Monitoring blood stream infection in neonatal intensive care units

A thesis presented for the degree of Doctor of Philosophy

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Declaration

I, Pamela Helen Leighton, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Comparisons of the incidence of blood stream infection (BSI) between neonatal intensive care units (NICUs) can promote sharing of potentially better practices for infection control. Comparisons should take into account differences in babies' vulnerability and the invasive procedures which can introduce infection. I carried out a systematic review of methods reported in the literature, or used by regional monitoring systems, for comparing the incidence of BSI among NICUs. I found substantial variation, especially in the risk factors used to adjust incidence estimates.

The use of routinely recorded administrative data would minimize and accelerate staff workload for BSI monitoring. I investigated which risk factors recorded in routine data should be adjusted for when comparing BSI incidence between NICUs. I linked microbiology laboratory records with administrative records collected over four years for three London NICUs. I analysed rates of BSI using various methods, including Poisson regression and logistic regression assuming a matched case control design. With both approaches, National Health Service level of care was the strongest predictor for BSI incidence. Using Poisson regression models, the rate ratio for BSI, adjusted for birth weight, inborn/outborn status and postnatal age, was 3.15 (95% confidence interval (CI) 2.01, 4.94) for intensive care and 6.58 (95% CI 4.18, 10.36) for high dependency care, relative to special care. The case control study gave slightly larger estimates of effect than the Poisson regression models. Total parenteral nutrition was significantly associated with BSI incidence but explained less of the variance among babies than level of care.

Using the results from the risk adjustment model, I demonstrated how routine data can be integrated into a method for prospective, risk adjusted monitoring. This method involved standardised infection ratios and a sequential probability ratio test. The method can evaluate changes in BSI rates over time and between NICUs. It could also be used to quantify improvements following infection control interventions.

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Many figures and tables cover a page or more. To facilitate reading, they were included at the end of each chapter, rather than distributed throughout the chapter, so as not to break up the text.

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Abbreviations

AIC – Akaike's information criterion

BAPM - British Association of Perinatal Medicine

BIC - Bayesian information criterion

BSI - blood stream infection

CDC - United States Centers for Disease Control and Prevention

CI - confidence interval

CONS - coagulase-negative staphylococcus

CVC - central venous catheter

HAI - hospital-acquired infection

KISS - Krankenhaus Infektions Surveillance System

MANNERS - Maternal and Neonatal Electronic Recording System

NEO-KISS - neonatal Krankenhaus Infektions Surveillance System

NeonIN - Neonatal Infection Network

NHS - National Health Service

NICU - neonatal intensive care unit

PAS - Patient Administration System

QIC - quasi-likelihood information criterion

SEND - Standardised Electronic Neonatal Database

SPRT - sequential probability ratio test

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1. Introduction and systematic literature review

1.1 Summary

Comparisons of the incidence of blood stream infection (BSI) between neonatal intensive care units (NICUs) can reveal important differences, which may be due to variation in infection control practices. Investigation of these differences can highlight NICUs with effective infection control, whose practices can be shared with other units. To examine variation in practice, infection incidence must be risk adjusted to control for differences between units in the vulnerability of babies and the intensity of invasive procedures which can introduce infection.

I reviewed methods for risk adjusting comparisons of BSI incidence between NICUs, both in the published literature and in reports published by regional and national NICU infection monitoring systems. PubMed and Embase were searched for studies reporting risk adjusted BSI incidence in more than one NICU. An internet search found NICU infection monitoring systems in Western industrialised countries.

In the ten studies that met the inclusion criteria, risk adjustment reduced but did not eliminate variation in BSI incidence between NICUs. In both the studies and the regional monitoring systems, adjustment for baby susceptibility generally involved stratification by factors measured at birth. Adjustment for length of stay and invasive procedures involved reporting incidence by days with a device, such as central venous catheter days.

Current methods for monitoring NICU infection lack consistency. Adjustment for factors measured at birth fails to capture changes in susceptibility throughout the NICU stay and adjustment for device days does not adequately reflect risk to babies without a device. There is a requirement for methods which adjust for variation in risk for *all* babies *throughout* their NICU stay.

1.2 The rise of neonatal intensive care units

NICUs were developed in the 1950s and 1960s, and are hospital units specialising in the care of premature or acutely ill newborn babies. They provide acute intensive and high dependency care, including cardiovascular and respiratory support. They also provide less intensive 'special care', including monitoring and support for feeding and temperature maintainance, for babies not sufficiently mature or well enough to be cared for by their mothers on postnatal wards. NICUs are run and staffed by neonatologists and neonatal nurses. Common conditions cared for in the NICU include: prematurity, extreme low birth weight, major birth defects, perinatal asphyxia, jaundice, blood stream infection and respiratory distress syndrome. In England, about 10% of all births are admitted to NICUs.[1]

In developed countries, NICUs have greatly increased the survival of extremely premature and very low birth weight babies. In the 1950s, most babies of less than 30 weeks gestation or less than 1400g birth weight died, whereas in the UK today 96% of these babies survive.[2] The limit of viability has decreased to 22/23 weeks and 500g birth weight.[3] The Extremely Preterm Infants in Sweden Study (EXPRESS) was a

prospective observational study covering Sweden's entire population, carried out during 2004-2007. 1011 babies were born before 27 weeks of gestational age, and 707 of these were liveborn. Of the liveborn babies, 497 (70%) survived to one year of age (95% confidence interval (CI) 67%-73%).[4] However, babies who survive at the limit of viability often have severe developmental difficulties.[5-7]

Several differences between NICUs and other intensive care environments are relevant for this project. In contrast to adult and paediatric intensive care, babies are rarely admitted to the NICU from the community, coming instead from labour wards in the NICU's neonatal network. Babies in NICUs can suffer from infections acquired from their mothers during delivery as well as infections from the NICU environment. These factors result in different colonising organisms and incidences of infection between NICUs and other intensive care units. Maternally transmitted infections will be discussed in more detail in Chapter 5. In addition, duration of stay in intensive care differs between adults, children and babies. In a prospective cohort study including 2060 adults admitted to 22 intensive care units in Austria in 2006/2007, the median length of stay was four days.[8] The UK Paediatric Intensive Care Audit Network (PICANet) estimated that in the south west of England in 2007/2008, children admitted to district general hospital intensive care units had a median length of stay of 13 hours and children admitted to paediatric high dependency units had a median length of stay of one day.[9] In contrast, babies spend longer periods in the NICU: the median length of stay was between 7 and 13 days for the two NICUs described in this project (discussed in Chapter 3). This means that babies can be exposed for long periods to invasive procedures which may introduce infection.

1.3 Hospital-acquired infections in NICU

Between 6% and 22% of babies who spend at least 48 hours in an NICU acquire a hospital-acquired infection (HAI).[10,11] HAIs are rather loosely defined as infections occurring in hospital or shortly after discharge, with no evidence that the infection was present or incubating at the time of admission.[12] In the United States (US), a national point prevalence survey carried out for one day in 1999 included 827 babies from 29 NICUs. HAI prevalence, defined according to United States Centers for Disease Control and Prevention (CDC) criteria,[13] was estimated at 11.4% of NICU inpatients. Blood stream infection (BSI) was the most common HAI, accounting for 53% of infections. This was followed by respiratory infections (13%), urinary tract infections (9%) and other infections (25%).[14] This PhD project focused on BSI, as it forms the majority of the most serious NICU-acquired infections.

Case definitions for blood stream infection

The US CDC established criteria to define hospital-acquired BSI in 1988 (updated in 2008), these criteria are summarised in the box below:

US Centers for Disease Control and Prevention (CDC) criteria to define hospital-acquired blood stream infection (abbreviated)[12,13]

Laboratory-confirmed BSI

At least one of the following criteria must be met:

1. Patient of any age has a recognised pathogen cultured from one or more blood cultures.

2. Patient of any age has at least one of the following signs or symptoms: fever (>38°C), chills, hypotension
and
a common skin contaminant is cultured from two or more blood cultures drawn on separate occasions.

3. Patient ≤1 year of age has at least one of the following signs or symptoms: fever (>38°C rectal), hypothermia (<37°C rectal), apnea, bradycardia
and
a common skin contaminant is cultured from two or more blood cultures drawn on separate occasions.

For 1, 2 and 3 signs and symptoms and positive laboratory results must not be related to an infection at another site.

Common skin contaminants are listed as: diphtheroids (*Corynebacterium*), *Bacillus* (not *B anthracis*), *Propionibacterium*, coagulase-negative staphylococci (including *S epidermidis*), viridans group streptococci, *Aerococcus*, *Micrococcus*.

Clinical sepsis

Clinical sepsis may be used to report primary BSI in neonates and infants.

The following criterion must be met:

1. Patient ≤1 year of age has at least one of the following signs or symptoms with no other recognised cause: fever (>38°C rectal), hypothermia (<37°C rectal), apnea, bradycardia
and
blood culture not done or no organisms detected in blood
and
no apparent infection at another site
and
physician institutes treatment for sepsis

For both laboratory-confirmed BSI and clinical sepsis, there must be no evidence that the infection was present or incubating at the time of admission to hospital. Infections in babies that result from passage through the birth canal are considered HAIs.

A systematic literature review of multicentre monitoring for BSI incidence in NICUs showed that about half of the studies reviewed based their case definitions for BSI on CDC criteria (five out of ten published studies and three out of seven regional monitoring systems). These criteria were not considered appropriate in every study. In particular, authors of the NEO-KISS infection monitoring system in Germany had reservations about classifying maternally-transmitted infections acquired from the birth canal as HAI. They instituted several modifications to the CDC case definition, the main one stipulating that only BSI occurring after 48 hours of life should be considered hospital-acquired.[15]

The main obstacle to the use of CDC criteria in research and infection monitoring is their complexity. They include clinical observations of signs of infection to help differentiate between clinically-relevant BSI and subclinical infection or contaminated blood cultures. However such clinical data are not routinely recorded and therefore require skilled data collection, which may not be possible. The systematic review showed that some studies relied to a greater degree on blood culture results,[16-18] which can be obtained from routine hospital laboratory data. The systematic review is described in Sections 1.5 to 1.8. The case definition used in this PhD project relied solely on blood culture results, it is described in Chapter 3, Section 3.3.2 and discussed in Chapter 5, Section 5.5. A method for differentiating between maternally-transmitted and hospital-acquired BSI is described in Chapter 5. Section 5.3.2.

Organisms giving rise to blood stream infection

The organisms most commonly contributing to NICU-acquired infection are Coagulase-negative staphylococci (CONS). In a surveillance study, Gaynes *et al.* (1996) evaluated 13,179 HAIs conforming to CDC case definitions, including 3833 BSIs, reported by 99 US NICUs from 1986 to 1994. CONS were implicated in 36% of all HAI and in 51% of BSI.[19] Commensal organisms such as CONS, which in healthy individuals can colonise the skin and gastrointestinal tract without giving rise to infection, were recognised as important pathogens 30 years ago, and have increasingly been implicated in NICU-acquired infection over the last 20 years. This is probably due to increased survival of very premature babies, who are vulnerable to otherwise harmless bacteria due to their immune immaturity and increased requirement for invasive procedures which can introduce infection.[20] Other organisms giving rise to BSI in NICUs include *Staphylococcus aureus*, Group B streptococci, Enterococci, Candida species and *Escherichia Coli.* The frequent and widespread use of antibiotics in NICUs, hospitals and the community has led to the emergence of antibiotic-resistant organisms such as Methicillin-resistant *S. aureus,* and vancomycin-resistant enterococci. Although the vast majority of organisms giving rise to NICU-acquired BSI are susceptible to antibiotics, sporadic outbreaks of resistant BSI have occurred.[21-23]

Mechanisms of blood stream infection

Newborn babies are particularly vulnerable to infection compared with older age groups. Figure 1.1 shows that in relation to other hospital departments, NICUs have a higher rate of BSI.[24] A newborn's immune system is functionally inferior to that of an older child or an adult, and is more naïve to antigens. For example, a baby's IgG levels

reach about 60% of adult levels by one year of age.[25] Because much of the maternal IgG is transferred to the fetus during the last trimester of pregnancy, premature babies have even lower levels of serum IgG than their term counterparts.[26] Colonisation with 'normal' flora in the first few days of life can deter colonisation with pathogenic organisms and in the NICU, this process can be disrupted by antimicrobial agents.[27] Premature babies also have immature skin and mucous membrane barriers, particularly in the gut, and insufficiently acidic gastrointestinal tracts, which can admit pathogens or commensals. Invasive procedures used in the NICU can provide portals for the entry of organisms, either at their insertion sites, or internally by causing physical trauma. Invasive procedures can provide an environment for colonisation, for example at the catheter hub, and intravenous infusions can become contaminated. In particular, intralipids infused as part of parenteral nutrition provide a favourable medium for organismal growth. Other issues specific to parenteral nutrition include its direct effects on both the immune system, perhaps through inhibition of interleukin-2,[28] and on the development of natural gastrointestinal defences.

Risk factors for blood stream infection

Throughout this thesis, I divide risk factors for BSI into those reflecting susceptibility to BSI at birth, and those reflecting susceptibility during the NICU stay, i.e. invasive procedure-related factors. In the paragraph above I described how the mechanisms for BSI involve multiple intrinsic factors and extrinsic exposures associated with the complexity of intensive care. Many of these risk factors act at the molecular or bacterial level, and most are not investigated or recorded on a routine basis. Population-based studies have tended to use markers for susceptibility to infection which are routinely

recorded, examples include gestational age and the use of invasive procedures, for example central venous catheters (CVCs) and parenteral nutrition. The results of these studies are summarised in the following three paragraphs.

Risk factors reflecting susceptibility to infection at birth

As shown in several studies, babies with low gestational ages and/or very low birth weights are at increased risk for BSI. In a prospective cohort study, Beck-Sague *et al*. (1994) evaluated 376 babies in 3 US NICUs from 1989 to 1991. The proportions of babies developing BSI according to CDC criteria were: 31 of 110 (28%) babies with a birth weight below 1500g, and 11 of 266 (4%) babies with a birth weight above 1500g (risk ratio 6.8, $p<0.01$, no CI available, adjusted for other factors related to babies' susceptibility to infection, such as admission diagnosis).[29] In another prospective cohort study, the National Institute of Child Health and Human Development Neonatal Research Network (2002) reported on babies of very low birth weight (below 1500g), admitted to 15 US NICUs between 1998 and 2000. BSI was defined as one or more positive blood cultures obtained after 72 hours of life, which were treated with antibiotics. Cultures positive for organisms generally considered to be contaminants were only included if they were found to indicate infection on clinical review. Of 6215 babies, 1313 (21%) experienced BSI, and the incidence of infection was inversely related to birth weight and gestational age. Forty three percent of babies with birth weights between 401 and 750g experienced infection, in contrast to 7% of babies with birth weights between 1251 and 1500g. Similarly, 46% of babies born before 25 weeks of gestation experienced BSI, which decreased to 2% for babies born after 32 weeks of

gestation (p<0.001 in unadjusted logistic regression models for BSI incidence, fitted with birth weight or gestational age as a covariate. Risk ratios and CIs not available).[30]

Many studies have shown associations between maternal risk factors and maternally-transmitted BSI occurring in the first few days of life.[31] The National Institute of Child Health and Human Development Neonatal Research Network carried out one of the largest of these studies, in which babies with very low birth weights (below 1500g), admitted to 12 US NICUs between 1991 and 1993, were enrolled in a prospective cohort. BSI was defined as one or more positive blood cultures obtained *before* 72 hours of life, accompanied by clinical signs of infection. Cultures positive for known contaminants were only included if they indicated infection on clinical review. Of 7861 babies, 147 (1.9%) experienced early-onset BSI, of which 45 (31%) experienced infection with Group B streptococcus. The time from rupture of membranes (rupture of the amniotic sac) to birth was a strong risk factor for BSI, because this interval reflects the potential exposure of the foetus to pathogenic organisms. If rupture of membranes occurred more than 24 hours before birth, the risk of BSI was more than four times greater than if this interval was less than 6 hours (p<0.01 adjusted for gestational age at birth. CI not available). Babies born by vaginal delivery can be exposed to potentially pathogenic organisms in the birth canal. Babies born by caesarean delivery were less likely to experience BSI than babies born by vaginal delivery (odds ratio 0.69, 95% CI 0.49, 0.96, p<0.05 adjusted for gestational age at birth).[32] This thesis concentrates on hospital-acquired BSI, by excluding probable maternally-transmitted BSI occurring during the first 48 hours of life. The threshold used to differentiate maternally-

transmitted BSI from hospital-acquired BSI is described in more detail in Chapter 5, Section 5.3.2.

Procedure-related risk factors reflecting susceptibility to infection during the NICU stay

Studies have shown associations between the use of invasive procedures and BSI.[33] The three invasive procedures most often associated with BSI are the use of parenteral nutrition, central venous catheters and assisted ventilation, as described by the following three prospective cohort studies. Holmes *et al*. (2007) evaluated 1367 babies admitted to one UK NICU between 2001 and 2003. BSI was defined as a positive blood culture, with the additional requirement of clinical symptoms if the culture revealed more than one organism or a skin contaminant. The rate of BSI was higher in the three days following treatment with parenteral nutrition (22.65 per 1000 baby days), than on other days (1.37 per 1000 baby days). The rate ratio was 14.2 (95% CI 8.8-22.9).[34] In another study, the Canadian Neonatal Network evaluated 19,507 babies admitted to 17 Canadian NICUs in 1996/1997. BSI was defined as one or more positive single organism blood cultures in babies with clinical suspicion of infection. The rate of BSI was higher on days treated with a CVC (7.2 to 13.1 per 1000 CVC days, depending on the type of CVC used) than on days not treated with a CVC (2.9 per 1000 noncatheter days). The rate ratio was 2.0 (95% CI 1.7, 2.5) to 3.5 (95% CI 3.0, 4.0).[35] In a subset of 16,497 babies from the Canadian Neonatal Network study, assisted ventilation was estimated to increase the odds of BSI 1.5 times (95% CI 1.1-2.0) in babies with birth weight below 1500g, and 2.9 times (95% CI 1.9-4.6) in babies with birth weight above

1500g (crude odds not available).[36] Risk ratio estimates for all three invasive procedures were adjusted for other factors related to babies' susceptibility to infection.

Outcomes of infection

Babies with BSI are at increased risk for neurodevelopmental impairment. The National Institute of Child Health and Human Development Neonatal Research Network (2004) carried out a prospective cohort study, which followed up 6093 babies in US NICUs, with birth weights between 401 and 1000g. Infection was defined as a positive culture from blood or cerebrospinal fluid, with antibiotic therapy for five or more days. Cultures positive for organisms generally considered to be contaminants were excluded. Of surviving babies at 18 to 22 months of corrected gestational age, those who experienced infection were significantly more likely to have cerebral palsy, impaired head growth, vision impairment and low scores on the mental and psychomotor development indices of the Bayley Scales of Infant Development II, than those who were not infected.[37]

Proposed mechanisms for neurodevelopmental impairment involve multiple, interacting prenatal, perinatal and postnatal insults, including intrauterine infections such as chorioamnionitis, hypoxic ischaemic events such as birth asphyxia, and postnatal infections such as BSI and meningitis. Periventricular leukomalacia, or lesions in white matter surrounding the cerebral ventricles, is the brain injury most commonly associated with both infection and adverse outcomes such as spastic diplegia, impaired vision, squints, sensorineural hearing loss and developmental delay.[38,39] In a retrospective case control study, Graham *et al.* (2004) evaluated all babies born at 23 to 34 weeks'

gestation, at a tertiary university hospital between 1994 and 2001. 150 babies with white matter lesions, diagnosed within the first six weeks of life, were matched for gestational age with controls without brain injury. The unadjusted odds of developing white matter injury was twice as high in babies with a positive blood culture, than in babies without a positive blood culture (43 cases had a positive blood culture versus 28 controls, 95% CI 1.04, 4.00).[40] One explanation for the association between infection and white matter lesions is that infection and inflammation may result in vascular compromise and cytotoxic injury to white matter. A possible mechanism suggests that the presence of pro-inflammatory cytokines inhibits proliferation of neuronal precursor cells, activates astrogliosis and stimulates oligodendrocyte death.[38]

BSI is associated with an increased risk of mortality, which varies depending on the infecting organism. In a prospective cohort study, Orsi *et al*. (2008) evaluated 575 babies admitted to an Italian NICU between 2003 and 2006. Thirty-five babies died (6.1%), and two of these deaths were attributable to HAI (attributable mortality 5.7% of 35), which was defined according to CDC criteria. Babies infected with BSI were almost four times more likely to die than babies not infected with BSI (risk ratio 3.89, 95% CI 1.76, 8.63), although this relationship was not adjusted for other factors related to babies' vulnerability.[41] The risk of death associated with BSI varies according to the infecting organism. In a prospective cohort study, Isaacs *et al*. (2003) evaluated admissions to 18 NICUs in Australia and New Zealand, between 1991 and 2000. BSI was defined as a positive blood culture accompanied by clinical symptoms. Of 1249 babies infected with CONS, between 4 and 24 (0.3% and 1.6%) were judged to have

died because of their infection. In contrast, 289 babies developed *Staphylococcus aureus* infection, of whom 38 (13.1%) died.[42]

Babies with BSI also tend to spend longer in hospital and have increased treatment costs. In a retrospective cohort study, the Vermont Oxford Network (2004) evaluated 2809 babies surviving to discharge from 17 US NICUs in 1998/1999. BSI was defined as a positive blood culture, with the additional requirement of clinical symptoms and antibiotic treatment if the culture revealed a commensal. BSI significantly increased lengths of stay by 4 to 7 days in babies of birth weight 401 to 1500g, and increased treatment costs by 15% to 21%, or by $6276 to $12,480, in babies of birth weight 751 to 1500g.[43]

Organisational measures to reduce infections in NICUs

Various intervention studies have shown that infection control practices implemented at the unit level have reduced the incidence of BSI in NICUs. Maas *et al*. (1998) evaluated the effect of a CVC care programme including aseptic techniques, such as the use of gloves and gowns when changing infusion sets, implemented in a Belgian NICU in 1989. BSI was defined according to modified CDC criteria. In the four year follow-up period, the proportion of babies acquiring BSI while treated with a CVC fell from 11/26 (42%) to 18/156 (12%) (adjusted risk ratio in the period before versus after the intervention, 2.96 95% CI 1.13, 7.79).[44] Pessoa-Silva *et al*. (2007) evaluated the effect of a hand hygiene promotion programme, including education on hand washing techniques, implemented in a Swiss NICU in 2001. HAI was defined according to CDC criteria. In the 27 month follow-up period, the rate of HAI in babies with birth weight

below 1500g fell from 15.5 to 8.8 per 1000 baby days (adjusted odds ratio 0.40 95% CI 0.19-0.85).[45] Isolation of babies known to be infected is recommended for serious, easily transmissible or hard to treat infections such as Methicillin-resistant *S. aureus*.[46] Changes to NICU environments and staffing can also affect BSI. The UK Neonatal Staffing Study Group (2005) evaluated 13,334 babies admitted to 54 UK NICUs in 1998/1999. 402 babies (2.97%) acquired BSIs, defined by a positive blood culture. The adjusted odds of BSI increased by 1.13 (95% CI 1.07, 1.20) for each additional special care cot per hand washbasin, and decreased by 0.53 (95% CI 0.35, 0.79) in units with an NICU infection control nurse compared with units without.[16]

1.4 Surveillance of blood stream infection in NICU

Surveillance can be defined as 'a comprehensive method of measuring outcomes and related processes of care, analysing the data, and providing information to members of the health care team to assist in improving those outcomes'.[47]

Surveillance of BSI in NICU could be used to:

- Assess the burden of infection
- Monitor changes in infection incidence over time and to trigger alarms if incidence increases significantly
- Encourage sharing of improved infection control practices between NICUs
- Monitor the outcome of interventions to improve infection control

An example of how surveillance can be used to assess the burden of BSI and to monitor changes over time is provided by the neonatal Krankenhaus Infektions Surveillance

System (NEO-KISS). NEO-KISS monitors babies with birth weights below 1500g cared for in German NICUs, and BSI is defined according to modified CDC criteria. Between 2000 and 2005, 24 NICUs each participated in the system for a period of three years, and submitted data for a total of 3856 babies. The overall burden of BSI was 8.3 per 1000 baby-days in the first year of participation, which for most units decreased over the study period to give a mean of 6.4 per 1000 baby-days (adjusted odds ratio 0.73, 95% CI 0.60, 0.89).[48] The programme includes biannual feedback to NICUs, including comparisons between hospitals and within hospitals over time. The authors inferred that taking part in surveillance may motivate NICU staff to reduce the risk of BSI. Further evidence for a positive effect of surveillance is provided by a systematic review of over 100 randomised controlled trials showing that audit and feedback alone produce small to moderate improvements in clinical practice.[49,50]

When comparative monitoring has been used to trigger sharing of improved practices between units, substantial reductions in infection incidence appear to have been achieved. Six NICUs in the Vermont Oxford Network, and 52 NICUs in the Hospital Corporation of America collaborated in separate but similar projects, both involving the sharing of infection control practices, between NICUs with consistently low rates of BSI and those with higher rates. Practices shared between units included protocols to reduce the contamination of invasive procedures, and to improve the accuracy of BSI diagnosis, for example by recommending a minimum blood sample of 1ml. The Vermont Oxford Network analysed CONS BSI only, the case definition was a blood culture testing positive for this organism, which was accompanied by clinical symptoms and treated with antibiotics. For babies of birth weight below 1500g, the mean

proportion infected across the participating NICUs decreased from 24.6% to 16.4%, from 1997 to 2000 (crude risk ratio 0.67, 95% CI 0.51, 0.87).[51,52] Across the Hospital Corporation of America network, the total incidence of all BSI, defined by positive blood culture, fell from 3.8 to 2.9 per 1000 baby-days, from 1997 to 1999. The average hospital cost per baby reduced from $60,826 to $48,916 (risk ratios and 95% CIs for decreases not available).[53] Neither study could definitively link the observed decreases in BSI with their initiatives, or with specific practice changes. It is also unclear to what extent decreases in BSI were due to infection control practices, or reductions in false positive blood cultures due to improved sampling for BSI. However, the Vermont Oxford Network demonstrated that the decrease in BSI was consistent in all but one NICU, and that practice changes were widely adopted, suggesting that the collaboration succeeded in improving practice.

A weakness of the Vermont Oxford Network and Hospital Corporation of America studies described above, is that some of the initial variation in BSI incidence observed between NICUs may have been attributable to factors other than quality of care, such as case mix, babies' length of stay and the invasive procedures carried out, all of which can influence hospital-acquired infection.[54] A robust multicentre monitoring system must *adjust* for these factors, in order to take into account variation in case mix. Any residual variation may be explained, at least in part, by factors amenable to change, such as hygiene practices. Developing a method for risk adjusting comparisons of BSI incidence between NICUs is a major challenge for infection monitoring, and is the focus of this thesis.

1.5 Aims of the systematic review

I performed a systematic review to determine:

- Methods used for risk adjustment in studies that compared infection incidence between NICUs
- How much infection incidence varied before and after risk adjustment
- The extent to which these approaches for risk adjustment are being used by regional surveillance systems for NICU-acquired infection around the world

I discuss different approaches for risk adjustment and suggest ways to improve robustness of comparisons.

1.6 Methods of the systematic review

1.6.1 Systematic review of studies reporting risk adjustment

Studies were included if they reported any measure of the frequency of BSI at more than one NICU and comparative results that were risk adjusted. I accepted any approach for risk adjustment, including stratification for risk factors, for example reporting infections as rates per catheter days, as well as the inclusion of risk factors in a statistical risk adjustment model. I accepted any definition for hospital-acquired BSI, but excluded studies concentrating on maternally-transmitted BSI in the first few days of life.

I combined three sets of search synonyms relating to NICU, BSI, and monitoring or risk adjustment to search PubMed and Embase databases (with Embase thesaurus mapping) in any language until October 2009. All titles and abstracts for potentially eligible articles were reviewed. Studies meeting the inclusion criteria were reviewed by myself and my primary supervisor. I also searched reference lists and 'related articles' of all included studies (using PubMed). Abstracts from relevant conferences were reviewed from January 2005 to October 2009. The Appendix to Chapter 1 contains details of the search strategies.

1.6.2 Review of regional monitoring systems

As both infections and organisational structures vary greatly among NICUs in developing countries, I included only monitoring systems from Europe, North America and Australasia to ensure generalisability. The search was performed in Google in 2007 and updated in October 2009, using short phrases and the region of interest, this is described in the Appendix to Chapter 1.

1.7 Results

1.7.1 Systematic review of studies reporting risk adjustment

Case definition

Ten studies met the inclusion criteria (Figure 1.2).[16,18,30,35,36,55-59] Case definitions for BSI varied in complexity from a first positive blood culture,[16,18] to hospital-acquired BSI defined by US CDC criteria.[13,56-59] Two studies excluded BSI acquired before

NICU admission as they were restricted to blood cultures taken at least 48 hours after admission.[36,55] CDC criteria state that 'there must be no evidence that the infection was present or incubating at the time of hospital admission', but give no time threshold.[13] All but two studies[57,59] distinguished hospital-acquired from maternally-transmitted BSI, using thresholds ranging from 48 to 72 hours after birth.

Risk adjustment

The third column of Table 1.1 shows that most studies took into account the duration of exposure, by reporting incidence per baby days of stay or per CVC days,[35,57-59] sometimes with Cox proportional hazards regression models or Kaplan-Meier analyses of time to infection.[55,56] Four studies did not take into account length of stay, reporting the proportion of babies experiencing one or more BSI.[16,18,30,36] Only three studies took recurrent infections into account, by reporting rates of BSI per baby or catheter days.[35,57,59]

The fourth to the sixth columns of Table 1.1 summarise adjustment for potential risk factors. Adjustment for factors reflecting susceptibility at birth was performed by stratifying BSI incidence by birth weight,[19,36,59] or by including factors in a risk adjustment model.[16,18,30,36,55,56,58] Adjustment for procedure-related factors was performed by reporting BSI per days with a CVC.[35,57,59] Other studies included invasive procedures in a risk adjustment model: some factors were included as binary variables (eg. CVC: yes/no),[56,58] some as durations censored at the onset of BSI or removal of the CVC or ventilator,[56,58] and others as daily variables which were updated continuously during a baby's stay.[55] Adjustment for organisational factors was performed by

including factors such as the provision of infection control nurses in a risk adjustment model.[16,18]

Two studies addressed the possibility that differences in blood sampling frequency between hospitals could influence comparisons, as the more samples taken the greater the risk of detecting asymptomatic BSI or a contaminated sample. The UK Neonatal Staffing Study Group (2005) found no association between the ratio of positive to all blood cultures and the incidence of BSI or any of their risk adjustment variables. Brodie *et al*. (2000) measured a two-fold variation in the frequency of blood sampling among NICUs, but reported that differences in BSI incidence between NICUs remained significant when results for the commonest contaminant, CONS, were removed from the analysis.

Five studies reported a reduction in the variation between NICUs after risk adjustment (third column of Table 1.2). All ten studies showed residual variation in BSI incidence between NICUs after risk adjustment. Perlman *et al*. (2007) also showed variation between two NICUs in the adjusted incidence of BSI with gram-positive organisms. In contrast, two subgroup analyses by Perlman *et al*. (2007) showed no significant variation in the adjusted incidence of BSI in babies who had at least one CVC placed during their NICU stay or in BSI occurring in the presence of a CVC (fourth column of Table 1.2).

1.7.2 Review of regional monitoring systems

Case definition

Table 1.3 summarises risk adjustment methods used by the seven regional monitoring systems included in the review.[17,60-65] Case definitions varied in complexity from a positive bacterial culture (excluding cultures for CONS)[17] to CDC case definitions,[63,64] while NEO-KISS modified the CDC case definition for use in neonates.[15] Four systems excluded BSI acquired before NICU admission by including only diagnostic blood cultures taken at least 48 hours after admission,[60,62] or rejecting infections with evidence that they were acquired elsewhere.[63,64] Two systems differentiated between maternally-transmitted and hospital-acquired BSI, using thresholds of 48[60] or 72[65] hours after birth.

Risk adjustment

Five systems provided some adjustment for duration of exposure, by reporting incidence by catheter days,[60,61,63] or by catheter days and baby days of stay.[62,64] (third column of Table 1.3)

The UK-based NeonIN was the only system not using any method of risk-adjustment. As the remaining six systems were based on the original US CDC surveillance system, they were remarkably similar. Adjustment for factors reflecting susceptibility at birth was performed by stratification into birth weight groups. Adjustment for procedure-related factors was performed by reporting incidence by catheter days. NEO-CAT incorporated several factors in a multivariable risk adjustment model (fourth column of Table 1.3).

While most systems did not directly adjust for differences in blood sampling frequency between NICUs, their case definitions attempted to control for differences in blood sample contamination by, for example, requiring that a positive blood culture be associated with clinical symptoms or a CVC.[61] The Vermont Oxford Network went further in proposing practices to standardise sampling techniques between participating NICUs, for example by recommending a minimum blood sample of 1ml.[51]

Most case definitions combined clinical evidence of infection with blood culture results and consequently required active reporting by clinicians. I found no evidence that any system exclusively used electronic hospital administrative data.

1.8 Discussion

Overall, risk adjustment attenuated but did not remove differences in infection incidence between NICUs. Residual variation could indicate differences in data quality, inadequate adjustment for case mix or procedure-related factors, or true differences in incidence. For example, Perlman *et al.* (2007) showed a significant difference between NICUs in overall BSI incidence adjusted for CVC use, but not for the subset of CVC-related BSI. This suggests that CVC use and study site were linked, and that probably the overall analysis was inadequately adjusted for CVC use. The UK Neonatal Staffing Study Group suggested that residual variation resulted from differences in quality of care. Measures of risk adjusted BSI showed statistically significant associations with NICU organisational factors, such as the provision of neonatal consultants and infection control nurses, and the availability of hand washbasins. Differences in quality of care

may have contributed to the localised outbreak of *Staphylococcus epidermidis,* which Perlman *et al.* (2007) suggested gave rise to the varying Gram-positive BSI incidences between NICUs. There is a consensus that risk adjustment is necessary, feasible and effective, but there is no agreement regarding the best method for carrying it out.

This review highlights the need for more consistent outcome measures and risk adjustment methods. A Europe-wide survey of hospital infection control physicians revealed that their strongest consensus research priority is standardisation of surveillance systems for international comparison of hospital-acquired infection incidence.[66] Consistency in the denominator used is the minimum requirement. Most studies and regional monitoring systems reported incidence by baby days or catheter days, controlling for variations between NICUs in duration of exposure to infections. Incidence rates also capture recurrent infections within the same baby, which is not possible if reporting consists of proportions of babies experiencing one or more BSI.

Meaningful comparisons also require consistency in the risk factors adjusted for, and in how these are measured and analysed. Most studies and regional monitoring systems adjusted for factors measured at birth, such as birth weight, however this does not adjust for *changes* in a baby's susceptibility *throughout* his or her NICU stay. Days with a CVC can provide such a *continuous* measure, but they exclude the 80% of NICU babies not treated with a CVC,[35] who may have widely differing risks of infection. The Canadian Neonatal Network Study (2002) (Table 1.1) suggested that only about 40% of BSI are CVC-related.[35] Holmes *et al.* questioned the use of CVC days for risk adjustment, as their multivariable analysis found parenteral nutrition to be a stronger

predictor of BSI than CVC use alone.[34] However again, parenteral nutrition is used to treat a minority, 24%, of babies in the NICU.[67] *Continuous composite* risk adjustment variables may be preferable, capturing multiple risk factors and all babies throughout their NICU stay. An example is days of stay at each level of care, which in some countries is updated daily and allocated to all babies according to clinical status. Levels of care used in the UK National Health Service (NHS) are described in the box below and in the Appendix to Chapter 3. The following chapters will examine level of care, as well as specific invasive procedures, as risk adjustment factors for comparisons of BSI between NICUs.

British Association of Perinatal Medicine, Categories of Neonatal Care (abbreviated)[68]

Intensive care
For babies: receiving any respiratory support via a tracheal tube, less than 29 weeks gestational age and less than 48 hours old, requiring complex clinical procedures or major surgery.
Recommended nurse to baby ratio 1:1.

High dependency care
For babies: receiving parenteral nutrition, requiring care of an intra-arterial catheter, with apneoa requiring stimulation.
Recommended nurse to baby ratio 1:2

Special care
For babies: requiring continuous monitoring of respiration or heart rate, receiving phototherapy, recovering from more specialist care.
Recommended nurse to baby ratio 1:4

The only regional monitoring system which did not perform risk adjustment was NeonIN, which aimed to provide simple, rapid determination of the patterns of organisms in NICUs, with data entry by busy clinicians. NeonIN highlights dual requirements for NICU monitoring: rapid data collection and feedback and more time-

consuming comparisons of risk adjusted rates. Both approaches are useful; the former can alert clinicians to sudden changes, the latter is essential for quality of care benchmarking. For both approaches, the use of routine electronic clinical records would accelerate data collection and minimise staff workload, but must be balanced against the use of case definitions that include clinical observations, which can require skilled data collection and stand-alone data systems.

This systematic literature review was published in the 'Journal of Hospital Infection' (included in the Publications Appendix).[69] The paper does not include the study by Perlman *et al.* (2007), which appeared on PubMed after its acceptance for publication.

Key conclusions of Chapter 1

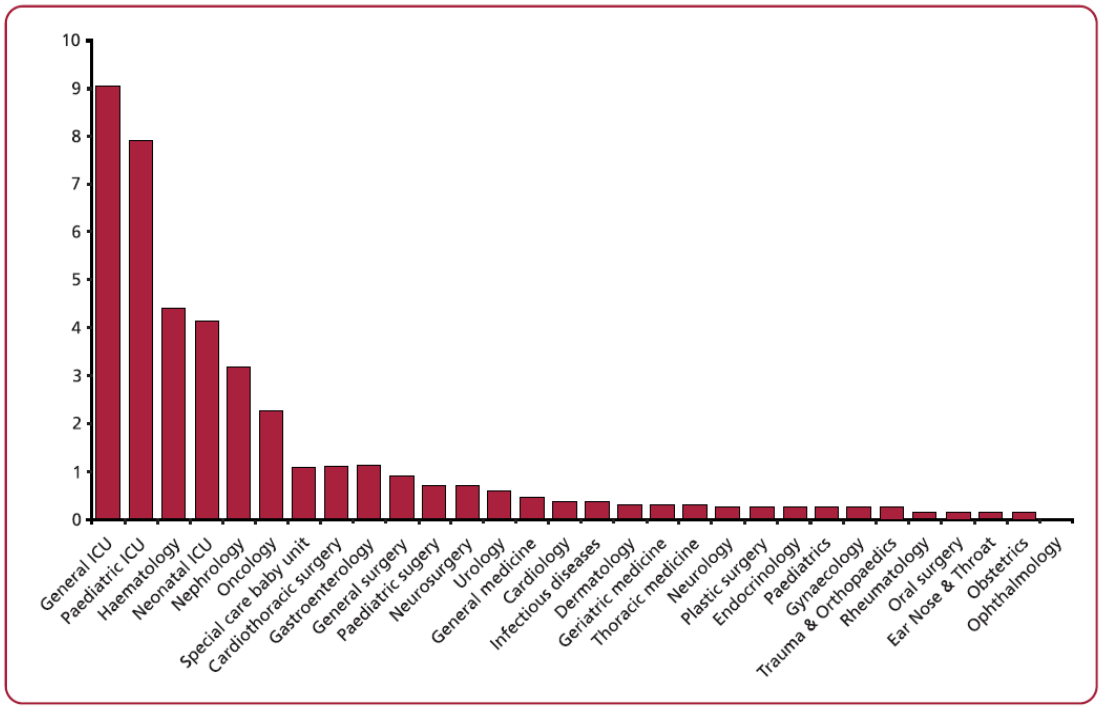
Findings

- Risk adjustment is widely recognised as necessary for meaningful comparisons of BSI incidence between NICUs, however there is a lack of consistency in the methods used.
- Most regional monitoring systems agreed that adjustment for duration of exposure and susceptibility at birth is a minimum requirement.

Conclusions

- Further research should investigate the possibility of adjustment for continuous, composite measures of risk from invasive procedures.
- The use of routine electronic data would accelerate data collection and minimise staff workload.

Figure 1.1 Number of hospital-acquired BSIs per 1000 patient-days, by specialty, in the UK 1997-2002



Nosocomial Infection National Surveillance Service (2002) 'Surveillance of Hospital-Acquired Bacteraemia in English Hospitals 1997-2002' Public Health Laboratory Service, London, UK. Permission to reproduce this graph was confirmed by the Health Protection Agency in January 2011.

