to 0.19)	0.11 (0.07 to 0.16)	0.11 (0.07 to 0.16)	0.10 (0.07 to 0.16)	0.11 (0.07 to 0.16)	0.13 (0.09 to 0.19)
Gestational age (weeks)							
< 26		1.00	1.00	1.00	1.00	1.00	1.00
26–28		0.66 (0.60 to 0.72) <sup>b</sup>	0.66 (0.60 to 0.73) <sup>b</sup>	0.66 (0.60 to 0.73) <sup>b</sup>	0.68 (0.62 to 0.75) <sup>b</sup>	0.73 (0.66 to 0.81) <sup>b</sup>	0.73 (0.66 to 0.80) <sup>b</sup>
28–32		0.61 (0.56 to 0.67) <sup>b</sup>	0.62 (0.56 to 0.68) <sup>b</sup>	0.62 (0.56 to 0.68) <sup>b</sup>	0.68 (0.62 to 0.76) <sup>b</sup>	0.58 (0.52 to 0.64) <sup>b</sup>	0.58 (0.52 to 0.64) <sup>b</sup>
32–37		0.65 (0.59 to 0.72) <sup>b</sup>	0.66 (0.59 to 0.73) <sup>b</sup>	0.66 (0.60 to 0.73) <sup>b</sup>	0.78 (0.70 to 0.88) <sup>b</sup>	0.48 (0.43 to 0.55) <sup>b</sup>	0.48 (0.42 to 0.54) <sup>b</sup>
≥ 37		1.00 (0.91 to 1.10)	1.00 (0.91 to 1.10)	1.00 (0.91 to 1.10)	1.16 (1.04 to 1.29)	0.65 (0.58 to 0.74) <sup>b</sup>	0.65 (0.58 to 0.73) <sup>b</sup>
Small for gestational age			0.91 (0.83 to 0.99) <sup>b</sup>	0.91 (0.83 to 0.99) <sup>b</sup>	0.91 (0.83 to 0.99) <sup>b</sup>	0.93 (0.85 to 1.02)	
Surgery							
				0.97 (0.78 to 1.19)			
Days of invasive ventilation							
0					1.00	1.00	1.00
1					1.28 (1.12 to 1.45) <sup>b</sup>	1.37 (1.20 to 1.55) <sup>b</sup>	1.37 (1.21 to 1.56) <sup>b</sup>
2–4					1.36 (1.22 to 1.50) <sup>b</sup>	1.47 (1.33 to 1.63) <sup>b</sup>	1.48 (1.33 to 1.64) <sup>b</sup>
5–6					1.51 (1.32 to 1.74) <sup>b</sup>	1.71 (1.49 to 1.97) <sup>b</sup>	1.72 (1.49 to 1.97) <sup>b</sup>
7–8					1.81 (1.56 to 2.11) <sup>b</sup>	2.11 (1.82 to 2.46) <sup>b</sup>	2.11 (1.82 to 2.46) <sup>b</sup>
9–12					1.73 (1.51 to 1.99) <sup>b</sup>	2.05 (1.78 to 2.36) <sup>b</sup>	2.06 (1.79 to 2.36) <sup>b</sup>
13–21					1.68 (1.47 to 1.92) <sup>b</sup>	2.04 (1.78 to 2.33) <sup>b</sup>	2.04 (1.78 to 2.33) <sup>b</sup>
≥ 22					1.56 (1.38 to 1.75) <sup>b</sup>	1.96 (1.74 to 2.21) <sup>b</sup>	1.96 (1.73 to 2.21) <sup>b</sup>

	Model, IRR (95% CI)						
	1	2	3	4	5	6	7 <sup>a</sup>
Days of non-invasive ventilation							
0						1.00	1.00
1						1.05 (0.93 to 1.20)	1.06 (0.93 to 1.20)
2-5						0.78 (0.70 to 0.86) <sup>b</sup>	0.78 (0.70 to 0.86) <sup>b</sup>
6-9						0.64 (0.56 to 0.73) <sup>b</sup>	0.64 (0.56 to 0.73) <sup>b</sup>
10-15						0.58 (0.50 to 0.66) <sup>b</sup>	0.58 (0.51 to 0.67) <sup>b</sup>
16-49						0.40 (0.36 to 0.45) <sup>b</sup>	0.40 (0.36 to 0.45) <sup>b</sup>
≥ 50						0.28 (0.25 to 0.32) <sup>b</sup>	0.28 (0.25 to 0.32) <sup>b</sup>
a	Selected model.						
b	Significant (CIs do not cross 0).						





## **Appendix 19** Additional information on the generalisability study: model-building for rate per 100 admissions

TABLE 80 The IRRs and 95% CIs for risk factors from forward stepwise multilevel Poisson regression of the rate of total late-onset BSIs (pathogens) per 100 admissions per month