Figure 1.2 Flow diagram of the process and results of the systematic literature review

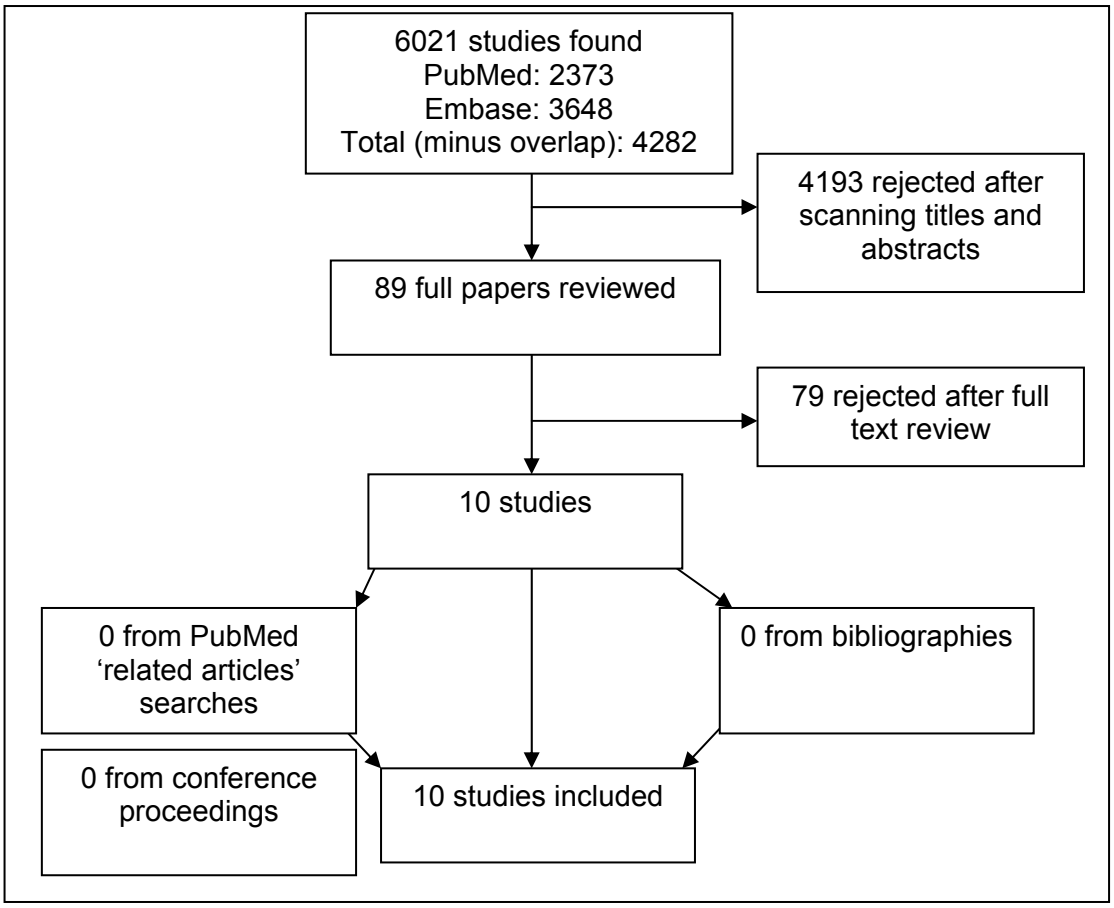


Table 1.1 Studies comparing risk adjusted BSI incidence between NICUs[a]

			Outcome measures adjusted for:		
Authors and setting (study period)	**Population**	**Outcome measure**	**Birth susceptibility factors**	**Procedure-related factors**	**Organisational factors**
Brodie *et al*, 2000[55] 6 US NICUs (1994-1996,1996-1997)	1354 babies with birth weight <1500g	Time to first BSI after admission	Birth weight, SGA	Duration of Broviac catheter parenteral nutrition (Daily variables)	No
The Canadian Neonatal Network, 2002, 2005 17 Canadian NICUs (1996-1997)	1) 19,507 babies[35]	1) Incidence per CVC days	1) Gestational age, outborn status, SNAP-II	1) Duration of CVC (by CVC type)	1) No
	2) 16,497 babies[36]	2) Proportion of babies with ≥1 BSI	2) Birth weight, gestational age, outborn status, SNAP-II	2) No	2) No
Carrieri *et al*, 2003[56] 21 Italian NICUs (1996-1997)	2160 babies with birth weight ≤1750g Babies with 15 defined 'minor' conditions excluded	1) Time to first BSI after admission	1) 3-10 day model: birth weight, sex, apgar score, respiratory distress syndrome, patent ductus arteriosus, intraventricular haemorrhage	1) 3-10 days: CVC ventilation (yes/no variables)	1) No
		2) Time to first BSI after admission	2) 10-35 day model: birth weight, maximum base excess, NEC	2) 10-35 days: Duration of CVC ventilation (censored at onset of BSI)	2) No
Gaynes *et al*, 1991[57] 35 US NICUs (1986-1990)	24,480 babies	Incidence per CVC days	Birth weight	Duration of CVC	No
The National Institute of Child Health and Human Development Neonatal Research Network (NICHD), 2002[30] 15 US NICUs	6215 babies with birth weight 401-1500g	Proportion of babies ≥1 BSI	Birth weight, gestational age, sex, ethnicity	No	No

(1998–2000)					
Perlman *et al*, 2007[58] 2 US NICUs (2001-2003)	2,935 babies	1) Number of first BSI/baby-days before first BSI	1) Birth weight	1) CVC Surgery Ventilation NC-CPAP (yes/no variables)	1) No
		2) Among babies treated with a CVC at any point: Number of first BSI/baby-days before first BSI	2) Birth weight	2) CVC Surgery Ventilation NC-CPAP (yes/no variables)	2) No
		3) Ratio of CVC-related BSI vs. non CVC-related BSI: Number of first BSI (CVC-related)/CVC days before first BSI Number of first BSI (non-CVC-related)/baby-days before first BSI	3) Birth weight	3) Surgery Ventilation NC-CPAP (yes/no variables) Duration of CVC (censored at onset of BSI)	3) No
		4) Ratio of BSI with gram-positive pathogens vs. BSI with gram-negative pathogens: Number of first BSI/baby-days before first BSI	4) Birth weight	4) CVC Surgery Ventilation NC-CPAP (yes/no variables)	4) No
Stover *et al*, 2001[59] 41 US NICUS (1997)	No number given	Incidence per CVC days	Birth weight	Duration of CVC	No

The UK Neonatal Staffing Study Group, 2002, 2005 54 UK NICUs (1998-1999)	13,334 babies <1 month old corrected for gestation	1) Proportion of babies ≥1 BSI[16]	1) Gestational age, SGA, sex, mode of delivery, diagnostic category, antenatal steroids	1) No	1) Provision of handwash basins and infection control nurse
		2) Proportion of babies ≥1 BSI[18]	2) Birth model: Gestational age, SGA, sex, mode of delivery, diagnostic category, antenatal steroids	2) No	2) Low birth weight patient volume, provision of consultants and nurses
		3) Proportion of babies ≥1 BSI[18]	3) 12hr model: admission temperature, blood analysis: most extreme PaCO2, mean appropriate FiO2 and lowest base excess	3) No	3) Low birth weight patient volume, provision of consultants and nurses

a – SGA - small for gestational age, CVC - central venous catheter, SNAP II - Score for Neonatal Acute Physiology II, NEC - necrotising enterocolitis, NC-CPAP - nasal cannula continuous positive airway pressure, CVC-related BSI - BSI in the presence of a CVC, with no other identifiable site of infection, non CVC-related BSI - BSI occurring without a CVC present, or with another identifiable site of infection.

Table 1.2 Variation in BSI incidence between NICUs before and after risk adjustment

Authors	Outcome measure	Between NICU variation reduced by risk adjustment?	How much residual variation between NICUs?
Brodie *et al*, 2000	Time to BSI after admission	Yes	Statistically significant variation between 3/6 NICUs
The Canadian Neonatal Network, 2002, 2005	1) Incidence per CVC days	1) Yes	1) Statistically significant variation for all CVC strata
	2) Proportion of babies with ≥1 BSI	2) Yes	2) Statistically significant variation for babies with birth weight <1500g
Carrieri *et al*, 2003	1) Time to BSI after admission	1) Unable to determine: no crude measures provided	1) BSI 3-10 days: statistically significant variation
	2) Time to BSI after admission	2) Unable to determine: no crude measures provided	2) BSI 11-35 days: statistically significant variation
Gaynes *et al*, 1991	Incidence per CVC days	Unable to determine: no crude measures provided	'Significant between centre differences', but no risk adjusted figures provided
NICHD, 2002	Proportion of babies ≥1 BSI	Unable to determine: no risk adjusted figures provided	'Statistically significant variation', but no risk adjusted figures provided
Perlman *et al*, 2007	1) Number of first BSI/baby-days before first BSI	1) Unable to determine: no crude measures provided	1) Statistically significant variation in the overall rate of BSI
	2) Among babies treated with a CVC at any point: Number of first BSI/baby-days before first BSI	2) Unable to determine: no crude measures provided	2) No statistically significant variation in the rate of BSI among babies treated with a CVC
	3) Ratio of CVC-related BSI vs. non CVC-related BSI Number of first BSI (CVC-related)/CVC days before first BSI Number of first BSI (non-CVC-related)/baby-days before first BSI	3) Unable to determine: no crude measures provided	3) No statistically significant variation in the ratio of CVC-related BSI vs. non CVC-related BSI

	4) Ratio of BSI with gram-positive pathogens vs. BSI with gram-negative pathogens: Number of first BSI/baby-days before first BSI	4) Unable to determine: no crude measures provided	4) Statistically significant variation in the ratio of BSI with gram-positive pathogens vs. BSI with gram-negative pathogens
Stover *et al*, 2001	Incidence per CVC days	Yes for babies with birth weight 1501-2500g	Variation remained, no information concerning statistical significance
The UK Neonatal Staffing Study Group, 2002, 2005	1) Proportion of babies with ≥1 BSI	1) Yes	1) Statistically significant variation in odds ratios between NICUs with >1 level 1 cot per handwash basin and NICUs with <1. More handwash basins led to lower outcomes Statistically significant variation in odds ratios between units with an infection control nurse and units without. Presence of an infection control nurse led to lower outcomes.
	2) Proportion of babies ≥1 BSI	2) Birth model: Yes	2) Statistically significant variation for NICUs allocated to different strata of consultant provision. Lower consultant availability led to lower odds ratios.
	3) Proportion of babies ≥1 BSI	3) 12hr model: Yes	3) Statistically significant variation for NICUs allocated to different strata of consultant provision. Lower consultant availability led to lower odds ratios.

Table 1.3 Risk adjustment in regional monitoring systems

System and setting (year established)	Population	Outcome measure	Outcome measures adjusted for:
The Canadian Nosocomial Infection Surveillance Program (CNISP)[62] Canada (2006)	21 hospitals Babies with a CVC inserted	Incidence of BSI per CVC days days of NICU stay	Birth weight Duration of CVC NICU stay
National Healthcare Safety Network (NHSN), previously the National Nosocomial Infections Surveillance System (NNIS)[64] USA NNIS (1970) NHSN (2005)	140 NICUs Babies with a CVC inserted, or on a ventilator	Incidence per CVC days days of NICU stay[b]	Birth weight Duration of CVC NICU stay
NEOCAT of CCLIN (Centre de Coordination de la Lutte contre les Infections Nosocomiales)[61] Paris and Western region, France (2006)	9 NICUs Babies with a CVC inserted for >48hrs	Incidence per CVC days	Baby susceptibility factors Procedure-related factors[c] Duration of CVC
NEO-KISS (Krankenhaus Infektions Surveillance System)[60] Germany (1997)	66 NICUs Babies with birth weight <1500g	Incidence per CVC days, peripheral VC days[d,e]	Birth weight Duration of CVC peripheral VC
Neonatal Infection Network (NeonIN) surveillance database[17] UK (2007)	12 NICUs (pending further expansion)	Frequency of BSI episodes[f]	None
Vermont Oxford Network[65] USA, UK (1998)	700 hospitals Babies with birth weight 501-1500g	Proportion of babies ≥ 1 BSI[f]	Birth weight
VICNISS Hospital Acquired Infection Surveillance System[63] Victoria, Australia (2002)	29 hospitals	Incidence per CVC days peripheral VC days	Birth weight Duration of CVC peripheral VC

b - Incidence of pneumonia also reported per ventilator days and days of NICU stay, and stratified by birth weight
c - Risk adjustment factors summarised for brevity

d - Peripheral venous catheter days
e - Incidence of pneumonia also reported per ventilator days and continuous positive airway pressure days. Incidence of necrotising enterocolitis reported by days of NICU stay
f - Outcome measures also reported for bacterial infection in cerebrospinal fluid and urine

2. Overview of areas addressed in this thesis

The main aim of this thesis was to establish risk factors for BSI incidence in NICUs, which could be adjusted for in order to give fair and meaningful comparisons of BSI incidence between hospitals. The results of various analytic approaches are compared and assembled to show a method of risk adjusted BSI monitoring that could be used in practice.

The study population comprised all babies admitted to three inner London NICUs from 2001 to 2005 (the precise months included varied according to the analysis). NICUs 1 and 2 are level 3 units, with approximately 260 (NICU 1) and 430 (NICU 2) admissions each year. NICU 3 is a level 1 to 2 unit, with approximately 250 admissions each year (Level 1, 2 and 3 NICUs are defined in the Appendix to Chapter 2).[62] All three units admit inborn babies and referrals.

All of the surveillance studies and regional monitoring systems reviewed in Chapter 1 relied on hospital staff entering the required information into a dedicated dataset. This study employed electronic, routine clinical records, which could accelerate data collection, minimise staff workload and cut costs in monitoring.

I analysed BSI episodes recorded in routine microbiology laboratory data, in relation to potential risk factors recorded in NICU administrative data. The potential risk factors analysed fell into the following categories: factors reflecting susceptibility to infection at birth (for example gestational age, birth weight and inborn/outborn status) and

procedure-related factors reflecting susceptibility during the NICU stay (for example level of care, total parenteral nutrition and ventilation).

I chose to present a *range* of analytic approaches for determining risk factors, for two reasons. Firstly, methods of data collection varied between NICUs. For example, for each baby, procedure-related factors could be recorded for each day of NICU stay, or as the sum of days treated with the procedure. This demanded a variety of corresponding statistical analyses. Secondly, I found that the most robust methods for determining risk factors were not appropriate in the context of routine monitoring, which demanded a simpler, more pragmatic approach. I present both simple and more complex methods, to assess consistency in their results. Table 2.1 gives a summary of the analytic approaches used. Wherever possible, analyses were performed for the hospitals separately and combined. This was to assess consistency in the effect of risk factors for BSI between NICUs, as well as to profit from a larger sample size with more explanatory power when the centres were combined.

I also discuss issues related to monitoring, such as the potential provided by routine hospital data, data requirements for monitoring, the establishment of a case definition for BSI, and difficulties in differentiating between: true BSI and contaminated blood culture results, and maternally-transmitted and hospital-acquired BSI.

Table 2.1 Summary of the analytic approaches used in this thesis

Chapter and analysis	Dataset	BSI episodes linked to individual babies?	Dates of BSI episodes analysed?	Birth susceptibility factors analysed?	Procedure-related factors analysed?	Outcome	Analytic approach	Relevance to NICU monitoring
Chapter 3 Aggregated analyses	Aggregated dataset containing monthly totals of BSI episodes and baby-days	No	Yes (by month only)	Yes	Yes	All BSI episodes Recurrent BSI episodes included	Analysed monthly rates of BSI Poisson generalised linear models	Simple risk adjusted analyses suitable for routine monitoring
Chapter 5								
1) Analyses of procedure-related factors recorded as the sum of days treated	1) Babies categorised according to baby susceptibility factors and the number of days treated with each invasive procedure	1) Yes	1) No	1) Yes	1) Yes	1) All BSI episodes occurring >48 hours after birth Recurrent BSI episodes included	1) Analysed rates of BSI by baby Poisson generalised linear models	1) An approach for analysing procedure-related factors recorded as the sum of days treated (as in the British Association of Perinatal Medicine minimum dataset prior to 2004)
2) Analyses of time to the development of BSI	2) As above	2) Yes	2) Yes	2) Yes	2) No	2) Number of days before first BSI episode occurring >48 hours after birth	2) Analysed time to first BSI episode Cox regression models Kaplan-Meier plots	2) Not appropriate for monitoring as cannot assess risk from procedure-related factors
Chapter 6 Analyses of factors predicting infection: poisson regression	Dataset with each baby-day labelled according to procedure-related exposures in	Yes	Yes	Yes	Yes, in the three days preceding a BSI episode	The first BSI episode occurring >48 hours after birth	Days with onset of a first BSI episode divided by total days of NICU stay. Baby-days censored at the first BSI episode.	A robust method to determine factors predicting BSI. Required data structure too complex for monitoring on a

	the previous three days						Poisson generalised linear models with generalised estimating equations	routine basis
Chapter 7 Analyses of factors predicting infection: case control study	Case control dataset, with censoring ages labelled according to procedure-related exposures in the previous three days	Yes	Yes	Yes	Yes, in the three days preceding a BSI episode	The first BSI episode occurring >48 hours after birth	Ratio of the odds of BSI in cases and controls Conditional logistic regression	As above
Chapter 8								
1) Method for prospective monitoring: yearly standardised infection ratios	1) Aggregated dataset containing monthly totals of BSI episodes and baby-days	1) No	1) Yes (by year only)	1) Yes	1) Yes	1) All BSI episodes occurring >48 hours after birth Recurrent BSI episodes included	1) Observed number of BSI episodes/expected number of BSI episodes	1) Robust method for routine monitoring
2) Method for prospective monitoring: quarterly sequential probability ratio test	2) As above	2) No	2) Yes (by quarter only)	2) Yes	2) Yes	2) As above	2) Observed number of BSI episodes/expected number of BSI episodes Thresholds to determine when observed deviates unacceptably from expected	2) As above

3. Simple risk adjusted analyses in electronic routine data

3.1 Summary

Hospital laboratory and administrative data were analysed for admissions over four years at two of the inner London NICUs. A dataset was generated of aggregated monthly totals of blood cultures, BSI episodes and baby-days for strata of level of care, gestational age at birth and hospital. The outcome was BSI episodes per 1000 baby-days. Level of care, and to a lesser extent, gestational age, were strong risk factors for BSI. The rate ratio for BSI, adjusted for gestational age and sampling frequency and relative to the baseline, special care, was 3.37 (95% CI 2.38, 4.77) in intensive care and 4.40 (95% CI 3.15, 6.15) in high dependency care.

I demonstrate how electronic routine National Health Service data could be aggregated for BSI monitoring in NICUs. Adjustment of BSI incidence by level of care and gestational age could produce risk adjusted rates for meaningful comparisons between NICUs. I present simple risk adjusted analyses that could be carried out by routine prospective monitoring systems.

3.2 Introduction

Hospital laboratory and administrative data were analysed for admissions over four years at two of the inner London NICUs. As NICUs participating in monitoring have

limited time and resources, a dataset was generated which would permit the analysis of BSI incidence with minimal data manipulation. This consisted of aggregated monthly totals of blood cultures, BSI episodes and baby-days, stratified by potential risk factors for BSI. The outcome was BSI episodes per 1000 baby-days at each stratum.

Potential risk factors were analysed in view of their suitability for risk adjusting between unit comparisons of BSI incidence. Gestational age at birth and NHS level of care were chosen for their existence and reliability in routine administrative records, and their likely association with BSI. Data concerning gestational age and level of care are routinely recorded and relatively complete because they are used for costing purposes.[1] The association between gestational age and BSI is well-known.[30,36] As a standardised measure of the intensity of care in NICUs, level of care[68] is likely to be associated with BSI and has not previously been evaluated in risk adjusted analyses. UK NHS levels of care are defined in detail in the Appendix to Chapter 3. I present simple risk adjusted analyses that could be carried out by routine prospective monitoring systems.

3.3 Methods

3.3.1 Study population

Data were analysed for babies who were inpatients at NICU 1 and NICU 2, from the 1st of May 2001 to the 28th of February 2005.

Records for NICU 3 could not be used in this analysis because they did not contain information on level of care for each day of NICU stay (this is explained further in Chapters 4 and 5).

3.3.2 Case definition

An episode of BSI was defined as one or more blood cultures in which the same bacterial organism was isolated within a seven day period. For a given baby, multiple positive cultures could relate to the same BSI episode. If this was the case, within the seven day period, the date of the first blood sample was taken as the date of the episode. In neonates, a proportion of blood cultures positive for CONS may reflect contamination by skin commensals. Huang *et al*. (2003) carried out a prospective cohort study in a Taiwanese hospital between 1998 and 2001. Of the babies and children admitted to the hospital's neonatal and paediatric intensive care units, 60 experienced a total of 67 episodes of CONS-positive blood cultures. Thirty (45%) of these episodes reflected contamination, if true BSI was defined as: the same strain of CONS in 'sequential' blood cultures or a positive blood culture accompanied by clinical symptoms. 'Sequential' blood cultures were not defined, and no information was given regarding the reasons for blood sampling. Patients with a blood culture result revealing more than one organism were excluded from the analysis.[70] To explore BSI potentially due to culture contamination, I performed separate analyses for total BSI, CONS, and non-CONS BSI. I also adjusted for differences in blood sampling frequency between hospitals as I expected that this could influence comparisons. The more cultures taken the greater the risk of detecting asymptomatic BSI or a contaminated culture.

3.3.3 Creating an aggregated dataset from electronic routine data

Linkage of administrative records with blood culture records is not routinely performed in NICUs. Chapter 4 proposes that records could be linked automatically within the hospital to facilitate BSI monitoring. For this chapter, a data manager performed data linkage and prepared the data for analysis. Microbiology laboratory records, and records from the Patient Administration System (PAS) were extracted from 2/10/1995 to 19/5/2005 for NICU 1, and from 1/1/2000 to 9/9/2005 for NICU 2. Blood cultures in the laboratory records were matched with PAS daily records using baby identity numbers and dates. Some blood sample dates fell just outside the corresponding baby's admission period. For these discrepancies in data entry, the rules in Figure 3.1 were applied. These rules applied to few blood cultures, 53 (1.18%) of the total 4482 blood cultures from NICU 1 and 28 of the 3151 (0.89%) blood cultures from NICU 2. 385 (8.6%) blood cultures from NICU 1 and 255 (8.1%) blood cultures from NICU 2 did not match baby identity numbers or admission periods in PAS records, and were excluded.

17 babies in NICU 1 and 3 babies in NICU 2 had missing gestational ages. For NICU 1, gestational ages were recovered for 305 babies from the unit's separate neonatal dataset. Daily records for each baby were aggregated to give monthly totals of blood cultures, infection episodes for CONS, non-CONS and total BSI and baby-days at each level of care and gestational age group. Datasets for the two hospitals were combined for the months for which they *both* supplied data; Jan 2000 to May 2005 inclusive. Within this period, an error in data extraction from the laboratories meant that blood culture data were missing for the months of: March to May 2005 for NICU 1; and January 2000 to April 2001 for NICU 2, so the data used for the analysis covered the complete months

of May 2001 to February 2005. The structure of this aggregated dataset is demonstrated in Figure 3.2.

3.3.4 Statistical analyses

Differences between NICUs were assessed for proportions of babies experiencing one or more BSI, proportions of BSI that were recurrent or repeat infections within babies (using two-sample *Z*-tests for proportions), and median length of NICU stay (using the Pearson chi-squared test of the equality of medians).

I calculated the rate of BSI per baby days of stay. Poisson generalised linear models were fitted to investigate relationships between BSI and level of care, gestational age at birth, NICU and the number of blood samples taken. I also examined the relationship between BSI and month, in order to detect changes over time. Adjusted models were constructed using a forward stepwise model selection strategy, that fitted covariates which showed statistically significant relationships ($p<0.01$) with BSI in crude analyses. Goodness of fit was compared between models using Akaike's information criterion (AIC, defined below).[71] When the optimal combination of covariates had been defined, the AIC was compared between models fitted with and without interactions between level of care and gestational age. I also fitted a Poisson generalised linear model to examine differences in the number of blood samples taken between NICUs.

The AIC is a parsimonious measure of goodness of fit for an estimated statistical model, which describes a trade-off between model precision (a greater log likelihood) and complexity (a higher number of parameters). Within a given dataset, competing models

may be ranked according to their AIC, with the one having the lowest AIC being considered as the best, ie. the model with the fewest parameters that still provides an adequate fit to the data. The AIC is defined as:

$AIC = - 2\ln(L) + 2k$

k = number of parameters in the model

L = maximised value of the likelihood function[71]

The analyses were repeated for total, CONS and non-CONS BSI, and for each of the hospitals separately and combined.

Monthly rates of total BSI were plotted by level of care for each NICU. Rates were aggregated for high dependency and intensive care because they were similar and because high dependency care had small numbers of babies for some months.

All analyses for this thesis were carried out using R 2.7.0[72], Stata 10.0[73] and Microsoft Office Excel 2003[74] in a Windows environment.

3.4 Results

There were 208 BSI episodes at NICU 1 and 225 BSI episodes at NICU 2. Table 3.1 shows the rates of BSI episodes for different organism classes. Similar distributions of organisms were found in both NICUs, with CONS predominating. In contrast to all subsequent chapters, results for statistical analyses in this chapter included probable

maternally-transmitted BSI occurring during the first 48 hours of life. Maternally-transmitted BSI will be discussed in Chapter 5.

I made a crude comparison between NICUs based on the proportion of babies who had one or more BSI episodes during their NICU stay. These proportions differed slightly, but non-significantly at the 1% level, for CONS BSI (10.9% for NICU 1 and 8.5% for NICU 2, two-sample *Z*-test p=0.04), and were similar for non-CONS BSI (3.4% for NICU 1 and 3.5% for NICU 2, p=0.86). Slightly more recurrent BSI occurred in NICU 1 compared with NICU 2, but this difference was not statistically significant: 20.8% of CONS episodes were recurrences in NICU 1 versus 13.3% in NICU 2 (p=0.07); 1.7% of non-CONS episodes were recurrences in NICU 1 versus 1.3% in NICU 2 (p=0.82). The median length of stay differed between NICUs (13 days in NICU 1 and 7 days in NICU 2 (Pearson chi-squared test p<0.001)). Tables 3.3, 3.4 and 3.5 show that crude and adjusted *rates* of BSI did not differ between NICUs and remained stable over time, whether measured as total BSI, CONS or non-CONS organisms.

In terms of the AIC, level of care was the strongest single risk factor for BSI, with those in high dependency and intensive care being most at risk. Table 3.2 shows how the best adjusted model was selected using the AIC. This model included both level of care and gestational age at birth. These findings did not change when CONS and non-CONS BSI were analysed separately (Tables 3.3, 3.4 and 3.5). No significant interactions were found between level of care and gestational age.

As expected, gestational age was significantly associated with the rate of BSI in adjusted analyses, and this finding remained when CONS and non-CONS BSI were analysed separately (Tables 3.3, 3.4 and 3.5). As the last column shows, BSI risk was highest in the most premature and in term babies. In comparison, premature babies born in the third trimester, between 32 and 37 weeks, had the lowest risk.

The rate of blood sampling per 1000 baby days was significantly higher in NICU 2 (78.71) than in NICU 1 (61.85); the crude rate ratio was 1.27, (95% CI 1.20-1.35, $p<0.001$). Sampling rate was also significantly associated with the rate of BSI (CONS and non-CONS) in crude analyses. These findings suggest that differences in sampling rate could confound comparisons of BSI rates between NICUs, so sampling rate was included in the adjusted analyses. However, in the final models, its effect was no longer statistically significant after adjustment for level of care and gestational age (Tables 3.3, 3.4 and 3.5).

Most of the above findings remained unchanged when the NICUs were analysed separately. However, gestational age was a weaker risk factor for BSI in NICU 1, as its relationship with CONS BSI diminished in adjusted analyses. The sampling rate in NICU 1 was also significantly associated with CONS BSI in adjusted analyses (Appendix to Chapter 3, Tables 3.6 to 3.11).

Figure 3.3 shows monthly rates of total BSI, by level of care for each NICU.

3.5 Discussion: the potential of electronic routine data for blood stream infection monitoring

Both hospitals used electronic, rather than paper-based records, which has several advantages. Electronic platforms can carry large amounts of information whilst using minimal storage space, and can be easily backed-up to prevent loss of data. They can be accessed remotely, admit several users simultaneously, and can be accessed in a controlled and secure way for data protection, for example by requiring passwords. They can also be continuously modified and updated, and exported in electronic format ready for analysis. Since 2005, in view of the advantages of electronic data, an NHS web platform called Neonatal.net was developed by Clevermed Ltd, and is currently used in 70% of UK NICUs.[1] Neonatal.net enables real-time electronic entry of patient data,[75] and was designed to be incorporated into the NHS National Programme for IT when this is rolled out nationally.[1]

In comparison with study-specific data collection, the use of routine hospital data may accelerate, facilitate and cut costs in NICU BSI monitoring. Because of this, it may also ensure that monitoring is sustainable over the long term. This chapter demonstrates a dataset that could be produced by hospital data managers relying exclusively on electronic routine data, and it demonstrates how this dataset could be used for risk adjusted monitoring of BSI in NICUs. Although the dataset would be suitable for monitoring once risk factors for BSI have been established, it had drawbacks for the initial identification of risk factors. A structure incorporating more variables was needed to evaluate more potential risk factors for BSI. In addition, the dataset could not reveal *predictive* associations between risk factors and BSI. For example, the association

found between level of care and BSI may be due to increased intensities of care *contributing to* BSI, but increased intensities of care may also be the *consequence* of infections causing babies' conditions to deteriorate. It would be useful to determine *predictive* factors for BSI, so that clinicians can identify high risk groups who could benefit from preventive action or close monitoring. To examine predictive associations, analyses must focus on potential risk factors in the days *preceding* the onset of BSI. Chapter 4 describes the preparation of a dataset suited to further exploratory analyses of risk factors for BSI and predictive associations. It also describes alternative strategies for data linkage, as this chapter revealed that around 8% of blood culture records did not match baby identity numbers or admission periods in PAS records. Chapter 4 also highlights further aspects of electronic routine data that are necessary if it is to be used for BSI monitoring.

The fact that NHS level of care was the strongest risk factor for BSI is not surprising as it is by definition a measure of vulnerability. The key implication is that adjustment of BSI incidence by level of care may be a simple method to give meaningful comparisons between NICUs. More specifically, the results suggest that BSI incidence could be stratified by both level of care and gestational age at birth as gestational age was also an independent risk factor for BSI in NICU 2. Data on gestational age and level of care is standardised across the NHS, routinely recorded and relatively complete and accurate because it is used for costing purposes.[1] In Chapter 9 I will explain how appropriate methods of risk adjustment may change as the availability of data expands.

The findings highlight the importance of taking into account length of stay. Median length of stay in NICU 1 was nearly twice as long as for NICU 2, so although NICU 1 may have had a slightly higher proportion of *babies* experiencing CONS BSI, the two units had similar numbers of CONS BSI episodes per *days of stay*. Despite these discrepancies, proportions of babies experiencing one or more infections are used in many studies reporting between-NICU comparisons.[30,36,52] Incidence rates based on the number of BSI episodes divided by the total days of NICU stay may be preferable. These take into account differences in length of stay and capture recurrent infections. An awareness of length of NICU stay and recurrent BSI would increase clinicians' understanding of reasons for variation between NICUs, in order to target infection control more effectively. Recurrent infections represented up to 20% of CONS episodes and up to 2% of non-CONS episodes. An increased length of stay may increase the risk of BSI, and may be amenable to reduction.

In most analyses, blood sampling rate in the unit was not a significant risk factor for BSI, but it was weakly and significantly associated with CONS BSI in NICU 1. This suggests that a proportion of the 'CONS episodes' recorded for NICU 1 may have been an artefact of sampling itself, reflecting contaminated blood cultures. Monitoring systems should be aware that differences in sampling frequency can confound associations with BSI. A disadvantage of routine data is the lack of clinical symptoms which help to differentiate between true BSI and contamination. Reporting rates by broad organism groupings, as in this analysis for CONS and non-CONS, may be the only way to differentiate between infections more or less likely to represent contamination. Reporting rates by finer organism classes would not be practical, as

numbers of BSI episodes by year or month would be sparse (as shown in Table 3.1). The case definition for BSI, adjustment for sampling frequency and a method for differentiating maternally-transmitted from hospital-acquired BSI are discussed further in Chapter 5.

Aspects of this analysis have been published in two letters to the 'Journal of Hospital Infection' (included in the Publications Appendix).[76,77]

Key conclusions of Chapter 3

Findings

- I demonstrated how a dataset relying exclusively on electronic routine data could be used for risk adjusted analyses of BSI incidence in NICUs.
- NHS level of care and gestational age at birth were the strongest independent risk factors for BSI.

Conclusions

- Electronic routine hospital data has the potential to facilitate long-term monitoring of BSI in NICUs.
- Adjustment of BSI rates by level of care and a factor reflecting susceptibility to BSI at birth, such as gestational age, may produce meaningful comparisons between NICUs.

Figure 3.1 Rules for assigning blood cultures to PAS admission days

A blood culture can be matched to a PAS admission day if:

1. PAS admission date < Blood sample date < PAS discharge date
OR
2. Blood sample date = PAS date of birth & PAS admission date = PAS date of birth + 1
OR
3. Blood sample date = PAS discharge date + 1

For condition 1, the blood sample date was not altered
For condition 2, the blood sample was assigned to the PAS admission date
For condition 3, the blood sample was assigned to the PAS discharge date

Figure 3.2 Diagram to describe stays in the NICU for three hypothetical babies over one month, and how these stays would be translated into the aggregated dataset

Special care	
High dependency	
Intensive care	

CONS infection episode	**C**
Non-CONS infection episode	**NC**
Blood sample taken	**S**

Days of May 2001 at NICU 1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**…**	**31**
Baby 1 Gestational age: 25 weeks Admitted 5/5/01 Died 12/5/01							**C S**			**NC S**												
Baby 2 Gestational age: 36 weeks Admitted 16/5/01 Discharged 20/05/01																**C S**						
Baby 3 Gestational age: 37 weeks Admitted 3/5/01 Discharged 7/5/01			**C S**		**S**																	

Figure 3.2 (continued) Aggregated dataset

				Totals of:				
Hospital	**Month**	**Level of care**	**Gestational age group**	**CONS infection episodes**	**Non-CONS infection episodes**	**All BSI infection episodes**	**Baby-days (denominator)**	**Blood samples taken[a]**
1	May 2001	Special care	<26	0	0	0	0	0
1	May 2001	Special care	26-<28	0	0	0	0	0
1	May 2001	Special care	28-<32	0	0	0	0	0
1	May 2001	Special care	32-<37	0	0	0	2	0
1	May 2001	Special care	≥37	0	0	0	1	0
1	May 2001	Special care	Missing	0	0	0	0	0
1	May 2001	High dependency care	<26	0	0	0	0	0
1	May 2001	High dependency care	26-<28	0	0	0	0	0
1	May 2001	High dependency care	28-<32	0	0	0	0	0
1	May 2001	High dependency care	32-<37	1	0	1	3	1
1	May 2001	High dependency care	≥37	0	0	0	1	0
1	May 2001	High dependency care	Missing	0	0	0	0	0
1	May 2001	Intensive care	<26	1	1	2	8	2
1	May 2001	Intensive care	26-<28	0	0	0	0	0
1	May 2001	Intensive care	28-<32	0	0	0	0	0
1	May 2001	Intensive care	32-<37	0	0	0	0	0
1	May 2001	Intensive care	≥37	1	0	1	3	2
1	May 2001	Intensive care	Missing	0	0	0	0	0

a - Blood samples only stratified by level of care, not by gestational age

Figure 3.3 Monthly rates of total BSI and 95% confidence intervals, by level of care for each NICU

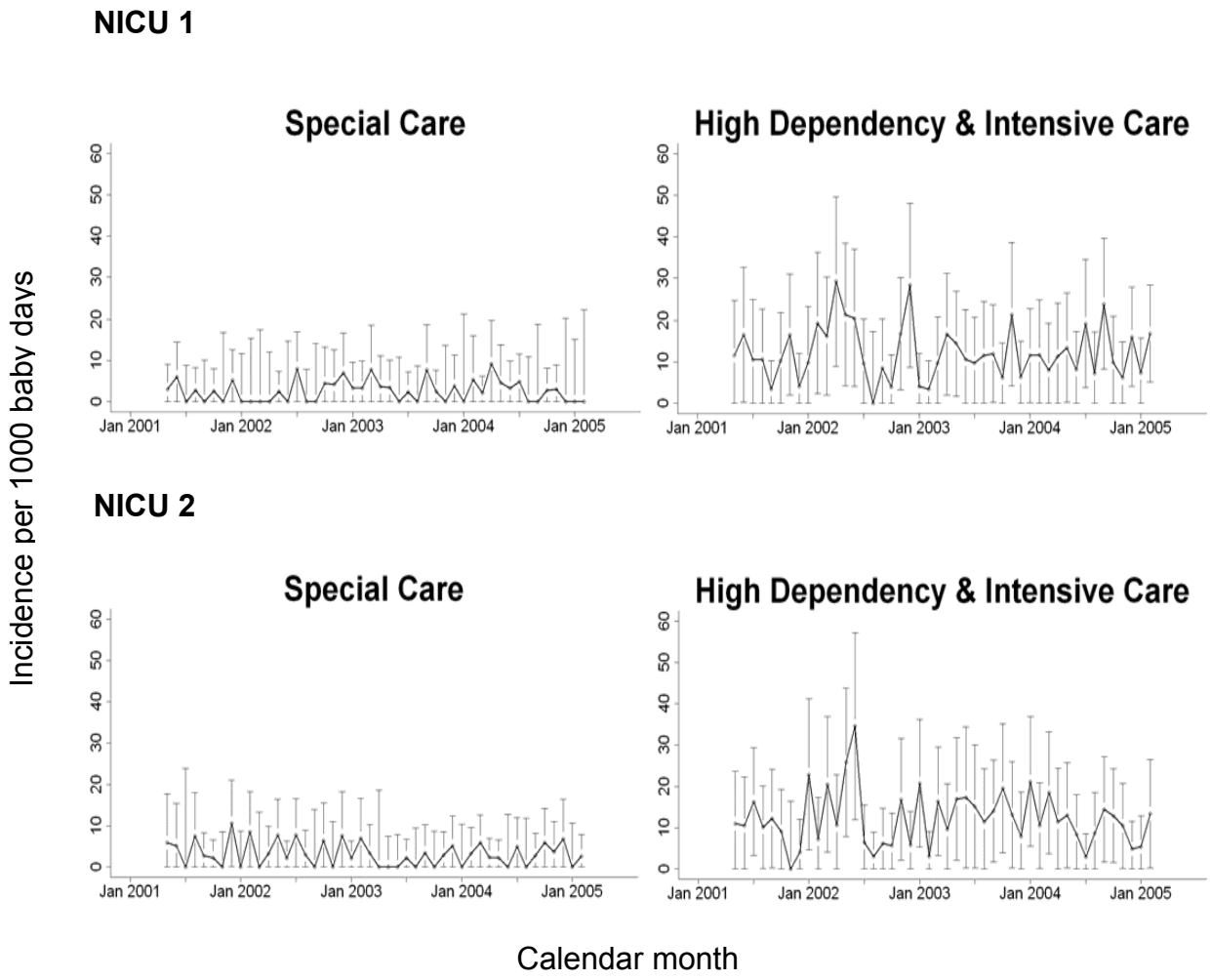


Table 3.1 Rates of BSI per 1000 baby days (numbers) according to organism groupings[b]

NICU 1								NICU 2						
Year	Total baby-days	CONS	Group B strep	Other GPos	Gneg	Yeasts	Total	Total baby-days	CONS	Group B strep	Other GPos	Gneg	Yeasts	Total
2001	4865	4.52(22)	0.41(2)	0(0)	1.03(5)	0(0)	5.96(29)	4843	4.54(22)	0(0)	1.45(7)	1.03(5)	0(0)	7.02(34)
2002	6838	6.43(44)	0.44(3)	0.88(6)	0.73(5)	0.15(1)	8.63(59)	7723	5.57(43)	0.26(2)	1.68(13)	0.65(5)	0.13(1)	8.29(64)
2003	7370	4.61(34)	0.27(2)	1.22(9)	0.54(4)	0(0)	6.65(49)	8086	5.44(44)	0.25(2)	0.62(5)	0.87(7)	0.12(1)	7.30(59)
2004	7315	5.47(40)	0.27(2)	1.09(8)	1.23(9)	0(0)	8.07(59)	8475	5.19(44)	0.59(5)	1.06(9)	0.35(3)	0(0)	7.20(61)
2005	1292	6.19(8)	0(0)	0.77(1)	1.55(2)	0(0)	8.51(11)	1389	4.32(6)	0(0)	0.72(1)	0(0)	0(0)	5.04(7)

b - Columns from left to right in each NICU refer to total baby-days, Coagulase-negative staphylococcus, Group B streptococcus, Gram-positive organisms other than Group B streptococcus, Gram-negative organisms, Yeasts, total

.

Table 3.2 NICU 1 and NICU 2 combined: forward model selection strategy for choosing the best adjusted model for total BSI

Potential risk factors included in model (factors were included if they showed statistically significant relationships (p<0.01) with total BSI in crude analyses)	**AIC**
Level of care	1524.9
Gestational age	1636.1
Number of blood samples taken	1636.7
Level of care and gestational age	1499.5
Level of care, gestational age and number of blood samples taken	1498 – lowest AIC indicates the best model
Level of care interacting with gestational age, and number of blood samples taken	1503.3

Table 3.3 NICU 1 and NICU 2 combined: crude and adjusted rate ratios for total BSI

Potential risk factor	BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value			Adjusted rate ratios (95% CI) *p*-value		
NHS level of care								
Intensive care	279/23,018	(12.12)	4.16	(3.27, 5.29)	<0.001	3.37	(2.38, 4.77)	<0.001
High dependency care	67/5177	(12.94)	4.11	(2.99, 5.65)	<0.001	4.40	(3.15- 6.15)	<0.001
Special care	87/30,001	(2.90)		1			1	
Total	**433/58,196**	**(7.44)**						
Gestational age (weeks)								
<26	136/11,977	(11.36)	1.29	(0.99, 1.67)	0.057	0.68	(0.51, 0.92)	0.011
26-<28	72/7698	(9.35)	1.05	(0.77, 1.42)	0.762	0.62	(0.45, 0.86)	0.004
28-<32	84/14,604	(5.75)	0.66	(0.49, 0.88)	0.005	0.51	(0.38, 0.69)	<0.001
32-<37	45/13,038	(3.45)	0.39	(0.28, 0.56)	<0.001	0.43	(0.30, 0.61)	<0.001
≥37	96/10,871	(8.83)		1			1	
Missing[c]	0/8							
Hospital								
NICU 2	225/30,516	(7.37)	0.98	(0.81, 1.19)	0.866			
NICU 1	208/27,680	(7.51)		1				
Number of blood samples taken								
Linear increase			1.03	(1.03, 1.04)	<0.001	1.01	(1.00, 1.03)	0.062
Month								
Linear increase			1.00	(0.99, 1.01)	0.881			

Table 3.4 NICU 1 and NICU 2 combined: crude and adjusted rate ratios for CONS BSI

Potential risk factor	CONS episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value			Adjusted rate ratios (95% CI) *p*-value		
NHS level of care								
Intensive care	202/23,018	(8.78)	4.36	(3.27, 5.82)	<0.001	3.14	(2.07, 4.74)	<0.001
High dependency care	45/5177	(8.69)	4.00	(2.72, 5.89)	<0.001	4.39	(2.93, 6.57)	<0.001
Special care	60/30,001	(2.00)		1			1	
Total	**307/58,196**	(**5.28**)						
Gestational age (weeks)								
<26	96/11,977	(8.02)	1.51	(1.09, 2.09)	0.014	0.80	(0.56, 1.15)	0.222
26-<28	57/7698	(7.40)	1.37	(0.95, 1.98)	0.089	0.81	(0.55, 1.20)	0.298
28-<32	65/14,604	(4.45)	0.84	(0.59, 1.20)	0.333	0.65	(0.45, 0.94)	0.021
32-<37	31/13,038	(2.38)	0.45	(0.29, 0.69)	<0.001	0.49	(0.31, 0.75)	0.001
≥37	58/10,871	(5.34)		1			1	
Missing[c]	0/8							
Hospital								
NICU 2	159/30,516	(5.21)	0.98	(0.78, 1.22)	0.839			
NICU 1	148/27,680	(5.35)		1				
Number of blood samples taken								
Linear increase			1.04	(1.03, 1.05)	<0.001	1.02	(1.00, 1.03)	0.044
Month								
Linear increase			1.00	(0.99, 1.01)	0.878			

Table 3.5 NICU 1 and NICU 2 combined: crude and adjusted rate ratios for non-CONS BSI

Potential risk factor	Non-CONS episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value			Adjusted rate ratios (95% CI) *p*-value		
NHS level of care								
Intensive care	77/23,018	(3.35)	3.70	(2.38, 5.73)	<0.001	4.01	(2.12, 7.60)	<0.001
High dependency care	22/5177	(4.25)	4.34	(2.47, 7.63)	<0.001	4.39	(2.43, 7.95)	<0.001
Special care	27/30,001	(0.90)		1			1	
Total	**126/58,196**	(**2.17**)						
Gestational age (weeks)								
<26	40/11,977	(3.34)	0.96	(0.61, 1.49)	0.848	0.51	(0.31, 0.85)	0.009
26-<28	15/7698	(1.95)	0.55	(0.30, 1.00)	0.051	0.32	(0.17, 0.61)	<0.001
28-<32	19/14,604	(1.30)	0.37	(0.22, 0.65)	<0.001	0.29	(0.17, 0.51)	<0.001
32-<37	14/13,038	(1.07)	0.31	(0.17, 0.57)	<0.001	0.34	(0.18, 0.63)	0.001
≥37	38/10,871	(3.50)		1			1	
Missing[c]	0/8							
Hospital								
NICU 2	66/30,516	(2.16)	1.00	(0.71, 1.42)	0.998			
NICU 1	60/27,680	(2.17)		1				
Number of blood samples taken								
Linear increase			1.03	(1.01, 1.04)	0.001	1.00	(0.98, 1.03)	0.763
Month								
Linear increase			1.00	(0.98, 1.01)	0.606			

c - Babies with missing variables were few and experienced few episodes of BSI. For this reason I considered it acceptable to remove them from the analyses.