	Model, IRR (95% CI)					
	1	2	3	4	5	6 <sup>a</sup>
Trend						
PREVAIL NICUs	0.996 (0.994 to 0.998) <sup>b</sup>	0.997 (0.995 to 0.999) <sup>b</sup>	0.997 (0.995 to 0.999) <sup>b</sup>	0.998 (0.995 to < 1.000) <sup>b</sup>	0.998 (0.995 to < 1.000) <sup>b</sup>	0.998 (0.995 to < 1.000) <sup>b</sup>
Non-PREVAIL NICUs	0.999 (0.998 to 1.001)	1.001 (0.999 to 1.003)	1.001 (0.999 to 1.003)	1.001 (0.999 to 1.003)	1.001 (0.999 to 1.003)	1.001 (0.999 to 1.003)
LNUs	0.994 (0.991 to 0.996) <sup>b</sup>	0.995 (0.993 to 0.998) <sup>b</sup>	0.995 (0.993 to 0.998)	0.997 (0.995 to < 1.000) <sup>b</sup>	0.997 (0.995 to < 1.000) <sup>b</sup>	0.997 (0.995 to < 1.000) <sup>b</sup>
Group						
PREVAIL NICUs	1.00	1.00	1.00	1.00	1.00	1.00
Non-PREVAIL NICUs	0.09 (0.01 to 0.62)	0.08 (0.01 to 0.55)	0.09 (0.01 to 0.67)	0.10 (0.01 to 0.73)	0.08 (0.01 to 0.61)	0.09 (0.01 to 0.62)
LNUs	1.92 (0.21 to 17.75)	1.90 (0.20 to 17.66)	2.08 (0.22 to 19.28)	1.39 (0.15 to 12.80)	1.38 (0.15 to 12.74)	1.39 (0.15 to 12.83)
NNU variance	0.16 (0.11 to 0.23)	0.15 (0.10 to 0.22)	0.12 (0.08 to 0.17)	0.10 (0.07 to 0.15)	0.13 (0.09 to 0.19)	0.13 (0.08 to 0.19)
Gestational age (weeks)						
< 26		1.00	1.00	1.00	1.00	1.00
26–28		0.58 (0.53 to 0.64) <sup>b</sup>	0.58 (0.53 to 0.64) <sup>b</sup>	0.83 (0.75 to 0.92) <sup>b</sup>	0.83 (0.75 to 0.92) <sup>b</sup>	0.79 (0.71 to 0.87) <sup>b</sup>
28–32		0.28 (0.25 to 0.31) <sup>b</sup>	0.28 (0.25 to 0.31) <sup>b</sup>	0.63 (0.57 to 0.70) <sup>b</sup>	0.63 (0.57 to 0.70) <sup>b</sup>	0.66 (0.60 to 0.74) <sup>b</sup>
32–37		0.12 (0.11 to 0.13) <sup>b</sup>	0.12 (0.11 to 0.13) <sup>b</sup>	0.36 (0.31 to 0.40) <sup>b</sup>	0.36 (0.32 to 0.40) <sup>b</sup>	0.42 (0.37 to 0.48) <sup>b</sup>
≥ 37		0.15 (0.14 to 0.17) <sup>b</sup>	0.15 (0.14 to 0.17) <sup>b</sup>	0.42 (0.37 to 0.47) <sup>b</sup>	0.42 (0.37 to 0.47) <sup>b</sup>	0.49 (0.43 to 0.55) <sup>b</sup>
Small for gestational age			1.19 (1.08 to 1.31) <sup>b</sup>	1.07 (0.97 to 1.18)		
Surgery			1.20 (0.96 to 1.49)			
Days of invasive ventilation						
0				1.00	1.00	1.00
1				1.58 (1.39 to 1.80) <sup>b</sup>	1.58 (1.39 to 1.80) <sup>b</sup>	1.54 (1.35 to 1.76) <sup>b</sup>
2–4				2.26 (2.03 to 2.51) <sup>b</sup>	2.26 (2.03 to 2.51) <sup>b</sup>	2.17 (1.95 to 2.41) <sup>b</sup>
5–6				3.75 (3.25 to 4.33) <sup>b</sup>	3.75 (3.25 to 4.32) <sup>b</sup>	3.50 (3.03 to 4.05) <sup>b</sup>
7–8				5.03 (4.29 to 5.91) <sup>b</sup>	5.04 (4.29 to 5.92) <sup>b</sup>	4.64 (3.95 to 5.45) <sup>b</sup>
9–12				5.82 (5.02 to 6.74) <sup>b</sup>	5.83 (5.03 to 6.76) <sup>b</sup>	5.28 (4.55 to 6.13) <sup>b</sup>
13–21				6.67 (5.79 to 7.69) <sup>b</sup>	6.69 (5.80 to 7.71) <sup>b</sup>	5.96 (5.16 to 6.89) <sup>b</sup>
≥ 22				9.49 (8.34 to 10.80) <sup>b</sup>	9.55 (8.40 to 10.86) <sup>b</sup>	8.26 (7.22 to 9.44) <sup>b</sup>

Model, IRR (95% CI)						
	1	2	3	4	5	6 <sup>a</sup>
Days of non-invasive ventilation						
0						1.00
1						0.90 (0.79 to 1.03)
2-5						0.88 (0.79 to 0.98)
6-9						1.06 (0.92 to 1.22)
10-15						1.25 (1.09 to 1.45) <sup>b</sup>
16-49						1.39 (1.25 to 1.54) <sup>b</sup>
≥ 50						1.44 (1.25 to 1.65) <sup>b</sup>

a Selected model.

b Significant (CIs do not cross 1.00).



## Appendix 20 Additional information on the generalisability study: bloodstream infection definitions

TABLE 81 Definitions of BSI used in this study

BSI term	Definition
1. BSI during PICC days at risk	BSI that occurs from 1 day after PICC insertion to 2 days after PICC removal
2. Early-onset BSI	BSI that occurs in babies aged < 2 days (excluding BSI during PICC days at risk)
3. Late-onset BSI (no PICC)	BSI that occurs from 2 days of age to 2 days after discharge (excluding BSI during PICC days at risk)
4. Total late-onset BSI	BSI that occurs during PICC days at risk plus BSIs that are late onset (no PICC)
5. Total BSI	All BSI that meet any of the criteria for terms 1–3 <sup>a</sup>

a Terms 1–3 are mutually exclusive, whereby if a BSI occurs during PICC days at risk, it cannot be early onset (no PICC) or late onset (no PICC).