4. Methods of data linkage and data requirements for monitoring

4.1 Summary

Further analyses of potential risk factors for BSI required the preparation of a dataset with a more complex structure to that described in Chapter 3, including the timing of potential risk factors occurring before infection. This chapter describes how I generated the more complex dataset, and how I employed various matching strategies to improve the linkage of laboratory blood culture records with administrative records.

Using the raw datasets for NICUs 1, 2 and 3, I linked blood culture records with administrative records using baby identity number and blood sample date. Records with no matches in this first step were linked using other identifiers such as date of birth and sex. Between 6% and 18% of blood culture records found no matches in administrative data. Datasets were prepared with records for each baby-day, including precise dates of BSI episodes and invasive procedures.

The data management was laborious, and it revealed aspects of electronic routine hospital data that could be improved to facilitate BSI monitoring. These include a common data system for all participating NICUs, automatic linkage of microbiology laboratory blood culture records with this common system, and the use of daily patient care records.

4.2 Introduction

As described in Chapter 3, after demonstrating the structure of a dataset suitable for routine monitoring, it was necessary to build a more complex dataset to determine risk factors for BSI and predictive associations. Factors predicting infection are useful for identifying high risk groups that may benefit from close monitoring or infection control interventions. To identify potentially *predictive* relationships, invasive procedures can be examined in the few days *prior* to the development of a BSI episode. The analyses in Chapter 3 relied on a dataset of aggregated monthly totals of infections and baby-days, for strata of potential risk factors. An analysis of *predictive* relationships required a dataset with a record for each baby-day, including precise dates of procedure-related factors and BSI episodes. In addition, as our data manager was unable to match approximately 8% of blood culture records with PAS records, I wanted to assess whether non-matches on baby identity number, possibly due to data entry errors, could be matched using other information, for example name, date of birth and sex.

In this chapter I describe the the development and structure of the raw datasets for NICUs 1, 2 and 3, before explaining the procedures I used for data linkage and data management at each NICU. The Discussion section relates the structure of the raw NICU patient data to requirements for BSI monitoring. Current developments in regional shared, electronic routine medical record systems form a background to this discussion.

4.3 Development and structure of the raw datasets

Raw datasets for all three NICUs were extracted by hospital data managers in 2005, before I started this PhD project in October 2006, except for the separate neonatal dataset from NICU 1, which was extracted in December 2006. I wrote to clinicians, a microbiologist and a data manager at the three NICUs to enquire about the development of the datasets, their responses form the basis of this section (personal communication, Dr Paul Ostro, University College London Hospitals NHS Trust, Dr Stephen Kempley and Dr Mike Millar, both at Barts and The London NHS Trust and Mayank Patel, Royal Free Hampstead NHS Trust). I also visited NICU 1 to learn about its clinical activities and data collection processes.

Two types of data systems were used to store administrative and care information: Patient Administration Systems (PAS) (NICUs 1 and 2), and separate neonatal data systems (NICUs 1 and 3). PAS were used primarily to organise administrative activities within the hospital: ordering blood tests and x-rays, organising appointments in clinic, producing annual statistics and providing information for costing. PAS data were mainly entered by trained ward clerks, using information provided by medical and nursing staff. PAS were descended from computerised hospital records installed in the 1970s, and had been updated in the 1980s at NICU 1 and in the 1990s at NICU 2.

In more recent years separate neonatal data systems were developed specifically for the NICU environment at NICUs 1 and 3 to help organise neonatal care, with information entered by clinical staff, often by junior doctors. Information concerning blood cultures

was stored separately in microbiology laboratory data systems, whose main function was to communicate the results of blood cultures to clinical staff.

Table 4.1 shows the structure and content of the raw datasets for all three NICUs. PAS data at NICU 1 were structured as a record for each NICU admission with dates and times of entry and exit to: the NICU, each level of care and other hospital specialties to which babies were admitted. The more modern PAS at NICU 2 incorporated a record for each baby-day and recorded procedure-related factors as either present or absent. The separate neonatal data systems at NICUs 1 and 3 contained a record for each baby including the sum of days treated with procedure-related factors. Microbiology laboratory data had a similar structure at all three NICUs, storing the date and result for each blood culture.

As PAS had hospital-wide applications, datasets extracted from these systems contained dates of discharge to other hospital specialties including surgery. No other information was recorded concerning care outside the NICU, so it was unclear how many of these periods involved transfer to another hospital. Because NICU 1 provides specialist surgical care, we can assume that most babies remained within the hospital. At NICUs 2 and 3, babies requiring specialist care would mostly have been discharged to a tertiary paediatric surgical unit nearby.

4.4 Data linkage for NICU 1

4.4.1 Data linkage

Conversion of Patient Administration System records to daily records

To match blood culture records with PAS admission days, PAS data had to be expanded to contain a record for each baby-day. Entry and exit to each level of care was denoted by a date and time, and some levels converged on the same day. For example, baby 1001 may have exited high dependency care and entered special care on the 11th July 2002 at midday. To expand the data into baby-days, such days had to be assigned a single level of care for simplicity, and I chose to assign the level of care to which the baby was entering. For the example above, for baby 1001, the 11th July 2002 would be assigned to special care. Another approach would have been to assign the highest level of care which the baby experienced that day. For the example above, the 11th July 2002 would be assigned to high dependency care. However this would have resulted in the more intensive levels of care being overrepresented in the dataset. Of the 66,491 baby-days in the raw PAS data, 64,192 (96.5%) were assigned to NICU levels of care, 1667 (2.5%) were assigned to other hospital specialties such as paediatrics or the maternity ward, and 632 (0.95%) were assigned to surgery.

Linking blood culture records with Patient Administration System records

Laboratory blood culture records were first linked to admission days in PAS using baby identity numbers and blood sample dates (using the rules for assigning blood cultures to PAS admission days described in Figure 3.1, Chapter 3). Blood culture records not

matching PAS admission days in this first step were matched using date of birth and sex (the only identifying information available in the laboratory data) and blood sample date. As date of birth and sex did not uniquely identify babies, hospital specialty information was also required to match. Of the remaining 264 blood cultures which could not be linked to PAS records, 27 tested positive for BSI and only 58 had hospital specialty recorded as NICU (either special care, high dependency or intensive care). Figure 4.1 summarises the linkage of blood culture records with PAS records, showing the numbers matched at each step.

Linking separate neonatal data system records with Patient Administration System records

The separate neonatal data system consisted of an admission dataset and a ventilation dataset. The admission dataset consisted of 2570 records (2570 babies). 2458 records were matched with babies in PAS records using baby identity number. A further 11 records were matched using date of birth, sex and date of admission. This left 101 records unmatched (4.1% of the total separate neonatal admission records). The ventilation dataset consisted of records for 1294 babies receiving ventilation, and 971 could be matched with babies in PAS records using baby identity number. Most of the remaining 323 records (25% of the total ventilation records) probably referred to babies admitted outside the time period for which PAS records were provided. This cannot be assessed as the ventilation records did not contain dates of birth or admission. This also meant that these remaining records could not be matched on other identifiers.

4.4.2 Data cleaning

For data fields included in both the PAS records and the separate neonatal data system, the PAS information was used for analysis unless variables were found to be missing. 325 babies had missing gestational ages at birth in PAS records, of which 304 had this information recovered from the separate neonatal records. Similarly, 350 babies had missing delivery method information in PAS records, of which 299 had this information recovered from the separate neonatal data. Data entry errors resulted in three babies with years of birth prior to 1980. These were corrected to correspond with the year of admission. Four babies had negative numbers recorded for their days with ventilation, and these were corrected by calculating the duration of ventilation by subtracting the admission date from the extubation date.

4.5 Data linkage for NICU 2

4.5.1 Data linkage

Preparation of Patient Administration System records

The version of PAS employed by NICU 2 consisted of baby, admission and daily care records, which matched up exactly using baby identity numbers. These three datasets matched exactly because they formed an integrated system. Baby and daily care information could not be entered without an admission record. Unlike data from NICU 1, data from NICU 2 did not include days spent in other hospital specialties or in surgery. These days could be inferred however, if a baby had been discharged from NICU then readmitted, using the field concerning where the baby was discharged to.

Calculating the days between discharge and readmission I was able to input and label these missing days. Of the resulting total 45,727 baby-days, 44,450 (97.21%) were assigned to NICU levels of care, 230 (0.50%) were assigned to other hospital specialties, 1,025 (2.24%) were assigned to surgery and 22 (0.05%) were missing a specialty.

Linking blood culture records with Patient Administration System records

Laboratory blood culture records were linked to admission days in PAS using baby identity numbers and blood sample dates (using the rules described in Figure 3.1, Chapter 3). 266 records (8.44% of the total blood culture records) found no matches, of which 32 tested positive for BSI. As the laboratory records contained no identifiers other than baby identity number, further matching was not possible, as shown in Figure 4.2.

4.5.2 Data cleaning

Four babies had dates of birth recorded as occurring after their admission dates. Either the date of birth or the admission date was corrected, by checking when babies were born and admitted to NICU in the daily care record.

Comparison with the data management described in Chapter 3 for NICUs 1 and 2

In comparison with the data linkage performed by a data manager for Chapter 3, there were discrepancies in the numbers of blood culture records linked by baby identity number and sample date for NICU 1 (4097 linked previously versus 4171) and NICU 2 (2896 versus 2885). There were two reasons for this, firstly our data manager took

account of the *time* of admission or discharge when assigning blood culture records. The data providers stated that these times were not reliable so I simply used admission and discharge dates. Secondly, I was interested in characterising time spent outside the NICU and in surgery, to investigate the BSI risk associated with these phases, and I was able to match more blood culture records to these periods, particularly for NICU 1.

4.6 Data linkage for NICU 3

4.6.1 Data linkage

Conversion of neonatal data system records to daily records

Neonatal data system records for NICU 3 contained admission and discharge dates, but did not contain any information concerning days spent in hospital specialties outside the NICU or in surgery. The records were expanded to contain a record for each baby day, giving 22,480 baby-days.

Linking blood culture records with neonatal data system records

Figure 4.3 summarises the linkage of blood culture records with neonatal data system days. Blood culture records were first linked to admission days using baby identity numbers and blood sample dates (using the rules for assigning blood cultures to admission days described in Figure 3.1, Chapter 3). Blood culture records not matching admission days in this first step were matched using surname, date of birth and sample date. As the blood culture and neonatal data system records had many discrepancies in the spelling of surnames, babies who could not be matched by name were matched by

date of birth and sample date. Further enquiries at NICU 3 revealed that many of the microbiology laboratory records were duplicates, existing simply to give further information regarding sample bottle type, rather than representing blood cultures themselves (personal communication, Mayank Patel, Royal Free Hampstead NHS Trust). These duplicates were removed from the matched and unmatched datasets. 333 records (18.03% of the total remaining blood culture records) found no matches, of which 12 tested positive for BSI.

4.6.2 Data cleaning

One baby had a gestational age recorded as one week, this was changed to missing. Thirty-six babies had no admission date, 20 babies had no discharge date and 12 had neither. For 19 of those missing an admission date only, this information could be imputed from dates of birth. The remaining babies were excluded as their total number of admission days could not be calculated for further analyses. Errors in the entry of year of admission or discharge resulted in seven babies with lengths of NICU stay longer than one year. Errors in year of admission were corrected using year of birth as a guide, errors in year of discharge were corrected by summing days at each level of care to calculate the length of NICU stay. Three babies had admission or discharge dates recorded as occurring before their dates of birth. The erroneous admission or discharge dates were changed to the date of birth.

4.7 Time coverage, quality and completeness of the final datasets for NICUs 1, 2 and 3

To ensure that datasets for NICU 1 and 2 covered the same time period as the analyses in Chapter 3, they were truncated to cover the complete months of May 2001 to February 2005. The dataset for NICU 3 was truncated to cover as much of this time period as possible, the complete months of May 2001 to July 2004. In contrast to the data management in Chapter 3, all complete *admissions* between the cut-off dates were included, rather than all *baby-days*. For example, consider a baby admitted before the cut-off date, on the 26th February 2005, and discharged after it, on the 2nd of March 2005. The data management process described in Chapter 3 would have excluded the last two days of the baby's NICU stay, whereas the dataset in this chapter would exclude the baby's entire stay. This enabled analyses in which potential risk factors were recorded per *baby*, rather than aggregated per *month* as in Chapter 3. The structure of the resulting datasets, which each contain a record for each baby-day, is shown in Figure 4.4. These datasets formed the basis for the statistical analyses in all subsequent chapters.

Table 4.2 compares data quality and completeness for various data fields, for the final datasets of the three NICUs. In terms of completeness, NICU 3 had the most missing data whereas NICU 2 had the least. Numbers of babies with unusual values for quantitative data can give an idea of data quality. In particular, 10 of the 1011 babies at NICU 1 (0.99%) had recorded gestational ages above 42 weeks, including one with a gestational age of 48 weeks. Seventeen of the 1612 babies at NICU 2 (1.05%) had recorded birth weights above 4500g, including one with a reported birth weight of

8913g. It is unclear how many of these extreme values represent errors in data entry, so they were left unchanged. In the analyses described in following chapters, gestational age and birth weight were analysed as categorical variables. For example, the baby with a birth weight recorded as 8913g would be categorised in the highest birth weight category. This tempered the potential bias presented by such outliers.

4.8 Discussion: further data requirements for blood stream infection monitoring in NICUs

Following the recommendations from Chapter 3 for electronic routine hospital data, the data linkage and data management processes in this chapter revealed further aspects of data that are necessary or could be improved if they are to be used for BSI monitoring.

It is essential that NICUs participating in monitoring use the same definitions and a common system for data capture and storage, to provide fair comparisons between each other. Although the three NICUs used similar definitions for most data fields, they differed in the extent of information stored concerning time spent away from the NICU. This could hinder fair comparisons, for example, of the effect of surgery on BSI. They also differed in data completeness and quality, as shown in Table 4.2. Data entry systems at NICU 2 incorporated automatic quality checks and mandatory fields, which explains the lower proportion of missing data when compared with the other two NICUs. Since 1997, the British Association of Perinatal Medicine (BAPM) has recommended a 'minimum dataset' of baby and unit level information, using common definitions, to standardise audits of activity and outcomes.[78] In addition, two common systems for capture and storage of neonatal data have been developed, which comply

with the BAPM minimum dataset and run on the Neonatal.net platform. The Standardised Electronic Neonatal Database (SEND) was established in 2004, and is currently used in most neonatal units in England, including the NICUs featured in this thesis.[75,79] The Maternal and Neonatal Electronic Recording System (MANNERS) was launched in 2007, and is used by several NICUs in the West Midlands.[80] Both systems support the day-to-day running of the NICU, for example by producing discharge summaries, and enabling patient transfers by locating suitable cots and sharing information with other hospitals. They also collect data for audits, such as the National Neonatal Audit Programme,[81] and for health service commissioning, such as the Payment by Results system.[82] Thus both SEND and MANNERS are able to support the daily activity of units, whilst providing data suitable for fair comparisons between units, using common definitions and data entry protocols. Recognising the potential of a common, routine administrative data system, the non-risk adjusted NeonIN surveillance system[17] reviewed in Chapter 1 intends to use SEND for its data capture in the future (personal communication, Dr. Paul Heath, St George's Healthcare NHS Trust).

To support infection monitoring, common data systems must automatically incorporate information concerning BSI, to reduce effort, maintain consistency between NICUs and improve data completeness and quality. *Crude* or *unadjusted* between-NICU comparisons of BSI incidence would be feasible without linking administrative and blood culture records by baby. Rates could be calculated using aggregated or total BSI episodes and baby-days from each data source respectively and separately. However, to provide *risk adjusted* comparisons, blood culture results must be linked to babies' characteristics and invasive procedures recorded in administrative records. Linking

blood culture and administrative records for the three NICUs was labour intensive, particularly for records not matching on baby identity number and sample date. These were linked on identifiers which varied in availability between NICUs, giving inconsistencies in the proportion of records matched at each unit. Between 6% and 18% of blood culture records found no matches with administrative data and were excluded, which may have affected data completeness. At NICU 1, 78% of non-matching blood cultures were recorded as having originated from other hospital specialties such as 'Well babies', indicating that they did not actually belong in data extraction for the NICU. This may also have been the case for non-matching blood cultures at NICU 2 and NICU 3 (personal communication, Dr Mike Millar, Barts and The London NHS Trust). Unlike identity numbers, names, dates of birth and sex do not uniquely identify babies, so matching records on these identifiers has potential for error and consequences for data quality. To avoid the pitfalls of data linkage, common data systems could incorporate blood culture information as patient records are created. Neonatal staff participating in the MANNERS system enter infection and pathogen details in daily patient care records. For participation in a monitoring system, the details required would depend on the agreed case definition for BSI. The case definition used in this project, described in Chapter 3 and justified in detail in Chapter 5, relies solely on blood culture results from the laboratory. These could be automatically linked with the common data system on a daily basis, to reduce the burden of data entry for neonatal staff and the potential for error associated with manual data entry.

Finally, *daily* patient records provide the best data format for infection monitoring, as they record precise dates for factors which change during the NICU stay and they can

improve data quality. In the three NICUs, factors which changed during the NICU stay, for example level of care and total parenteral nutrition, were recorded in three ways: the sum of days treated with the particular factor (NICU 1 and NICU 3), start and end dates for treatment (NICU 1) and in daily records (treatment with the factor on each day, yes/no) (NICU 2). To provide risk adjusted BSI rates for monitoring, the timing of BSI episodes in relation to potential risk factors must be known, to assess their association. The sum of days treated with a factor does not convey if treatment coincided with BSI. Start and end dates convey more timing information, but do not easily record, for example, if treatment was suspended for single days. Daily records precisely convey the timing of procedures in relation to BSI episodes, and provide a versatile format which is suited to data analysis software. BSI episodes and baby-days can be summed by month (as in Chapter 3), by quarter or year, or by days with potential risk factors, depending on the requirements of the monitoring system. Daily rather than retrospective data entry probably improves data quality, as events are fresh in the minds of staff. There is also a stronger incentive to maintain the quality of daily records, as they can provide a 'live' system for NICU management and neonatal network-wide cot-sharing. Both SEND and MANNERS use daily patient records in this way.

Key conclusions of Chapter 4

- I created datasets for the three London NICUs, suitable for more complex analyses of various potential risk factors for BSI and predictive associations.
- The data management process highlighted aspects of data collection that differed between NICUs.
- Retrospective data linkage was time-consuming and between 6% and 18% of blood culture records found no matches in administrative data.
- Daily patient care records conveyed the timing of procedures and BSI episodes with the greatest precision.

Conclusions

Aspects of electronic routine hospital data that are necessary if they are to be used for BSI monitoring include:

- a common data system for all participating NICUs
- automatic linkage of laboratory blood culture results with this common system, avoiding workload and error associated with manual data entry
- the use of daily patient care records

These recommendations are feasible, as shown by newly developed data systems such as SEND and MANNERS.

Figure 4.1 NICU 1: linking blood culture records with Patient Administration System records

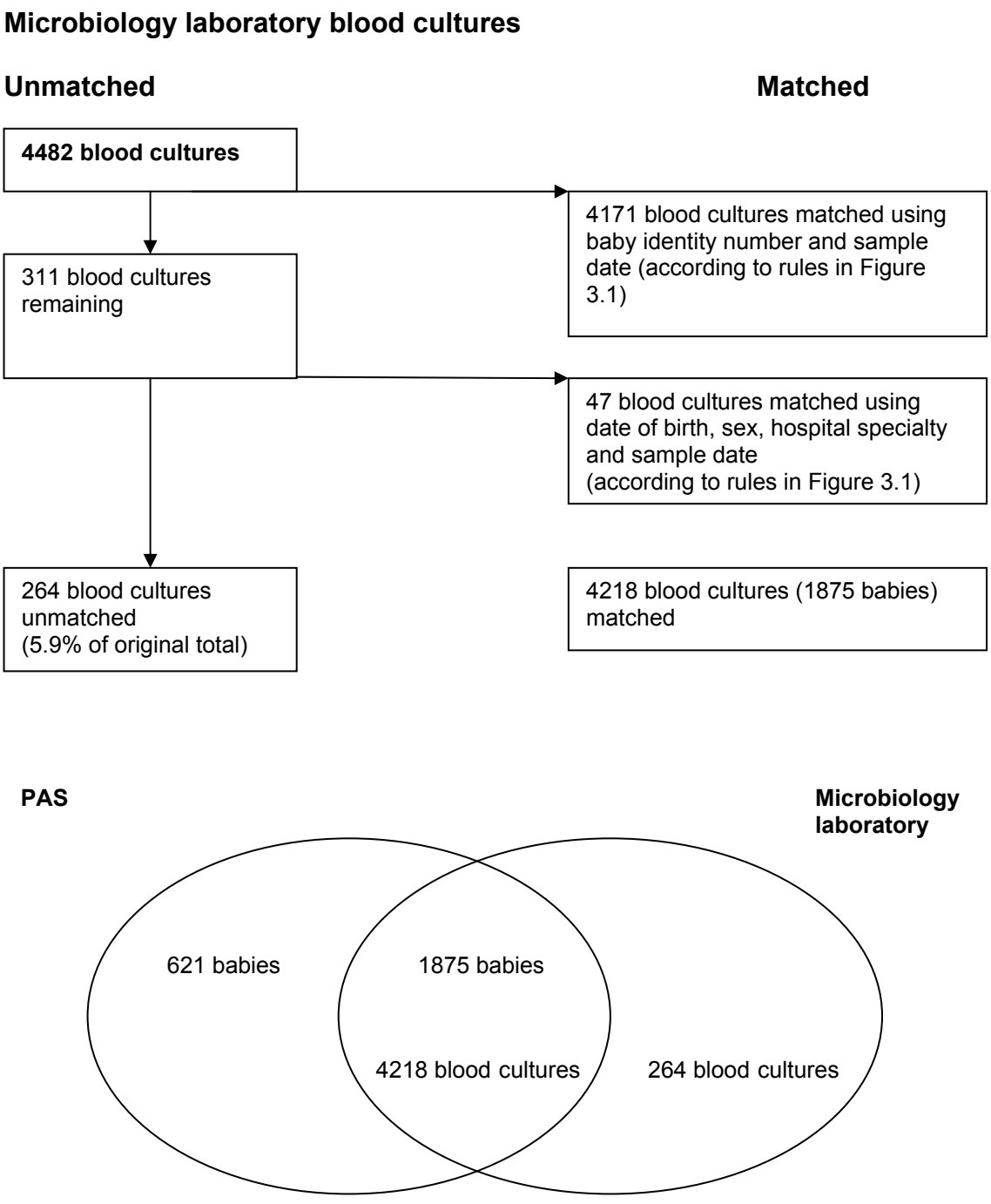


Figure 4.2 NICU 2: linking blood culture records with Patient Administration System records

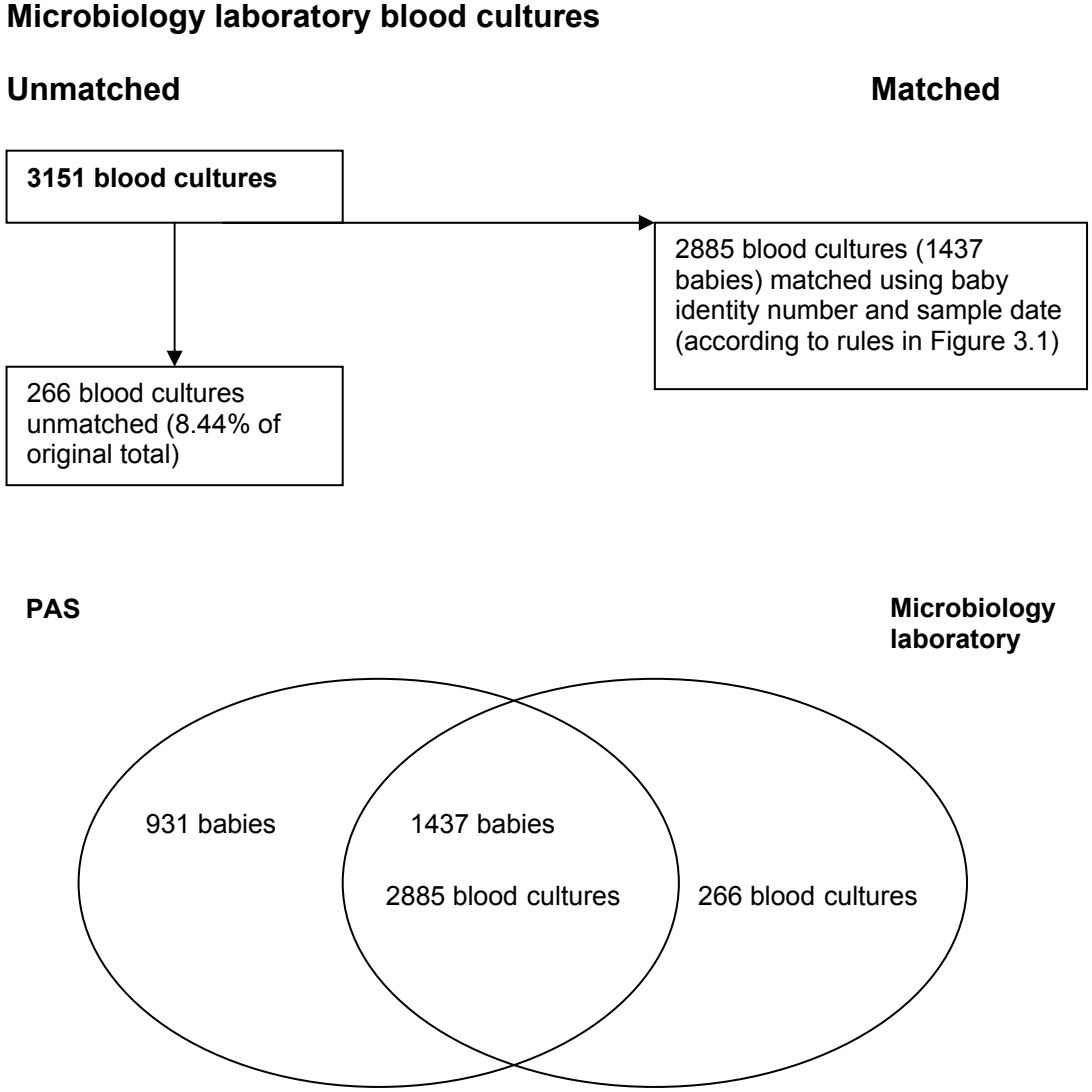


Figure 4.3 NICU 3: linking blood culture records with administrative records

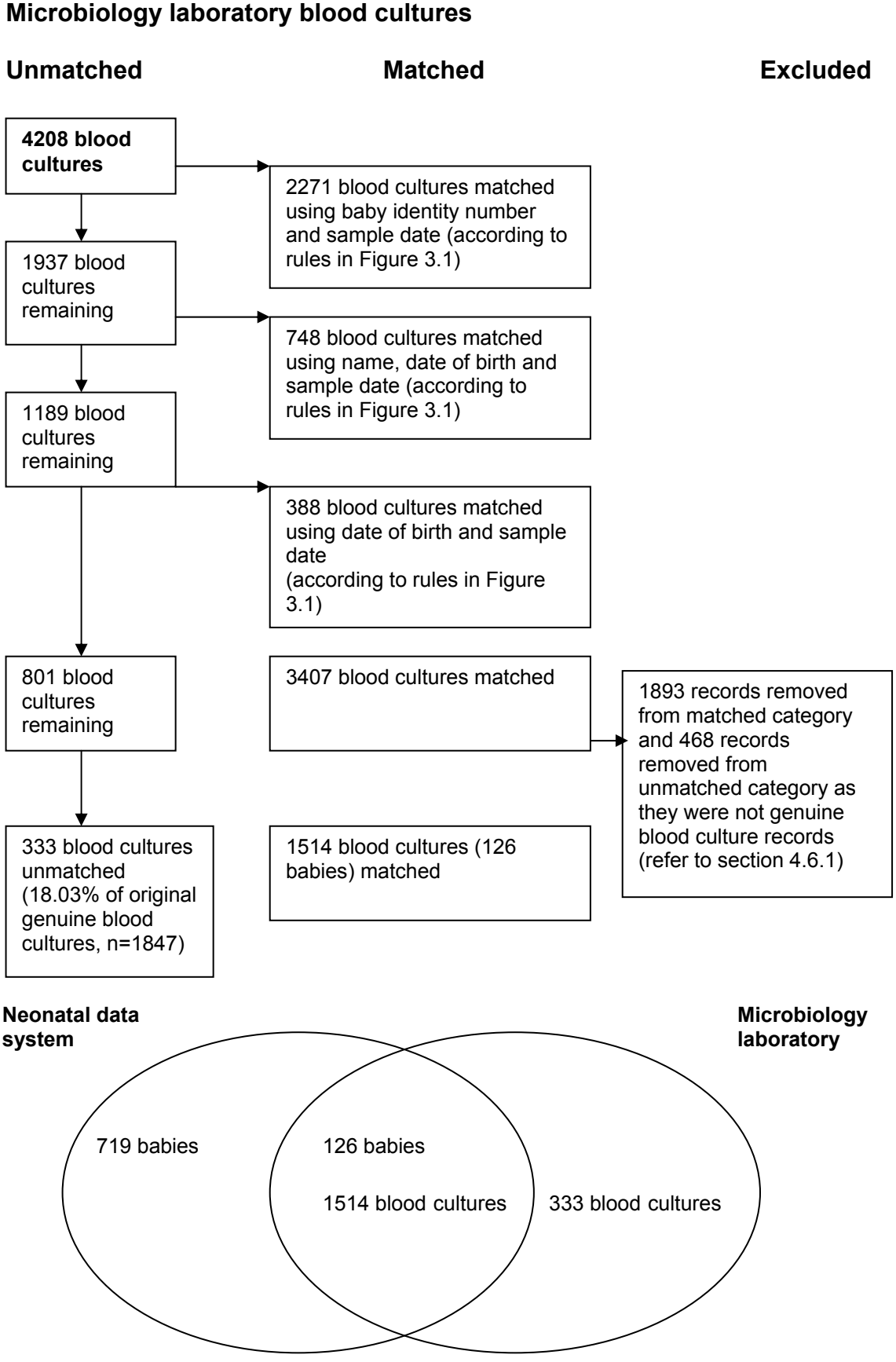


Figure 4.4 Diagram to describe stays in the NICU for three hypothetical babies, and how these stays would be translated into a dataset with a record for each baby-day

Special care	
High dependency	
Intensive care	

CONS infection episode	**C**
Non-CONS infection episode	**NC**
Blood sample taken	**S**

Invasive procedure, eg.	
Total parenteral nutrition	**T**
Ventilation	**V**

Days of May 2001 at NICU 1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**…**	**31**
Baby 1 (25 weeks, 753g)[a] Male Inborn, vaginal delivery Admitted 5/5/01 Died 12/5/01					**T V**	**T V**	**C S T V**	**T V**	**T V**	**NC S T V**	**T V**	**T V**											
Baby 2 (36 weeks, 2425g) Female Inborn, vaginal delivery Admitted 16/5/01 Discharged 20/05/01																**C S**							
Baby 3 (37 weeks, 2600g) Male Inborn, vaginal delivery Admitted 3/5/01 Discharged 7/5/01			**C S**		**S**																		

a - (Gestational age at birth, birth weight)

Figure 4.4 (continued) Dataset with a record for each baby-day

Baby	Date	Gestational age (wks)	Birth weight (g)	Sex	Inborn/ Outborn	Delivery method	Level of care	Total parenteral nutrition	Ventilation	CONS episode	Non-CONS episode	Blood sample taken
1	5/5/2001	<26	700-<1200	Male	Inborn	Vaginal	Intensive care	Yes	Yes	0	0	0
1	6/5/2001	<26	700-<1200	Male	Inborn	Vaginal	Intensive care	Yes	Yes	0	0	0
1	7/5/2001	<26	700-<1200	Male	Inborn	Vaginal	Intensive care	Yes	Yes	1	0	1
1	8/5/2001	<26	700-<1200	Male	Inborn	Vaginal	Intensive care	Yes	Yes	0	0	0
1	9/5/2002	<26	700-<1200	Male	Inborn	Vaginal	Intensive care	Yes	Yes	0	0	0
1	10/5/2001	<26	700-<1200	Male	Inborn	Vaginal	Intensive care	Yes	Yes	0	1	1
1	11/5/2001	<26	700-<1200	Male	Inborn	Vaginal	Intensive care	Yes	Yes	0	0	0
1	12/5/2001	<26	700-<1200	Male	Inborn	Vaginal	Intensive care	Yes	Yes	0	0	0
2	16/5/2001	32-<37	≥1200	Female	Inborn	Vaginal	High dependency care	No	No	1	0	1
2	17/5/2001	32-<37	≥1200	Female	Inborn	Vaginal	High dependency care	No	No	0	0	0
2	18/5/2001	32-<37	≥1200	Female	Inborn	Vaginal	High dependency care	No	No	0	0	0
2	19/5/2001	32-<37	≥1200	Female	Inborn	Vaginal	Special care	No	No	0	0	0
2	20/5/2001	32-<37	≥1200	Female	Inborn	Vaginal	Special care	No	No	0	0	0
3	3/5/2001	≥37	≥1200	Male	Inborn	Vaginal	Intensive care	No	No	1	0	1
3	4/5/2001	≥37	≥1200	Male	Inborn	Vaginal	Intensive care	No	No	0	0	0
3	5/5/2001	≥37	≥1200	Male	Inborn	Vaginal	Intensive care	No	No	0	0	1
3	6/5/2001	≥37	≥1200	Male	Inborn	Vaginal	High dependency care	No	No	0	0	0
3	7/5/2001	≥37	≥1200	Male	Inborn	Vaginal	Special care	No	No	0	0	0

Table 4.1 Structure of the raw datasets for NICUs 1, 2 and 3

Dataset	Time period covered	Structure One record for each:	Data fields
NICU 1			
PAS	1/1/1996 to 6/3/2005 Datasets covered various time periods. They were truncated to cover the minimum period for which reliable data was received from the microbiology laboratory.	NICU admission	Baby identity number, date of birth, name, sex, gestational age at birth, delivery method, inborn/outborn status, dates and times of admission and discharge to the NICU, dates and times of admission and discharge to each level of care or other hospital specialty to which the baby was admitted
Microbiology laboratory		Blood culture	Baby identity number, date of birth, sex, date the sample was taken, hospital specialty where the sample was taken, organism class and genus cultured
Separate neonatal data system: admission		Baby	Baby identity number, date of birth, sex, gestational age at birth, birth weight, delivery method, date of admission to the NICU
Separate neonatal data system: ventilation			Baby identity number, date of extubation, sum of days treated with: ventilation, nasal continuous positive airway pressure
NICU 2			
PAS: baby	1/1/2000 to 9/9/2005	Baby	Baby identity number, date of birth, sex, gestational age at birth, birth weight, delivery method, inborn/outborn status
PAS: admission		NICU admission	Baby identity number, where the baby was discharged to, dates and times of admission and discharge
PAS: daily care		Day of NICU stay	Baby identity number, date, level of care, treatment with: ventilation, total parenteral nutrition (yes/no variables)
Microbiology laboratory		Blood culture	Baby identity number, date the sample was taken, organism class and genus cultured
NICU 3			
Neonatal data system	2/3/2001 to 30/7/2004	Baby	Baby identity number, date of birth, name, sex, gestational age at birth, birth weight, delivery method, dates of admission and discharge, sum of days cared for in: special care, high dependency care, intensive care, sum of days treated with: nasal continuous positive airway pressure, total parenteral nutrition, long line, umbilical arterial catheter, umbilical venous catheter
Microbiology laboratory:		Blood culture	Baby identity number, date of birth, name, date the sample was taken, organism

positive blood cultures			class and genus cultured
Microbiology laboratory: negative blood cultures		Blood culture	Baby identity number, date of birth, name, date the sample was taken

Table 4.2 Data quality and completeness in the final datasets

	NICU 1	NICU 2	NICU 3
Time period covered	01/05/2001 to 28/02/2005	01/05/2001 to 28/02/2005	01/05/2001 to 31/07/2004
Number of babies included	1011	1612	762
Data completeness:			
Number of babies missing the following data fields (% of babies at each NICU):			
Gestational age at birth	16 (1.58)	0	10 (1.31)
Birth weight	20 (1.98)	0	9 (1.18)
Inborn/outborn status	31 (3.07)	0	36 (4.72)
Sex	0	0	23 (3.02)
Delivery method	17 (1.68)	5 (0.31)	62 (8.14)
Data quality:			
Number of babies with gestational age at birth (range in weeks):			
<25 weeks	37 (21, 24)	42 (22-24)	11 (23, 24)
>42 weeks	10 (43, 48)	3 (43)	0
Number of babies with birth weight (range in g):			
<500g	6 (376, 493)	6 (356, 485)	3 (458, 480)
>4500g	4 (4550, 4600)	17 (4576, 8913)	17 (4570, 5294)

5. Exploring crude associations between potential risk factors and blood stream infection

5.1 Summary

This chapter explores associations between BSI and potential risk factors reflecting susceptibility at birth and between BSI and procedure-related factors which change during the NICU stay. The analysis made use of procedure-related factors which were recorded as the sum of days treated, and treatment periods of varying length were analysed in relation to the development of BSI.

Birth weight and inborn/outborn status were significant independent risk factors for NICU-acquired BSI. When compared with babies weighing 1200g or more at birth, the rate ratio for BSI adjusted for inborn/outborn status was 2.00 (95% CI 1.54, 2.60) in babies weighing 700g to 1200g, and 3.43 (95% CI 2.60, 4.53) in babies weighing less than 700g. Babies with lower birth weights and outborn babies also contracted BSI earlier upon entry to the NICU. Days of stay in each of the NHS levels of care and days of treatment with total parenteral nutrition and ventilation were all significantly associated with BSI, however as these factors were correlated they could not be analysed together in multivariable models.

Birth weight and inborn/outborn status could be used to adjust BSI rates to give risk adjusted comparisons between NICUs. More complex analyses are required to explore associations between BSI and procedure-related factors.

5.2 Introduction

This chapter examines crude associations between BSI and procedure-related factors which change during the NICU stay, such as level of care and total parenteral nutrition. Chapters 6 and 7 will focus on associations which predict infection, by restricting analyses to procedure-related factors that preceded BSI episodes. This chapter provides a preliminary analysis, by analysing associations between varying durations of treatment with invasive procedures, and the development of BSI at any time during the NICU stay. This analysis was required to investigate certain procedures which were only recorded as the sum of days treated, which would otherwise be lost to the study.

I also included an analysis of associations between BSI and factors reflecting susceptibility to infection at birth, such as birth weight and gestational age at birth. This analysis included Cox regression models to describe the effects of potential risk factors on how quickly babies were infected with BSI upon entering the NICU.

5.3 Methods

5.3.1 Study population

The datasets with records for each baby-day, described in Chapter 4, were used for the analysis. Because the dataset for NICU 3 included babies who were admitted on or after 1st May 2001 and discharged up to and including 31st July 2004, the analyses for the other two NICUs were restricted to this time period to enable comparisons between all three NICUs.

5.3.2 Case definition and a method to differentiate maternally-transmitted from hospital-acquired blood stream infection

As in Chapter 3, an episode of BSI was defined as one or more blood cultures in which the same bacterial organism was isolated within a 7-day period.

A method to differentiate maternally-transmitted from hospital-acquired blood stream infection

The focus of this and the following chapters is on comparing rates of hospital-acquired infection between NICUs, to inform infection control practices. There is no easy way to differentiate maternally-transmitted from hospital-acquired BSI, apart from using timing of infection. Previous studies have used arbitrary thresholds between two and three days of age.[16,30] I derived a threshold, by exploring age at first BSI episode using finite mixture latent class regression models with normally distributed components.[83] I used the R library `flexmix` to fit models in this class.[84] Because this threshold was to be used for the rest of this study, which concentrates mainly on NICUs 1 and 2, only data

for these two hospitals were used for its calculation, for the period 1st May 2001 to 28th February 2005.

For these analyses I based my model selection strategy on the Bayesian information criterion (BIC). Like the AIC described in Chapter 3, Section 3.3.4, the BIC is another parsimonious measure of goodness of fit for an estimated statistical model, which describes the trade-off between model precision and complexity. Within a given dataset, competing models may be ranked according to their BIC values, with the one having the lowest BIC being the best. The BIC differs from the AIC in that the penalty for additional parameters is larger, thus it is more robust against over-parametrisation. This is an important aspect when fitting latent class mixture models, which may have many parameters. The BIC is given by:

$$\mathrm{BIC} = -2\ln(L) + k\ln(n)$$

L = maximised value of the likelihood function

k = number of parameters in the model

n = the number of independent observations used to fit the model, or the sample size[85]

The optimal model had four components, and I calculated pairwise maximal differences in the empirical cumulative probability functions of these components. One of the maximal differences was at 2.23 days, indicating that the frequency of first BSI episodes drops sharply at this age. I hypothesised that this is due to a shift in the aetiology of BSI from maternally-transmitted to hospital-acquired at around day two of life. Figure 5.1 shows how this threshold was derived.

Figure 5.2 shows the organisms giving rise to BSI episodes by day of life. It also indicates a shift in the aetiology of BSI at around day two of life, as CONS, Group B streptococcus and Gram positive organisms other than Group B streptococcus show marked decreases. The importance of Group B streptococcal infections in the first two to three days of life has been described previously.[32,86] CONS is less frequently a pathogen during this period,[86] so the early spike in the number of CONS episodes may be partly the result of a high blood sampling frequency. In the first few days of life, blood samples may be taken more frequently as part of standard care as babies are often in an emergency situation. The blood sampling rate in days 1 and 2 of life (445.07 per 1000 baby-days, 95% CI 424.32, 466.58) was significantly greater than the rate in days 3 and 4 of life (70.67 per 1000 baby-days, 95% CI 62.54, 79.57). As described in Chapter 3 (Section 3.3.2 and Section 3.5), the more blood samples taken the greater the risk of detecting asymptomatic BSI or a blood culture contaminated with a commensal organism such as CONS.

To concentrate on hospital-acquired BSI and to reduce blood sampling bias, I excluded BSI episodes from the first 48 hours of life. All further analyses in this thesis are based on BSI episodes occurring after the first 48 hours of life.

5.3.3 Factors reflecting baby susceptibility at birth

Babies were divided into categories of gestational age at birth in weeks (<26, 26-<28, 28-<32, 32-<37, ≥37) and birth weight in grams (<700, 700-<1200, ≥1200). These strata were chosen to be comparable with a study by Holmes *et al.* (2008), which is described in Chapter 6.[34] I modified this study's categories by dividing babies with gestational

ages above 27 weeks into three categories rather than one, as variability in gestational age within this group was found to have a statistically significant relationship with BSI.

Poisson generalised linear models

I fitted Poisson generalised linear models to investigate relationships between BSI and gestational age, birth weight, inborn/outborn status, hospital, sex and delivery method. Adjusted models were constructed using forward fitting of covariates which showed statistically significant relationships ($p<0.01$) with BSI in crude analyses. As gestational age at birth and birth weight were correlated, separate adjusted models were built for each of these variables. Goodness of fit was compared between models using the AIC.

Analyses of time to the development of blood stream infection

Cox regression models were fitted to investigate relationships between potential risk factors reflecting susceptibility at birth, and the time to infection with a first BSI episode. Babies entered this analysis at the latest date of either their NICU admission or day three of life, and exited it at the earliest date of their first BSI episode or discharge from the NICU. The construction of multivariable models proceeded as for the Poisson generalised linear models described above. Kaplan-Meier plots were used to display time to BSI, for strata of risk factors shown to have a statistically significant effect on BSI in the Cox regression multivariable models.

5.3.4 Procedure-related factors which change during the NICU stay

This analysis made use of procedure-related potential risk factors which were recorded as the sum of days of treated (refer to Chapter 4, 'Data fields' section of Table 4.1),

rather than dates starting and stopping treatment, or daily records. These comprised all of the procedure-related variables for NICU 3 (level of care, total parenteral nutrition, ventilation, nasal continuous positive airway pressure (CPAP), long line, umbilical arterial catheter, umbilical venous catheter), and two for NICU 1 (total parenteral nutrition and ventilation). For this analysis, the remaining procedure-related variables (level of care at NICU 1 and all procedure-related variables at NICU 2) were converted to this format, by summing days of treatment using the records for each baby-day in the three datasets created in Chapter 4. Babies were categorised according to their number of days treated with each procedure-related factor (0, 1-3, 4-6 and ≥7 days). Again, these strata were chosen to be comparable with Holmes *et al.* (2008), who judged that the maximum time from BSI to the manifestation of clinical symptoms was about three days.[34] Babies were also categorised according to number of blood samples taken (0-3, 4-6, ≥7). By definition, babies with no blood samples taken had no BSI episodes, so they were grouped with babies with one to three blood samples. The structure of the datasets used, with babies categorised according to the sum of days treated with each invasive procedure, is demonstrated in Figure 5.3.

Poisson generalised linear models

I fitted Poisson generalised linear models to investigate relationships between BSI and procedure-related factors, which varied in availability between NICUs. Procedure-related factors were not combined in multivariable models, as they were highly correlated.

It was not possible to analyse time to the development of BSI with procedure-related factors. As procedure-related factors were recorded as the sum of days treated for this analysis, their timing was not recorded in relation to BSI episodes.

All analyses were repeated for total BSI, CONS and non-CONS BSI. Poisson regression analyses were repeated for the NICUs separately as well as combined.

5.4 Results

5.4.1 Factors reflecting baby susceptibility at birth

Poisson generalised linear models

There were no significant differences between NICUs in BSI rates per 1000 baby-days, whether measured as total BSI (6.14 at NICU 1, 6.29 at NICU 2 and 5.24 at NICU 3), CONS (4.42 at NICU 1, 4.53 at NICU 2 and 4.41 at NICU 3) or non-CONS (1.72 at NICU 1, 1.77 at NICU 2 and 0.83 at NICU 3) infection episodes (refer to Tables 5.1, 5.2 and 5.3). It is important to note that, despite the relatively large sample size (2562 babies and 58,046 baby-days), these rate ratios are underpowered. A power of 80% or above is desirable, but for the analysis of total BSI, this would have required between double and triple the sample size obtained (between about 5000 and 8000 babies, or between 115,000 and 180,000 baby-days), which was not feasible for this study. Figure 5.4 demonstrates this for total BSI rate ratios at NICU 1 and NICU 2. It shows that even with twice the sample size studied, the power to detect a rate ratio of two for NICU 2 compared with NICU 1 would still only be about 45%.

Gestational age at birth, birth weight and inborn/outborn status were significantly associated with total BSI in crude analyses. As in the analyses for Chapter 3, BSI risk was highest in the most premature and in term babies. Preterm babies born in the third trimester, between 32 and 37 weeks, had the lowest risk. Babies with birth weights below 1200g were at increased risk for BSI, as were babies transferred to the NICU from another hospital after birth. Birth weight increased with gestational age (Figure 5.5). As these two factors were correlated they could not be combined in the same multivariable model. In terms of the AIC, the optimal adjusted model included birth weight and inborn/outborn status (Table 5.1).

These findings broadly remained when CONS and non-CONS BSI were analysed separately, except that non-CONS BSI was not significantly associated with inborn/outborn status (Tables 5.2, 5.3). When the NICUs were analysed separately, gestational age was a weaker risk factor for BSI in NICU 1 and NICU 2. Inborn/outborn status had no significant effect on non-CONS BSI at either NICU 1 or NICU 2, or on any BSI at NICU 3. As the study population at NICU 3 was relatively small, it contained too few non-CONS BSI episodes to permit some stratified analyses (Tables 5.10 to 5.18, Appendix to Chapter 5).

Neither sex nor delivery method had significant effects on total BSI, CONS or non-CONS infection episodes.

Analyses of time to the development of blood stream infection

The results shown in Table 5.4 are based on hazard rates, which for any point in time, describe the rate of first BSI episodes in the group of babies currently being observed. The hazard ratios compare rates at which babies are experiencing first BSI episodes, for different strata of various potential risk factors. For example, a hazard ratio of 2 indicates twice the instantaneous rate of first BSI episodes in relation to the baseline comparison group. Hazard ratios can be interpreted as comparisons of the time to first BSI episode between strata. There were no significant differences between NICUs in the time to first BSI episode after admission to the NICU, whether measured as total BSI, CONS or non-CONS infection episodes.

Gestational age, birth weight and inborn/outborn status were significantly associated with total BSI in crude analyses. In terms of the AIC, the optimal adjusted model included birth weight and inborn/outborn status (Table 5.4). Again, these findings remained when CONS and non-CONS BSI were analysed separately, except that non-CONS BSI was not significantly associated with inborn/outborn status in crude analyses (Tables 5.5, 5.6). Figures 5.5 to 5.9 illustrate differential time to infection in strata of birth weight and inborn/outborn status for all BSI and CONS BSI, and in strata of birth weight for non-CONS BSI. The proportion of babies without BSI decreased over time. This decline was steeper for the more common CONS BSI than for non-CONS BSI.

5.4.2 Procedure-related factors which change during the NICU stay

Procedure-related factors were highly positively correlated ($p<0.001$), an increase in one was significantly associated with increases in the others (Figure 5.5), so these factors could not be combined in multivariable models.

Poisson generalised linear models

Throughout this section, days of stay at each level of care and days of treatment with each invasive procedure are referred to as 'short' (1 to 3 days), 'medium' (4 to 6 days) or 'long' (7 or more days) periods. Risk ratios are expressed in relation to the baseline of 0 days, or no exposure to the procedure-related factor.

Each level of care was strongly associated with total BSI, and BSI rates increased with the intensity of care. Any time spent in special care was associated with a halving in the risk of BSI. Long stays in high dependency care were associated with an increase in the risk of BSI by 50%. For intensive care, the risk of BSI increased between two-fold for short stays and four-fold for long stays (Table 5.7). These findings broadly remained when CONS and non-CONS BSI were analysed separately. However for non-CONS BSI, short and medium stays in special care were associated with a weaker protective effect and long stays in intensive care were associated with a greater risk (Tables 5.8 and 5.9). When the NICUs were analysed separately, special care had no significant effect on any BSI at NICU 1. Intensive care had no significant effect on non-CONS BSI at NICU 2. The effect of intensive care appeared to be particularly strong at NICU 3. Compared with no days spent in this level, long stays were associated with an eleven-fold increase in the risk of total BSI (Tables 5.19 to 5.27, Appendix to Chapter 5). As

the study population at NICU 3 was relatively small, the high rate ratios observed for some potential risk factors were accompanied by large confidence intervals.

Information concerning specific procedure-related factors varied in availability between NICUs. Total parenteral nutrition was strongly associated with both CONS and non-CONS BSI at the two NICUs where its use was recorded. At NICU 2, long periods of treatment with total parenteral nutrition were associated with a four-fold increase in the risk of total BSI. This association appeared to be stronger at NICU 3, where risk increased between eight and eleven-fold, depending on the length of treatment. Long periods of ventilation were associated with a three-fold increase in the risk of total BSI at all three NICUs. When the NICUs were analysed separately, ventilation was not significantly associated with CONS BSI at NICU 1, nor with non-CONS BSI at NICU 2. Again associations with ventilation appeared to be stronger at NICU 3, with between three and seven-fold increases in BSI risk, depending on the length of treatment (Tables 5.7 to 5.9 and Tables 5.19 to 5.27, Appendix to Chapter 5).

Nasal continuous positive airway pressure was recorded at NICUs 1 and 3. It was not associated with any BSI at NICU 1, but long periods of treatment were associated with a three-fold increase in total BSI at NICU 3. Treatment with a long line, an umbilical arterial catheter or an umbilical venous catheter was recorded at NICU 3 and all three procedures were associated with increased risks of BSI. Surgery was recorded for NICUs 1 and 2 and was associated with a two-fold increase in the risk of total BSI, compared with no surgery (Tables 5.19 to 5.27, Appendix to Chapter 5). The number of blood samples taken was strongly associated with the risk of total BSI; in relation to 0

to 3 blood samples, 4 or more blood samples were associated with a four to five-fold increase in the risk of total BSI (Table 5.7).

5.5 Discussion

Of the factors reflecting baby susceptibility at birth, birth weight and inborn/outborn status were the strongest risk factors for BSI in both Poisson and Cox regression multivariable analyses. Babies with lower birth weights and outborn babies were at greater risk of developing BSI, and they also developed BSI *earlier* upon entering the NICU. This indicates that BSI rates could be adjusted for these two risk factors to compare rates between NICUs. I found no significant differences between NICUs in either total BSI, CONS or non-CONS infection rates. In contrast to Chapter 3, the analyses in this chapter included more potential risk factors reflecting baby susceptibility at birth, and found birth weight to be a stronger risk factor for BSI than gestational age at birth. In crude analyses for both chapters, babies born in the third trimester but before term (28-<32 or 32-<37 weeks gestation), were at lowest risk for BSI. This has not previously been reported but is plausible, as these babies are usually admitted to NICU for observation and help with feeding, but are otherwise healthy and not requiring invasive procedures. In contrast, more premature and term babies may be more prone to infection, either from extreme prematurity, or in term babies, from other serious complications such as congenital anomalies which may require invasive surgical care.

Most procedure-related factors were found to be strongly associated with BSI and the risk of BSI increased with the intensity of care. Babies spending any time in special care

had a lower risk of BSI than babies who spent no time in special care. This is because, by definition, babies who spent no time in special care were exclusively looked after in the more intensive levels. In high dependency and intensive care, BSI risk increased with the duration of care, and intensive care was associated with the greatest risk.

These analyses enabled exploration of risk factors recorded only as the sum of days treated. It also provided a simple exploration of risk factors which change over time, by analysing associations between treatment periods of varying length, and the development of BSI at any time during the NICU stay. Disadvantages of these analyses include the fact that factors analysed in this way were correlated with each other. As sicker babies received more intensive care and spent longer in the NICU, their days of stay at each of the levels of care and days of treatment with intensive procedures were positively correlated. It was therefore impossible to perform multivariable analyses, and associations found in univariable analyses may be subject to many confounders. For example, the association between BSI and total parenteral nutrition may be due to the fact that more vulnerable babies were treated with parenteral nutrition in the first place, or may be due to another invasive procedure correlated with parenteral nutrition, rather than to any effect of parenteral nutrition itself. Babies with longer periods of treatment with procedure-related factors spent more time in the NICU, which would also increase the probability of succumbing to BSI, as shown by the Kaplan-Meier plots.

Because the timing of procedure-related factors in relation to BSI episodes was not taken into account, associations between them may reflect either cause or consequence. The procedure may contribute to the infection, or the procedure may have been

necessary as a result of deteriorating symptoms of infection. The disadvantages I have described in this and the preceding paragraph illustrate the limited value of factors recorded as the sum of days treated. Recognising this, the BAPM revised its recommendations for the neonatal 'minimum dataset' in 2004, to include daily records rather than the sum of days treated with procedure-related factors. It recommended daily recording of invasive procedures, such as parenteral nutrition, and all other factors necessary for defining NHS levels of care.[87] Chapters 6 and 7 provide more complex analyses, using daily records of procedure-related factors and a method which enabled the levels of care to be analysed in the same multivariable model. These analyses described procedure-related factors which predict infection, as they were restricted to risk factors that preceded BSI episodes.

In contrast to the analyses in Chapter 3, blood sampling frequency was strongly associated with BSI rates. This is because this chapter analysed the relationship between blood sampling frequency and BSI in individual babies, whereas Chapter 3 analysed this relationship at the unit level. Within individual babies, the number of blood samples taken was, by definition, strongly correlated with the number of BSI episodes, as blood samples were used to diagnose infection and to monitor the response to treatment. Within units, blood sampling frequency and BSI were less strongly correlated, as the experiences of many babies were combined. In addition, in Chapter 3, the relationship between blood sampling frequency and BSI rates was adjusted for the confounding effects of gestational age and days spent at each level of care. As my project focused on differences in BSI rates at the unit level, the approach for Chapter 3 was most relevant. This approach found that blood sampling rate was not a risk factor for total BSI.

As mentioned in Chapter 1, previous studies have used clinical symptoms to differentiate between 'true' BSI and contamination. However, Gastmeier *et al.* (2008) warn that differences between hospitals in the sensitivity and specificity of clinical diagnoses may lead to differences in HAI rates that are not necessarily associated with infection control. They chose 10 case studies from real adult patient records, including 13 HAI defined by CDC criteria and agreed upon by an expert panel. In 169 adult intensive care units participating in the German Krankenhaus Infektions Surveillance System (KISS), the diagnosis of HAI for the case studies ranged in sensitivity from 31% to 100% (median 69%) and ranged in specificity from 65% to 100% (median 94%).[88] As mentioned in Chapter 3, Section 3.5, reporting BSI rates by organisms, for example by CONS and non-CONS, may be the only way to differentiate between infections more or less likely to represent contamination using routine data. Reporting rates of CONS may also be useful for monitoring and addressing contamination itself, as false positive blood cultures can lead to increased antibiotic use and longer durations of hospital stay. As results for CONS and non-CONS were similar, I focus on total BSI in the following four chapters.

Key conclusions of Chapter 5

Findings

- Birth weight and inborn/outborn status were strong independent risk factors for BSI.
- NHS levels of care and other procedure-related factors may be strongly associated with BSI.
- Recording the sum of days exposed to procedure-related factors had limited value for risk adjusted analyses.
- Differences in sampling frequency did not confound comparisons of BSI rates between NICUs.

Conclusions

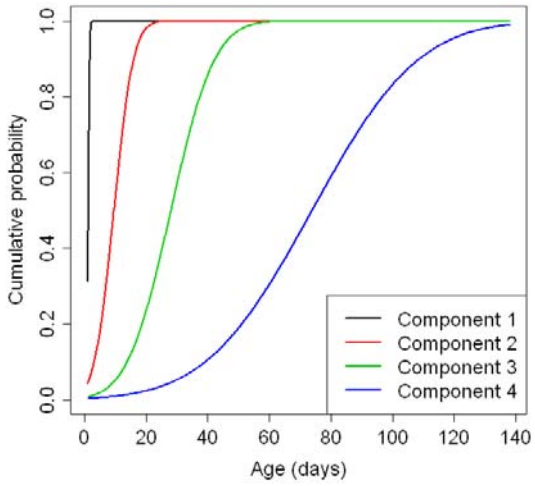
- Birth weight and inborn/outborn status could be used to adjust BSI rates to give risk adjusted comparisons between NICUs.
- More complex analyses are required to determine if BSI rates could be adjusted by days at each level of care, or days with other procedure-related factors, to give risk adjusted comparisons between NICUs.
- A monitoring system for hospital-acquired BSI in NICUs employing routine data could rely on rates of CONS, non-CONS or total BSI occurring after the first 48 hours of life.

Figure 5.1 Deriving a threshold to differentiate between maternally-transmitted and hospital-acquired BSI

Age at first BSI episode was explored using finite mixture latent class regression models. These were fitted with up to five components, and models were compared using the BIC.

Number of components in model	BIC
1	2761.40
2	2503.80
3	2480.70
4	2351.63 – lowest BIC indicates the best model
5	2351.64

Cumulative probabilities of the four model components against age at first BSI episode



Maximal difference in cumulative probability between component 1 and component 2

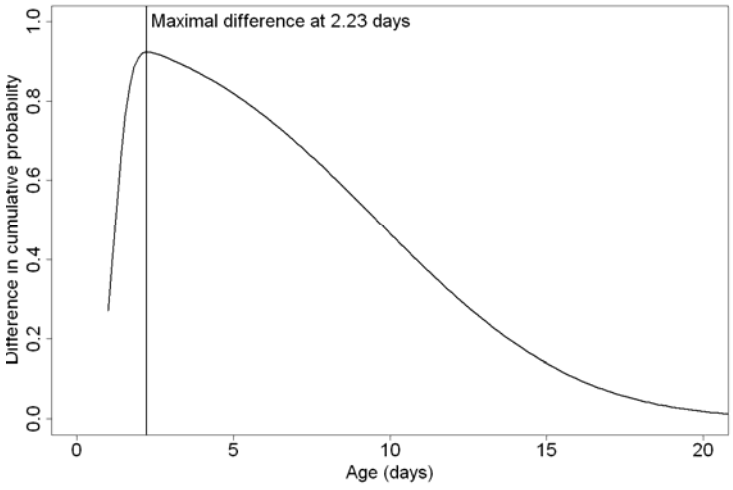


Figure 5.2 Organisms giving rise to BSI episodes by day of life. Graph includes babies admitted to NICUs 1 and 2 between May 2001 and February 2005 inclusive

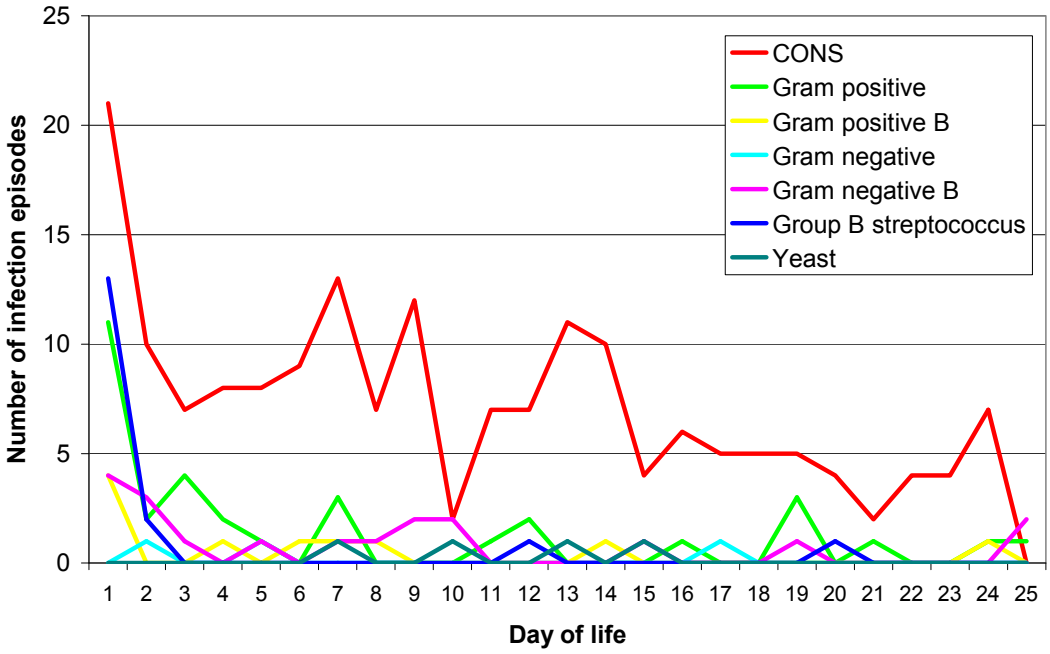


Figure 5.3 Diagram to describe stays in the NICU for three hypothetical babies, and how these stays would be translated into a dataset with babies categorised according to the sum of days exposed to each procedure-related factor

Special care	
High dependency	
Intensive care	

CONS infection episode	**C**
Non-CONS infection episode	**NC**
Blood sample taken	**S**

Procedure-related factor, eg.	
Total parenteral nutrition	**T**
Ventilation	**V**

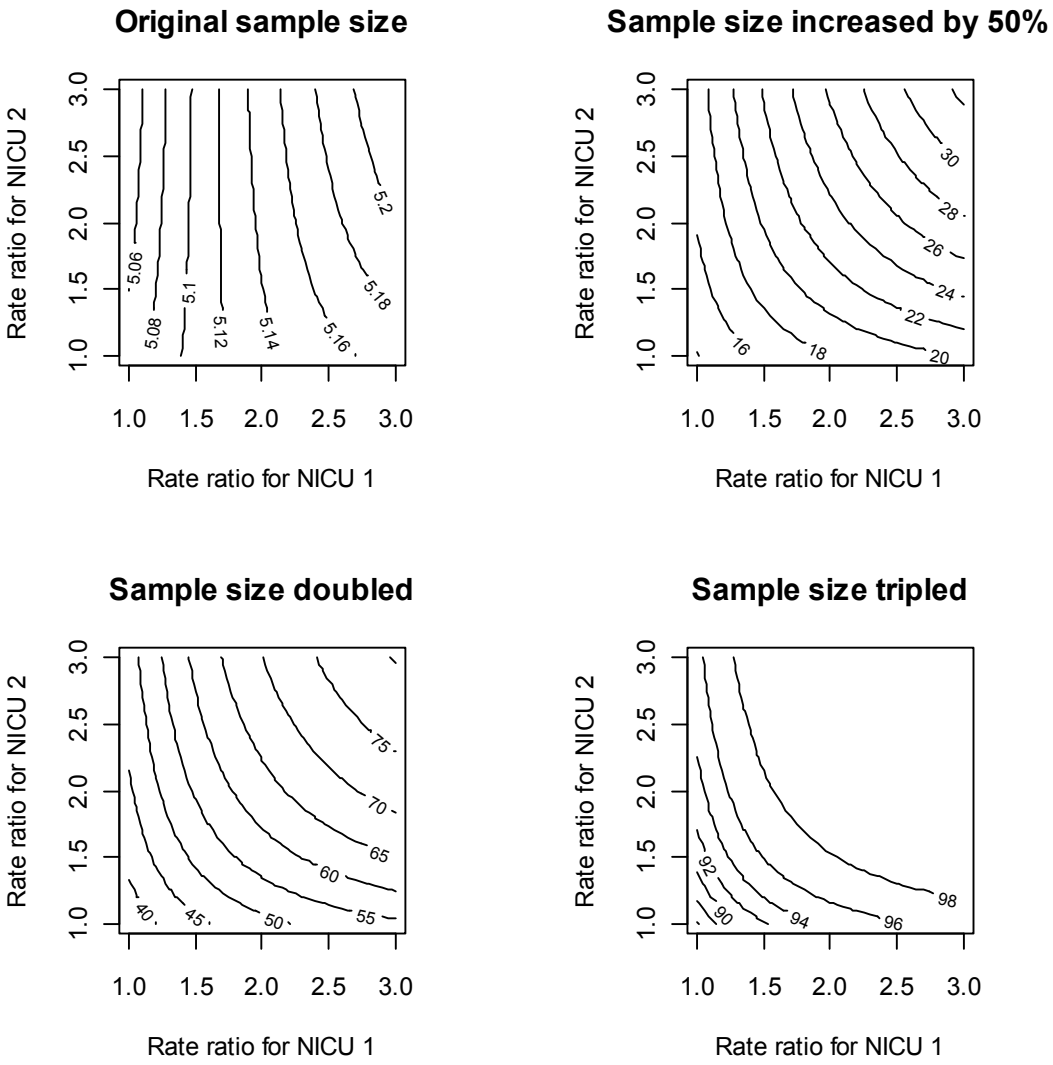
Days of May 2001 at NICU 1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**…**	**31**
Baby 1 (25 weeks, 753g)[a] Male Inborn, vaginal delivery Admitted 5/5/01 Died 12/5/01					**T V**	**T V**	**C S T V**	**T V**	**T V**	**NC S T V**	**T V**	**T V**											
Baby 2 (36 weeks, 2425g) Female Inborn, vaginal delivery Admitted 16/5/01 Discharged 20/05/01																**C S**							
Baby 3 (37 weeks, 2600g) Male Inborn, vaginal delivery Admitted 3/5/01 Discharged 7/5/01			**C S**		**S**																		

a - (Gestational age at birth, birth weight)

Figure 5.3 (continued) Dataset with babies categorised according to the sum of days exposed to each procedure-related factor

Baby	Gestational age (wks)	Birth weight (g)	Sex	Inborn/ Outborn	Delivery method	Number of days treated in/with:					Total CONS episodes	Total non-CONS episodes	Total baby-days	Total blood samples taken
						Special care	High dependency care	Intensive care	Total parenteral nutrition	Ventilation				
1	<26	700-<1200	Male	Inborn	Vaginal	0	0	≥7	≥7	≥7	1	1	8	0-3
2	32-<37	≥1200	Female	Inborn	Vaginal	1-3	1-3	0	0	0	1	0	5	0-3
3	≥37	≥1200	Male	Inborn	Vaginal	1-3	1-3	1-3	0	0	1	0	5	0-3

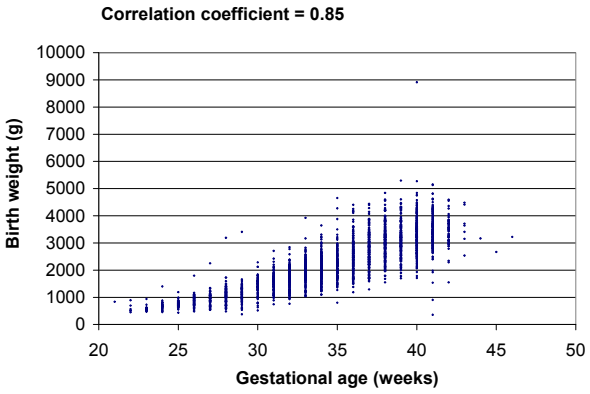
Figure 5.4 Graphs showing statistical power for increasing sample sizes and rate ratios, for total BSI.



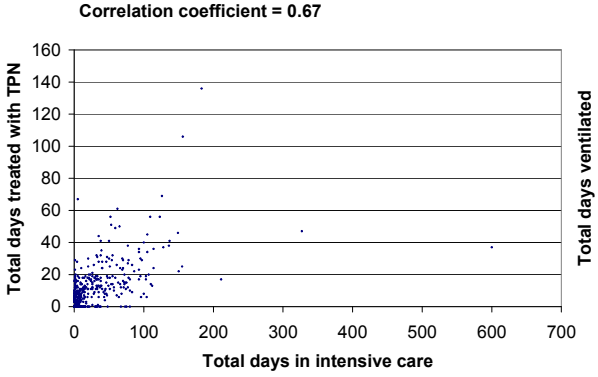
Each plot corresponds to a multiple of the sample size. The contour lines show the statistical power to detect hypothetical rate ratios for total BSI incidence at each NICU. To read each graph, find the intersection of the rate ratios of interest, and read the statistical power on the corresponding contour line. For example, if the sample size was doubled, the statistical power to detect a rate ratio of two at NICU 2 and one at NICU 1 would be about 45%.

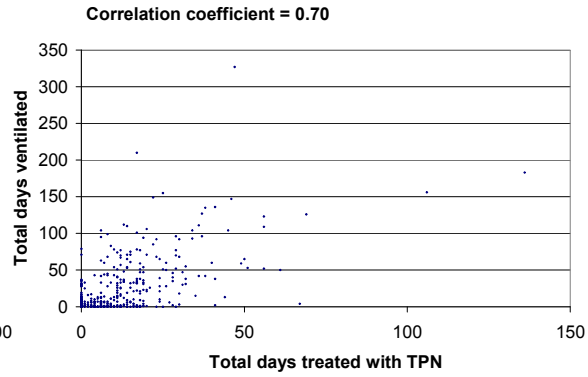
Figure 5.5 Graphs showing correlations between potential risk factors[b, c]

Factors reflecting baby susceptibility at birth



Procedure-related factors





Correlation coefficients:

+1 indicates positive correlation
-1 indicates negative correlation
0 indicates no correlation

For all correlations, *p*-value for the null hypothesis of no correlation was <0.001 (H_0=correlation coefficient of 0)

b - Outliers were identified for some variables, for example one baby had a birth weight of 8913g, another baby was in intensive care for 600 days. As mentioned in Chapter 4, it was often unclear whether extreme values represented errors in data entry, so they were left unchanged. Factors were analysed as categorical variables, which tempered the potential bias presented by outliers.
c - TPN- total parenteral nutrition

Figure 5.6 Kaplan-Meier estimates showing time to infection with total BSI, by birth weight[d]

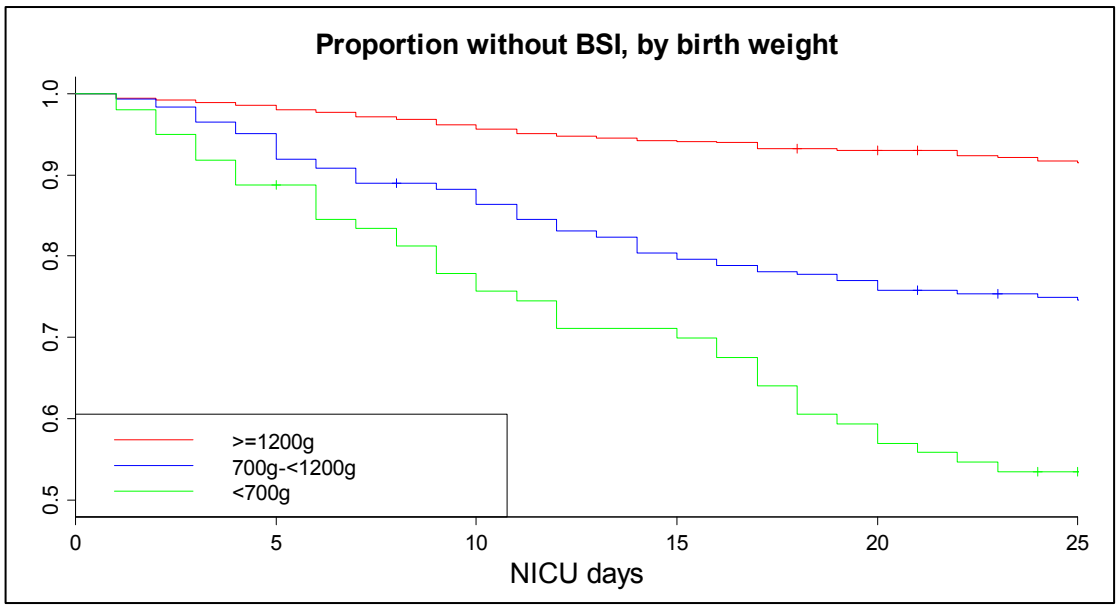


Figure 5.7 Kaplan-Meier estimates showing time to infection with total BSI, by inborn/outborn status[d]

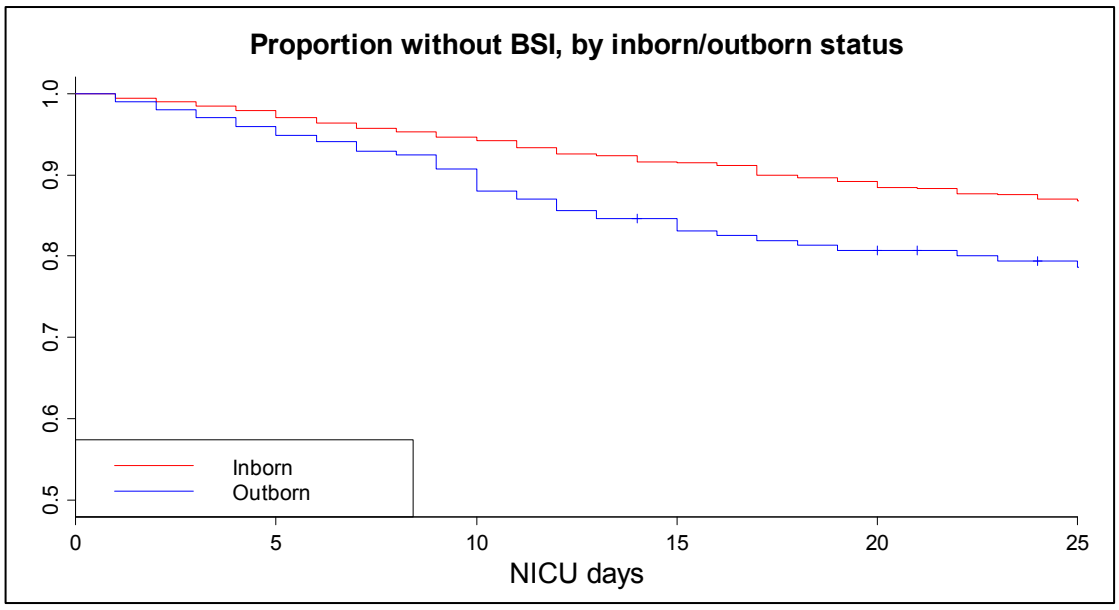


Figure 5.8 Kaplan-Meier estimates showing time to infection with CONS BSI, by birth weight[d]

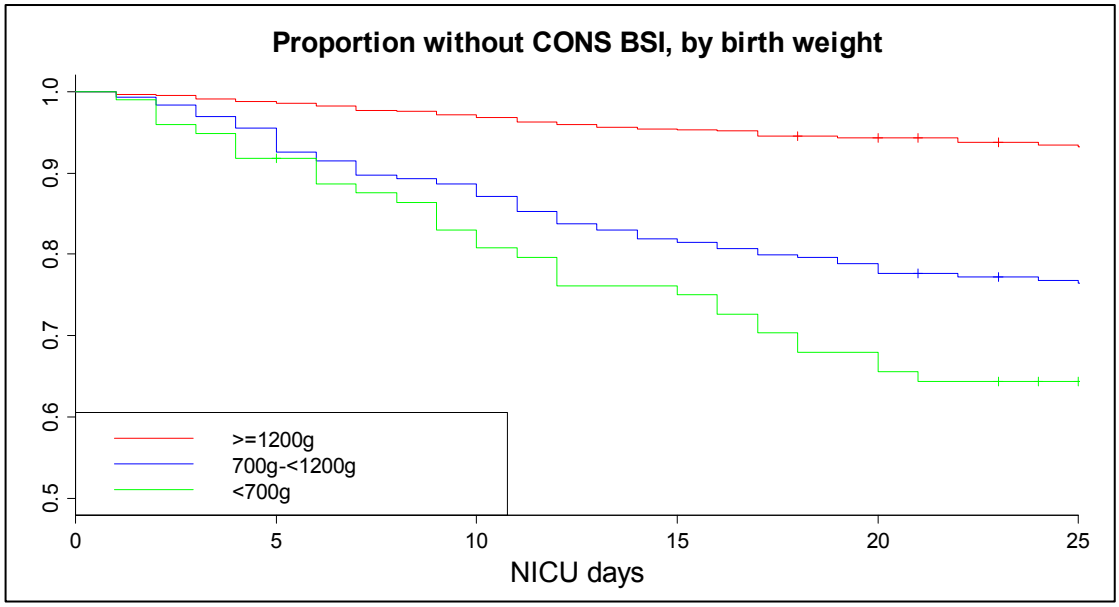


Figure 5.9 Kaplan-Meier estimates showing time to infection with CONS BSI, by inborn/outborn status[d]

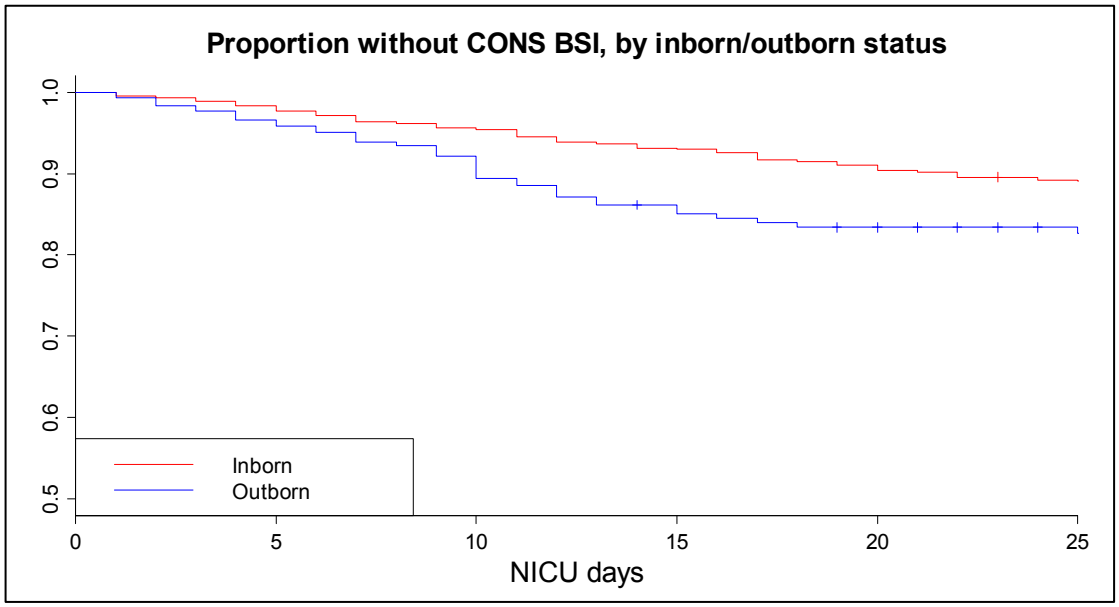
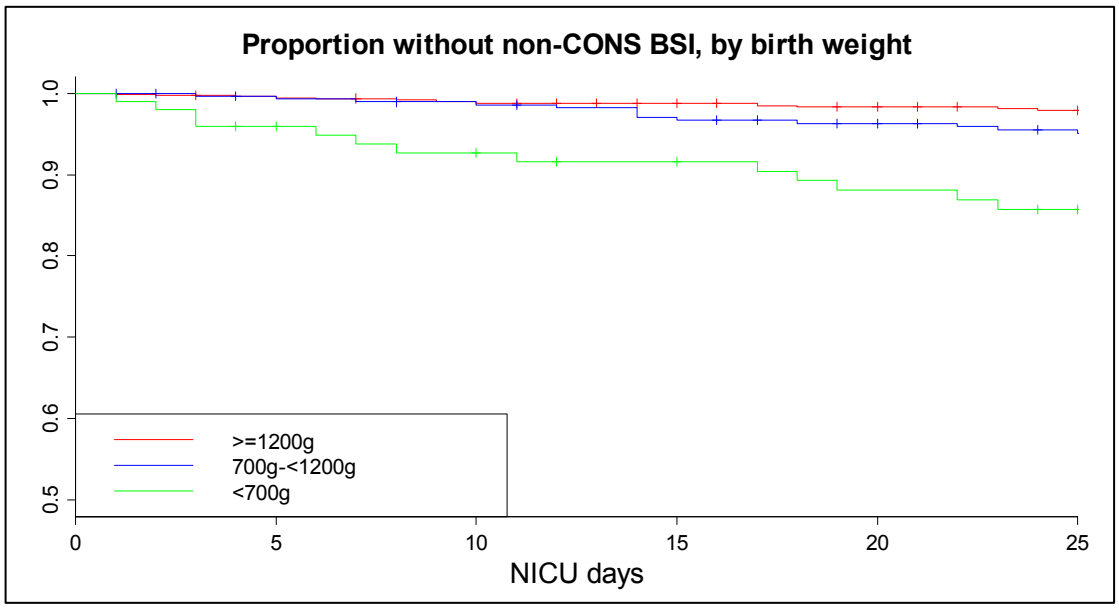


Figure 5.10 Kaplan-Meier estimates showing time to infection with non-CONS BSI, by birth weight[d]



d - The *y*-axis shows the proportion of babies in the NICU population who had never experienced a hospital-acquired BSI episode (total BSI, CONS or non-CONS, depending on the graph). The *x*-axis shows the number of days since NICU admission or day 3 of life, whichever came first. Vertical tick marks indicate when an uninfected baby was discharged from the NICU.