## Appendix 21 Additional information on the generalisability study: flow diagram of included PREVAIL babies

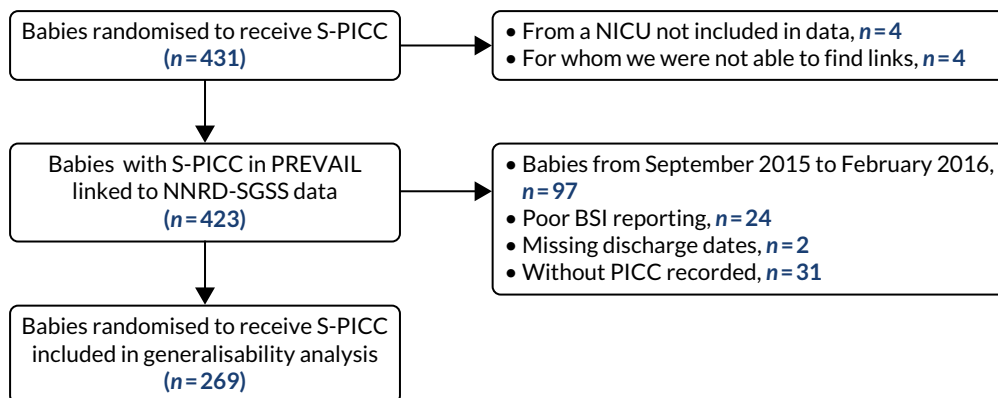


FIGURE 26 Flow diagram to show babies randomised to receive S-PICCs in PREVAIL who were linked to the NNRD and included in the generalisability analysis.





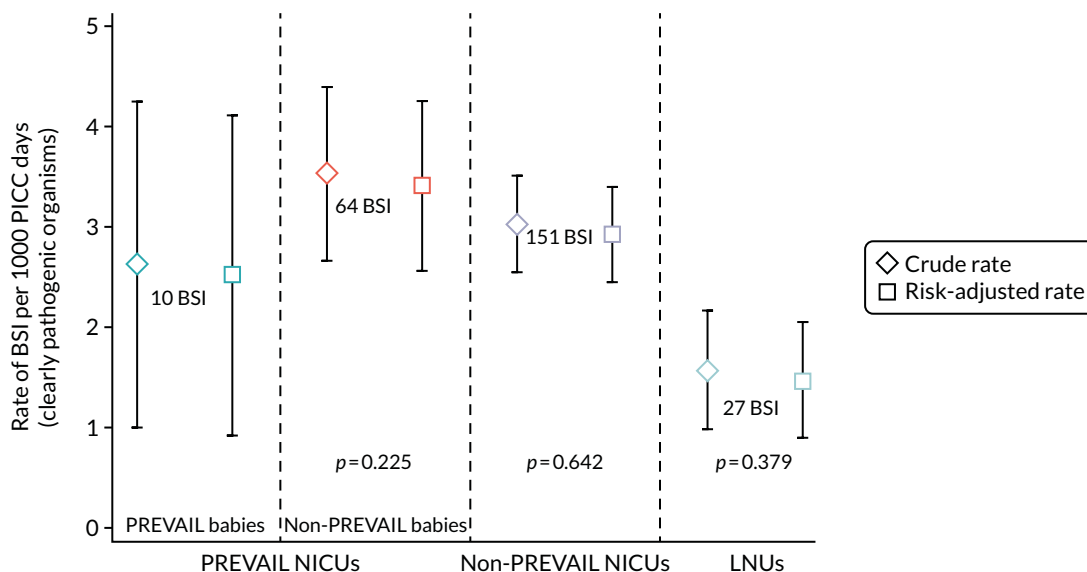
## Appendix 22 Additional information on the generalisability study: causative organisms

TABLE 82 The distribution of causative organisms of the first BSI during PICC days at risk per admission in the PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs during the PREVAIL trial period (August 2015–January 2017)

Organism	PREVAIL NICUs (n = 44)	Non-PREVAIL NICUs (n = 28)	LNUs (n = 68)
Number of babies	5433	3754	2381
Number of admissions	5958	4061	2485
Number of admissions with a BSI	189	338	92
Clearly pathogenic organisms, n (%)			
<i>E. coli</i>	22 (8)	62 (11)	10 (5)
Group B streptococci	8 (3)	20 (4)	11 (5)
Other Gram negative	29 (11)	55 (10)	21 (10)
Other Gram positive	17 (6)	19 (4)	9 (4)
<i>Staphylococcus aureus</i>	20 (8)	45 (8)	14 (7)
Other organisms, n (%)			
CoNS	151 (57)	322 (58)	135 (64)
Other	17 (7)	20 (4)	11 (5)
p-value from chi-squared test comparing with PREVAIL NICUs		0.593	0.238
<b>Note</b> Fungi were excluded from the table as a result of small cell counts.			



## Appendix 23 Additional information on the generalisability study: rates of bloodstream infection per 1000 peripherally inserted central venous catheter days



**FIGURE 27** Crude and risk-adjusted rates of BSI (pathogens) per 1000 PICC days in babies who received S-PICCs in NICUs and LNUs according to enrolment in the PREVAIL trial during the PREVAIL trial period (August 2015 to January 2017). Adjusted for gestational age at birth, age at first PICC and days of invasive and non-invasive ventilation. *p*-value for effect of group (PREVAIL babies in NICU, babies in non-PREVAIL trial NICUs, babies in LNUs) on BSI rate in comparison to babies in the PREVAIL trial. Period for NICUs that participated in the PREVAIL trial depends on NICU start and end date of recruitment; period for other NICUs and LNUs is August 2015 to January 2017 (whole PREVAIL trial recruitment period).