Table 5.1 Poisson regression models for the effect of birth susceptibility factors on total BSI, for NICUs 1, 2 and 3

Potential risk factor	BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value			Adjusted rate ratios (95% CI) *p*-value		
Gestational age (weeks)								
<26	117/10,101	(11.58)	2.57	(1.85, 3.58)	<0.001			
26-<28	55/7097	(7.75)	1.71	(1.17, 2.51)	0.006			
28-<32	88/16,369	(5.38)	1.18	(0.83, 1.67)	0.347			
32-<37	37/14,331	(2.58)	0.55	(0.36, 0.84)	0.006			
≥37	50/10,090	(4.96)		1				
Missing[e]	0/58							
Birth weight (g)								
<700	104/8543	(12.17)	3.65	(2.79, 4.78)	<0.001	3.43	(2.60, 4.53)	<0.001
700-<1200	135/18,792	(7.18)	2.15	(1.67, 2.77)	<0.001	2.00	(1.54, 2.60)	<0.001
≥1200	108/30,658	(3.52)		1			1	
Missing[e]	0/53							
Where born								
Outborn	101/11,389	(8.87)	1.73	(1.37, 2.18)	<0.001	1.28	(1.01, 1.63)	0.041
Inborn	242/46,197	(5.24)		1			1	
Missing[e]	4/460							
Hospital								
NICU 3	76/14,499	(5.24)	0.85	(0.64, 1.13)	0.254			
NICU 2	146/23,199	(6.29)	1.02	(0.80, 1.29)	0.890			
NICU 1	125/20,348	(6.14)		1				
Sex								
Male	182/29,940	(6.08)	1.03	(0.83, 1.27)	0.811			
Female	165/28,030	(5.89)		1				
Missing[e]	0/76							
Delivery method								
Emergency CS[f]	145/22,096	(6.56)	1.11	(0.89, 1.39)	0.357			
Elective CS[f]	43/9251	(4.65)	0.78	(0.56, 1.10)	0.154			
Vaginal	156/26,144	(5.97)		1				
Missing[e]	3/555							

Table 5.2 Poisson regression models for the effect of birth susceptibility factors on CONS BSI, for NICUs 1, 2 and 3

Potential risk factor	CONS BSI episodes/baby-days (Rate per 1000 baby-days)	Crude rate ratios (95% CI) *p*-value	Adjusted rate ratios (95% CI) *p*-value
Gestational age (weeks)			
<26	82/10,101 (8.12)	2.50 (1.69, 3.70) <0.001	
26-<28	43/7097 (6.06)	1.86 (1.20, 2.90) 0.006	
28-<32	70/16,369 (4.28)	1.30 (0.87, 1.95) 0.194	
32-<37	28/14,331 (1.95)	0.58 (0.35, 0.94) 0.029	
≥37	36/10,090 (3.57)	1	
Missing[e]	0/58		
Birth weight (g)			
<700	76/8543 (8.90)	3.61 (2.63, 4.93) <0.001	3.36 (2.43, 4.65) <0.001
700-<1200	103/18,792 (5.48)	2.21 (1.65, 2.96) <0.001	2.04 (1.50, 2.76) <0.001
≥1200	80/30,658 (2.61)	1	1
Missing[e]	0/53		
Where born			
Outborn	77/11,389 (6.76)	1.79 (1.37, 2.34) <0.001	1.33 (1.01, 1.76) 0.043
Inborn	178/46,197 (3.85)	1	1
Missing[e]	4/460		
Hospital			
NICU 3	64/14,499 (4.41)	0.99 (0.72, 1.37) 0.954	
NICU 2	105/23,199 (4.53)	1.02 (0.77, 1.35) 0.913	
NICU 1	90/20,348 (4.42)	1	
Sex			
Male	135/29,940 (4.51)	1.01 (0.79, 1.29) 0.919	
Female	124/28,030 (4.42)	1	
Missing[e]	0/76		
Delivery method			
Emergency CS[f]	115/22,096 (5.20)	1.23 (0.95, 1.59) 0.121	
Elective CS[f]	30/9251 (3.24)	0.76 (0.51, 1.14) 0.182	
Vaginal	112/26,144 (4.28)	1	
Missing[e]	2/555		

Table 5.3 Poisson regression models for the effect of birth susceptibility factors on non-CONS BSI, for NICUs 1, 2 and 3

Potential risk factor	Non-CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
Gestational age (weeks)					
<26	35/10,101	(3.47)	2.75	(1.48, 5.11)	0.001
26-<28	12/7097	(1.69)	1.34	(0.62, 2.89)	0.461
28-<32	18/16,369	(1.20)	0.86	(0.43, 1.73)	0.679
32-<37	9/14,331	(0.63)	0.48	(0.21, 1.10)	0.083
≥37	14/10,090	(1.39)		1	
Missing[e]	0/58				
Birth weight (g)					
<700	28/8,543	(3.28)	3.79	(2.25, 6.41)	<0.001
700-<1200	32/18,792	(1.70)	1.96	(1.18, 3.26)	0.009
≥1200	28/30,658	(0.91)		1	
Missing[e]	0/53				
Where born					
Outborn	24/11,389	(2.11)	1.55	(0.97, 2.48)	0.066
Inborn	64/46,197	(1.39)		1	
Missing[e]	0/460				
Hospital					
NICU 3	12/14,499	(0.83)	0.48	(0.25, 0.92)	0.027
NICU 2	41/23,199	(1.77)	1.02	(0.65, 1.60)	0.931
NICU 1	35/20,348	(1.72)		1	
Sex					
Male	47/29,940	(1.57)	1.07	(0.70, 1.62)	0.764
Female	41/28,030	(1.46)		1	
Missing[e]	0/76				
Delivery method					
Emergency CS[f]	30/22,096	(1.36)	0.82	(0.51, 1.30)	0.390
Elective CS[f]	13/9251	(1.41)	0.84	(0.45, 1.56)	0.577
Vaginal	44/26,144	(1.68)		1	
Missing[e]	1/555				

Table 5.4 Cox regression models for the effect of birth susceptibility factors on total BSI, for NICUs 1, 2 and 3

Potential risk factor	BSI episodes/baby-days	Crude hazard ratios (95% CI) *p*-value			Adjusted hazard ratios (95% CI) *p*-value		
Gestational age (weeks)							
<26	70/4963	4.59	(3.10, 6.80)	<0.001			
26-<28	39/4418	2.68	(1.72, 4.18)	<0.001			
28-<32	68/12,979	1.46	(0.98, 2.16)	0.060			
32-<37	33/13,328	0.51	(0.32, 0.80)	0.003			
≥37	44/9263		1				
Missing[e]	0/58						
Birth weight (g)							
<700	61/3314	7.33	(5.28, 10.16)	<0.001	6.80	(4.84, 9.54)	<0.001
700-<1200	96/13,143	3.16	(2.35, 4.24)	<0.001	2.86	(2.10, 3.90)	<0.001
≥1200	97/28,494		1			1	
Missing[e]	0/58						
Where born							
Outborn	73/7671	2.06	(1.56, 2.71)	<0.001	1.29	(0.97, 1.72)	0.085
Inborn	177/37,005		1			1	
Missing[e]	4/333						
Hospital							
NICU 3	56/10,787	0.88	(0.63, 1.23)	0.467			
NICU 2	108/18,171	1.08	(0.81, 1.42)	0.612			
NICU 1	90/16,051		1				
Sex							
Male	139/23,526	1.10	(0.86, 1.40)	0.462			
Female	115/21,407		1				
Missing[e]	0/76						
Delivery method							
Emergency CS[f]	99/16,645	1.01	(0.77, 1.32)	0.942			
Elective CS[f]	34/8032	0.75	(0.51, 1.09)	0.135			
Vaginal	118/19,911		1				
Missing[e]	3/421						

Table 5.5 Cox regression models for the effect of birth susceptibility factors on CONS BSI, for NICUs 1, 2 and 3

Potential risk factor	CONS BSI episodes/baby-days	Crude hazard ratios (95% CI) *p*-value			Adjusted hazard ratios (95% CI) *p*-value		
Gestational age (weeks)							
<26	60/5490	4.90	(3.16, 7.60)	<0.001			
26-<28	34/4749	2.90	(1.78, 4.74)	<0.001			
28-<32	60/13,330	1.66	(1.08, 2.56)	0.022			
32-<37	25/13,526	0.49	(0.29, 0.83)	0.008			
≥37	34/9396		1				
Missing[e]	0/58						
Birth weight (g)							
<700	53/3803	7.53	(5.26, 10.78)	<0.001	7.11	(4.89, 10.33)	<0.001
700-<1200	84/13,789	3.49	(2.53, 4.83)	<0.001	3.22	(2.30, 4.53)	<0.001
≥1200	76/28,899		1			1	
Missing[e]	0/58						
Where born							
Outborn	61/8146	2.00	(1.48, 2.70)	<0.001	1.21	(0.88, 1.65)	0.243
Inborn	148/38,070		1			1	
Missing[e]	4/333						
Hospital							
NICU 3	53/10,970	1.05	(0.74, 1.50)	0.784			
NICU 2	87/18,778	1.07	(0.79, 1.47)	0.650			
NICU 1	73/16,801		1				
Sex							
Male	113/24,414	1.02	(0.78, 1.34)	0.884			
Female	100/22,059		1				
Missing[e]	0/76						
Delivery method							
Emergency CS[f]	89/17,025	1.15	(0.86, 1.53)	0.356			
Elective CS[f]	27/8199	0.75	(0.49, 1.15)	0.183			
Vaginal	95/20,853		1				
Missing[e]	2/472						

Table 5.6 Cox regression models for the effect of birth susceptibility factors on non-CONS BSI, for NICUs 1, 2 and 3

Potential risk factor	Non-CONS BSI episodes/baby-days	Crude hazard ratios (95% CI) *p*-value		
Gestational age (weeks)				
<26	28/8696	4.21	(2.03, 8.72)	<0.001
26-<28	11/6168	1.98	(0.84, 4.66)	0.119
28-<32	16/15,468	1.03	(0.47, 2.25)	0.941
32-<37	9/14,042	0.52	(0.22, 1.25)	0.143
≥37	12/9882		1	
Missing[e]	0/58			
Birth weight (g)				
<700	24/6649	6.89	(3.80, 12.50)	<0.001
700-<1200	27/17,603	2.56	(1.44, 4.54)	0.001
≥1200	25/30,004		1	
Missing[e]	0/58			
Where born				
Outborn	21/10,413	1.63	(0.98, 2.70)	0.060
Inborn	55/43,441		1	
Missing[e]	0/460			
Hospital				
NICU 3	10/13,728	0.48	(0.23, 0.98)	0.044
NICU 2	37/21,783	1.12	(0.68, 1.82)	0.657
NICU 1	29/18,803		1	
Sex				
Male	41/28,518	1.08	(0.69, 1.70)	0.739
Female	35/25,720		1	
Missing[e]	0/76			
Delivery method				
Emergency CS[f]	25/20,641	0.77	(0.46, 1.27)	0.305
Elective CS[f]	12/8973	0.85	(0.45, 1.63)	0.629
Vaginal	38/24,196		1	
Missing[e]	1/504			

e - Babies with missing variables were few and experienced few episodes of BSI. For this reason I considered it acceptable to remove them from the analyses.
f - CS- Caesarean section

Table 5.7 Poisson regression models for the effect of procedure-related factors on total BSI, for NICUs 1, 2 and 3

Potential risk factor	BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
No of blood samples taken					
≥7	170/13,907	(12.22)	5.06	(3.91, 6.55)	<0.001
4-6	89/9625	(9.25)	3.79	(2.82, 5.09)	<0.001
0-3	88/34,514	(2.55)		1	
Number of days spent in:					
Special care					
≥7	216/44,969	(4.80)	0.39	(0.31, 0.50)	<0.001
4-6	11/2457	(4.48)	0.32	(0.17, 0.60)	<0.001
1-3	14/2087	(6.71)	0.46	(0.26, 0.80)	<0.006
0	106/8533	(12.42)		1	
High dependency care					
≥7	103/12,396	(8.31)	1.53	(1.20, 1.94)	<0.001
4-6	19/3719	(5.11)	0.93	(0.58, 1.49)	0.756
1-3	34/8024	(4.24)	0.76	(0.52, 1.09)	0.133
0	191/33,907	(5.63)		1	
Intensive care					
≥7	259/30,368	(8.53)	3.90	(2.78, 5.45)	<0.001
4-6	18/3847	(4.68)	2.07	(1.19, 3.62)	0.011
1-3	31/7246	(4.28)	1.88	(1.17, 3.01)	0.009
0	39/16,585	(2.35)		1	
Number of days treated with:					
Ventilation					
≥7	214/24,110	(8.88)	2.61	(2.03, 3.37)	<0.001
4-6	15/2716	(5.52)	1.59	(0.92, 2.75)	0.100
1-3	36/8538	(4.22)	1.21	(0.82, 1.79)	0.348
0	82/22,682	(3.62)		1	

Table 5.8 Poisson regression models for the effect of procedure-related factors on CONS BSI, for NICUs 1, 2 and 3

Potential risk factor	CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
No of blood samples taken					
≥7	124/13,907	(8.92)	4.78	(3.55, 6.42)	<0.001
4-6	67/9625	(6.96)	3.69	(2.63, 5.17)	<0.001
0-3	68/34,514	(1.97)		1	
Number of days spent in:					
Special care					
≥7	167/44,969	(3.71)	0.43	(0.33, 0.56)	<0.001
4-6	7/2457	(2.85)	0.29	(0.13, 0.63)	0.002
1-3	10/2087	(4.79)	0.46	(0.24, 0.89)	0.022
0	75/8533	(8.79)		1	
High dependency care					
≥7	75/12,396	(6.05)	1.50	(1.14, 1.99)	0.004
4-6	17/3719	(4.57)	1.12	(0.68, 1.86)	0.647
1-3	26/8024	(3.24)	0.78	(0.52, 1.19)	0.252
0	141/33,907	(4.16)		1	
Intensive care					
≥7	193/30,368	(6.36)	3.65	(2.50, 5.34)	<0.001
4-6	15/3847	(3.90)	2.17	(1.17, 4.03)	0.014
1-3	20/7246	(2.76)	1.52	(0.87, 2.67)	0.142
0	31/16,585	(1.87)		1	
Number of days treated with:					
Ventilation					
≥7	155/24,110	(6.43)	2.46	(1.84, 3.30)	<0.001
4-6	13/2716	(4.79)	1.79	(0.99, 3.25)	0.056
1-3	28/8538	(3.28)	1.22	(0.78, 1.91)	0.378
0	63/22,682	(2.78)		1	

Table 5.9 Poisson regression models for the effect of procedure-related factors on non-CONS BSI, for NICUs 1, 2 and 3

Potential risk factor	Non-CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
No of blood samples taken					
≥7	46/13,907	(3.31)	6.03	(3.57, 1.02)	<0.001
4-6	22/9625	(2.29)	4.12	(2.25, 7.55)	<0.001
0-3	20/34,514	(0.58)		1	
Number of days spent in:					
Special care					
≥7	49/44,969	(1.09)	0.31	(0.19, 0.48)	<0.001
4-6	4/2457	(1.63)	0.40	(0.14, 1.14)	0.088
1-3	4/2087	(1.92)	0.45	(0.16, 1.27)	0.130
0	31/8533	(3.63)		1	
High dependency care					
≥7	28/12,396	(2.26)	1.58	(1.00, 2.52)	0.051
4-6	2/3719	(0.54)	0.37	(0.09, 1.53)	0.172
1-3	8/8024	(1.00)	0.68	(0.32, 1.43)	0.310
0	50/33,907	(1.47)		1	
Intensive care					
≥7	66/30,368	(2.17)	4.84	(2.32, 0.10)	<0.001
4-6	3/3847	(0.78)	1.68	(0.45, 6.35)	0.441
1-3	11/7246	(1.52)	3.24	(1.31, 8.07)	0.011
0	8/16,585	(0.48)		1	
Number of days treated with:					
Ventilation					
≥7	59/24,110	(2.45)	3.11	(1.85, 5.21)	<0.001
4-6	2/2716	(0.74)	0.91	(0.21, 3.92)	0.903
1-3	8/8538	(0.94)	1.16	(0.51, 2.64)	0.729
0	19/22,682	(0.84)		1	

6. Analyses of factors predicting infection: Poisson regression

6.1 Summary

Clinicians need to know which factors predict BSI in order to identify high risk groups who could benefit from preventive action or close monitoring. I determined which procedure-related factors predict infection, by restricting analyses to risk factors that preceded BSI episodes. In comparison with Chapters 3 and 5, this chapter provides more complex analyses to determine which potential risk factors should be adjusted for when comparing BSI rates between NICUs.

NHS level of care, total parenteral nutrition, birth weight, inborn/outborn status and postnatal age were significant independent risk factors for BSI, with level of care and total parenteral nutrition being the strongest. The rate ratio for BSI, adjusted for birth weight, inborn/outborn status and postnatal age, was 3.15 (95% confidence interval 2.01, 4.94) for intensive care and 6.58 (4.18, 10.36) for high dependency care, relative to special care. Total parenteral nutrition was significantly associated with BSI incidence but explained less of the variance among babies than level of care.

Days at each level of care, birth weight, inborn/outborn status and postnatal age are risk factors that should be adjusted for when comparing BSI rates between NICUs. The next chapter will address bias associated with differences in the length of hospital stay.

6.2 Introduction

In this chapter I present analyses to determine which *predictive* risk factors should be adjusted for when comparing BSI rates between NICUs. In Chapter 3 and Chapter 5 I described simple associations between procedure-related factors and BSI. As described in Chapter 5, Section 5.5, because the timing of procedure-related exposures in relation to BSI episodes was not taken into account, some associations may have reflected *consequences* of infection. It would be useful for clinicians to know which factors *precede* or *predict* BSI, in order to identify high risk groups who could benefit from preventive action or close monitoring. In Chapter 6 and Chapter 7, I determine which procedure-related factors are most strongly predictive of BSI, by restricting analyses to factors preceding BSI episodes. As mentioned in Chapter 5, this was only possible for factors for which precise dates were recorded by NICU staff. This meant that data for NICUs 1 and 2 only could be included.

6.3 Methods

6.3.1 Study population

The datasets described in Chapter 4 for NICUs 1 and 2, each of which contain a record for each baby-day, were used for the analysis. Data were analysed for babies admitted on or after the 1st May 2001 and discharged up to and including the 28th February 2005.

6.3.2 Case definition

As in Chapter 5, an episode of BSI was defined as one or more blood cultures in which the same bacterial organism was isolated within a seven day period, and BSI episodes and baby-days from the first 48 hours of life were excluded from the analyses.

6.3.3 Potential risk factors

As in Chapter 5, potential risk factors reflecting susceptibility to BSI at birth included gestational age at birth in weeks (<26, 26-<28, 28-<32, 32-<37, ≥37), birth weight in grams (<700, 700-<1200, ≥1200), inborn/outborn status, NICU, sex and delivery method.

In Chapter 3 and Chapter 5 I suggested that procedure-related factors which change during the NICU stay may be associated with an increased risk of BSI. In this chapter, I determine which procedure-related factors *predict* BSI, and may therefore be amenable to infection control interventions. Factors which change during the NICU stay included: NHS level of care, total parenteral nutrition, ventilation, postnatal age in days (3-<10, 10-<20, 20-<30, 30-<40, 40-<50, ≥50), the number of blood samples taken and surgery.

Precise dates of treatment with total parenteral nutrition and ventilation were only available for NICU 2. To identify risk factors which may have a predictive role in BSI, I analysed procedure-related factors recorded in the three days preceding infection. For this three day period, the most intensive level of care was recorded and total parenteral nutrition and ventilation were labelled as either present or absent. The structure of the

datasets used, with each baby-day labelled according to procedure-related exposures in the previous three days, is shown in Figure 6.1.

6.3.4 Statistical analyses

Poisson regression models for rates of blood stream infection with potential risk factors

The advantage of this approach was that it allowed comparisons with findings reported by Holmes *et al*. (2008).[34] Following their methods, I calculated rates of BSI as days with onset of a first BSI episode divided by total days of NICU stay, for each level of each potential risk factor. To differentiate days of stay that may contribute to BSI from days of stay that may be the consequence of BSI, baby-days were counted up until the first BSI episode for infected babies and up until discharge from NICU for uninfected babies. Thus only risk factors preceding BSI episodes were included in the analyses. Poisson generalised linear models were fitted to estimate crude rate ratios for BSI, for each potential risk factor in turn. The models were fitted using generalised estimating equations, to account for the fact that days pertaining to the same baby were not independent. Poisson generalised linear models fitted using generalised estimating equations yield parameter estimates adjusted for within-subject correlation.[89] Potential risk factors with significant associations with BSI ($p<0.01$) were examined in combination using Poisson generalised linear models and forward stepwise model selection for risk factors based on the quasi-likelihood information criterion (the QIC is defined in the paragraph below).[90] As gestational age at birth and birth weight were correlated, separate adjusted models were built for each of these variables. A similar approach was taken for total parenteral nutrition and ventilation, which were also

correlated with each other and with level of care (for all correlations, the *p*-value for the null hypothesis of no correlation was <0.001) (refer to Chapter 5, Figure 5.5). The combination of risk factors giving the lowest QIC was included in the final adjusted model.[90]

The QIC was used to assess goodness of fit as Poisson generalised linear models using generalised estimating equations do not satisfy the assumptions associated with the AIC and the BIC. The QIC is another measure of goodness of fit of an estimated statistical model, similar to the AIC described in Chapter 3, Section 3.3.4, and the BIC described in Chapter 5, section 5.3.2. However, the QIC is different in that it adjusts for over-dispersion, or lack of fit, with a variance inflation factor *c,* and it is suitable for models fitted with generalised estimating equations. The QIC can be written as:

$$QIC = -(1/c)2\ln(L) + 2k$$

k = number of parameters in the model

c = variance inflation factor

L = maximised value of the likelihood function[90]

The analyses were repeated for each hospital separately.

6.3.5 Sensitivity analyses incorporating five and eight categories of birth weight and birth weight standardised for gestational age

Analyses incorporating five and eight categories of birth weight

It is possible that the three, broad birth weight categories used for the main analysis, and chosen by Holmes *et al.* (2008) (<700, 700-<1200, ≥1200g), may mask variations in BSI risk in babies with birth weights above 1200g. The ≥1200g birth weight category may include both babies born moderately preterm who are otherwise healthy and growing, and term babies undergoing surgery who may have more complex problems. This variation in risk was observed in Chapter 5 (Section 5.5) as babies with gestational ages between 28 and 36 weeks were at lower risk for BSI than term babies born at 37 weeks or above. This variation in risk is more likely in this study than in Holmes *et al.* (2008). While both study populations were drawn from inner London, level 3 NICUs admitting inborn babies and referrals, this study included one NICU (NICU 1) admitting specialist surgical cases. In this sensitivity analysis I analysed the effect on BSI of birth weight split into five and eight categories, to differentiate effects in preterm and term babies, who I expected to differ slightly in birth weight.

The following birth weight categories were used for the sensitivity analysis:

1. Five categories: <700, 700<-1200, 1200-<2500, 2500-<3500, ≥3500g. These categories were comparable with those chosen by Holmes *et al*. (2008), except that babies with birth weights above 1200g were split into three groups rather than one.

2. Eight categories: <500, 500-<1000, 1000-<1500, 1500-<2000, 2000-<2500, 2500-<3000, 3000-<3500, ≥3500g standard 500g birth weight groups.

Analyses incorporating birth weight standardised for gestational age

Chapter 5 showed that birth weight and gestational age were risk factors for BSI in separate analyses. This may signify that babies born smaller than expected for their gestational age are at increased risk for BSI. I therefore analysed the effect of birth weight standardised for gestational age, expressed as standard deviation scores, calculated using the `lmsGrowth` add-in to Microsoft Excel.[91] Reference centile curves show the distribution of birth weight as it changes according to gestational age. The LMS method uses the British 1990 growth reference centiles,[92] and it summarises this changing distribution using three curves representing the median (μ), coefficient of variation (σ) and skewness (λ) of birth weight against gestational age. The program standardised the birth weight (y) measurements in the dataset against this reference, using values appropriate for each baby's gestational age and sex. Standard deviation scores (Z) were calculated thus:

$$Z = \begin{cases} \dfrac{\left(y/\mu\right)^{\lambda} - 1}{\lambda\,\sigma} & \text{if } \lambda \neq 0 \\ \dfrac{\ln\left(y/\mu\right)}{\sigma} & \text{if } \lambda = 0 \end{cases}$$

The standard deviation score measured the number of standard deviations a baby's birth weight lay, above or below the mean birth weight for his or her gestational age and sex

in the reference population. Babies with birth weights corresponding to the mean had a score of 0, those with birth weights above or below the mean had positive and negative scores, respectively. Because standard deviation score represents a single variable combining birth weight and gestational age, it enabled the two factors to be combined in the same Poisson regression model. However, it must be stressed that the score is a standardised measure and therefore cannot be used to assess the simple effects of either factor.

6.4 Results

A total of 236 first episodes of BSI were recorded, of which: 176 were Coagulase-negative staphylococcus, 2 were Group B streptococcus, 27 were Gram positive organisms other than Group B streptococcus, 17 were Gram negative organisms, and 4 were yeasts. Ten episodes were mixed cultures, of which six contained CONS. The analysis included 2269 babies (940 from NICU 1 and 1329 from NICU 2). The two NICUs had similar rates of BSI, of around 6 per 1000 baby-days.

Level of care was the single strongest risk factor for BSI, in terms of optimising the QIC. Intensive care accounted for 36% of total NICU days (14,443/40,218) and 58% of BSI (138/236) and high dependency care accounted for 9% of NICU days (3603/40,218) and 20% of BSI (47/236) (Table 6.2). The optimal adjusted model consisted of level of care, birth weight, inborn/outborn status and postnatal age (Table 6.3).

Total parenteral nutrition was the second strongest risk factor for BSI. In NICU 2, it accounted for 16% of NICU days (3375/21,281) and 56% of BSI (72/129). Total parenteral nutrition could not be adjusted for in models already including level of care, as these variables were correlated. The optimal adjusted model incorporating total parenteral nutrition also included birth weight, inborn/outborn status and postnatal age (Table 6.5). The effect of ventilation was attenuated by adjustment for birth weight, inborn/outborn status and postnatal age (adjusted rate ratio 1.30, 95% confidence interval 0.81, 2.11, p=0.277).

As in Chapter 5, BSI risk was highest in the most premature and in term babies, with preterm babies born in the third trimester having the lowest risk. Babies with birth weights below 1200g were also at higher risk for BSI than heavier babies. The optimal adjusted model retained birth weight as an independent risk factor for BSI (Table 6.3).

Outborn babies had a higher risk for BSI than inborn babies. The risk of BSI was highest between days 3 and 20 of life in crude analyses, and this effect remained after adjustment for level of care, birth weight and inborn/outborn status (Table 6.3). No significant associations were found between BSI and NICU, sex, delivery method, the number of blood samples taken or surgery.

Similar results were found when the NICUs were analysed separately (Tables 6.3 and 6.4). For NICU 1, birth weight was a strong risk factor for BSI in crude analyses, but it was not included in the multivariable model as it did not optimise the QIC (Table 6.4). Postnatal age was only a significant risk factor for BSI at NICU 2 (Table 6.5).

6.4.1 Sensitivity analyses incorporating five and eight categories of birth weight and birth weight standardised for gestational age

Analyses incorporating five and eight categories of birth weight

The sensitivity analyses based on five categories of birth weight revealed a reverse J-shaped relationship. While babies with very low birth weights (below 700g) were at highest risk for BSI, babies with low to moderately low birth weights (between 1200g and 3500g) were at lowest risk. Babies weighing between 1200g and 3500g at birth were at lower risk than babies weighing more than 3500g. A similar relationship was found when birth weight was categorised into eight 500g birth weight groups, but confidence intervals were wide due to the small number of babies in some strata (n=10 in the <500g birth weight group) (Table 6.2). In the multivariable analysis, variation in risk in babies with birth weights above 1200g diminished after adjustment for level of care, inborn/outborn status and postnatal age. As a result, the best fitting model, based on the QIC for goodness of fit, grouped babies with birth weights above 1200g into a single category (Table 6.3).

Analyses incorporating birth weight standardised for gestational age

I found no significant association between standard deviation scores and BSI in crude or adjusted analyses. Figure 6.2 describes the standard deviation scores which standardised birth weight measurements for gestational age. Scores could not be calculated for seven babies born at 21-22 weeks' gestation, as reference centiles were not available for gestational ages below 23 weeks. Birth weight standardised for gestational age had no

significant effect on BSI in crude analyses, so it was not included in the adjusted models (Table 6.2).

6.5 Discussion

High intensity care and total parenteral nutrition in the previous three days were the strongest single risk factors for BSI. The optimal adjusted models combined these factors with birth weight, inborn/outborn status and postnatal age.

In this chapter I used similar statistical methods to those of the study by Holmes *et al*. (2008)[34] However, Holmes *et al.* analysed the risk associated with various specific invasive procedures in one NICU, whereas I also included NHS level of care as a composite potential risk factor and I analysed a larger study population spanning two NICUs. Holmes *et al*. identified parenteral nutrition and gestational age at birth below 26 weeks as the only significant independent risk factors for BSI, and recommended stratification by these factors for BSI monitoring. I found similar results for total parenteral nutrition and a similarly strong association between BSI and NHS level of care. The effects of total parenteral nutrition and level of care on BSI could not be compared together in the same model as they were correlated. Which factors should be used for risk adjustment depend on the clinical and health service questions being addressed. When comparing overall quality of care between NICUs, adjustment for daily level of care may be preferable because it includes all babies across the full spectrum of risk. In contrast, only a minority (24%)[67] of NICU patients receive parenteral nutrition, and the remaining babies have widely differing risks of BSI. Comparisons between NICUs could be based on BSI rates stratified by level of care.

This would describe BSI rates by their location and clinical team, which is useful for targeting infection control measures. Additional stratification of BSI rates by parenteral nutrition may be useful for monitoring infection control interventions focused on parenteral nutrition.

In addition to level of care, the optimal multivariable model included birth weight, inborn/outborn status and postnatal age, indicating that these factors may also need to be adjusted for when comparing BSI incidence between NICUs. Birth weight and inborn/outborn status were described as independent risk factors for BSI in Chapter 5. In the crude model for both NICUs combined, babies between 3 and 20 days of age experienced twice the risk of BSI, compared with babies above 50 days of age (Table 6.2). This effect was only evident at NICU 2 (Tables 6.4 and 6.5). It may be due to chance or because, as described in Section 6.3.5, babies at NICU 2 were predominantly born preterm, thus those surviving above 50 days of age were likely to be mostly healthy, growing and more resistant to BSI than newborn babies. In contrast, NICU 1 included babies referred for neonatal surgery whose clinical course may have been more complex.

As mentioned in Chapter 5 (Section 5.5), associations between potential risk factors and infections are not necessarily causal; they can arise from chance, from confounding by other risk factors, or they can reflect the consequence of infection. To determine factors predicting BSI, procedure-related factors were analysed for the three days preceding BSI. It is important to note that relationships found between BSI episodes and the risk factors closely preceding BSI are not necessarily *causal* relationships. Chronology is

only one requirement for establishing causality, another requirement is a biological mechanism for infection by invasive procedures, which is beyond the scope of this thesis. It is also important to remember that, as explained in Chapter 1 (Section 1.8), level of care is a *composite* risk factor that reflects a number of specific procedures and baby susceptibility factors, that could themselves be associated with infection.

Length of hospital stay is an example of a potential risk factor which could have a complex association with BSI. A longer length of stay may increase the risk of infection, but it can also be the consequence of an infection which causes a baby's condition to deteriorate. To determine factors predicting BSI, follow-up time was truncated at infection. However, this truncation is prone to bias, as it may result in systematic differences in follow-up time between infected and uninfected individuals (Figure 6.3).[93] Studies in NICUs are more prone to this type of bias than studies in adult intensive care, as babies tend to have longer lengths of stay in intensive care. A novel, alternative analytical method to overcome bias associated with length of follow-up is presented in Chapter 7.

Results for this analysis were similar to those for Chapter 5, except that neither the number of blood samples taken nor surgery showed significant relationships with BSI, in contrast with the previous chapter. This is likely to be because neither factor had a *predictive* relationship with BSI, which the analysis in this chapter was designed to detect. As described in Chapter 5, a baby's overall number of blood samples taken was, by definition, strongly correlated with his or her number of BSI episodes, as blood samples were used to diagnose infection. This chapter found that the number of blood

samples taken in the three-day period of relevant exposure before a first BSI episode did not predict that episode. This suggests that increases in the frequency of blood sampling do not result in a greater risk of detecting asymptomatic BSI or a contaminated sample. This finding was in keeping with the results for Chapter 3, which showed no significant association between the number of blood samples taken and total BSI at the unit level in adjusted analyses. Similarly, Chapter 5 showed that babies undergoing surgery *at any time* during their NICU stay were more likely to experience BSI episodes, whereas the analysis in this chapter showed that, during the relevant period of exposure, treatment with surgery did not predict the development of a first BSI episode. The association found in Chapter 5 was probably due to the fact that babies undergoing surgery were likely to be susceptible to BSI through their more serious clinical conditions and increased requirement for invasive procedures, rather than through any effect of the surgery itself. In this chapter, blood sampling frequency and surgery did not predict the development of BSI episodes.

6.5.1. Sensitivity analyses incorporating five and eight categories of birth weight and birth weight standardised for gestational age

Analyses incorporating five and eight categories of birth weight

The three birth weight categories chosen by Holmes *et al.* (2008) (<700, 700-<1200, ≥1200g) were suitable for risk adjusting comparisons of BSI incidence between NICUs in this study. Variation in risk among babies with birth weights above 1200g diminished with adjustment for level of care, inborn/outborn status and postnatal age. The three birth weight categories therefore produced a more parsimonious model, which

optimised the QIC. This suggests that the study populations in Holmes *et al*. (2008) and this study were fairly similar, which is supported by the similarity in findings regarding parenteral nutrition described above. This similarity may indicate that the findings of both studies could be transportable to other level 3 NICUs, including those providing specialist surgical care.

Analyses incorporating birth weight standardised for gestational age

Birth weight standardised for gestational age had no significant effect on BSI in this study. This may be the result of a selection effect, as the babies most at risk of BSI, those who were very preterm (23 to 28 weeks' gestation) and small for gestational age, were also those least likely to survive and be represented in the unit.

Bartels *et al.* (2007) described an increased risk of BSI among babies born at 24 to 28 weeks' gestation who were also small for gestational age. They evaluated babies born between 2000 and 2004, within 47 German NICUs participating in the NEO-KISS infection surveillance system. The outcome was at least one episode of hospital-acquired BSI, defined using modified CDC criteria.[15] 42% (163/392) of small for gestational age babies, defined as below the 10th percentile, experienced BSI episodes. 87% (787/2526) of appropriate for gestational age babies, between the 10th and the 90th percentile, experienced BSI episodes (odds ratio 1.41, 95% CI 1.05 to 1.89, adjusted for various birth susceptibility and procedure-related factors) The authors speculated that this increased risk was due to interactions between nutritional status and immunological function.[94] Low counts of white blood cells involved in immune function (total neutrophils, immature neutrophils, lymphocytes and monocytes) have been observed in

preterm small for gestational age babies, in comparison with their appropriate for gestational age counterparts.[95]

Babies described as being most at risk from BSI, those who were very preterm (24 to 28 weeks' gestation) and small for gestational age, were few in this study (Table 6.1, refer to the first two columns of the first two rows in the table). This was probably due to a selection effect, which was not so evident in Bartels *et al.* (2008) as their study population was very large, covering 47 NICUs. Larger babies and babies with greater gestational ages may have been more likely to survive and be represented in the unit, as well as being more resistant to BSI. Studies investigating the risk of BSI in babies above 28 weeks' gestation and small for gestational age are scarce, and they give conflicting results.[94,96,97] Because my focus was to determine factors which could adjust for BSI risk in the entire NICU population, birth weight standardised for gestational age was not included in the final risk adjustment model.

Key conclusions of Chapter 6

Findings

- I identified level of care, total parenteral nutrition, birth weight, gestational age, inborn/outborn status and postnatal age as significant independent risk factors for BSI.
- The analysis described in this chapter was able to elaborate predictive associations between procedure-related risk factors and BSI episodes.

Conclusions

- Adjustment of BSI rates by level of care, birth weight, inborn/outborn status and postnatal age could provide fair and meaningful comparisons between NICUs.
- The analysis was prone to bias associated with differences in the length of follow-up between babies. This bias will be addressed in the following chapter.

Figure 6.1 Diagram to describe stays in the NICU for three hypothetical babies, and how these stays would be translated into a dataset with each baby-day labelled according to procedure-related exposures in the previous three days

Special care	
High dependency	
Intensive care	

CONS infection episode	**C**
Non-CONS infection episode	**NC**
Blood sample taken	**S**

Invasive procedure, eg.	
Total parenteral nutrition	**T**
Ventilation	**V**

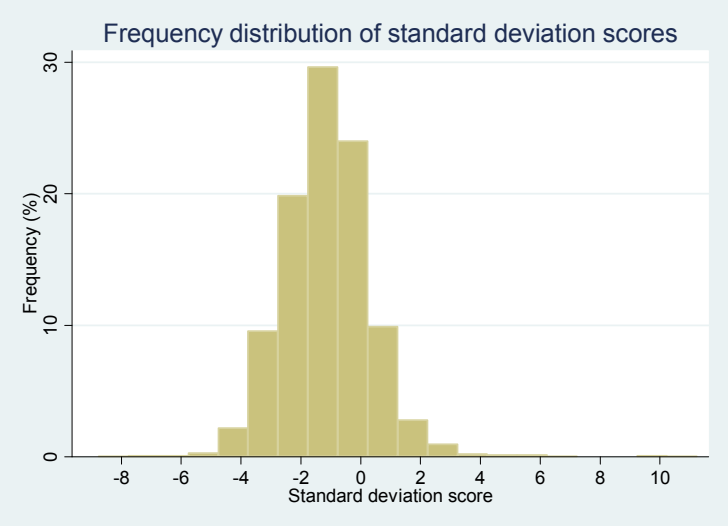
Days of May 2001 at NICU 1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**…**	**31**
Baby 1 (25 weeks, 753g)[a] Male Inborn, vaginal delivery Admitted 5/5/01 Died 12/5/01					**T V**	**T V**	**C S T V**	**T V**	**T V**	**NC S T V**	**T V**	**T V**										
Baby 2 (36 weeks, 2425g) Female Inborn, vaginal delivery Admitted 16/5/01 Discharged 20/05/01																**C S**						
Baby 3 (37 weeks, 2600g) Male Inborn, vaginal delivery Admitted 3/5/01 Discharged 7/5/01			**C S**		**S**																	

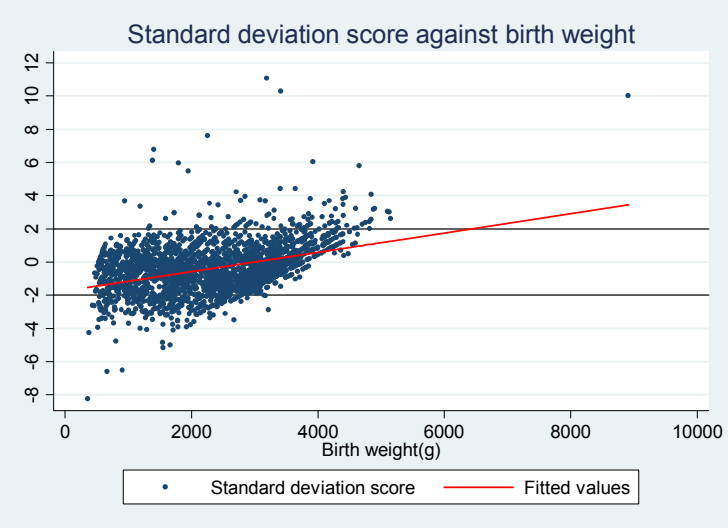
a - (Gestational age at birth, birth weight)

Figure 6.1 (continued) Dataset with each baby-day labelled according to procedure-related exposures in the previous three days. For infected babies, baby-days were truncated at the first infection episode

Baby	Date	Gestational age (wks)	Birth weight (g)	Sex	Inborn/ Outborn	Delivery method	In previous three days:				CONS episode	Non-CONS episode
							Highest level of care	Total parenteral nutrition?	Ventilation?	Number of blood samples taken		
1	5/5/2001	<26	700-<1200	Male	Inborn	Vaginal	Other	No	No	0	0	0
1	6/5/2001	<26	700-<1200	Male	Inborn	Vaginal	Intensive care	Yes	Yes	0	0	0
1	7/5/2001	<26	700-<1200	Male	Inborn	Vaginal	Intensive care	Yes	Yes	0	1	0
2	16/5/2001	32-<37	≥1200	Female	Inborn	Vaginal	Other	No	No	0	1	0
3	3/5/2001	≥37	≥1200	Male	Inborn	Vaginal	Other	No	No	0	1	0

Figure 6.2 Description of standard deviation scores standardising birth weight measurements for gestational age





Standard deviation score and birth weight were positively correlated, showing a linear relationship:

Correlation coefficient = 0.40
p-value for the null hypothesis of no correlation <0.001
(H_0 = correlation coefficient of 0)

Linear regression coefficient = 0.0006 (95% CI 0.0005, 0,0006)
p-value for the null hypothesis of no linear relationship <0.001

The dataset contained outliers for birth weight and gestational age. As mentioned in Chapter 5, Figure 5.5, factors were analysed as categorical variables, which tempered the potential bias presented by outliers.