TABLE 83 Crude and risk-adjusted rates of BSI per 1000 PICC days for babies in PREVAIL trial NICUs, non-PREVAIL trial NICUs and LNUs during the PREVAIL trial period (August 2015 to January 2017)

BSI per 1000 PICC days	NICUs (n = 16) participating in PREVAIL <sup>a</sup>		NICUs (n = 27) and LNUs (n = 67) not participating in PREVAIL	
	Admissions in PREVAIL	Admissions not in PREVAIL	Admissions to NICU <sup>b</sup>	Admissions to LNU <sup>b</sup>
Babies (n)	269	1608	3745	2358
Admissions (n)	325	1522	4051	2460
PICC days (n)	3809	18,115	49,902	17,187
All BSIs				
Number of BSIs	31	185	379	96
Crude BSI rate (95% CI)	8.1 (5.3 to 11.0)	10.2 (8.7 to 11.7)	7.6 (6.8 to 8.4)	5.6 (4.5 to 6.9)
Adjusted BSI rate <sup>b</sup> (95% CI)	7.8 (5.0 to 10.6)	9.9 (8.5 to 11.4)	7.4 (6.6 to 8.1)	5.0 (3.9 to 6.0)
<i>p</i> -value <sup>c</sup>				
BSI due to clearly pathogenic organisms				
Number of BSI	10	64	151	27
Crude BSI rate (95% CI)	3.2 (1.4 to 4.9)	3.3 (2.5 to 4.1)	3.2 (2.7 to 3.7)	1.5 (0.9 to 2.1)
Adjusted BSI rate <sup>b</sup> (95% CI)	2.5 (0.9 to 4.1)	3.4 (2.6 to 4.3)	2.9 (2.4 to 3.4)	1.5 (0.9 to 2.0)
<i>p</i> -value <sup>c</sup>		0.225	0.642	0.379

a Admissions to PREVAIL trial NICUs are restricted to NICU-specific trial recruitment period, whereas admissions to other NICUs and LNUs include the whole recruitment period (August 2015 to January 2017).  
b Adjusted for gestational age at birth, age at first PICC and days of invasive and non-invasive ventilation.  
c *p*-value comparing difference in rate compared with PREVAIL babies.

## Appendix 24 Additional information on the generalisability study: trends in bloodstream infection risk factors

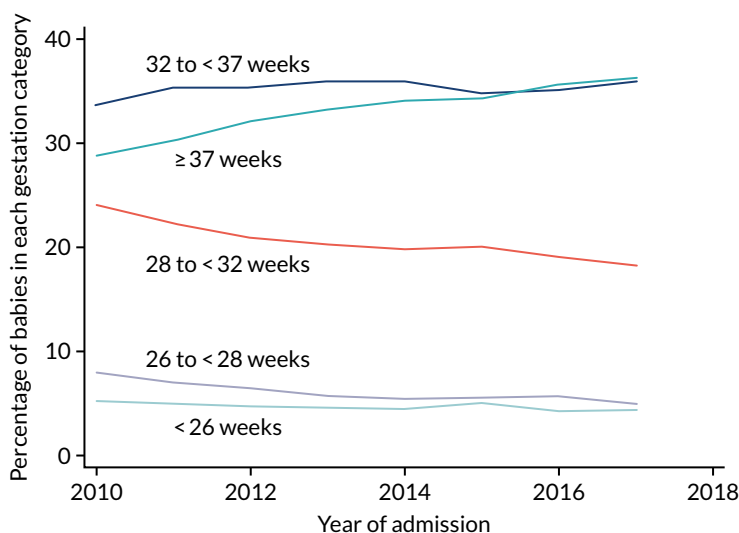


FIGURE 28 The percentage of babies admitted to NICUs and LNUs according to gestational age and by year.

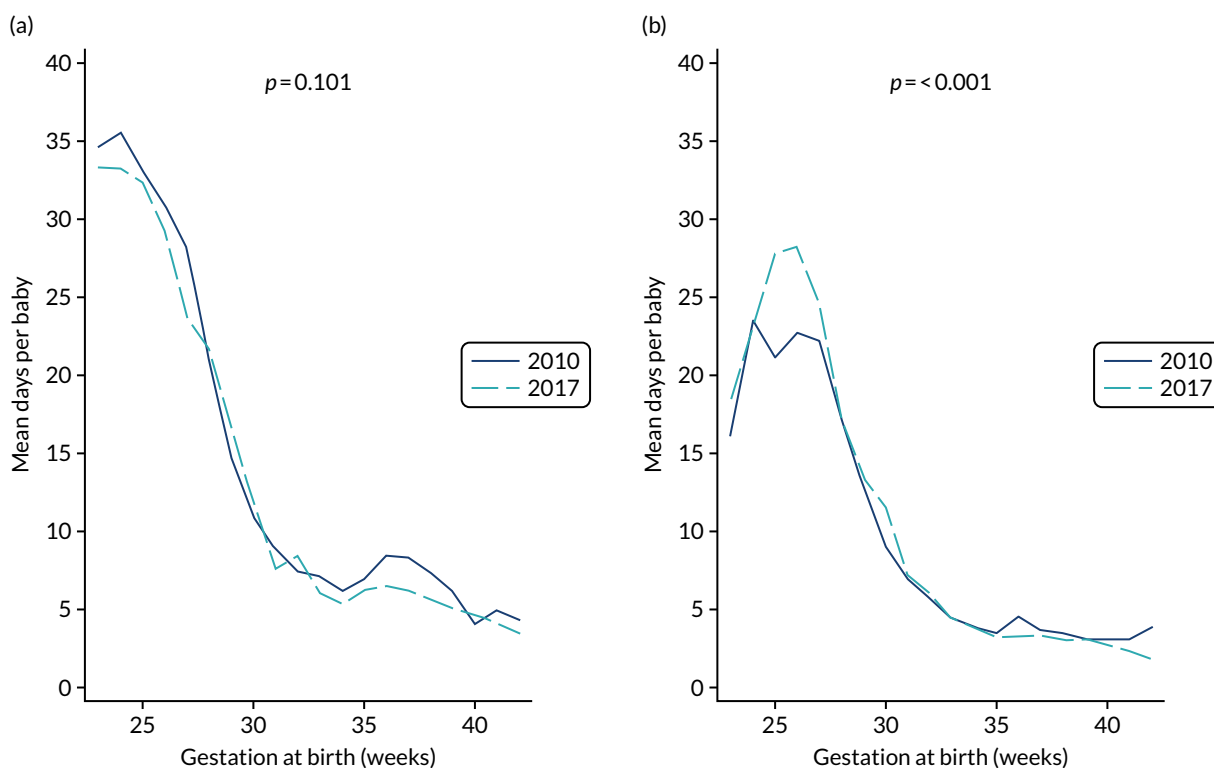


FIGURE 29 The mean number of days of intensive and high-dependency care per baby in NICUs and LNUs by week of gestational age at birth. (a) Days of stay in NICUs; and (b) days of stay in LNUs.  $p$ -value from two-way ANOVA demonstrating whether or not the mean is significantly different by week of gestation in 2010, compared with 2017.

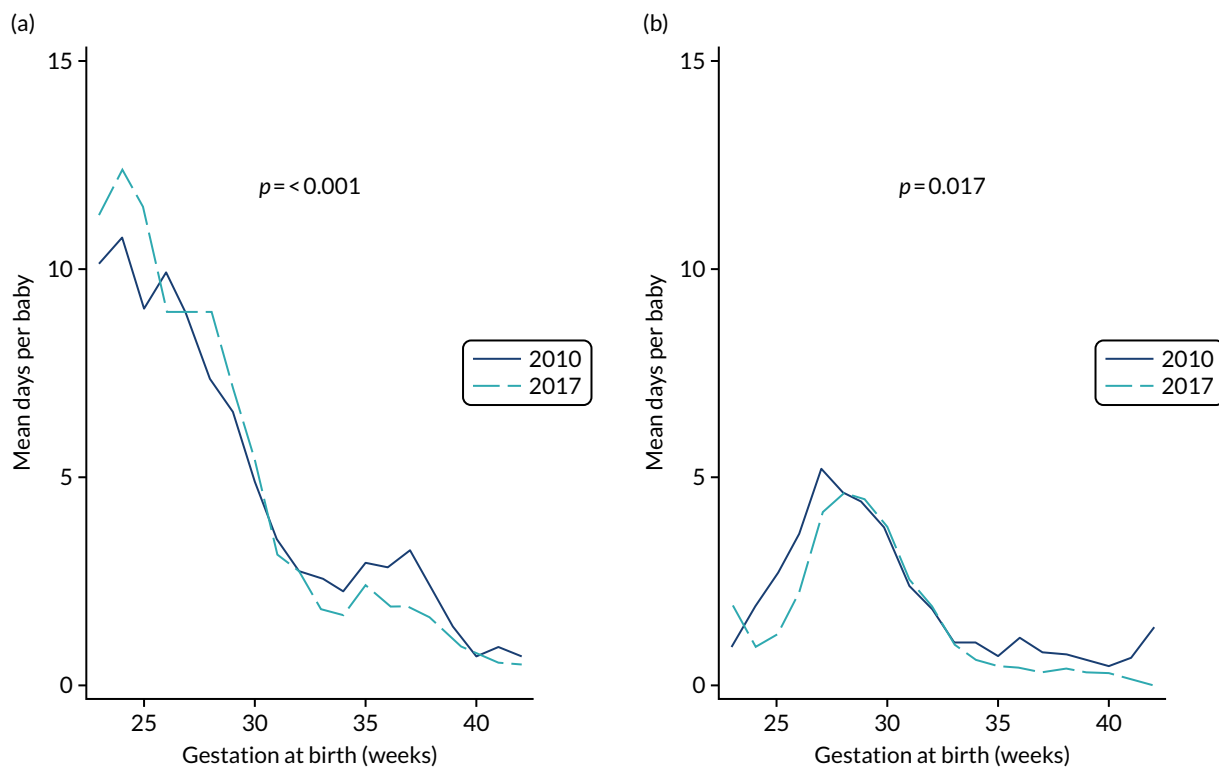


FIGURE 30 The mean number of PICC days per baby in NICUs and LNUs by week of gestational age at birth. (a) PICCs in NICUs; and (b) PICCs in LNUs. *p*-value from two-way ANOVA demonstrating whether or not the mean is significantly different by week of gestation in 2010, compared with 2017.