Figure 6.3 If only days preceding infection are analysed, uninfected babies can contribute more person-time to the analysis. Example showing a baby with an infection at day 7 and discharge from NICU at day 14

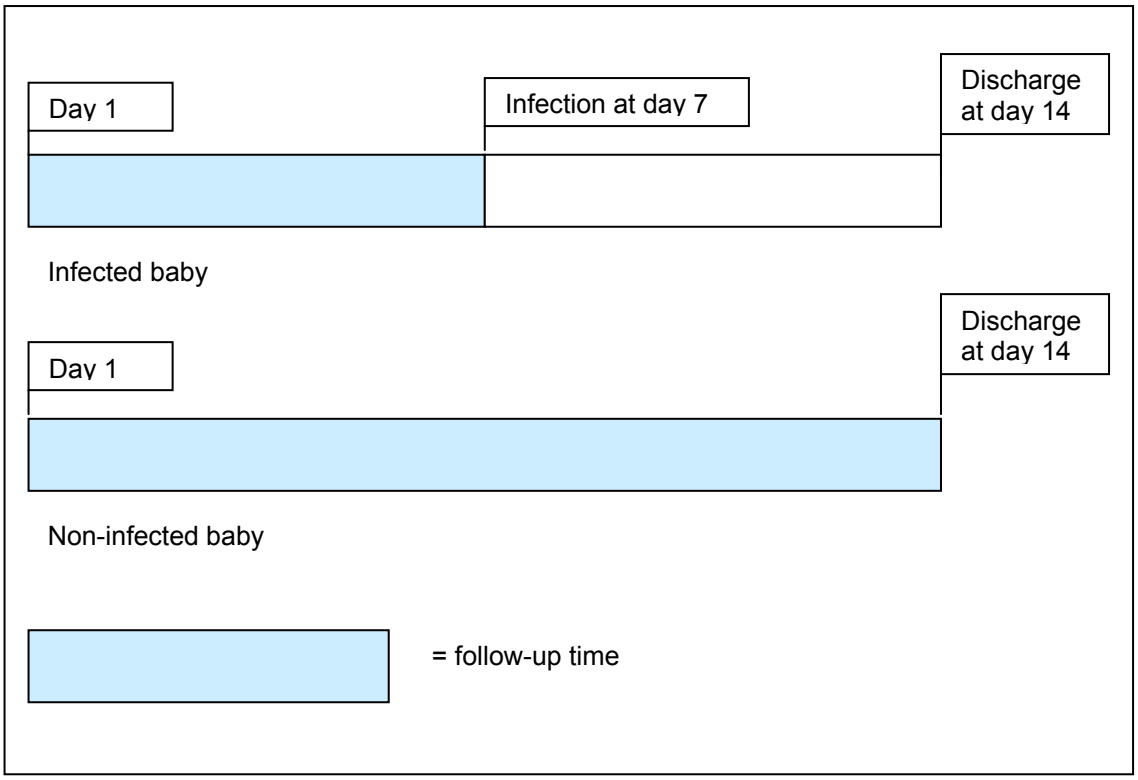


Table 6.1 Number of babies by gestational age and standard deviation score

	Standard deviation score						
Gestational age (weeks)	**<-2**	**-2-<-1**	**-1-<0**	**0-<1**	**1-<2**	**≥2**	**Missing**
<26	1	11	46	48	9	4	7
26-<28	9	21	33	26	12	5	0
28-<32	39	58	92	87	35	12	0
32-<37	94	122	186	141	68	38	1
≥37	132	234	309	237	98	40	2
Missing	0	0	0	0	0	0	12

Table 6.2 Crude Poisson regression models for NICU 1 and NICU 2 combined

Potential risk factor	Days with onset of BSI/Total baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
Highest level of care[b]					
Intensive care	138/14,443	(9.55)	5.42	(3.78, 7.77)	<0.001
High dependency care	47/3603	(13.04)	7.30	(4.76, 11.19)	<0.001
Special care	36/20,919	(1.72)		1	
Other[c]	15/1253				
Gestational age (weeks)					
<26	72/5619	(12.81)	2.67	(1.80, 3.94)	<0.001
26-<28	35/4398	(7.96)	1.58	(1.00, 2.48)	0.050
28-<32	53/11,319	(4.68)	0.92	(0.61, 1.37)	0.668
32-<37	30/10,620	(2.82)	0.51	(0.32, 0.81)	0.005
≥37	46/8233	(5.59)		1	
Missing[d]	0/29				
Birth weight (g)					
<700g	62/3634	(17.06)	4.82	(3.39, 6.85)	<0.001
700g-<1200g	78/12,400	(6.29)	1.76	(1.29, 2.40)	<0.001
≥1200g	96/24,146	(3.98)		1	
Missing[d]	0/38				
Postnatal age (days)					
3-<20	153/20,991	(7.29)	1.97	(1.24, 3.13)	0.004
20-<56	63/13,804	(4.56)	1.24	(0.75, 2.04)	0.407
≥56	20/5423	(3.69)		1	
Inborn status					
Outborn	80/7571	(10.57)	2.21	(1.68, 2.89)	<0.001
Inborn	154/32,476	(4.74)		1	
Missing[d]	2/171				
Hospital					
NICU 2	129/21,281	(6.06)	1.08	(0.84, 1.41)	0.544
NICU 1	107/18,937	(5.65)		1	
Sex					
Male	130/21,015	(6.19)	1.12	(0.86, 1.45),	0.413
Female	106/19,203	(5.52)		1	
Delivery method					
Emergency CS[e]	92/15,531	(5.92)	0.97	(0.73, 1.29)	0.824
Elective CS[e]	33/6789	(4.86)	0.79	(0.53, 1.17)	0.237
Vaginal	110/17,856	(6.16)		1	
Missing[d]	1/42				
Number of blood samples taken[b]					
≥2	2/388	(5.15)	0.78	(0.19, 3.24)	0.734
1	27/6169	(4.38)	0.69	(0.46, 1.02)	0.060
0	207/33,661	(6.15)		1	
Surgery[b]					
Yes	5/935	(5.35)	0.89	(0.38, 2.10)	0.796
No	231/39,283	(5.88)		1	
Sensitivity analyses					

incorporating five and eight categories of birth weight and birth weight standardised for gestational age					
Birth weight (g)					
<700	62/3634	(17.06)	2.28	(1.25, 4.17)	0.007
700-<1200	78/12,400	(6.29)	0.83	(0.47, 1.49)	0.537
1200-<2500	58/16,404	(3.54)	0.42	(0.24, 0.77)	0.004
2500-<3500	24/6108	(3.93)	0.46	(0.24, 0.90)	0.022
≥3500	14/1634	(8.57)		1	
Missing[d]	0/38				
Birth weight (g)					
<500	5/272	(18.38)	2.63	(0.79, 8.72)	0.114
500-<1000	115/11,116	(10.35)	1.41	(0.80, 2.48)	0.238
1000-<1500	46/10,232	(4.50)	0.57	(0.31, 1.05)	0.071
1500-<2000	20/6957	(2.87)	0.35	(0.17, 0.69)	0.002
2000-<2500	12/3861	(3.11)	0.36	(0.17, 0.79)	0.011
2500-<3000	8/3180	(2.52)	0.28	(0.12, 0.67)	0.004
3000-<3500	16/2928	(5.46)	0.66	(0.32, 1.37)	0.262
≥3500	14/1634	(8.57)		1	
Missing[d]	0/38				
Standard deviation score					
<-2	38/5660	(6.71)	1.04	(0.68, 1.59)	0.849
-2-<-1	49/7811	(6.27)	0.97	(0.66, 1.42)	0.855
-1-<0	62/12,529	(4.95)	0.77	(0.54, 1.10)	0.147
0-<1	61/9446	(6.46)		1	
1-<2	18/3052	(5.90)	0.91	(0.53, 1.55)	0.714
≥2	6/1365	(4.40)	0.66	(0.30, 1.45)	0.296
Missing[d]: gest age <23 weeks	2/317				
Missing[d]: birth weight missing or birth weight and gest age missing	0/38				

Table 6.3 Adjusted Poisson regression models for NICU 1 and NICU 2 combined

Potential risk factor	Optimal risk adjustment model Adjusted rate ratios (95% CI) *p*-value QIC for model: 2526			Sensitivity analyses incorporating five and eight categories of birth weight Model including five birth weight categories Adjusted rate ratios (95% CI) *p*-value QIC for model: 2529			Model including eight birth weight categories Adjusted rate ratios (95% CI) *p*-value QIC for model: 2537		
Highest level of care[b]									
Intensive care	3.15	(2.01, 4.94)	<0.001	3.16	(2.02, 4.94)	<0.001	2.90	(1.85, 4.54)	<0.001
High dependency care	6.58	(4.18, 10.36)	<0.001	6.61	(4.19, 10.43)	<0.001	6.57	(4.15, 10.38)	<0.001
Special care		1			1			1	
Other[c]									
Birth weight (g)									
<700g	3.69	(2.37, 5.74)	<0.001						
700g-<1200g	1.60	(1.09, 2.35)	0.016						
≥1200g		1							
Missing[d]									
Postnatal age (days)									
3-<10	2.79	(1.64, 4.74)	<0.001	2.79	(1.64, 4.75)	<0.001	3.01	(1.76, 5.14)	<0.001
10-<20	2.94	(1.78, 4.83)	<0.001	2.94	(1.78, 4.83)	<0.001	3.08	(1.87, 5.07)	<0.001
20-<30	1.93	(1.10, 3.39)	0.023	1.93	(1.10, 3.39)	0.022	1.98	(1.13, 3.48)	0.017
30-<40	2.15	(1.19, 3.89)	0.011	2.15	(1.19, 3.88)	0.011	2.20	(1.22, 3.97)	0.009
40-<50	1.42	(0.68, 2.96)	0.358	1.41	(0.68, 2.96)	0.358	1.42	(0.68, 2.96)	0.349
≥50		1			1			1	
Inborn status									
Outborn	1.51	(1.12, 2.04)	0.007	1.51	(1.12, 2.03)	0.007	1.45	(1.08, 1.95)	0.014
Inborn		1			1			1	
Missing[d]									
Birth weight (g)									

<700g	3.00	(1.32, 6.80)	0.009			
700g-<1200	1.30	(0.59, 2.87)	0.513			
1200-<2500	0.84	(0.39, 1.81)	0.653			
2500-<3500	0.70	(0.30, 1.62)	0.403			
≥3500		1				
Missing[d]						
Birth weight (g)						
<500				3.65	(1.24, 10.75)	0.019
500-<1000				2.23	(1.00, 4.94)	0.049
1000-<1500				1.03	(0.47, 2.27)	0.934
1500-<2000				0.77	(0.33, 1.79)	0.537
2000-<2500				0.59	(0.22, 1.56)	0.286
2500-<3000				0.55	(0.21, 1.45)	0.225
3000-<3500				0.89	(0.35, 2.26)	0.804
≥3500					1	
Missing[d]						

Table 6.4 Poisson regression models for NICU 1

Potential risk factor	Days with onset of BSI/Total baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value			Adjusted rate ratios (95% CI) *p*-value QIC for model: 1196		
Highest level of care[b]								
Intensive care	60/6400	(9.38)	5.68	(3.24, 9.97)	<0.001	5.02	(2.65, 9.52)	<0.001
High dependency care	28/2418	(11.58)	7.02	(3.75, 13.14)	<0.001	7.40	(3.84, 14.26)	<0.001
Special care	16/9540	(1.68)		1			1	
Other[c]	3/579							
Gestational age (weeks)								
<26	33/2653	(12.44)	2.63	(1.49, 4.64)	0.001			
26-<28	17/2753	(6.18)	1.30	(0.67, 2.53)	0.442			
28-<32	28/5237	(5.35)	1.11	(0.61, 2.01)	0.730			
32-<37	10/4422	(2.26)	0.46	(0.21, 1.00)	0.048			
≥37	1/3843	(4.94)		1				
Missing[d]	0/29							
Birth weight (g)								
<700g	41/10,432	(3.93)	3.75	(2.21, 6.37)	<0.001			
700g-<1200g	42/6743	(6.23)	1.65	(1.07, 2.56)	0.025			
≥1200g	24/1724	(13.92)		1				
Missing[d]	0/38							
Postnatal age (days)								
3-<10	26/4970	(5.23)	1.18	(0.62, 2.26)	0.614			
10-<20	35/4589	(7.63)	1.72	(0.93, 3.20)	0.085			
20-<30	13/3082	(4.22)	0.95	(0.45, 2.03)	0.898			
30=<40	11/2053	(5.36)	1.21	(0.55, 2.66)	0.638			
40-<50	9/1317	(6.83)	1.54	(0.67, 3.56)	0.312			
≥50	13/2926	(4.44)		1				
Inborn status								
Outborn	50/4696	(10.65)	2.71	(1.86, 3.95)	<0.001	1.78	(1.17, 2.73)	0.008
Inborn	55/14,070	(3.91)					1	
Missing[d]	2/171							

Sex					
Male	58/9917	(5.85)	1.08	(0.74, 1.58)	0.705
Female	49/9020	(5.43)		1	
Delivery method					
Emergency CS[e]	46/8138	(5.65)	0.95	(0.64, 1.41)	0.793
Elective CS[e]	8/2069	(3.87)	0.65	(0.31, 1.35)	0.248
Vaginal	52/8698	(5.98)		1	
Missing[d]	1/32				
Number of blood samples taken[b]					
≥2	1/181	(5.52)	0.93	(0.13, 6.90)	0.944
1	13/2670	(4.87)	0.83	(0.47, 1.48)	0.533
0	93/16,086	(5.78)		1	
Surgery[b]					
Yes	2/291	(6.87)	1.22	(0.31, 4.84)	0.781
No	105/18,646	(5.63)		1	

Table 6.5 Poisson regression models for NICU 2

Potential risk factor	Days with onset of BSI/Total baby-days (Rate per 1000 baby-days)	Crude rate ratios (95% CI) *p*-value	Adjusted rate ratios incorporating level of care (95% CI) *p*-value QIC for model: 1323	Adjusted rate ratios incorporating total parenteral nutrition (95% CI) *p*-value QIC for model:1450
Highest level of care[b]				
Intensive care	78/8043 (9.70)	5.36 (3.37, 8.52) <0.001	2.48 (1.34, 4.59) 0.004	
High dependency care	19/1185 (16.03)	8.38 (4.61, 15.23) <0.001	7.25 (3.73, 14.13) <0.001	
Special care	20/11,379 (1.76)	1	1	
Other[c]	12/674			
Gestational age (weeks)				
<26	39/2966 (13.15)	2.90 (1.70, 4.96) <0.001		
26-<28	18/1645 (10.94)	2.15 (1.14, 4.04) 0.018		
28-<32	25/6082 (4.11)	0.80 (0.46, 1.39) 0.420		
32-<37	20/6198 (3.23)	0.54 (0.30, 0.96) 0.036		
≥37	27/4390 (6.15)	1		
Missing[d]	0/0			
Birth weight (g)				
<700g	38/1910 (19.90)	5.88 (3.69, 9.36) <0.001	5.78 (3.27, 10.22) <0.001	2.66 (1.58, 4.48) <0.001
700g-<1200g	36/5657 (6.36)	1.94 (1.24, 3.03) 0.004	2.22 (1.27, 3.86) 0.005	1.19 (0.71, 1.98) 0.508
≥1200g	55/13,714 (4.01)	1	1	1
Missing[d]	0/0			
Postnatal age (days)				
3-<10	56/6347 (8.82)	3.29 (1.66, 6.51) 0.001	5.06 (2.31, 11.09) <0.001	3.13 (1.45, 6.74) 0.004
10-<20	36/5085 (7.08)	2.63 (1.29, 5.36) 0.008	4.09 (1.90, 8.80) <0.001	2.04 (0.90, 4.63) 0.086
20-<30	15/3014 (4.98)	1.85 (0.82, 4.16) 0.138	2.93 (1.26, 6.81) 0.013	1.73 (0.72, 4.15) 0.218
30-<40	11/1881 (5.85)	2.17 (0.91, 5.15) 0.079	2.98 (1.25, 7.13) 0.014	1.98 (0.78, 5.04) 0.153
40-<50	1/1284 (0.78)	0.29 (0.04, 2.31) 0.239	0.38 (0.05, 2.93) 0.351	0.26 (0.03, 2.33) 0.229
≥50	10/3670 (2.72)	1	1	1
Inborn status				
Outborn	30/2875 (10.43)	1.95 (1.27, 3.00) 0.002	1.67 (1.12, 2.50) 0.013	1.58 (1.06, 2.35) 0.024
Inborn	99/18,406 (5.38)	1	1	1
Missing[d]	0/0			

Sex								
Male	72/11,098	(6.49)	1.14	(0.80, 1.64)	0.467			
Female	57/10,183	(5.60)		1				
Delivery method								
Emergency CS[e]	46/7393	(6.22)	0.99	(0.66, 1.48)	0.965			
Elective CS[e]	25/4720	(5.30)	0.83	(0.51, 1.33)	0.431			
Vaginal	58/9158	(6.33)		1				
Missing[d]	0/10							
Number of blood samples taken [b]								
≥2	1/207	(4.83)	0.68	(0.10, 4.85)	0.703			
1	14/3499	(4.00)	0.59	(0.35, 0.99)	0.047			
0	114/17,575	(6.49)		1				
Surgery[b]								
Yes	3/644	(4.66)	0.73	(0.25, 2.16)	0.573			
No	126/20,637	(6.11)		1				
Total parenteral nutrition[b]								
Yes	72/3375	(21.33)	6.50	(4.53, 9.33)	<0.001	4.30	(2.63, 7.04)	<0.001
No	57/17,906	(3.18)		1			1	
Ventilation[b]								
Yes	75/7093	(10.57)	2.80	(1.99, 3.93)	<0.001			
No	54/14,188	(3.81)		1				

b - In the previous three days

c - 'Other' indicates that for the previous three days, the baby was outside the NICU. For example at another hospital or undergoing surgery.

d - Days/babies with missing variables were few and represented few episodes of BSI. For this reason I considered it acceptable to remove them from the analyses.

e - CS- Caesarean section

7. Analyses of factors predicting infection: Case control study

7.1 Summary

In Chapter 6 I suggested that adjustment of BSI rates by level of care, birth weight, inborn/outborn status and postnatal age could provide meaningful comparisons between NICUs. This chapter provides an alternative analysis to that described in Chapter 6. It presents a novel method which can describe predictive associations between procedure-related risk factors and BSI episodes, whilst removing bias in the length of follow-up.

I used a case control study design: cases were babies experiencing at least one episode of BSI, and controls were babies who were present in the NICU at the same age (in days) as their matched case's age at first BSI. This age was taken as the censoring day for both cases and controls. In conditional logistic regression models, NHS level of care, total parenteral nutrition, birth weight, gestational age at birth and inborn/outborn status were significant independent risk factors for BSI, with level of care being the strongest. The effect of postnatal age could not be evaluated in this analysis as this factor was used to match cases and controls. The odds ratio for BSI adjusted for birth weight and inborn/outborn status was 4.38 (95% CI 2.32, 8.27) in intensive care and 14.63 (95% CI 6.94, 30.83) in high dependency care, relative to the baseline special care. The case control study gave larger risk estimates than the Poisson regression analyses described in Chapter 6.

The true effects on BSI of the risk factors analysed were likely to be between the effects estimated by the analytical approaches described in Chapter 6 and this chapter. Despite the methodological differences between the two analyses, they yielded similar conclusions.

7.2 Introduction

The previous chapter identified various significant independent risk factors for BSI, and suggested that adjustment of BSI rates by NHS level of care, birth weight, inborn/outborn status and postnatal age could provide meaningful comparisons between NICUs. A strength of the analysis in Chapter 6 was its comparability with a previous study that had used similar analytic methods,[34] however it was prone to bias associated with differences in the length of follow-up between babies with and without BSI.

This chapter provides an alternative analysis to that described in Chapter 6, using logistic regression models assuming a matched case control design. Cases and controls were chosen from the same dataset used for Chapter 6. This is a novel method which can describe predictive associations between procedure-related risk factors and BSI episodes, whilst removing bias in the length of follow-up.

7.3 Methods

7.3.1 Study population, case definition and potential risk factors

The study population, case definition and potential risk factors were defined as for Chapter 6 (refer to Sections 6.3.1, 6.3.2 and 6.3.3). Probable maternally-transmitted BSI episodes occurring during the first 48 hours of life were excluded.

In a case control study, factors used to match cases and controls cannot be analysed in regression models. Age at infection was used for matching cases and controls in this study, which ensured consistent follow-up time for babies within each matched pair, but it meant that the effect of postnatal age could not be analysed. To be able to investigate the BSI risk associated with the other potential risk factors, only age at infection was used for matching.

7.3.2 Selection of controls

Babies experiencing at least one episode of BSI were defined as cases. Controls were babies who were present in the NICU at the same age (in days) as their matched case's age at first BSI. Controls were defined using the following control selection strategies:

1 - Babies who had no episodes of BSI during their NICU stay

2 - Babies who had no episodes of BSI on or before the age used for matching

3 - Babies who had no episodes of BSI in the eight days up to and including the age used for matching

With control selection strategy 1, controls were babies who remained completely free of infection. Control selection strategy 3 included the greatest number of babies with potential experience of infection.

For each control selection strategy, each case was matched with two controls. Except for one to two cases described in footnotes to the results tables, controls were not selected twice, so the vast majority of cases did not share controls. Each control selection strategy was carried out for the hospitals combined and separate. When the hospitals were combined, matched cases and controls did not necessarily come from the same NICU. When the hospitals were separated, all cases and controls were taken from the same NICU.

Each case's age at first BSI was the age used for matching, and this was taken as the censoring age for both cases and controls. In contrast to the Poisson regression models described in Chapter 6, this removed bias due to differences in follow-up by ensuring that infected and uninfected babies were observed for similar lengths of time. For each baby, I recorded the presence of each procedure-related factor in the three days prior to the censoring age. The structure of the datasets used, with censoring ages labelled according to the procedure-related exposures in the previous three days, is shown in Figure 7.1.

7.3.3 Statistical analyses

Conditional logistic regression models[98] were fitted to estimate the ratio of the odds of BSI in cases and controls, between separate strata of each potential risk factor. Potential

risk factors significantly associated with BSI (p<0.01) were examined in combination using conditional logistic regression and stepwise forward selection of risk factors based on the AIC. As in Chapter 6, due to correlations between covariates, separate adjusted models were built incorporating gestational age at birth, birth weight, total parenteral nutrition and ventilation. The set of risk factors corresponding to the lowest AIC was included in the final adjusted model. Once the optimal combination of risk factors was defined, the AIC was compared between models fitted with and without interactions between level of care, total parenteral nutrition or ventilation and gestational age, birth weight or inborn/outborn status. The analyses were repeated for each control selection strategy and for each hospital separately.

7.3.4 Sensitivity analyses incorporating five and eight categories of birth weight and birth weight standardised for gestational age

As in Chapter 6, Section 6.3.5, I carried out the following sensitivity analyses:

Analyses incorporating five and eight categories of birth weight

To investigate effects in babies with birth weights above 1200g, I analysed the effect on BSI of birth weight split into five and eight categories:

1. 700, 700<-1200, 1200-<2500, 2500-<3500, ≥3500g
2. <500, 500-<1000, 1000-<1500, 1500-<2000, 2000-<2500, 2500-<3000, 3000-<3500, ≥3500g

Analyses incorporating birth weight standardised for gestational age

I also investigated whether babies born smaller than expected for their gestational age were at increased risk for BSI, by analysing the effect of birth weight standardised for gestational age, expressed as standard deviation scores.

7.4 Results

The 236 first episodes of BSI included in the analysis for Chapter 6 (whose constituent organisms are listed in Chapter 6, Section 6.4) were used to define the cases. When the hospitals were combined, each control selection strategy included 708 babies (236 cases and 472 controls), split roughly equally between both hospitals.

Control selection strategy 1

In keeping with the results from Chapter 6, level of care was the single strongest risk factor for BSI, in terms of optimising the AIC. The odds of infection were eleven to twelve times higher in babies recently cared for in high dependency or intensive care, rather than in special care (Table 7.1). The optimal adjusted model consisted of level of care, birth weight and inborn/outborn status (Table 7.2). No significant interactions were found between level of care and birth weight or between level of care and inborn/outborn status.

Total parenteral nutrition was the second strongest risk factor for BSI. In NICU 2, the odds of infection were about ten times higher in babies recently treated with total parenteral nutrition, than in babies not recently treated with this procedure. The optimal

adjusted model incorporating total parenteral nutrition also included gestational age at birth and inborn/outborn status (Table 7.4). The effect of ventilation was attenuated by adjustment for gestational age and inborn/outborn status (adjusted odds ratio 1.74, 95% CI 0.84, 3.58, p=0.135). No significant interactions were found between total parenteral nutrition or ventilation and gestational age, or inborn/outborn status.

As in Chapters 5 and 6, BSI risk was highest in the most premature and in term babies, in babies with birth weights below 1200g, and in outborn babies. The optimal adjusted model retained birth weight and inborn/outborn status as independent risk factors for BSI (Table 7.2). No significant associations were found between BSI and NICU, sex, delivery method, the number of blood samples taken or surgery (Table 7.1).

Similar results were found when the NICUs were analysed separately (Tables 7.3 and 7.4). However, for NICU 1, the optimal adjusted model included level of care, gestational age and inborn/outborn status, rather than level of care, birth weight and inborn/outborn status (Table 7.3).

Control selection strategies 2 and 3

By definition, the controls selected in strategy 1 could not include any babies with BSI episodes. For control selection strategies 2 and 3, babies could be counted twice in the analyses, as both case and control. When both hospitals were combined, 39 out of 708 babies were counted twice in strategy 2, and 100 out of 708 babies were counted twice in strategy 3.

Analyses based on control selection strategy 2 gave similar results to those based on strategy 1. However, both crude and adjusted estimates of effect generally decreased (Tables 7.5, 7.6, 7.7, Appendix to Chapter 7). In addition, in crude analyses, gestational age was not significantly associated with BSI incidence at NICU 1 (Table 7.6, Appendix to Chapter 7) and inborn/outborn status was not significantly associated with BSI incidence at NICU 2 (Table 7.7, Appendix to Chapter 7).

Analyses based on control selection strategy 3 also gave similar results to those based on strategy 1, but estimates of effect were decreased even further than those resulting from strategy 2 (Tables 7.8, 7.9, 7.10, Appendix to Chapter 7). In addition, when both hospitals were combined, the optimal adjusted model included level of care, gestational age and inborn/outborn status, rather than level of care, birth weight and inborn/outborn status (Table 7.8, Appendix to Chapter 7). At NICU 1, the optimal adjusted model included level of care and inborn/outborn status only (Table 7.9, Appendix to Chapter 7). At NICU 2, inborn/outborn status was not significantly associated with BSI incidence in crude analyses (Table 7.10, Appendix to Chapter 7).

7.4.1 Sensitivity analyses incorporating five and eight categories of birth weight and birth weight standardised for gestational age

Analyses incorporating five and eight categories of birth weight

The sensitivity analyses did not reveal any significant variation in BSI risk for babies with birth weights above 1200g (Table 7.1). In the multivariable analysis, the model

including three birth weight categories was optimal, having the smallest AIC (Table 7.2).

Analyses incorporating birth weight standardised for gestational age

Birth weight standardised for gestational age had no significant effect on BSI in crude analyses, so it was not included in the multivariable models (Table 7.1).

The results of these sensitivity analyses were consistent with the results of the Poisson regression analyses in Chapter 6, described in Section 6.4.1 and discussed in Section 6.5.1.

7.5 Discussion

As in Chapter 6, highest NHS level of care and total parenteral nutrition in the previous three days were the strongest single risk factors for BSI. The optimal adjusted models combined these risk factors with either birth weight or gestational age at birth and inborn/outborn status.

In this chapter I present a novel, alternative analytical method in the case control study design. As described in Chapter 6 (Section 6.5), previous analyses of predictive relationships between potential risk factors and BSI episodes have truncated follow-up time at infection for infected babies, and at discharge from the NICU for uninfected babies.[34] This approach is prone to bias as follow-up time differs systematically between infected and uninfected individuals.[93] The case control analyses avoided this bias, as infected and uninfected babies were followed up for similar lengths of time. By

simulating censoring dates for controls, I created equivalent, age-matched time points for cases and controls. However, as explained in Section 7.3.1, whilst ensuring consistent follow-up for cases and controls, this approach precluded the analysis of postnatal age, which was found to be a significant independent risk factor for BSI in the Poisson regression analyses described in Chapter 6.

Whereas the Poisson regression models in Chapter 6 compared admission days with and without infection, the analyses based on control selection strategy 1 in this chapter compared babies experiencing infection with babies *never* having experienced infection. These babies may differ in susceptibility in ways that are not measured, and that may be correlated with potential risk factors. The associations found between potential risk factors and BSI may thus be partly due to these unmeasured confounders. This confounding may explain why the associations found in the case control study were stronger than those established by the Poisson regression models. Associations may also have been stronger for the case control study because conditional logistic regression models estimate odds ratios, which are larger than rate ratios for non-rare events. Confidence intervals were also wider for the results of the case control study in comparison with the results of the Poisson regression models, because of the smaller number of subjects analysed. On the other hand, the Poisson regression analyses included prolonged periods of follow up of uninfected babies, during which more mature babies exposed to potential risk factors would have been less susceptible to infection than at earlier ages. This may have attenuated associations between risk factors and BSI. The true effects on BSI of the risk factors analysed are therefore likely to be in between the effects estimated by these two analytical approaches. Despite the

methodological differences between the two analyses, in practice they yielded similar conclusions. I would recommend using both approaches when analysing risk factors for BSI in NICUs.

The unmeasured differences in susceptibility between cases and controls described above may also explain why effect estimates decreased with control selection strategies 2 and 3. From strategy 1 to strategy 3, the rule specifying that controls should not have had a BSI episode was progressively relaxed, and controls became closer in susceptibility to cases. Differences between cases and controls in unmeasured confounders may therefore have reduced, which may have decreased the estimates of effect for the risk factors I analysed. The results for control selection strategy 1 described factors which predict whether a baby experiences *any* infection during the NICU stay. The results for control selection strategy 3 described factors which predict *when* a baby experiences infection. In this respect, control selection strategy 3 was closest to the Poisson regression method described in Chapter 6. In terms of infection monitoring, control selection strategy 3 may be the most relevant, provided the assumption that eight days following a BSI episode is sufficient time for a baby's infection risk to return to his or her baseline. This assumption is reasonable, as following an infection episode, we could expect about five days of antibiotic treatment, followed by about three days for the development of clinical symptoms of a new infection, prompting a repeat blood culture. In strategies 2 and 3, some babies featured as both cases and controls. This may have introduced bias as cases spending longer periods in the NICU were more likely to also be included as controls. Babies remaining for longer in the NICU may have more complex conditions requiring very invasive care,

which would make them more susceptible to BSI and would decrease estimates of effect. However, babies spending longer in the NICU may also be more mature and less susceptible to infections, which would increase estimates of effect.

Key conclusions of Chapter 7

Findings

- Optimal adjusted models generally included level of care, birth weight and inborn/outborn status as the strongest independent predictors for BSI when the NICUs were combined.

Conclusions

- This confirmed the conclusion of Chapter 6 that adjustment of BSI rates by these factors could provide meaningful comparisons between NICUs.
- The case control study design is a novel, alternative analytical method which can elaborate predictive associations between risk factors and BSI, whilst minimising bias associated with the length of follow-up.
- However, this approach did preclude the evaluation of postnatal age, which was found to be a significant independent risk factor for BSI in Chapter 6.

Figure 7.1 Diagram to describe stays in the NICU for three hypothetical cases and their controls. NICU stays were translated into a dataset with censoring ages labelled according to procedure-related exposures in the previous three days

Special care	
High dependency	
Intensive care	

CONS infection episode	**C**
Non-CONS infection episode	**NC**
Blood sample taken	**S**

Invasive procedure, eg.	
Total parenteral nutrition	**T**
Ventilation	**V**

Cases

Age (in days) at NICU 1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Baby 1 (25 weeks, 753g)[a] Male Inborn, vaginal delivery Born 4/5/01 Admitted 5/5/01 Died 12/5/01		**T V**	**T V**	**C S T V**	**T V**	**T V**	**NC S T V**	**T V**	**T V**
Baby 2 (36 weeks, 2425g) Female Inborn, vaginal delivery Born 15/5/01 Admitted 16/5/01 Discharged 20/5/01		**C S**							
Baby 3 (37 weeks, 2600g) Male Inborn, vaginal delivery Born 3/5/01 Admitted 3/5/01 Discharged 7/5/01	**C S**		**S**						

Controls selected according to control scheme 1

Age (in days)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Baby 4 (control for baby 1) (38 weeks, 2671g)[a] Female Inborn, elective CS[b] Born 3/6/02 Admitted 3/6/02 Discharged 12/6/02		**S**								
Baby 5 (control for baby 2) (24 weeks, 697g) [a] Male Outborn, vaginal delivery Born 7/7/03 Admitted 7/7/03 Died 15/7/01	**T V**	**S T V**	**T V**	**T V**	**T V**	**S T V**	**T V**	**T V**	**T V**	
Baby 6 (control for baby 3) (37 weeks, 2650g) [a] Male Inborn, vaginal delivery Born 1/12/04 Admitted 1/12/04 Discharged 2/12/04										

a - (Gestational age at birth, birth weight)
b - CS- Caesarean section

Figure 7.1 (continued) Dataset with censoring ages labelled according to procedure-related exposures in the previous three days. Baby-days were truncated at the censoring age

Baby	Censoring age (days)	Gestational age (wks)	Birth weight (g)	Sex	Inborn/ Outborn	Delivery method	In three days prior to censoring age:				CONS episode	Non-CONS episode	Total baby-days in NICU up to and including censoring age
							Highest level of care	Total parenteral nutrition?	Ventilation?	Number of blood samples taken			
1	4	<26	700-<1200	Male	Inborn	Vaginal	Intensive care	Yes	Yes	0	1	0	3
4	4	≥37	≥1200	Female	Inborn	Elective CS	High dependency care	No	No	1	0	0	4
2	2	32-<37	≥1200	Female	Inborn	Vaginal	Other	No	No	0	1	0	1
5	2	<26	<700	Male	Outborn	Vaginal	Intensive care	Yes	Yes	0	0	0	2
3	1	≥37	≥1200	Male	Inborn	Vaginal	Other	No	No	0	1	0	1
6	1	≥37	≥1200	Male	Inborn	Vaginal	Other	No	No	0	0	0	1

Table 7.1 Case control study, control selection strategy 1. Crude results for NICU 1 and NICU 2 combined

Potential risk factor	Number of cases	Number of controls	Crude odds ratios (95% CI) p-value		
Highest level of care[c]					
Intensive care	138	130	11.16	(6.51, 19.13)	<0.001
High dependency care	47	41	12.32	(6.32, 23.98)	<0.001
Special care	36	286		1	
Other[d]	15	15			
Gestational age (weeks)					
<26	72	32	7.43	(3.97, 13.89)	<0.001
26-<28	35	39	3.35	(1.69, 6.64)	0.001
28-<32	53	127	1.23	(0.71, 2.12)	0.460
32-<37	30	159	0.48	(0.28, 0.82)	0.007
≥37	46	114		1	
Missing[e]	0	1			
Birth weight (g)					
< 700g	62	21	18.26	(8.99, 37.09)	<0.001
700g-<1200g	78	107	3.61	(2.31, 5.61)	<0.001
≥1200g	96	342		1	
Missing[e]	0	2			
Inborn status					
Outborn	80	78	2.78	(1.88, 4.11)	<0.001
Inborn	154	389		1	
Missing[e]	2	5			
Hospital					
NICU 2	129	240	1.16	(0.85, 1.58)	0.344
NICU 1	107	232		1	
Sex					
Male	130	245	1.14	(0.83, 1.55)	0.426
Female	106	227		1	
Delivery method					
Emergency CS[f]	92	181	0.98	(0.69, 1.39)	0.895
Elective CS[f]	33	79	0.79	(0.50, 1.27)	0.333
Vaginal	110	211		1	
Missing[e]	1	1			
Number of blood samples taken[c]					
≥2	2	2	1.77	(0.24, 12.77)	0.572
1	27	66	0.77	(0.46, 1.31)	0.342
0	207	404		1	
Surgery[c]					
Yes	5	12	0.83	(0.29, 2.37)	0.732
No	231	460		1	
Sensitivity analyses incorporating five and eight categories of birth weight and birth weight standardised for gestational age					
Birth weight (g)					
<700	62	21	10.01	(3.61, 27.77)	<0.001

700-<1200	78	107	1.96	(0.82, 4.67)	0.128
1200-<2500	58	234	0.48	(0.21, 1.13)	0.092
2500-<3500	24	81	0.61	(0.25, 1.50)	0.285
≥3500	14	27		1	
Missing[e]	0	2			
Birth weight (g)					
<500	5	1	16.28	(1.50, 176.87)	0.022
500-<1000	115	79	4.09	(1.70, 9.85)	0.002
1000-<1500	46	117	0.92	(0.38, 2.25)	0.856
1500-<2000	20	105	0.33	(0.13, 0.86)	0.024
2000-<2500	12	60	0.35	(0.13, 0.97)	0.044
2500-<3000	8	42	0.34	(0.12, 1.02)	0.054
3000-<3500	16	39	0.83	(0.31, 2.23)	0.711
≥3500	14	27		1	
Missing[e]	0	2			
Standard deviation score					
<-2	38	68	0.95	(0.56, 1.61)	0.843
-2-<-1	49	85	0.93	(0.58, 1.50)	0.773
-1-<0	62	146	0.68	(0.43, 1.05)	0.083
0-<1	61	98		1	
1-<2	18	51	0.57	(0.31, 1.07)	0.081
≥2	6	19	0.50	(0.19, 1.32)	0.164
Missing[e]: gest age <23 weeks	2	3			
Missing[e]: birth weight missing or birth weight and gest age missing	0	2			

Table 7.2 Case control study, control selection strategy 1. Adjusted results for NICU 1 and NICU 2 combined.

Potential risk factor	Optimal risk adjustment model Adjusted odds ratios (95% CI) *p*-value AIC for model: 291			Sensitivity analyses incorporating five and eight categories of birth weight Model including five birth weight categories Adjusted odds ratios (95% CI) *p*-value AIC for model: 294			Model including eight birth weight categories Adjusted odds ratios (95% CI) *p*-value AIC for model: 299		
Highest level of care[c]									
Intensive care	4.38	(2.32, 8.27)	<0.001	4.42	(2.33, 8.38)	<0.001	4.84	(2.49, 9.38)	<0.001
High dependency care	14.63	(6.94, 30.83)	<0.001	14.36	(6.83, 30.19)	<0.001	15.50	(7.24, 33.20)	<0.001
Special care	1			1			1		
Other[d]									
Birth weight (g)									
< 700g	12.03	(4.76, 30.43)	<0.001						
700g-<1200g	2.37	(1.35, 4.16)	0.003						
≥1200g	1								
Missing[e]									
Inborn status									
Outborn	1.97	(1.16, 3.35)	0.012	2.04	(1.19, 3.47)	0.009	1.65	(0.99, 2.75)	0.057
Inborn	1			1			1		
Missing[e]									
Birth weight (g)									
<700g				7.77	(1.81, 33.39)	0.006			
700g-<1200				1.52	(0.43, 5.34)	0.513			
1200-<2500				0.59	(0.18, 1.97)	0.389			
2500-<3500				0.72	(0.20, 2.63)	0.623			
≥3500				1					
Missing[e]									
Birth weight (g)									
<500							17.26	(1.04, 287.64)	0.047
500-<1000							2.91	(0.84, 10.16)	0.093
1000-<1500							0.78	(0.23, 2.64)	0.688

1500-<2000		0.45	(0.12, 1.67)	0.235
2000-<2500		0.41	(0.10, 1.74)	0.228
2500-<3000		0.37	(0.09, 1.52)	0.168
3000-<3500		1.32	(0.31, 5.71)	0.710
≥3500			1	
Missing[e]				

Table 7.3 Case control study, control selection strategy 1. Results for NICU 1[g]

Potential risk factor	Number of cases	Number of controls	Crude odds ratios (95% CI) p-value			Adjusted odds ratios (95% CI) p-value		
Highest level of care[c]								
Intensive care	60	41	12.64	(5.82, 27.49)	<0.001	8.30	(2.96, 23.25)	<0.001
High dependency care	28	27	10.51	(4.23, 26.09)	<0.001	15.08	(5.06, 44.97)	<0.001
Special care	16	139		1			1	
Other[d]	3	7						
Gestational age (weeks)								
<26	33	16	11.76	(4.30, 32.15)	<0.001	2.15	(0.57, 8.07)	0.256
26-<28	17	20	3.82	(1.47, 9.95)	0.006	0.73	(0.20, 2.65)	0.637
28-<32	28	51	2.07	(0.98, 4.40)	0.058	1.31	(0.49, 3.49)	0.593
32-<37	10	66	0.38	(0.14, 1.01)	0.053	0.30	(0.08, 1.05)	0.060
≥37	19	60		1			1	
Missing[e]	0	1						
Birth weight (g)								
≤ 700g	24	12	16.77	(5.62, 49.98)	<0.001			
700g-<1200g	42	57	3.81	(2.02, 7.21)	<0.001			
≥1200g	41	144		1				
Missing[e]	0	1						
Inborn status								
No	50	38	3.41	(2.06, 5.67)	<0.001	1.72	(0.83, 3.59)	0.146
Yes	55	172		1			1	
Missing[e]	2	4						
Sex								
Male	58	100	1.29	(0.84, 2.00)	0.242			
Female	49	114		1				
Delivery method								
Emergency CS[f]	46	83	1.16	(0.71, 1.91)	0.546			
Elective CS[f]	8	22	0.77	(0.33, 1.82)	0.555			
Vaginal	52	108		1				
Missing[e]	1	1						

Number of blood samples taken[c]					
≥2	1	1	2.18	(0.13, 35.21)	0.583
1	13	20	1.37	(0.65, 2.91)	0.411
0	93	193		1	
Surgery[c]					
Yes	2	3	1.33	(0.22, 7.98)	0.753
No	105	211		1	

Table 7.4 Case control study, control selection strategy 1. Results for NICU 2

Potential risk factor	Number of cases	Number of controls	Crude odds ratios (95% CI) p-value			Adjusted odds ratios incorporating level of care (95% CI) p-value AIC= 171.45			Adjusted odds ratios incorporating total parenteral nutrition (95% CI) p-value AIC= 192.39		
Highest level of care[c]											
Intensive care	78	76	9.32	(4.64, 18.70)	<0.001	3.60	(1.54, 8.39)	0.003			
High dependency care	19	15	10.40	(4.13, 26.19)	<0.001	10.61	(4.02, 28.01)	<0.001			
Special care	20	156		1			1				
Other[d]	12	11									
Gestational age (weeks)											
<26	39	14	10.66	(4.18, 27.22)	<0.001				3.07	(1.01, 9.34)	0.048
26-<28	18	14	4.72	(1.81, 12.34)	0.002				1.72	(0.58, 5.12)	0.333
28-<32	25	64	1.09	(0.50, 2.36)	0.827				0.62	(0.25, 1.52)	0.296
32-<37	20	99	0.50	(0.25, 1.00)	0.051				0.48	(0.22, 1.04)	0.062
≥37	27	67		1						1	
Missing[e]	0	0									
Birth weight (g)											
≤ 700g	38	14	11.12	(5.17, 23.94)	<0.001	6.16	(2.29, 16.57)	<0.001			
700g-<1200g	36	44	3.56	(1.96, 6.47)	<0.001	2.21	(1.01, 4.82)	0.046			
≥1200g	55	200		1			1				
Missing[e]	0	0									
Inborn status											
No	30	23	3.18	(1.72, 5.90)	<0.001	1.83	(0.83, 4.04)	0.133	2.21	(0.96, 5.07)	0.062
Yes	99	235		1			1			1	
Missing[e]	0	0									
Sex											
Male	72	139	1.09	(0.70, 1.70)	0.706						
Female	57	119		1							
Delivery method											
Emergency CS[f]	46	92	0.98	(0.61, 1.57)	0.943						
Elective CS[f]	25	51	0.97	(0.55, 1.70)	0.914						

Vaginal	58	114		1				
Missing[e]	0	1						
Number of blood samples taken[c]								
≥2	1	2	0.94	(0.08, 10.36)	0.956			
1	14	39	0.64	(0.32, 1.29)	0.215			
0	114	217		1				
Surgery[c]								
Yes	3	6	1	(0.25, 4.00)	1.00			
No	126	252		1				
Total parenteral nutrition[c]								
Yes	72	29	9.98	(5.38, 18.49)	<0.001	6.32	(3.14, 12.70)	<0.001
No	57	229		1			1	
Ventilation[c]								
Yes	75	63	4.86	(2.92, 8.11)	<0.001			
No	54	195		1				

c - In the three days prior to the censoring age
d - 'Other' indicates that for the three days prior to the censoring age, the baby was outside the NICU. For example at another hospital or undergoing surgery.
e - Babies with missing variables were few and represented few episodes of BSI. For this reason I considered it acceptable to remove them from the analyses.
f - CS- Caesarean section
g - For cases with higher ages (in days) at BSI, the number of controls available for selection became scarce. For control selection strategy 1 at NICU 1, two cases with ages at BSI of 111 and 132 days had to share controls with other cases.