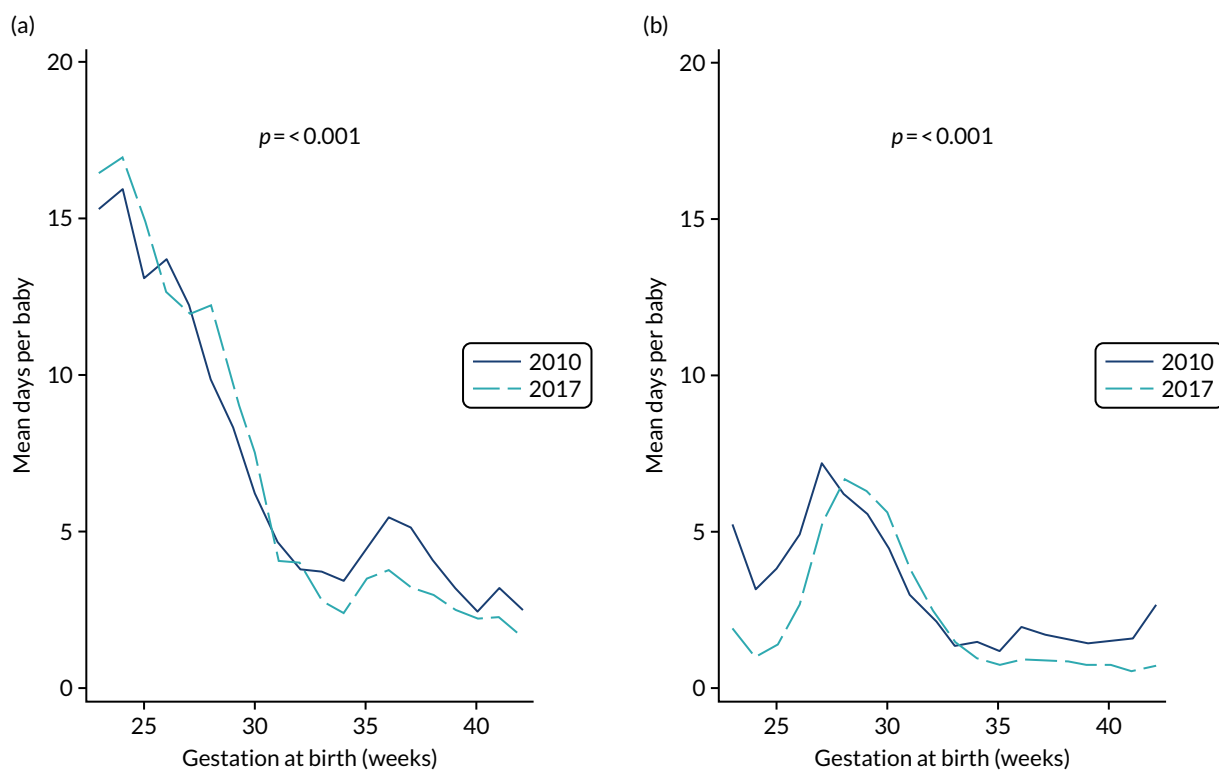


FIGURE 31 The mean number of central line days per baby in NICUs and LNUs by week of gestational age at birth. (a) Central lines in NICUs; and (b) central lines in LNUs. *p*-value from two-way ANOVA demonstrating whether or not the mean is significantly different by week of gestation in 2010, compared with 2017.

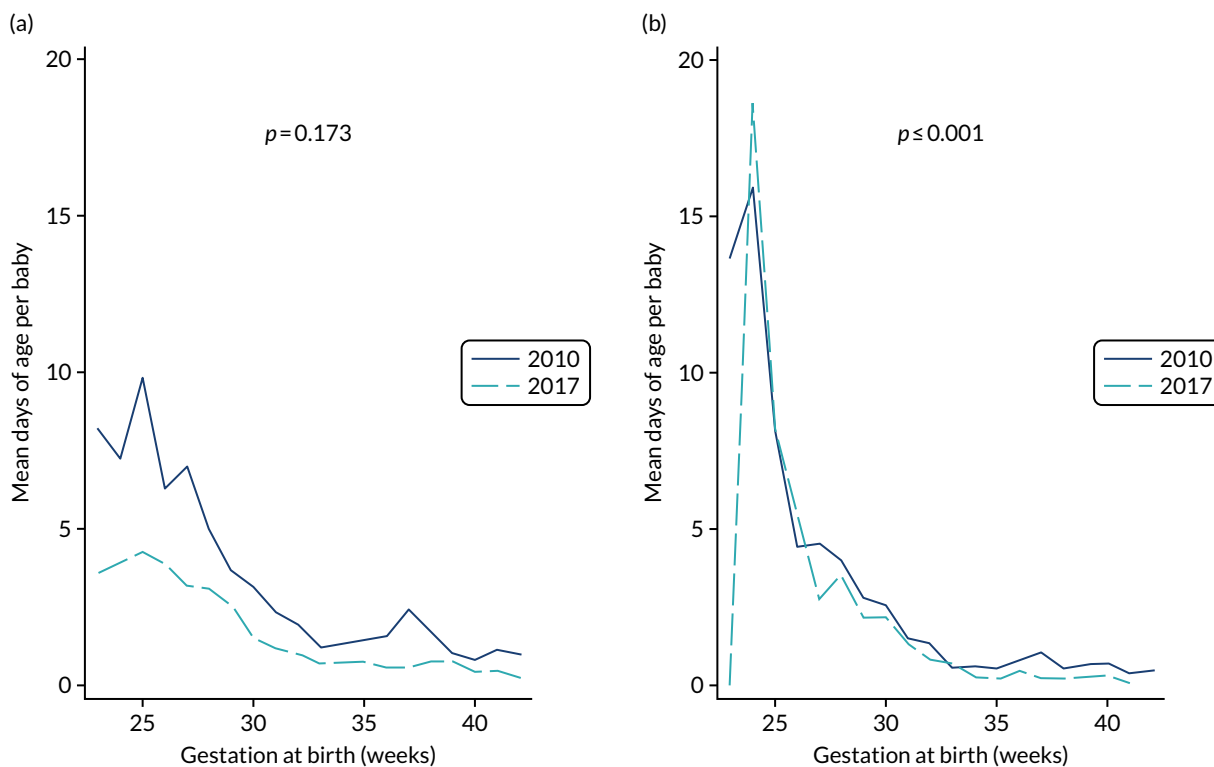


FIGURE 32 The mean age at first PICC insertion in NICUs and LNUs by week of gestational age at birth. (a) NICUs; and (b) LNUs.  $p$ -value from two-way ANOVA demonstrating whether or not the mean is significantly different by week of gestation in 2010, compared with 2017.