8. A method for monitoring blood stream infection in neonatal intensive care units

8.1 Summary

Findings from previous chapters are collated to propose a method for prospective monitoring of NICU-acquired BSI. The method is demonstrated for NICUs 1 and 2, to illustrate how it could be applied to a larger group of units. Two monitoring techniques are demonstrated which could be used in tandem. Both relied on comparisons of observed numbers of BSI episodes at each NICU with expected numbers derived from both units. Comparisons were adjusted for differences between hospitals and over time in the distributions of: baby-days spent at each NHS level of care, birth weight, inborn/outborn status and postnatal age.

Firstly, to give standardised infection ratios, observed numbers of BSI episodes were divided by expected numbers for each NICU and year. These showed no significant differences between hospitals, except for a slightly increased incidence for NICU 1 in 2002 (standardised infection ratio 1.43, 95% CI 1.08, 1.85). Secondly, a sequential probability ratio test (SPRT) can trigger alarms if BSI incidence increases significantly over time. No significant increases or decreases were observed for either NICU over the time period.

Both monitoring techniques are easy to implement with software available to NICUs. They can monitor changes in infection incidence over time and could encourage sharing of improved infection control practices between NICUs.

8.2 Introduction: synthesis of thesis findings into a method for prospective monitoring

This chapter brings together findings from the previous chapters to propose a method for prospective monitoring of BSI in NICUs that could be used in practice.

Findings from the various analytic approaches used in Chapters 3, 5, 6 and 7 consistently showed that there was no significant difference in the incidence of BSI between the NICUs analysed. In this chapter I demonstrate a method for comparative monitoring in NICUs 1 and 2, which could be applied to a wider group of NICUs which may display significant differences.

The analytic approaches used in previous chapters showed that the strongest predictors for BSI incidence recorded in routine data were: NHS level of care, total parenteral nutrition, birth weight, gestational age, and inborn/outborn status. The risk adjustment model which most consistently provided a good fit to the data, whilst describing risk for all babies throughout their NICU stay, included level of care, birth weight and inborn/outborn status. The analytic approach described in Chapter 6 enabled the evaluation of postnatal age, and its results indicated that this factor should also be included in the risk adjustment model. I will demonstrate a method for monitoring BSI

incidence, adjusted for differences between hospitals and over time in the distributions of: baby-days spent at each NHS level of care, baby-days grouped according to postnatal age, and babies cared for with various birth weights and inborn/outborn status.

As described in Chapter 5, if a monitoring system is to rely on current routine data systems, positive blood cultures provide the only information on which to base a case definition for BSI. If NICUs wish to differentiate between infections more or less likely to represent blood sample contamination, rates can be reported separately for CONS and non-CONS BSI. As I found patterns in CONS and non-CONS BSI incidence to be broadly similar, I will demonstrate a method for monitoring total BSI incidence. In Chapter 5 I also described a shift in the aetiology of BSI from maternally-transmitted to hospital-acquired at around day two of life. In this chapter I used data from day three of life to demonstrate monitoring for hospital-acquired BSI.

I will describe a monitoring method encompassing two approaches: yearly standardised infection ratios and a quarterly sequential probability ratio test (SPRT).

8.3 Methods

8.3.1 Study population and case definition

As mentioned in Chapter 5, adjustment of BSI incidence by procedure-related factors was only possible if precise dates were recorded for these variables, so the risk adjusted monitoring method could only be demonstrated for NICUs 1 and 2, and not for NICU 3.

The study population and case definition were defined as in Chapters 6 and 7 (refer to Sections 6.3.1 and 6.3.2). I excluded probable maternally-transmitted BSI episodes occurring during the first 48 hours of life. Chapters 6 and 7 included only the first episode of BSI per baby, in order to concentrate on predictive risk factors for infection. In this chapter I aimed to monitor the burden of infection in NICUs, so all BSI episodes were included.

8.3.2 Creating an aggregated dataset

In Chapter 3, I demonstrated an aggregated dataset relying on routine data, which would permit the monitoring of BSI incidence with minimal data manipulation (refer to Figure 3.2). Instead of re-using this dataset, I aggregated the datasets created in Chapter 4 (Figure 4.4), which contain a record for each baby-day, because they were created using the more thorough strategies to match blood cultures with administrative data. I generated a dataset with a structure resembling that described in Chapter 3 (Figure 3.2), consisting of aggregated quarterly totals of BSI episodes and baby-days, stratified by NHS level of care, birth weight, inborn/outborn status and postnatal age. The following birth weight strata were chosen: <700g, 700-<1200g, ≥1200g, as these categories best described variation in BSI risk in Chapters 6 and 7 (Section 6.4.1 and Section 7.4.1). Strata of 3-<20 days and ≥20 days of postnatal age were chosen, as the risk of BSI was significantly greater in babies below 20 days of age than in older babies (Chapter 6, Section 6.5). BSI episodes and baby-days from the first two days of life were removed, as early-onset BSI is likely to reflect maternally-transmitted infection. Baby-days pertaining to babies with missing birth weights and/or missing inborn/outborn status were also removed, as these could not be stratified. Rates were aggregated by quarter

rather than by month, as I judged that quarterly monitoring would maintain continuity of surveillance whilst minimising workload for NICUs.

8.3.3 Estimating expected numbers of BSI episodes

Both the yearly standardised infection ratios and the quarterly SPRT were based on a comparison of the observed number of BSI episodes against the number expected according to a risk adjustment procedure. Expected numbers were estimated using a Poisson generalised linear model. The model included data for both hospitals over the whole time period. The outcome was episodes of BSI, the offset or denominator was baby-days, and level of care, birth weight category, inborn/outborn status and postnatal age category were included as covariates. The model's coefficients referred to the expected rate of BSI for each risk stratum (refer to the worked example in Figure 8.1). These rates were multiplied by the numbers of stratified baby-days for each hospital and year (for standardised infection ratios) and for each hospital and quarter (for the SPRT). This gave the number of BSI episodes expected, given variations between hospitals and over time in the number of baby-days at each risk stratum.

8.3.4 Yearly standardised infection ratios

Standardised infection ratios were calculated by dividing the observed by the expected number of BSI episodes, for each hospital and year.[99] Confidence limits assuming Poisson counts were defined for each ratio.

8.3.5 Quarterly sequential probability ratio test

The SPRT is a method for continuous monitoring first developed by Wald.[100] It defines thresholds to determine when the observed outcome diverges unacceptably from the expected. These thresholds could be set for a single time point using confidence intervals. However, this does not allow for the fact that, with many time points, the true null hypothesis is likely to be eventually rejected, which could result in unfair accusations of poor performance. The SPRT allows for multiple time points and is described below.

The test statistic[100,101]

The SPRT was designed to carry out a test of a null hypothesis H_0, versus an alternative H_1 defined as:

H_0 : no increase in observed numbers of BSI episodes over expected

H_1 : a level of performance considered importantly divergent.

I considered H_1 as a 30% increase over the expected number of BSI episodes. An 'important' change in BSI incidence has not been defined for the NICU context, so this was an arbitrary figure, chosen as Kilbride *et al.* (2003) considered a 30% change in BSI incidence to be an important indicator of infection control practices within the Vermont Oxford Network of NICUs.[52] The choice of H_1 is discussed further in Chapter 9.

The SPRT involves plotting, for each yearly quarter, t:

$X_t = X_{t-1} + W_t$

$X_0 = 0$

Where t = 1,2,3… is the yearly quarters numbered sequentially for the whole time period

For each value of t, the probability of witnessing the observed number of BSI episodes, Y_t, is proportional to: L_{0t} under H_0, and L_{1t} under H_1

$W_t = \log(L_{1t}/L_{0t})$

The observed numbers of BSI episodes follow a Poisson distribution, so W_t can be calculated thus:

$W_t = Y_t\log(R_1) - \lambda_0(R_1-1)$

where

Y_t = observed number of BSI episodes

λ_0 = expected number of BSI episodes

$R_1 = \lambda_1 / \lambda_0$ = change to be measured

I assumed $\lambda_1 / \lambda_0 = 1.3$, corresponding to a 30% increase as previously defined.

Thresholds[100,101]

Values of the test statistic lie between lower and upper thresholds denoted *a* and *b*. When the test statistic exceeds *b,* H_1 is accepted over H_0, and when it is less than *a,* H_0 is accepted over H_1. The thresholds form horizontal lines, and are defined as:

$a = \log[\beta/(1-\alpha)]$

$b = \log[(1-\beta)/\alpha)]$

where

α - probability of eventually rejecting H_0 when it is true (Type I error)

β - probability of eventually rejecting H_1 when it is true (Type II error)

The values of α and β can be chosen to reflect the relative costs of making the two types of error. Because they are defined for the whole SPRT process, rather than for each quarter, they account for multiple testing. Several values can be chosen for α and β respectively, to denote different degrees of urgency, for example 'alert' and 'alarm'. I chose equal values for α and β, which gave the following values for *a* and *b*:

$\alpha = \beta = 0.01$ for 'alert', corresponding to:
$a = -4.6$
$b = 4.6$

$\alpha = \beta = 0.001$ for 'alarm', corresponding to:
$a = -6.91$
$b = 6.91$

The calculation of the test statistic was restarted (by bringing the cumulative calculation back to 0) when the 'accept H_0' boundary *a* was crossed. This avoided the build-up of credit, where unacceptable increases in infection rates are masked by previous decreases.

I also constructed an SPRT for which H_1 was defined as a 30% *decrease* below the expected number of BSI episodes. The test statistic was calculated the same way, except that R_1 was defined as 0.7 ($\lambda_1 / \lambda_0 = 0.7$).

Finally, I constructed an SPRT to detect increases in infection incidence without risk adjustment. Expected numbers of BSI episodes were estimated by multiplying the single, non-stratified rate of BSI for both hospitals over the whole time period, by the numbers of baby-days in each quarter, for each hospital.

8.4 Results

A total of 322 episodes of BSI were included in the monitoring method, of which: 232 were CONS, 4 were Group B streptococcus, 46 were Gram positive organisms other than Group B streptococcus, 35 were Gram negative organisms and 5 were yeasts. 2230 babies were included (901 from NICU 1 and 1329 from NICU 2). The slight discrepancy compared with the number of babies analysed in Chapter 6 (2269) is because baby-days that could not be stratified were excluded. 24 babies not cared for in either special care, high dependency or intensive care after day two of life (for example because they were treated in surgery) were excluded, as were 15 babies with missing birth weights and/or missing inborn/outborn status.

Tables 8.2 to 8.6 (Appendix to Chapter 8) show the stratified observed numbers of BSI episodes and baby-days for each hospital and year. Figure 8.2 shows quarterly rates of BSI, for both hospitals. As the study period ran from May 2001 to February 2005 inclusive, the first and last years and quarters did not contain data for the full time interval. This did not affect the analysis, as expected numbers of BSI episodes were calculated for the truncated numbers of baby-days observed.

8.4.1 Yearly standardised infection ratios

Table 8.1 shows standardised infection ratios for each hospital and year. The ratios were mostly close to 1, indicating no statistically significant difference between observed and expected numbers of BSI episodes. However in 2002, NICU 1 had more BSI episodes than expected, and this difference was significant (56 observed/39.26 expected, ratio 1.43, 95% CI (1.08, 1.85), observed BSI rate 9.18 per 1000 baby-days).

8.4.2 Quarterly sequential probability ratio test

Figure 8.3 shows the risk adjusted SPRTs to detect increases in BSI incidence. Far from indicating any problems with infection control, the test statistic crossed the lower threshold, *a,* during April to June 2004 for NICU 1, and during January to February 2005 for NICU 2. This indicated an acceptance of H_0 over H_1, and the assurance that a 30% increase in observed numbers of BSI episodes over expected numbers had not occurred. Calculation of the test statistic was restarted at this point.

Figure 8.4 shows the SPRTs to detect decreases in BSI incidence. The test statistic crossed the lower threshold, *a*, during April to June 2002 for both hospitals. This indicated an acceptance of H_0 over H_1, signifying that a 30% decrease in observed numbers of BSI episodes over expected numbers had not occurred. The relatively early acceptance of H_0 corresponded with a small, but non-significant, rise in BSI incidence during April to June 2002 for both NICUs, visible in Figure 8.2. Calculation of the test statistic was restarted at this point, and remained between the two thresholds for the rest of the study period.

Figure 8.5 shows the SPRTs to detect increases in BSI incidence, constructed without risk adjustment. It is similar to the corresponding risk adjusted chart, except that the test statistic crossed the lower 'accept H_0' threshold, *a,* two yearly quarters earlier for NICU 2 (July to September 2004).

8.5 Discussion

In keeping with the findings in previous chapters, there was no significant difference in BSI incidence between NICUs or over time. This chapter demonstrates what could be carried out in larger groups of NICUs, which may display significant differences.

Standardised infection ratios provide a straightforward method for comparing hospitals and can be included in annual reports. Infection control investigations could be targeted at units with BSI incidence significantly above expected (with a standardised infection ratio significantly above one). However, this measure does not take account of the fact that, with increasing hospitals and time points, it becomes more likely that a ratio will

exceed one significantly, simply by chance. This multiple testing problem may have given rise to the slightly increased ratio for NICU 1 in 2002. Monitoring systems should be aware of this problem, to avoid unfairly penalising units with single high ratios. Standardised infection ratios should be used in conjunction with the SPRT, which is better suited to continuous monitoring over shorter intervals because it takes multiple time points into account. It can also include an adjustment for multiple hospitals, like the one described below.

The SPRT can trigger alarms if BSI incidence increases significantly over time. As the priority of a monitoring system is to detect unacceptable increases in incidence, the SPRT to detect *decreases* is not useful for long-term surveillance. However, it could be used to detect target decreases in incidence following infection control interventions. The SPRT is a novel approach to infection monitoring in NICUs. It is a robust method for comparisons over time, but it provides less information concerning differences between hospitals than the standardised infection ratios. Spiegelhalter *et al.* (2003)[102] recommend the following modifications to the SPRT, depending on a system's priorities. H_1 should be defined so that the chart detects the lowest range in incidence deemed acceptable. Different values for α and β can be chosen to reflect the relative costs of making Type I and Type II error. If a monitoring system wishes to avoid falsely identifying a satisfactory NICU as 'higher risk', then α should be very small. If it is keen not to miss a 'higher risk' NICU, then β should be very small. When comparing a large number of NICUs, more stringent thresholds are appropriate. For example, if $\alpha = \beta = 0.1$ is chosen, of 10 units performing normally, we would expect one to cross the threshold just by chance. When monitoring n units, $\alpha = \beta$ could be adjusted to $0.1/n$ for

'alert' or 0.01/*n* for 'alarm'. Resetting of the test statistic when it crosses the 'accept H_0' boundary can retain sensitivity to changes in performance. However, NICUs should be aware that a series of these restarts avoids acceptance of the hypothesis that there is no increase in observed numbers of BSI episodes over expected (or avoids the acceptance of H_0). This would, overall, *increase* the probability of falsely concluding that there *is* a significant increase (or increase the chance of a Type I error to 1) and *decrease* the probability of falsely concluding that there is *no* significant increase (or decrease the chance of a Type II error to 0).[102]

Tables 8.2 to 8.6 (Appendix to Chapter 8) show that both monitoring techniques relied on small numbers of baby-days for some strata. This should not matter in practice, but for simplicity NICUs may prefer to group high dependency care, which includes the fewest babies, with intensive care, which shares a similar risk of BSI. As an alternative to using the Poisson regression model, expected rates can be calculated by dividing BSI episodes by baby-days in each risk stratum, for both hospitals over the whole time period, which gives almost identical results. Neither monitoring technique takes account of the fact that hospitals may have varying numbers of BSI episodes which are recurrent within babies. The risk adjustment model described would not be strictly accurate in this case, as babies experiencing one infection may be more or less likely to experience another, over and above the risk factors already adjusted for. This is difficult to correct for with aggregated datasets, as recurrent infections are no longer linked with babies and cannot be identified. However, the development of datasets with daily records for each baby could allow regression models which estimate expected rates adjusted for recurrencies. In the NICUs I analysed, the proportions of recurrencies within hospital-

acquired BSI episodes were similar: 30% were recurrent at NICU 1 and 25% were recurrent at NICU 2 (95% CI for difference - 0.04, 0.15, $p = 0.315$). These percentages differ from the proportions of recurrent infections given in Chapter 3, Section 3.5, because they exclude probable maternally-transmitted BSI episodes from the first 48 hours of life.

Key conclusions of Chapter 8

Findings

- Standardised infection ratios showed that BSI incidence, analysed on a yearly basis, was similar for NICUs 1 and 2.
- The SPRTs showed no substantial changes in BSI incidence over time.
- Both monitoring techniques were adjusted for differences between hospitals and over time in the distributions of: baby-days spent at each NHS level of care, baby-days grouped according to postnatal age and babies cared for with various birth weights and inborn/outborn status.
- Standardised infection ratios are most informative concerning differences between hospitals, whereas SPRTs are more robust for monitoring changes over time.

Conclusions

- Used together, standardised infection ratios and SPRTs could provide a powerful tool for evaluating risk-adjusted changes in BSI incidence between NICUs.

Figure 8.1 Expected BSI rates

Exponentiated coefficients of the Poisson generalised linear model

Intercept (baseline rate of BSI) Corresponding to special care, birth weight ≥1200g, inborn and postnatal age ≥20 days	0.001
Rate ratios corresponding to changes in the baseline to:	
High dependency care	5.73
Intensive care	4.36
Birth weight 700g-<1200g	1.08
Birth weight <700g	1.76
Outborn status	1.23
Postnatal age 3-<20 days	1.76

Worked example: calculating an expected rate

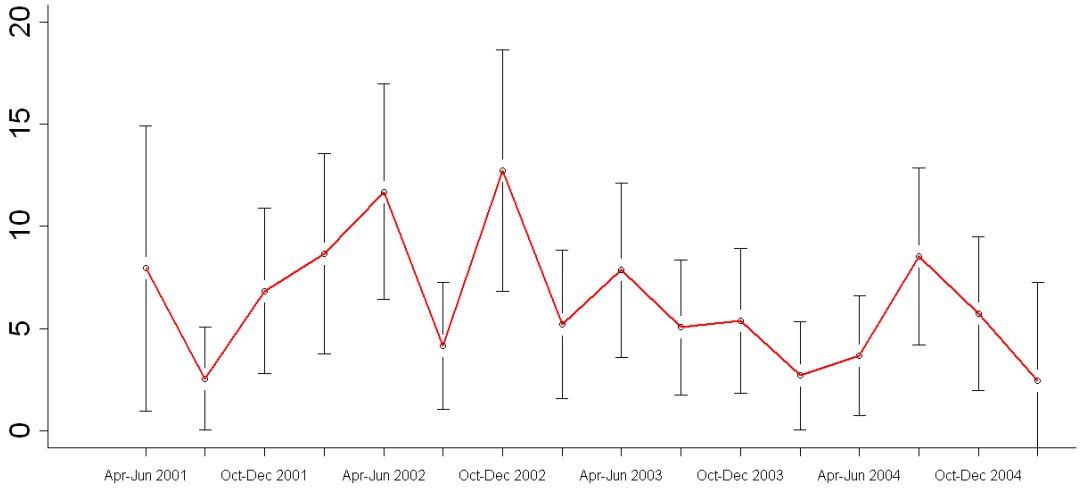
For the stratum defined by intensive care, birth weight 700g-<1200g, outborn status and postnatal age 3-<20 days
BSI rate estimated by the model 0.001 x 4.36 x 1.08 x 1.23 x 1.76 = 0.01 or ~10 per 1000 baby-days

Expected rates (per 1000 baby-days) for each risk stratum (calculated using exact coefficients, rather than the rounded coefficients shown above)

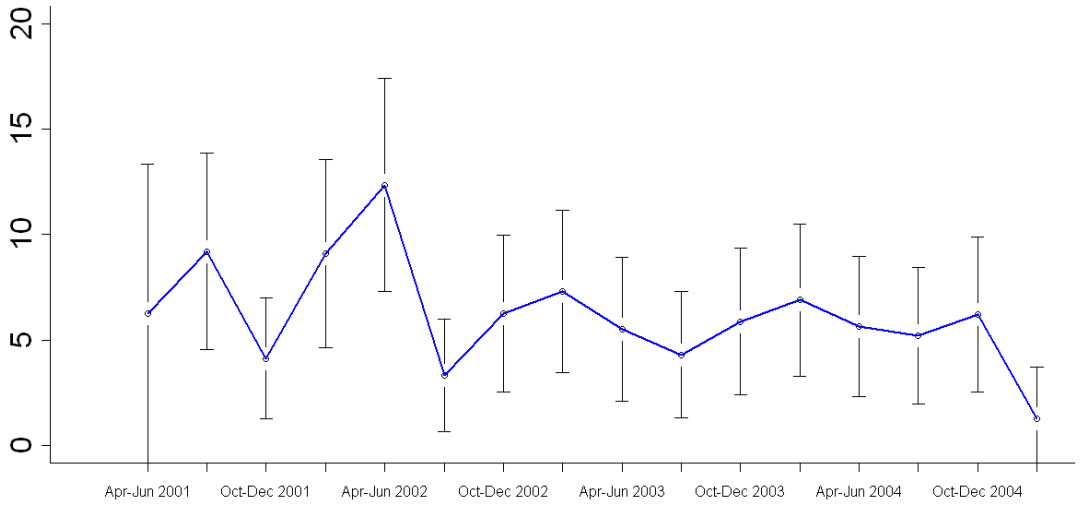
Birth weight (g)	**<700**				**700g-<1200**				**≥1200**			
Inborn/outborn status	**Inborn**		**Outborn**		**Inborn**		**Outborn**		**Inborn**		**Outborn**	
Postnatal age (days)	**3-<20**	**≥20**	**3-<20**	**≥20**	**3-<20**	**≥20**	**3-<20**	**≥20**	**3-<20**	**≥20**	**3-<20**	**≥20**
Level of care												
Special care	4.44	2.53	5.48	3.12	2.72	1.55	3.36	1.91	2.52	1.43	3.11	1.77
High dependency care	25.43	14.46	31.37	17.84	15.58	8.86	19.22	10.93	14.41	8.20	17.78	10.11
Intensive care	19.37	11.02	23.89	13.59	11.87	6.75	14.64	8.33	10.98	6.24	13.54	7.70

Figure 8.2 Quarterly rates of BSI episodes, per 1000 baby-days[a]

NICU 1



NICU 2



a - As the study period ran from May 2001 to February 2005 inclusive, the first and last quarters did not contain the full three months of data. The vertical lines are 95% CIs.

Figure 8.3 Risk adjusted SPRTs to detect a 30% increase in BSI episodes

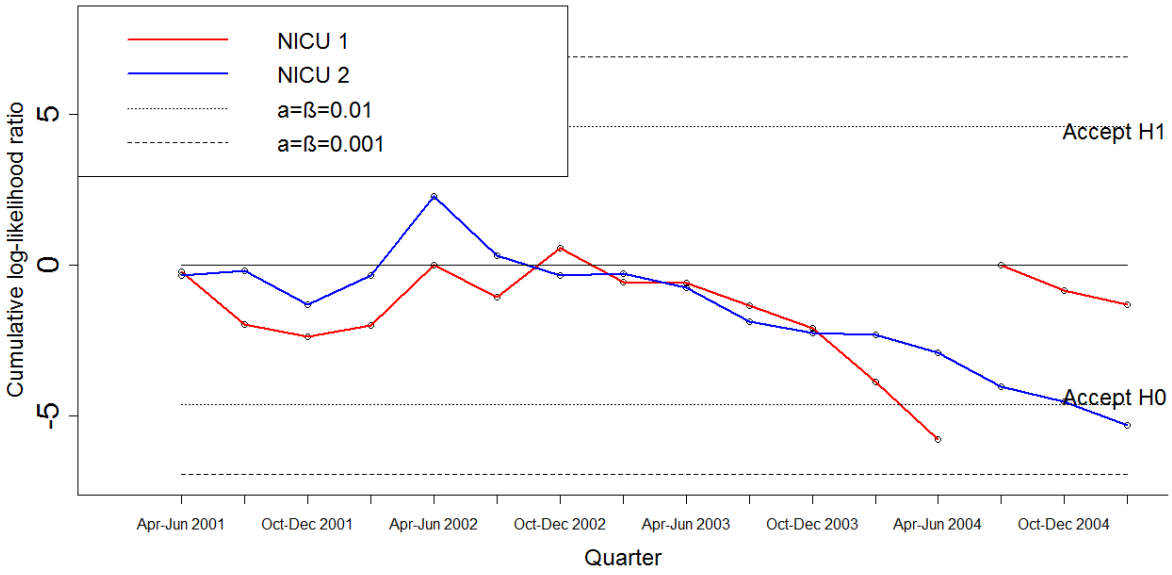


Figure 8.4 Risk adjusted SPRTs to detect a 30% decrease in BSI episodes

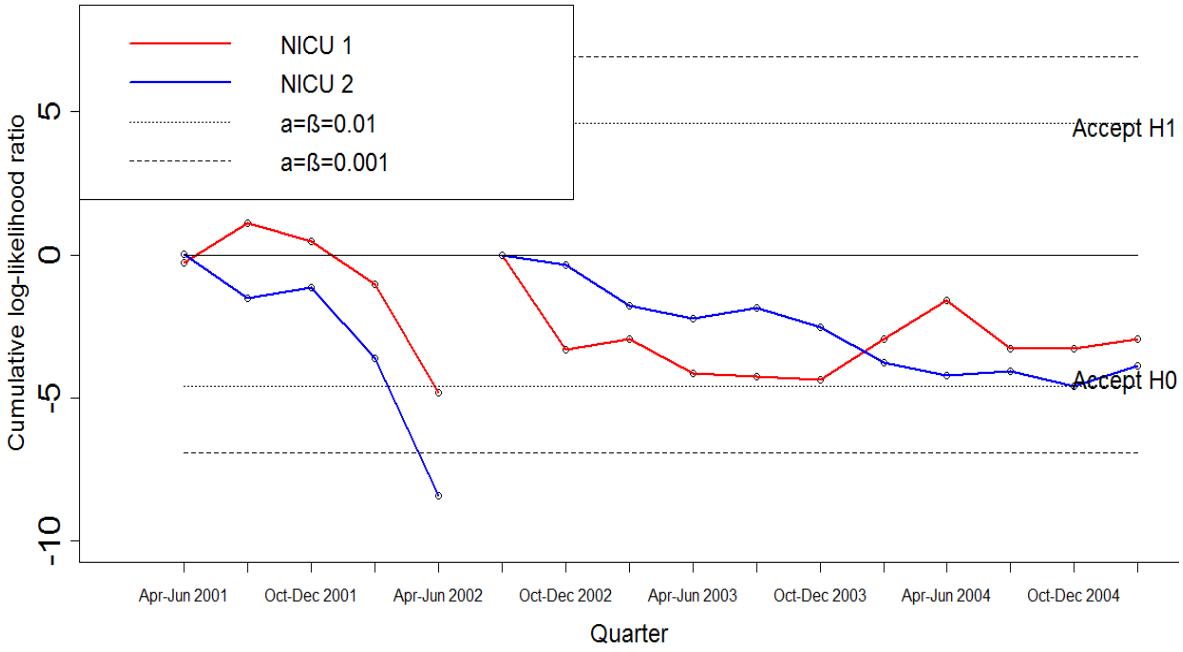


Figure 8.5 Crude SPRTs to detect a 30% increase in BSI episodes

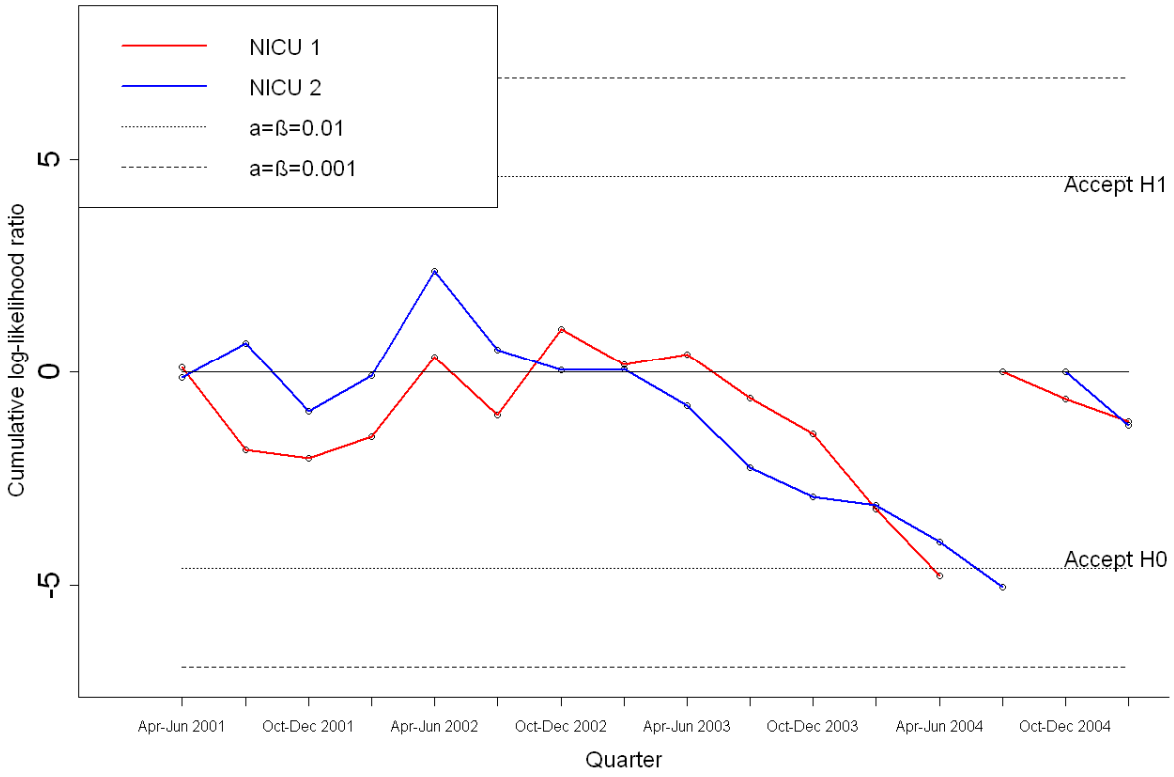


Table 8.1 Standardised infection ratios (95% CI) by NICU and year

Year	NICU 1	NICU 2
2001	0.79 (0.48, 1.22)	0.96 (0.63, 1.41)
2002	1.43 (1.08, 1.85)	1.22 (0.92, 1.59)
2003	0.91 (0.65, 1.24)	0.98 (0.71, 1.32)
2004	0.77 (0.54, 1.08)	0.96 (0.70, 1.28)
2005	0.41 (0.01, 2.31)	0.28 (0.01, 1.56)

9. Discussion and future directions for research

9.1 Summary of thesis findings

The premise of this thesis was that comparisons between NICUs can reveal important differences in BSI incidence, which may result from variations in infection control practices. Examination of these differences can reveal NICUs with potentially better practices, which can be shared with other units. The systematic literature review in Chapter 1 showed that adjustment for case mix and the use of invasive procedures is commonly regarded as necessary for fair and meaningful comparisons of BSI incidence between NICUs. However, there is no consensus on how risk adjustment should be carried out. The review also indicated that the use of electronic routine hospital data would accelerate data collection and minimise staff workload in monitoring.

The main aim of the thesis was to establish risk factors for BSI incidence recorded in routine data at three London NICUs. These risk factors could be adjusted for to give meaningful comparisons between NICUs. I presented a *range* of analytic approaches to determine risk factors (summarised in Chapter 2, Table 2.1) for two reasons. Firstly, the way in which procedure-related factors were recorded varied between NICUs, which required a variety of analytic methods. Secondly, I explored various methods for establishing risk factors to determine a robust approach. These methods included analyses of aggregate data (Chapter 3), analyses of procedure-related factors recorded as the sum of days treated (Chapter 5), investigation of time to the development of BSI (Chapter 5), and analyses of risk factors predicting BSI (Chapter 6 and Chapter 7). I

assessed consistency in the results, and the advantages and disadvantages of each method.

Chapter 6 and Chapter 7 provided the two most robust methods for determining risk factors for BSI, these methods involved Poisson regression and a case control study. The two methods had different strengths, so I recommended using both approaches when analysing risk factors for BSI incidence in NICUs. They focused on risk factors preceding BSI, which can therefore be regarded as predictors, rather than potential consequences of BSI. Predictive risk factors can identify high risk groups who could benefit from preventive action or close monitoring. The Poisson regression method described in Chapter 6 permitted the investigation of postnatal age, which was found to be a significant independent risk factor for BSI, but it was prone to bias associated with the length of follow-up. The case control study method in Chapter 7 removed this bias, but it led to larger estimates of effect. The true effects of the risk factors analysed were likely to be in between the effects estimated by the two analytical approaches. Despite the differences between the two analyses, in practice they yielded similar conclusions. These conclusions were consistent with the interpretation of the results in previous chapters. In the dataset used for this thesis, daily level of care, birth weight, inborn/outborn status and postnatal age were significant independent risk factors for BSI.

In Chapter 8 I demonstrated a method for prospective, comparative monitoring of BSI incidence, adjusted for the risk factors I had established, using a pragmatic aggregated

dataset. The prospective monitoring method demonstrated what could be carried out in larger groups of NICUs to achieve the objectives of monitoring described in Chapter 1:

- Assess the burden of infection
- Monitor changes in infection incidence over time and to trigger alarms if incidence increases significantly
- Encourage sharing of improved infection control practices between NICUs
- Monitor the outcome of interventions to improve infection control

To inform NICUs concerning infection burden, feedback to NICUs could include yearly or quarterly observed and expected rates of BSI episodes. Rates could be stratified by predictive risk factors to display groups at higher risk who may benefit from close monitoring or preventive action. The standardised infection ratio method could encourage sharing of improved practices between NICUs. In any units with BSI incidence significantly below expected (with a standardised infection ratio significantly below one), infection control practices could be investigated as potentially better practices. These could be shared with any units with BSI incidence significantly above the expected. Risk adjusted standardised ratios are increasingly being used to investigate differences in outcomes between hospitals with a view to improving the overall quality of care. They are used to measure variations in adult surgical site infections within the German Krankenhaus Infektions Surveillance System (KISS),[99] as well as variations in hospital mortality within several countries.[103,104]

The risk adjusted SPRT is a novel approach to infection monitoring in NICUs. It can trigger alarms if BSI incidence increases significantly over time, which could prompt investigation into the cause of the increase and the instigation of measures to control infection. As the priority of a monitoring system is to detect unacceptable increases in incidence, the SPRT to detect decreases is not useful for long-term surveillance. However it could be used to detect target decreases in incidence following infection control interventions.

Used together, standardised infection ratios and the SPRT could provide risk adjusted monitoring using minimal time, effort and expense. Standardised infection ratios provide a straightforward method for comparing hospitals and can be included in annual reports, whereas the SPRT is better suited to continuous monitoring over time. Both rely on existing data collection systems, and can be calculated using software easily available to NICUs, such as Microsoft Excel. A data manager could arrange procedures for the extraction of the necessary information in to pre-prepared spreadsheets on a quaterly basis. Ward clerks or NICU staff would then require only minimal training to understand the necessary concepts and to produce the statistics in tables and graphs such as those shown in Chapter 8, which could be included in regular reports and audits.

9.2 Thesis findings in the current UK context

These findings are timely as they comply with recent recommendations made to the UK Department of Health. The second National Audit Office report on HAI recommended the development of infection surveillance initiatives in high risk areas such as adult, paediatric and neonatal intensive care.[105] In response to this, the Steering Group on

Healthcare Associated Infection convened the 'Surveillance in adult, paediatric and neonatal intensive care and high dependency units' subgroup in April 2006, to provide advice to the Health Protection Agency and the Department of Health. In 2007, the work of the Steering Group was passed to the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI), which published recommendations for HAI surveillance in February 2010. A key recommendation was that surveillance should use routine patient management systems to minimise costs and staff workload, thus ensuring long-term buy-in from hospital management and staff. It noted that the reporting of childhood infections by paediatricians was low in several studies conducted through the British Paediatric Surveillance Unit, underlining the need to 'become more innovative and use routinely available data sources rather than conducting a series of individual and more expensive projects.' The Appendix to Chapter 9 gives the full criteria for HAI surveillance established in the report.[106]

The recommendation to exploit routine data is possible due to recent developments in the collection and storage of neonatal records, described in Chapter 4 (Section 4.8). Firstly, NICUs are increasingly using the same definitions and common systems for data capture and storage, which will facilitate risk adjusted comparisons between them. This began with the recording of 'minimum datasets' using standard definitions, such as the Neonatal Critical Care Minimum Dataset and the BAPM dataset.[78] Common neonatal data systems, the most widespread of which is SEND, now incorporate these minimum datasets. Secondly, information collected by systems such as SEND is likely to be fairly complete and accurate. SEND is used for the day-to-day running of the NICU, as well as for collecting data for audits and health service commissioning. There is therefore considerable incentive to keep its content complete, accurate and current.

This is enhanced by the inclusion of automatic quality checks and mandatory fields in the data entry process.[75] The exciting potential of SEND as a resource for monitoring and research has been recognised by the Neonatal Data Analysis Unit, which exploits it for the National Neonatal Audit Programme and the Newborn Patient Safety Programme among other projects.[106]

As described in Chapter 4 (Section 4.8), further aspects of SEND are relevant to the monitoring method devised in this thesis. Firstly, SEND currently records all the factors used to adjust for differences in risk between NICUs, as levels of care, birth weight, inborn/outborn status and date of birth (used to calculate postnatal age) are required for each baby by the BAPM minimum dataset.[78] Secondly, SEND records data items used to calculate levels of care on a daily basis, as this is also a BAPM requirement.[87] Daily patient records provide the best format for infection monitoring, as BSI episodes and baby-days can be reported by days with potential risk factors.

If a routine neonatal data system is to be used for infection monitoring, it must be linked with information concerning infection episodes. The case definition used for monitoring BSI represents an important trade-off. On the one hand, case definitions including clinical symptoms help to differentiate between clinically-relevant BSI and subclinical infection or contaminated blood cultures, but they require skilled data collection by clinicians. On the other hand, case definitions based on blood cultures alone may be more ambiguous, but they could rely on routine data from hospital microbiology laboratories. This would reduce the burden of data collection and may therefore provide a monitoring system that is more practical and sustainable than one relying on clinician

reporting. In Chapter 4 (Section 4.8) I argued that microbiology laboratory data should be automatically linked with neonatal data systems.

An advantage of using routine microbiology laboratory data in BSI monitoring is that blood sampling frequency can be measured and taken into account. As explained in Chapter 3, Section 3.3.2, variations in blood sampling frequency could confound comparisons of BSI incidence, although confounding by blood sampling frequency was not detected in the population studied for this thesis. As explained in Chapter 5 (Section 5.5), if NICUs wish to differentiate between infections more or less likely to represent blood sample contamination using routine data, rates can be reported separately for CONS and non-CONS BSI. I found patterns in CONS and non-CONS BSI incidence to be broadly similar.

The NeonIN surveillance system described in Chapter 1 is similar to the monitoring system proposed in this thesis because it relies on positive blood cultures (excluding cultures for CONS) and it plans to link with neonatal data systems such as SEND (personal communication, Dr. Paul Heath, St George's Healthcare NHS Trust). It differs from the system proposed here because it relies on reporting of infection episodes by clinicians. In addition, it is not risk-adjusted, its aim being to determine patterns of bacterial organisms in NICUs, not to provide multicentre comparisons to improve the overall quality of care.[17]

9.3 Future directions for research

The approach for monitoring described in Chapter 8 should be validated using a larger number of NICUs. As I analysed only two NICUs from the same city, the scope for detecting variation was small. Even before risk adjustment, they had similar incidences of infection which changed little over time, as shown by the similar curves for the crude and risk adjusted SPRTs. This was compounded by the fact that expected rates were based on data for both the hospitals combined. The consistency found may partly be the result of comparing 'like with like'. A greater number of NICUs would increase the potential to detect variation, and would provide more generalisable expected rates based on the overall average. The time period used to calculate expected rates should also be considered carefully. For example, following an infection control intervention leading to an overall, sustained decrease in infection incidence, expected rates should be recalculated to maintain sensitivity to increases in incidence.

Ideally, performance of the monitoring system should be tested in about five or six NICUs, which equates to a neonatal network. This is convenient as neonatal networks are more likely to share common data systems, which would facilitate monitoring. A BSI monitoring system based on routine data must be constantly reevaluated as neonatal data systems evolve. The case definition for BSI could include some clinical symptoms, where these are captured by data systems. Similarly, the appropriate method of risk adjustment may evolve with neonatal data systems, as risk adjustment factors were chosen for their existence and reliability in routine data as well as for their association with BSI. As any statistical monitoring technique may include unforeseen bias and inaccuracies, the comparison of multiple techniques is most informative. I have

demonstrated two techniques in Chapter 8 which could be used in conjunction with each other, but NICUs may wish to develop more depending on the time and resources available to them.

I found no evidence that differences in sampling frequency affected comparisons of BSI incidence between the NICUs analysed. However, differences in sampling frequency should always be investigated before NICUs are included in a monitoring system. If these differences are shown to confound comparisons of BSI incidence in multivariable analyses, measures can be taken to standardise blood sampling protocols between NICUs. Standardisation of blood sampling protocols is always desirable. This could involve the definition of clinical signs required before a blood sample is taken, as well as criteria for the method of sampling itself. Between 1997 and 2000, six NICUs in the Vermont Oxford Network implemented standardisation guidelines relating to the sampling method. These guidelines included: a requirement for two blood cultures on suspicion of BSI, protocols to prepare the skin for phlebotomy, and a recommended blood sample volume of 1ml.[52]

In addition to the further research described above, a successful monitoring system will require thorough consultation with the stakeholders. Firstly, neonatologists and infection control specialists should define the threshold used to determine an 'unacceptable' increase in infection over time. For the SPRT described in Chapter 8, I defined this threshold (H_1) as a 30% increase over the expected number of BSI episodes. NICUs participating in a monitoring system should decide on their own threshold, based on their priorities, resources and current infection rates. Secondly,

NICU staff must decide on the actions they will take in the event of significant variation in infection incidence between units or over time. As described in Chapter 1 (Section 1.3 and Section 1.4), interventions could include the introduction of aseptic techniques for invasive procedures, hygiene promotion programmes and changes to NICU environments and staffing.[16,44,45] Collaborative quality improvement initiatives could be introduced at the group level.[51-53] ARHAI recommended that the economic effects of surveillance and infection control interventions must be assessed during the planning phase. Although investment could be more than offset by decreases in BSI and its associated effects such as hospital stays, treatment, readmissions, re-operations and social support, this economic benefit should not be taken for granted.[106]

Thirdly, consultation among stakeholders should determine who will have access to the results of surveillance. The purpose of this thesis was to provide an approach for improving the care of babies in NICU, by alerting staff to clinically important increases in BSI incidence and by triggering the sharing of improved practices between units. As a minimum, feedback to NICUs should include their own performance in relation to the overall group. Issues such as whether NICUs should have access to the BSI rates of other participating units, or whether the results of monitoring should be made available to other stakeholders or the general public are beyond the scope of this thesis. Research and consultation will be necessary to determine best practice in these areas, to avoid the negative connotations associated with ranking or penalising units, which may have adverse effects on the morale of staff. Experience from other infection surveillance systems stresses that engagement with staff is fundamental to the success of any monitoring system.[52,99,107,108]

Key conclusions of Chapter 9

- I achieved the main aim of this PhD project, which was to establish risk factors for BSI incidence in NICUs, which could be adjusted for to give meaningful comparisons of BSI incidence between hospitals.
- The Poisson regression method described in Chapter 6 and the case control study method described in Chapter 7 have different strengths, and should be used together for determining risk factors for BSI incidence in NICUs.
- The thesis demonstrated a method for risk adjusted, comparative monitoring of BSI incidence, relying exclusively on routine data.
- Standardised infection ratios, used in conjunction with SPRTs can fulfill the objectives of monitoring BSI incidence in NICUs.
- The findings of this thesis are timely. Recent recommendations made to the UK Department of Health call for infection surveillance in intensive care units and the exploitation of recent developments in routine electronic data systems.
- The approach to monitoring must be validated in a wider group of NICUs. Research and consultation must determine ways to optimise the potential benefits of monitoring, whilst engaging NICU staff in the process.