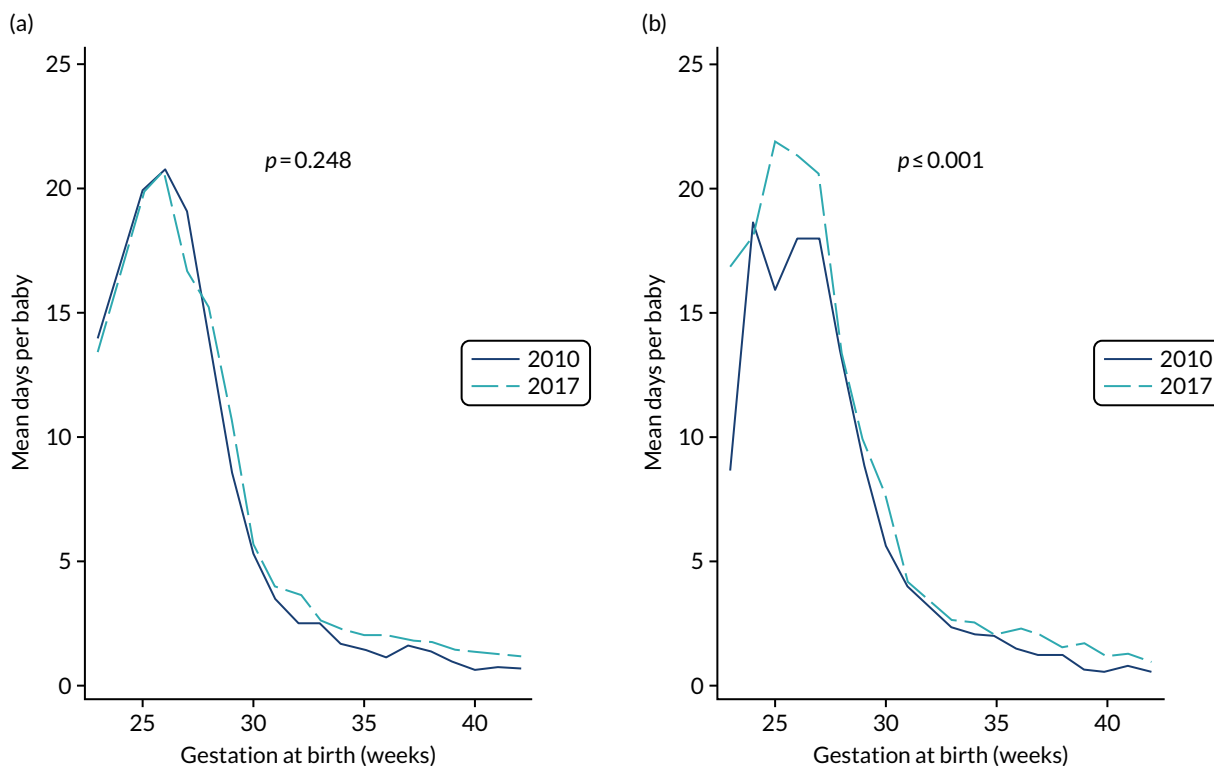


FIGURE 33 The mean number of non-invasive ventilation days per baby in NICUs and LNUs by week of gestational age at birth. (a) NICUs; and (b) LNUs.  $p$ -value from two-way ANOVA demonstrating whether or not the mean is significantly different by week of gestation in 2010, compared with 2017.



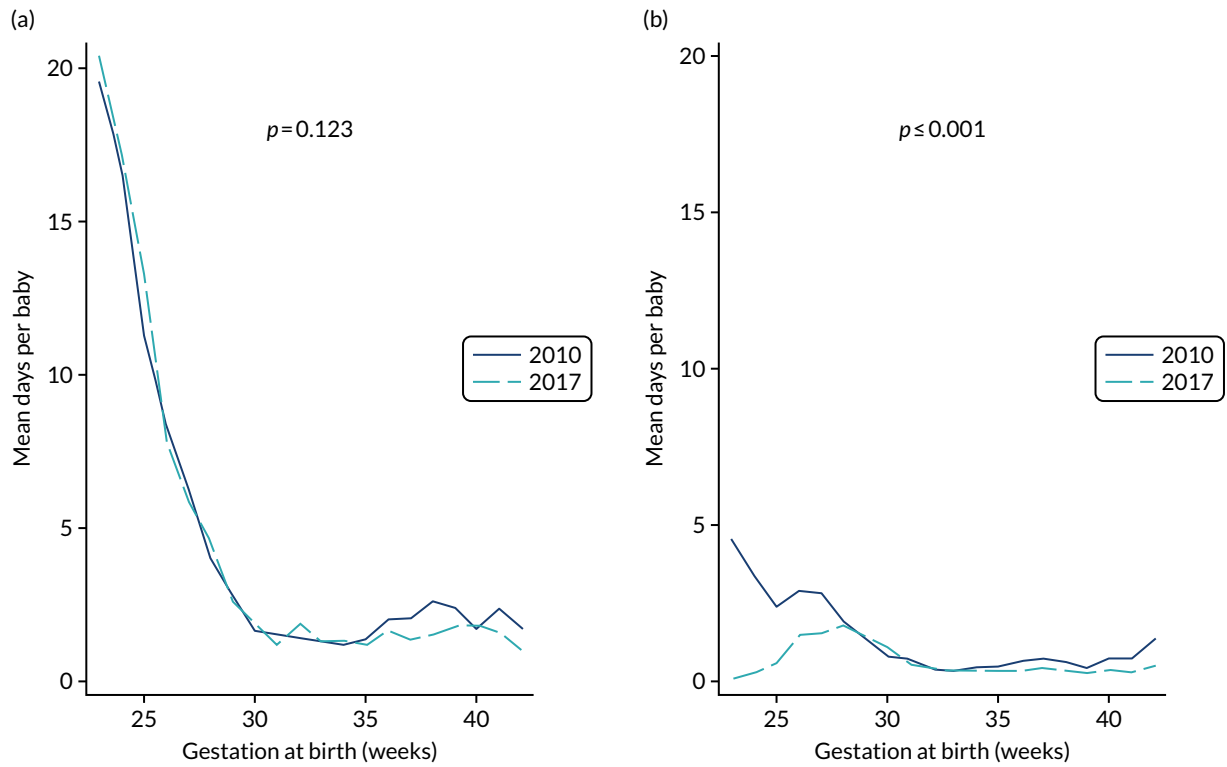


FIGURE 34 The mean number of invasive ventilation days per baby in NICUs and LNUs by week of gestational age at birth. (a) NICUs; and (b) LNUs.  $p$ -value from two-way ANOVA demonstrating whether or not the mean is significantly different by week of gestation in 2010, compared with 2017.

## Appendix 25 Additional information on the generalisability study: flow diagrams

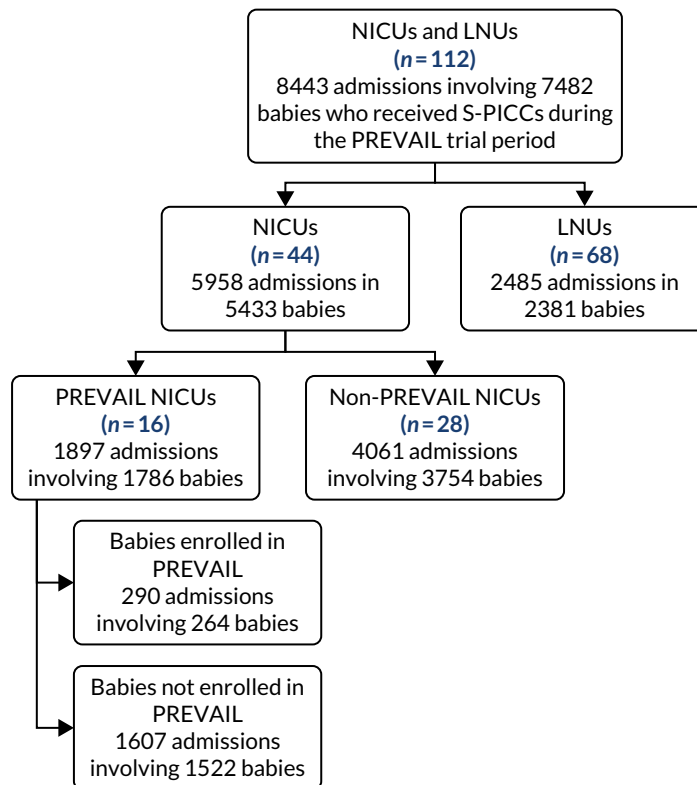


FIGURE 35 The number of admissions and babies receiving S-PICCs according to NNU level and enrolment in the PREVAIL trial for the PREVAIL trial period (August 2015 to January 2017).

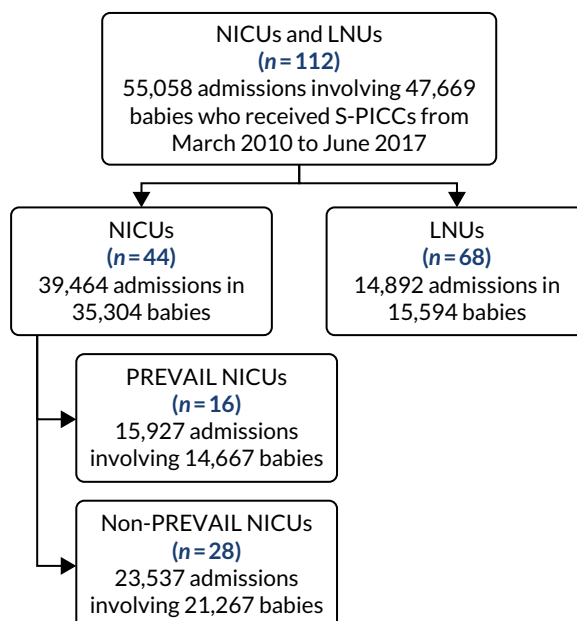


FIGURE 36 The number of admissions and babies who received PICCs from March 2010 to June 2017 and who were included in the analysis of changes over time in BSI during PICC days at risk.

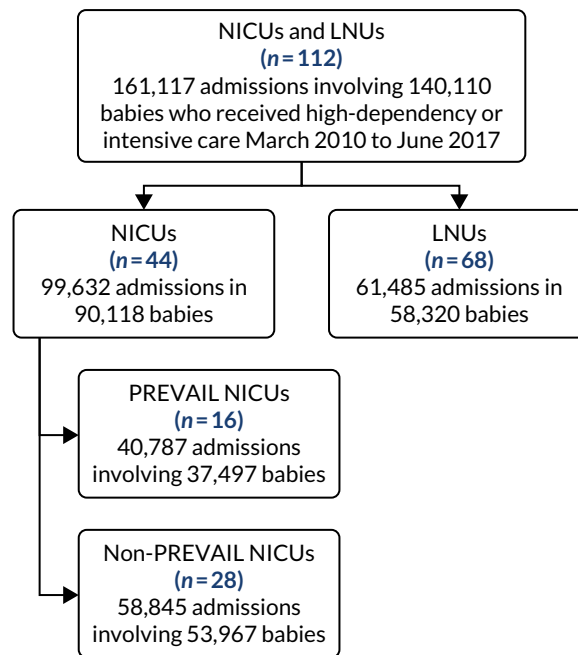


FIGURE 37 The number of admissions and babies who received intensive or high-dependency care from March 2010 to June 2017 and who were included in the analysis of changes over time in late-onset BSI.



EME  
HS&DR  
**HTA**  
PGfAR  
PHR

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