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Appendix to Chapter 1

Pubmed literature search terms

Search 1 - premature OR low birth weight OR very low birth weight OR neonatal intensive care OR neonatal intensive care unit OR neonatal intensive care units OR neonatal ICU OR neonatal ICUs OR NICU OR NICUs OR newborn intensive care OR newborn intensive care unit OR newborn intensive care units OR newborn ICU OR newborn ICUs OR neonatal critical care OR neonatal critical care unit OR neonatal critical care units OR neonatal high dependency OR neonatal high dependency care OR neonatal high dependency care unit OR neonatal high dependency care units OR neonatal high dependency unit OR neonatal high dependency units OR special care OR special care unit OR special care units OR special care baby unit OR special care baby units OR SCBU OR SCBUs
Results: 145,776 studies

Search 2 - bacteraemia OR bacteremia OR bloodstream infection OR bloodstream infections OR blood stream infection OR blood stream infections OR sepsis OR septic OR septicaemia OR septicaemic OR septicemia OR septicemic
Results: 115,480 studies

Search 3 – monitoring OR surveillance OR incidence OR risk-adjusted OR risk adjusted OR adjusted OR stratified OR time trends OR longterm OR long term OR long-term
Results: 1,778,491 studies

Search #1 AND #2 AND #3
Results: 2372 studies

Embase free text literature search terms

Search 1 - premature OR low birth weight OR very low birth weight
Results: 76,845 studies

Search 2 - neonatal intensive care OR neonatal intensive care unit OR neonatal intensive care units OR neonatal ICU OR neonatal ICUs OR NICU OR NICUs OR newborn intensive care OR newborn intensive care unit OR newborn intensive care units OR newborn ICU OR newborn ICUs OR neonatal critical care OR neonatal critical care unit OR neonatal critical care units
Results: 10,434 studies

Search 3 - neonatal high dependency OR neonatal high dependency care OR neonatal high dependency care unit OR neonatal high dependency care units OR neonatal high dependency unit OR neonatal high dependency units
Results: 1 study

Search 4 - special care OR special care unit OR special care units OR special care baby unit OR special care baby units OR SCBU OR SCBUs
Results: 2325 studies

Search 5 - bacteraemia OR bacteremia OR bloodstream infection OR bloodstream infections OR blood stream infection OR blood stream infections OR sepsis OR septic OR septicaemia OR septicaemic OR septicemia OR septicemic
Results: 101,335 studies

Search 6 - monitoring OR surveillance OR incidence OR risk-adjusted OR risk adjusted OR adjusted OR stratified OR time trends OR longterm OR long term OR long-term
Results: 1,037,069 studies

Search (#1 OR #2 OR #3 OR #4) AND #5 AND #6
Results: 1105 studies

Embase thesaurus mapping literature search terms

Search 1 - LOW-BIRTH-WEIGHT.DE. OR PREMATURE-LABOR.DE. OR PREMATURITY.W..DE. OR VERY-LOW-BIRTH-WEIGHT.DE. OR NEWBORN-SEPSIS.DE. OR NEWBORN-MORTALITY.DE. OR SEPSIS.W..DE. OR INFECTION.W..DE.
Results: 155,485 studies

Search 2 - PREMATURITY.W..DE. OR NEWBORN-INTENSIVE-CARE.DE. OR PREMATURE-LABOR.DE. OR HOSPITAL-INFECTION.DE. OR VERY-LOW-BIRTH-WEIGHT.DE. OR CENTRAL-VENOUS-CATHETERIZATION.DE. OR SEPSIS.W..DE. OR EXTUBATION.W..DE. OR NEWBORN-CARE.DE. OR NEWBORN-SEPSIS.DE. OR NEWBORN-DISEASE.DE. OR LOW-BIRTH-WEIGHT.DE. OR NEWBORN-INFECTION.DE.
Results: 129,754 studies

Search 3 - PREGNANCY.W..DE. OR DELIVERY.W..DE. OR INTENSIVE-CARE.DE
Results: 219,324 studies

Search 4 - NEWBORN-CARE.DE. OR INTENSIVE-CARE.DE. OR PREMATURE-LABOR.DE. OR HOSPITALIZATION.W..DE. OR SEPSIS.W..DE.
Results: 139,565 studies

Search 5 - SEPSIS.W..DE. OR BACTEREMIA.W..DE. OR SEPTIC-SHOCK.DE. OR INTENSIVE-CARE.DE. OR NEWBORN-SEPSIS.DE. OR BACTERIAL-INFECTION.DE. OR HOSPITAL-INFECTION.DE. OR GRAM-NEGATIVE-INFECTION.DE. OR MYCOSIS.W..DE. OR HYGIENE.W..DE. OR INFECTION.W..DE. OR SEPTICEMIA.W..DE. OR MENINGOCOCCOSIS.W..DE. OR LOW-BIRTH-WEIGHT.DE. OR NEWBORN-MORTALITY.DE. OR ENTEROBACTER-INFECTION.DE. OR MORBIDITY.W..DE.
Results: 342,313 studies

Search 6 - HOSPITAL-INFECTION.DE. OR HEALTH-CARE-PLANNING.DE. OR BACTEREMIA.W..DE. OR MICROBIOLOGY.W..DE. OR INFECTION-CONTROL.DE. OR MYCOSIS.W..DE
Results: 97,534 studies

Search (#1 or #2 or #3 or #4) and #5 and #6
Results: 28,622 studies

Limits imposed: only studies in humans and children
Results: 2570 studies (overlap with Embase free text search: 27 studies)

Searching bibliographies of shortlisted papers

Bibliographies of the ten final shortlisted studies were reviewed for relevance.

Searching related articles

For each of the ten shortlisted studies, the first 20 studies in the 'related articles' function within PubMed were reviewed for relevance.

Searching conference proceedings

Reviewed from January 2005 to October 2009**:**

- Annual Meeting for the European Society for Paediatric Infectious Diseases (ESPID)
- European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)
- Neonatal Updates
- UK Paediatric Research Society

Searching regional surveillance systems

Google search

Search 1- *Country/region* hospital infection monitoring
Search 2- *Country/region* hospital infection surveillance

Search 3- *Country/region* hospital infection neonatal intensive care monitoring
Search 4- *Country/region* hospital infection neonatal intensive care surveillance

Substitute *country/region* for:

UK
Netherlands
Germany
Belgium
France
Europe
USA
Canada
Australia
International

This resulted in 40 Google searches (4 searches × 10 countries).
The first 30 search results for each were scanned for relevance.

Appendix to Chapter 2

British Association of Perinatal Medicine (2001) 'Standards for Hospitals providing Neonatal Intensive and High Dependency Care (Second Edition) and Categories of Babies requiring Neonatal Care', British Association of Perinatal Medicine, London, UK. Permission to reproduce this information was confirmed by the BAPM in January 2011.

Designation of Neonatal Units

Level 1

Units provide Special Care but do not aim to provide any continuing High Dependency or Intensive Care. This term includes units with or without resident medical staff.

Level 2

Units provide High Dependency Care and some short-term Intensive Care as agreed within the network.

Level 3

Units provide the whole range of medical neonatal care but not necessarily all specialist services such as neonatal surgery.

Appendix to Chapter 3

British Association of Perinatal Medicine (2001) 'Standards for Hospitals providing Neonatal Intensive and High Dependency Care (Second Edition) and Categories of Babies requiring Neonatal Care', British Association of Perinatal Medicine, London, UK. Permission to reproduce this information was confirmed by the BAPM in January 2011.

Designation of levels of care

Intensive Care

These babies have the most complex problems. They need 1:1 care by a nurse with a neonatal qualification. The possibility of acute deterioration is such that there should be the constant availability of a competent doctor.

1. receiving any respiratory support via a tracheal tube and in the first 24 hours after its withdrawal
2. receiving NCPAP for any part of the day and less than five days old
3. below 1000g current weight and receiving NCPAP for any part of the day and for 24 hours after withdrawal
4. less than 29 weeks gestational age and less than 48 hours old
5. requiring major emergency surgery, for the pre-operative period and post-operatively for 24 hours
6. requiring complex clinical procedures:
    - Full exchange transfusion
    - Peritoneal dialysis
    - Infusion of an inotrope, pulmonary vasodilator or prostaglandin and for 24 hours afterwards
7. any other very unstable baby considered by the nurse-in-charge to need 1:1 nursing
8. a baby on the day of death.

High Dependency Care

A nurse should not be responsible for the care of more than two babies in this category

1. receiving NCPAP for any part of the day and not fulfilling any of the criteria for intensive care
2. below 1000g current weight and not fulfilling any of the criteria for intensive care
3. receiving parenteral nutrition
4. having convulsions
5. receiving oxygen therapy and below 1500g current weight
6. requiring treatment for neonatal abstinence syndrome
7. requiring specified procedures that do not fulfil any criteria for intensive care:
    - Care of an intra-arterial catheter or chest drain
    - Partial exchange transfusion
    - Tracheostomy care until supervised by a parent
8. requiring frequent stimulation for severe apnoea.

Special Care

A nurse should not be responsible for the care of more than four babies receiving Special or Normal Care.

Special care is provided for all other babies who could not reasonably be expected to be looked after at home by their mother.

Normal Care

Is provided for babies who themselves have no medical indication to be in hospital.

Table 3.6 NICU 1: crude and adjusted rate ratios for total BSI

Potential risk factor	BSI episodes/baby-days (Rate per 1000 baby days)		Crude rate ratios (95% CI) *p*-value			Adjusted rate ratios (95% CI) *p*-value		
NHS level of care								
Intensive care	122/9809	(12.44)	4.68	(3.24, 6.75)	<0.001	1.89	(1.05, 3.41)	0.035
High dependency care	49/3846	(12.74)	4.59	(3.00, 7.04)	<0.001	4.74	(3.09, 7.28)	<0.001
Special care	37/14,025	(2.64)		1			1	
Total	**208/27,680**	(**7.51**)						
Gestational age (weeks)								
<26	62/5078	(12.21)	1.60	(1.07, 2.38)	0.022	1.03	(0.67, 1.60)	0.891
26-<28	42/4628	(9.08)	1.18	(0.77, 1.83)	0.448	0.84	(0.53, 1.33)	0.455
28-<32	50/7352	(6.80)	0.90	(0.59, 1.36)	0.610	0.82	(0.54, 1.25)	0.360
32-<37	15/5513	(2.72)	0.36	(0.20, 0.65)	0.001	0.41	(0.22, 0.74)	0.003
≥37	39/5101	(7.65)		1			1	
Missing[c]	0/8							
Number of blood samples taken								
Linear increase			1.06	(1.04, 1.07)	<0.001	1.05	(1.02,1.08)	<0.001
Month								
Linear increase			1.00	(0.99, 1.01)	0.389			

Table 3.7 NICU 1: crude and adjusted rate ratios for CONS BSI

Potential risk factor	CONS episodes/baby-days (Rate per 1000 baby days)		Crude rate ratios (95% CI) *p*-value			Adjusted rate ratios (95% CI) *p*-value		
NHS level of care								
Intensive care	89/9809	(9.07)	4.67	(3.04, 7.19)	<0.001	1.83	(0.91, 3.68)	0.088
High dependency care	32/3846	(8.32)	4.11	(2.46, 6.86)	<0.001	4.25	(2.54, 7.12)	<0.001
Special care	27/14,025	(1.93)		1			1	
Total	**148/27,680**	(**5.34**)						
Gestational age (weeks)								
<26	42/5078	(8.27)	1.76	(1.06, 2.90)	0.028	1.12	(0.65, 1.92)	0.683
26-<28	34/4628	(7.35)	1.56	(0.92, 2.63)	0.097	1.09	(0.62, 1.89)	0.771
28-<32	39/7352	(5.30)	1.14	(0.68, 1.89)	0.622	1.03	(0.62, 1.73)	0.906
32-<37	9/5513	(1.63)	0.35	(0.16, 0.75)	0.007	0.39	(0.18, 0.85)	0.017
≥37	24/5101	(4.70)		1			1	
Missing[c]	0/8							
Number of blood samples taken								
Linear increase			1.06	(1.04, 1.08)	<0.001	1.05	(1.02, 1.09)	0.003
Month								
Linear increase			1.00	(0.99, 1.01)	0.754			

Table 3.8 NICU 1: crude and adjusted rate ratios for non-CONS BSI

Potential risk factor	Non-CONS episodes/baby-days (Rate per 1000 baby days)		Crude rate ratios (95% CI) *p*-value			Adjusted rate ratios (95% CI) *p*-value		
NHS level of care								
Intensive care	33/9809	(3.36)	4.68	(2.31, 9.49)	<0.001	2.04	(0.67, 6.27)	0.212
High dependency care	17/3846	(4.42)	5.90	(2.70, 12.88)	<0.001	6.05	(2.76, 13.28)	<0.001
Special care	10/14,025	(0.71)		1			1	
Total	**60/27,680**	(**2.17**)						
Gestational age (weeks)								
<26	20/5078	(3.94)	1.34	(0.69, 2.62)	0.392	0.89	(0.42, 1.88)	0.778
26-<28	8/4628	(1.73)	0.59	(0.25, 1.38)	0.223	0.43	(0.17, 1.07)	0.069
28-<32	11/7352	(1.50)	0.51	(0.24, 1.12)	0.093	0.48	(0.22, 1.05)	0.066
32-<37	6/5513	(1.09)	0.37	(0.14, 0.96)	0.040	0.43	(0.17, 1.12)	0.086
≥37	15/5101	(2.94)		1			1	
Missing[c]	0/8							
Number of blood samples taken								
Linear increase			1.05	(1.02, 1.08)	<0.001	1.05	(1.00, 1.11)	0.054
Month								
Linear increase			1.01	(0.99, 1.03)	0.266			

Table 3.9 NICU 2: crude and adjusted rate ratios for total BSI

Potential risk factor	BSI episodes/baby-days (Rate per 1000 baby days)		Crude rate ratios (95% CI) *p*-value			Adjusted rate ratios (95% CI) *p*-value		
NHS level of care								
Intensive care	157/13,209	(11.89)	3.78	(2.75, 5.20)	<0.001	4.29	(2.55, 7.20)	<0.001
High dependency care	18/1331	(13.52)	3.64	(2.12, 6.24)	<0.001	3.90	(2.10, 7.25)	<0.001
Special care	50/15,976	(3.13)		1			1	
Total	**225/30,516**	(**7.37**)						
Gestational age (weeks)								
<26	74/6899	(10.73)	1.09	(0.77, 1.54)	0.625	0.47	(0.32, 0.70)	<0.001
26-<28	30/3070	(9.77)	0.97	(0.62, 1.51)	0.890	0.44	(0.28, 0.71)	0.001
28-<32	34/7252	(4.69)	0.48	(0.31, 0.73)	0.001	0.31	(0.20, 0.49)	<0.001
32-<37	30/7525	(3.99)	0.41	(0.26, 0.63)	<0.001	0.42	(0.27, 0.66)	<0.001
≥37	57/5770	(9.88)		1			1	
Missing[c]	0							
Number of blood samples taken								
Linear increase			1.04	(1.02, 1.05)	<0.001	1.00	(0.98, 1.03)	0.695
Month								
Linear increase			0.99	(0.98, 1.00)	0.293			

Table 3.10 NICU 2: crude and adjusted rate ratios for CONS BSI

Potential risk factor	CONS episodes/baby-days (Rate per 1000 baby days)		Crude rate ratios (95% CI) *p*-value			Adjusted rate ratios (95% CI) *p*-value		
NHS level of care								
Intensive care	113/13,209	(8.55)	4.13	(2.80, 6.08)	<0.001	3.47	(1.86, 6.50)	<0.001
High dependency care	13/1331	(9.77)	3.98	(2.10, 7.57)	<0.001	5.14	(2.45, 10.78)	<0.001
Special care	33/15,976	(2.07)		1			1	
Total	**159/30,516**	(**5.21**)						
Gestational age (weeks)								
<26	54/6899	(7.83)	1.33	(0.87, 2.05)	0.189	0.58	(0.36, 0.95)	0.029
26-<28	23/3070	(7.49)	1.25	(0.73, 2.11)	0.416	0.57	(0.32, 1.01)	0.054
28-<32	26/7252	(3.59)	0.61	(0.37, 1.02)	0.059	0.41	(0.24, 0.69)	0.001
32-<37	22/7525	(2.92)	0.50	(0.29, 0.85)	0.011	0.52	(0.30, 0.89)	0.017
≥37	34/5770	(5.89)		1			1	
Missing[c]	0							
Number of blood samples taken								
Linear increase			1.04	(1.03, 1.06)	<0.001	1.02	(1.00, 1.05)	0.189
Month								
Linear increase			1.00	(0.99, 1.01)	0.929			

Table 3.11 NICU 2: crude and adjusted rate ratios for non-CONS BSI

Potential risk factor	Non-CONS episodes/baby-days (Rate per 1000 baby days)		Crude rate ratios (95% CI) *p*-value			Adjusted rate ratios (95% CI) *p*-value		
NHS level of care								
Intensive care	44/13,209	(3.33)	3.12	(1.78, 5.46)	<0.001	7.21	(2.86, 18.14)	<0.001
High dependency care	5/1331	(3.76)	2.97	(1.10, 8.06)	0.032	2.03	(0.65, 6.36)	0.224
Special care	17/15,976	(1.06)		1			1	
Total	**66/30,516**	(**2.16**)						
Gestational age (weeks)								
<26	20/6899	(2.90)	0.73	(0.40, 1.33)	0.303	0.31	(0.16, 0.62)	0.001
26-<28	7/3070	(2.28)	0.56	(0.24, 1.31)	0.180	0.26	(0.10, 0.63)	0.003
28-<32	8/7252	(1.10)	0.28	(0.12, 0.62)	0.002	0.18	(0.08, 0.42)	<0.001
32-<37	8/7525	(1.06)	0.27	(0.12, 0.60)	0.001	0.28	(0.13, 0.63)	0.002
≥37	23/5770	(3.99)		1			1	
Missing[c]	0							
Number of blood samples taken								
Linear increase			1.02	(1.00, 1.05)	0.055	0.97	(0.93, 1.01)	0.184
Month								
Linear increase			0.98	(0.97, 1.00)	0.073			

c - Babies with missing variables were few and experienced few episodes of BSI. For this reason I considered it acceptable to remove them from the analyses.

Appendix to Chapter 5

Table 5.10 Poisson regression models for the effect of birth susceptibility factors on total BSI, for NICU 1

Potential risk factor	BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value			Adjusted rate ratios (95% CI) *p*-value		
Gestational age (weeks)								
<26	43/3937	(10.92)	2.32	(1.35, 3.98)	0.002			
26-<28	18/3218	(5.59)	1.19	(0.62, 2.26)	0.605			
28-<32	34/5573	(6.10)	1.28	(0.73, 2.24)	0.388			
32-<37	11/3836	(2.87)	0.59	(0.28, 1.23)	0.157			
≥37	19/3760	(5.05)		1				
Missing[e]	0/24							
Birth weight (g)								
<700	31/2623	(11.82)	2.86	(1.80, 4.55)	<0.001	2.27	(1.39, 3.70)	0.001
700-<1200	51/7759	(6.57)	1.59	(1.06, 2.38)	0.025	1.28	(0.83, 1.98)	0.258
≥1200	43/9933	(4.33)		1			1	
Missing[e]	0/33							
Where born								
Outborn	59/5895	(10.01)	2.26	(1.59, 3.22)	<0.001	1.91	(1.30, 2.79)	<0.001
Inborn	64/14,227	(4.50)		1			1	
Missing[e]	2/226							
Sex								
Male	64/10,530	(6.08)	0.97	(0.69, 1.38)	0.880			
Female	61/9818	(6.21)		1				
Missing[e]	0/0							
Delivery method								
Emergency CS[f]	51/8814	(5.79)	0.88	(0.61, 1.27)	0.496			
Elective CS[f]	11/2135	(5.15)	0.78	(0.41, 1.49)	0.454			
Vaginal	62/9321	(6.65)		1				
Missing[e]	1/78							

Table 5.11 Poisson regression models for the effect of birth susceptibility factors on CONS BSI, for NICU 1

Potential risk factor	CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) p-value			Adjusted rate ratios (95% CI) p-value		
Gestational age (weeks)								
<26	27/3937	(6.86)	1.85	(0.98, 3.47)	0.057			
26-<28	14/3218	(4.35)	1.17	(0.56, 2.42)	0.676			
28-<32	27/5573	(4.84)	1.29	(0.69, 2.42)	0.432			
32-<37	7/3836	(1.82)	0.47	(0.19, 1.16)	0.101			
≥37	15/3760	(3.99)		1				
Missing[e]	0/24							
Birth weight (g)								
<700	21/2623	(8.01)	2.53	(1.46, 4.37)	<0.001	1.91	(1.06, 3.41)	0.030
700-<1200	36/7759	(4.64)	1.46	(0.91, 2.34)	0.115	1.12	(0.67, 1.87)	0.659
≥1200	33/9933	(3.32)		1			1	
Missing[e]	0/33							
Where born								
Outborn	44/5895	(7.46)	2.46	(1.62, 3.73)	<0.001	2.18	(1.39, 3.43)	<0.001
Inborn	44/14,227	(3.09)		1			1	
Missing[e]	2/226							
Sex								
Male	45/10,530	(4.27)	0.93	(0.61, 1.40)	0.722			
Female	45/9818	(4.58)		1				
Missing[e]	0/0							
Delivery method								
Emergency CS[f]	39/8814	(4.42)	0.95	(0.62, 1.46)	0.806			
Elective CS[f]	7/2135	(3.28)	0.70	(0.32, 1.56)	0.385			
Vaginal	44/9321	(4.72)		1				
Missing[e]	0/78							

Table 5.12 Poisson regression models for the effect of birth susceptibility factors on non-CONS BSI, for NICU 1

Potential risk factor	Non-CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
Gestational age (weeks)					
<26	16/3937	(4.06)	4.10	(1.37, 12.27)	0.012
26-<28	4/3218	(1.24)	1.25	(0.31, 5.00)	0.751
28-<32	7/5573	(1.26)	1.25	(0.37, 4.28)	0.720
32-<37	4/3836	(1.04)	1.01	(0.25, 4.04)	0.988
≥37	4/3760	(1.06)		1	
Missing[e]	0/24				
Birth weight (g)					
<700	10/2623	(3.81)	3.97	(1.65, 9.55)	0.002
700-≤1200	15/7759	(1.93)	2.01	(0.90, 4.47)	0.087
≥1200	10/9933	(1.01)		1	
Missing[e]	0/33				
Where born					
Outborn	15/5895	(2.54)	1.84	(0.94, 3.60)	0.074
Inborn	20/14,227	(1.41)		1	
Missing[e]	0/226				
Sex					
Male	19/10,530	(1.80)	1.10	(0.57, 2.14)	0.775
Female	16/9818	(1.63)		1	
Missing[e]	0/0				
Delivery method					
Emergency CS[f]	12/8814	(1.36)	0.71	(0.34, 1.48)	0.363
Elective CS[f]	4/2135	(1.87)	0.98	(0.33, 2.90)	0.972
Vaginal	18/9321	(1.93)		1	
Missing[e]	1/78				

Table 5.13 Poisson regression models for the effect of birth susceptibility factors on total BSI, for NICU 2

Potential risk factor	BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value			Adjusted rate ratios (95% CI) *p*-value		
Gestational age (weeks)								
<26	52/4960	(10.48)	1.77	(1.10, 2.86)	0.019			
26-<28	25/2447	(10.22)	1.72	(0.99, 3.00)	0.054			
28-<32	25/6297	(3.97)	0.66	(0.38, 1.16)	0.149			
32-<37	19/5747	(3.31)	0.53	(0.29, 0.97)	0.040			
≥37	25/3748	(6.67)		1				
Missing[e]	0/0							
Birth weight (g)								
<700	52/4278	(12.16)	3.22	(2.18, 4.76)	<0.001	3.04	(2.02, 4.58)	<0.001
700-<1200	45/6706	(6.71)	1.77	(1.18, 2.66)	0.006	1.72	(1.14, 2.59)	0.010
≥1200	49/12,215	(4.01)		1			1	
Missing[e]	0/0							
Where born								
Outborn	38/4081	(9.31)	1.69	(1.17, 2.45)	0.005	1.21	(0.82, 1.78)	0.346
Inborn	108/19,118	(5.65)		1			1	
Missing[e]	0/0							
Sex								
Male	80/12,574	(6.36)	1.02	(0.74, 1.41)	0.912			
Female	66/10,625	(6.21)		1				
Missing[e]	0/0							
Delivery method								
Emergency CS[f]	52/7505	(6.93)	1.12	(0.78, 1.60)	0.551			
Elective CS[f]	26/4840	(5.37)	0.86	(0.55, 1.35)	0.513			
Vaginal	68/10,844	(6.28)		1				
Missing[e]	0/10							

Table 5.14 Poisson regression models for the effect of birth susceptibility factors on CONS BSI, for NICU 2

Potential risk factor	CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value			Adjusted rate ratios (95% CI) *p*-value		
Gestational age (weeks)								
<26	38/4960	(7.66)	2.16	(1.19, 3.93)	0.012			
26-<28	18/2447	(7.36)	2.07	(1.04, 4.10)	0.038			
28-<32	19/6297	(3.02)	0.84	(0.43, 1.66)	0.618			
32-<37	15/5747	(2.61)	0.70	(0.34, 1.44)	0.335			
≥37	15/3748	(4.00)		1				
Missing[e]	0/0							
Birth weight (g)								
<700	38/4278	(8.88)	3.61	(2.25, 5.77)	<0.001	3.35	(2.04, 5.48)	<0.001
700-<1200	35/6706	(5.22)	2.11	(1.31, 3.41)	0.002	2.02	(1.24, 3.29)	0.005
≥1200	32/12,215	(2.62)		1			1	
Missing[e]	0/0							
Where born								
Outborn	29/4081	(7.11)	1.83	(1.20, 2.81)	0.005	1.27	(0.81, 1.99)	0.296
Inborn	76/19,118	(3.98)		1			1	
Missing[e]	0/0							
Sex								
Male	58/12,574	(4.61)	1.04	(0.71, 1.52)	0.853			
Female	47/10,625	(4.42)		1				
Missing[e]	0/0							
Delivery method								
Emergency CS[f]	41/7505	(5.46)	1.33	(0.87, 2.03)	0.187			
Elective CS[f]	19/4840	(3.93)	0.95	(0.56, 1.62)	0.850			
Vaginal	45/10,844	(4.15)		1				
Missing[e]	0/10							

Table 5.15 Poisson regression models for the effect of birth susceptibility factors on non-CONS BSI, for NICU 2

Potential risk factor	Non-CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
Gestational age (weeks)					
<26	14/4960	(2.82)	1.19	(0.53, 2.69)	0.669
26-<28	7/2447	(2.86)	1.21	(0.46, 3.17)	0.704
28-<32	6/6297	(0.95)	0.40	(0.14, 1.10)	0.075
32-<37	4/5747	(0.70)	0.28	(0.09, 0.90)	0.032
≥37	10/3748	(2.67)		1	
Missing[e]	0/0				
Birth weight (g)					
<700	14/4278	(3.27)	2.50	(1.23, 5.07)	0.011
700-<1200	10/6706	(1.49)	1.14	(0.52, 2.48)	0.750
≥1200	17/12,215	(1.39)		1	
Missing[e]	0/0				
Where born					
Outborn	9/4081	(2.21)	1.35	(0.65, 2.83)	0.424
Inborn	32/19,118	(1.67)		1	
Missing[e]	0/0				
Sex					
Male	22/12,574	(1.75)	0.97	(0.53, 1.80)	0.930
Female	19/10,625	(1.79)		1	
Missing[e]	0/0				
Delivery method					
Emergency CS[f]	11/7505	(1.47)	0.70	(0.34, 1.43)	0.327
Elective CS[f]	7/4840	(1.45)	0.68	(0.29, 1.60)	0.380
Vaginal	23/10,844	(2.12)		1	
Missing[e]	0/10				

Table 5.16 Poisson regression models for the effect of birth susceptibility factors on total BSI, for NICU 3

Potential risk factors	BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
Gestational age (weeks)					
<26	22/1204	(18.27)	8.61	(3.49, 21.24)	<0.001
26-<28	12/1432	(8.38)	3.94	(1.48, 10.50)	0.006
28-<32	29/4499	(6.45)	3.02	(1.25, 7.27)	0.014
32-<37	7/4748	(1.47)	0.67	(0.22, 1.98)	0.464
≥37	6/2582	(2.32)		1	
Missing[e]	0/34				
Birth weight (g)					
<700	21/1642	(12.79)	7.20	(3.76, 13.80)	<0.001
700-<1200	39/4327	(9.01)	5.05	(2.82, 9.04)	<0.001
≥1200	16/8510	(1.88)		1	
Missing[e]	0/20				
Where born					
Outborn	4/1413	(2.83)	0.52	(0.19, 1.43)	0.208
Inborn	70/12,852	(5.45)		1	
Missing[e]	2/234				
Sex					
Male	38/6836	(5.56)	1.10	(0.70, 1.72)	0.681
Female	38/7587	(5.01)		1	
Missing[e]	0/76				
Delivery method					
Emergency CS[f]	42/5777	(7.27)	1.69	(1.04, 2.76)	0.035
Elective CS[f]	6/2276	(2.64)	0.61	(0.25, 1.48)	0.271
Vaginal	26/5979	(4.35)		1	
Missing[e]	2/467				

Table 5.17 Poisson regression models for the effect of birth susceptibility factors on CONS BSI, for NICU 3

Potential risk factors	CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
Gestational age (weeks)					
<26	17/1204	(14.12)	6.65	(2.62, 16.88)	<0.001
26-<28	11/1432	(7.68)	3.61	(1.34, 9.77)	0.011
28-<32	24/4499	(5.33)	2.50	(1.02, 6.11)	0.045
32-<37	6/4748	(1.26)	0.57	(0.18, 1.77)	0.331
≥37	6/2582	(2.32)		1	
Missing[e]	0/34				
Birth weight (g)					
<700	17/1642	(10.35)	6.22	(3.11, 12.45)	<0.001
700-<1200	32/4327	(7.40)	4.42	(2.39, 8.17)	<0.001
≥1200	15/8510	(1.76)		1	
Missing[e]	0/20				
Where born					
Outborn	4/1413	(2.83)	0.63	(0.23, 1.74)	0.632
Inborn	58/12,852	(4.51)		1	
Missing[e]	2/234				
Sex					
Male	32/6836	(4.68)	1.10	(0.67, 1.79)	0.706
Female	32/7587	(4.22)		1	
Missing[e]	0/76				
Delivery method					
Emergency CS[f]	35/5777	(6.06)	1.59	(0.94, 2.70)	0.082
Elective CS[f]	4/2276	(1.76)	0.46	(0.16, 1.32)	0.149
Vaginal	23/5979	(3.85)		1	
Missing[e]	2/467				

Table 5.18 Poisson regression models for the effect of birth susceptibility factors on non-CONS BSI, for NICU 3

Potential risk factors	Non-CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
Gestational age (weeks)					
<26	5/1204	(4.15)		-	
26-<28	1/1432	(0.70)		-	
28-<32	5/4499	(1.11)		-	
32-<37	1/4748	(0.21)		-	
≥37	0/2582			-	
Missing[e]	0/34				
Birth weight (g)					
<700	4/1642	(2.44)	21.95	(2.45, 19.62)	0.006
700 - <1200	7/4327	(1.62)	14.51	(1.79, 117.87)	0.012
≥1200	1/8510	(0.12)		1	
Missing[e]	0/20				
Where born					
Outborn	0/1413	(0.0)		-	
Inborn	12/12,852	(0.93)		-	
Missing[e]	0/234				
Sex					
Male	6/6836	(0.88)	1.10	(0.35, 3.41)	0.870
Female	6/7587	(0.79)		1	
Missing[e]	0/76				
Delivery method					
Emergency CS[f]	7/5777	(1.21)	2.44	(0.63, 9.45)	0.195
Elective CS[f]	2/2276	(0.88)	1.75	(0.29, 10.50)	0.538
Vaginal	3/5979	(0.50)		1	
Missing[e]	0/467				

e - Babies with missing variables were few and experienced few episodes of BSI. For this reason I considered it acceptable to remove them from the analyses.
f - CS- Caesarean section

Table 5.19 Poisson regression models for the effect of procedure-related factors on total BSI, for NICU 1

Potential risk factors	BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
No of blood samples taken					
≥7	68/5277	(12.89)	5.33	(3.48, 8.15)	<0.001
4-6	26/2847	(9.13)	3.75	(2.23, 6.32)	<0.001
0-3	31/12,224	(2.54)		1	
Number of days spent in:					
Special care					
≥7	92/16,015	(5.74)	0.78	(0.49, 1.24)	0.296
4-6	4/786	(5.09)	0.62	(0.21, 1.80)	0.382
1-3	7/658	(10.64)	1.28	(0.55, 3.00)	0.566
0	22/2889	(7.62)		1	
High dependency care					
≥7	63/7287	(8.65)	1.86	(1.26, 2.76)	0.002
4-6	4/1321	(3.03)	0.64	(0.23, 1.79)	0.399
1-3	17/3216	(5.29)	1.12	(0.64, 1.97)	0.692
0	41/8524	(4.81)		1	
Intensive care					
≥7	92/11,110	(8.28)	3.40	(1.94, 5.96)	<0.001
4-6	8/1532	(5.22)	2.09	(0.88, 4.99)	0.096
1-3	11/2311	(4.76)	1.90	(0.86, 4.19)	0.110
0	14/5395	(2.59)		1	
Number of days treated with:					
Ventilation					
≥7	66/7779	(8.48)	1.96	(1.32, 2.92)	<0.001
4-6	4/735	(5.44)	1.23	(0.44, 3.45)	0.691
1-3	16/3248	(4.93)	1.12	(0.63, 2.01)	0.701
0	39/8586	(4.54)		1	
Nasal continuous positive airway pressure					
≥7	63/8630	(7.30)	1.38	(0.95, 2.00)	0.094
4-6	2/754	(2.65)	0.49	(0.12, 2.03)	0.329
1-3	11/2172	(5.06)	0.93	(0.49, 1.80)	0.839
0	49/8792	(5.57)		1	
Surgery					
Yes	34/3562	(9.55)	1.81	(1.22, 2.68)	0.003
No	91/16,786	(5.42)		1	

Table 5.20 Poisson regression models for the effect of procedure-related factors on CONS BSI, for NICU 1

Potential risk factors	CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
No of blood samples taken					
≥7	46/5277	(8.72)	4.14	(2.57, 6.65)	<0.001
4-6	17/2847	(5.97)	2.82	(1.53, 5.17)	<0.001
0-3	27/12,224	(2.21)		1	
Number of days spent in:					
Special care					
≥7	68/16,015	(4.25)	0.91	(0.51, 1.61)	0.738
4-6	3/786	(3.82)	0.73	(0.21, 2.55)	0.625
1-3	5/658	(7.60)	1.44	(0.52, 4.00)	0.484
0	14/2889	(4.85)		1	
High dependency care					
≥7	45/7287	(6.18)	1.95	(1.22, 3.12)	0.006
4-6	3/1321	(2.27)	0.71	(0.21, 2.32)	0.566
1-3	14/3216	(4.35)	1.35	(0.71, 2.57)	0.357
0	28/8524	(3.28)		1	
Intensive care					
≥7	64/11,110	(5.76)	2.76	(1.49, 5.11)	0.001
4-6	7/1532	(4.57)	2.14	(0.84, 5.42)	0.111
1-3	7/2311	(3.03)	1.41	(0.56, 3.59)	0.467
0	12/5395	(2.22)		1	
Number of days treated with:					
Ventilation					
≥7	44/7779	(5.66)	1.65	(1.04, 2.61)	0.033
4-6	3/735	(4.08)	1.16	(0.36, 3.80)	0.804
1-3	12/3248	(3.69)	1.06	(0.54, 2.06)	0.870
0	31/8586	(3.61)		1	
Nasal continuous positive airway pressure					
≥7	46/8630	(5.33)	1.49	(0.95, 2.33)	0.080
4-6	2/754	(2.65)	0.73	(0.18, 3.06)	0.672
1-3	9/2172	(4.14)	1.14	(0.54, 2.37)	0.736
0	33/8792	(3.75)		1	
Surgery					
Yes	23/3562	(6.46)	1.66	(1.03, 2.67)	0.036
No	67/16,786	(3.99)		1	

Table 5.21 Poisson regression models for the effect of procedure-related factors on non-CONS BSI, for NICU 1

Potential risk factors	Non-CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
No of blood samples taken					
≥7	22/5277	(4.17)	13.35	(4.60, 38.75)	<0.001
4-6	9/2847	(3.16)	10.06	(3.10, 32.67)	<0.001
0-3	4/12,224	(0.33)		1	
Number of days spent in:					
Special care					
≥7	24/16,015	(1.50)	0.56	(0.25, 1.25)	0.155
4-6	1/786	(1.27)	0.43	(0.05, 3.42)	0.423
1-3	2/658	(3.04)	1.01	(0.21, 4.75)	0.992
0	8/2889	(2.77)		1	
High dependency care					
≥7	18/7287	(2.47)	1.68	(0.82, 3.43)	0.154
4-6	1/1321	(0.76)	0.51	(0.07, 3.87)	0.513
1-3	3/3216	(0.93)	0.62	(0.18, 2.19)	0.461
0	13/8524	(1.53)		1	
Intensive care					
≥7	28/11,110	(2.52)	7.24	(1.73, 30.40)	0.007
4-6	1/1532	(0.65)	1.83	(0.17, 20.19)	0.622
1-3	4/2311	(1.73)	4.85	(0.89, 26.46)	0.068
0	2/5395	(0.37)		1	
Number of days treated with:					
Ventilation					
≥7	22/7779	(2.83)	3.19	(1.42, 7.17)	0.005
4-6	1/735	(1.36)	1.50	(0.19, 12.00)	0.702
1-3	4/3248	(1.23)	1.37	(0.41, 4.54)	0.611
0	8/8586	(0.93)		1	
Nasal continuous positive airway pressure					
≥7	17/8630	(1.97)	1.14	(0.57, 2.25)	0.712
4-6	0/754	(0.00)	-	-	-
1-3	2/2172	(0.92)	0.520	(0.12, 2.26)	0.384
0	16/8792	(1.82)		1	
Surgery					
Yes	11/3562	(3.09)	2.22	(1.09, 4.53)	0.029
No	24/16,786	(1.43)		1	

Table 5.22 Poisson regression models for the effect of procedure-related factors on total BSI, for NICU 2

Potential risk factors	BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
No of blood samples taken					
≥7	61/5683	(10.73)	3.42	(2.33, 5.03)	<0.001
4-6	40/4028	(9.93)	3.14	(2.05, 4.81)	<0.001
0-3	45/13,488	(3.34)		1	
Number of days spent in:					
Special care					
≥7	74/17,088	(4.33)	0.29	(0.20, 0.40)	<0.001
4-6	7/1220	(5.74)	0.33	(0.15, 0.73)	0.006
1-3	6/992	(6.05)	0.32	(0.14, 0.75)	0.009
0	59/3899	(15.13)		1	
High dependency care					
≥7	19/2382	(7.98)	1.32	(0.81, 2.16)	0.261
4-6	5/865	(5.78)	0.95	(0.39, 2.33)	0.910
1-3	16/2894	(5.53)	0.89	(0.53, 1.51)	0.674
0	106/17,058	(6.21)		1	
Intensive care					
≥7	106/13,085	(8.10)	2.55	(1.58, 4.11)	<0.001
4-6	6/1362	(4.41)	1.33	(0.54, 3.32)	0.535
1-3	14/2980	(4.70)	1.41	(0.71, 2.79)	0.326
0	20/5772	(3.47)		1	
Number of days treated with:					
Ventilation					
≥7	106/12,737	(8.32)	2.00	(1.32, 3.01)	<0.001
4-6	6/1276	(4.70)	1.09	(0.45, 2.64)	0.840
1-3	5/2781	(1.80)	0.41	(0.16, 1.06)	0.066
0	29/6405	(4.53)		1	
Total parenteral nutrition					
≥7	106/10,965	(9.67)	3.92	(2.57, 5.98)	<0.001
4-6	9/1331	(6.76)	2.71	(1.27, 5.75)	0.010
1-3	4/686	(5.83)	2.33	(0.82, 6.66)	0.114
0	27/10,217	(2.64)		1	
Surgery					
Yes	53/5507	(9.62)	1.91	(1.36, 2.68)	<0.001
No	93/17,692	(5.26)		1	

Table 5.23 Poisson regression models for the effect of procedure-related factors on CONS BSI, for NICU 2

Potential risk factors	CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
No of blood samples taken					
≥7	45/5683	(7.92)	3.55	(2.26, 5.58)	<0.001
4-6	28/4028	(6.95)	3.09	(1.86, 5.13)	<0.001
0-3	32/13,488	(2.37)		1	
Number of days spent in:					
Special care					
≥7	55/17,088	(3.22)	0.30	(0.20, 0.45)	<0.001
4-6	4/1220	(3.28)	0.27	(0.10, 0.75)	0.012
1-3	4/992	(4.03)	0.30	(0.11, 0.85)	0.023
0	42/3899	(10.77)		1	
High dependency care					
≥7	13/2382	(5.46)	1.26	(0.70, 2.27)	0.437
4-6	5/865	(5.78)	1.32	(0.54, 3.27)	0.543
1-3	11/2894	(3.80)	0.86	(0.46, 1.61)	0.632
0	76/17,058	(4.46)		1	
Intensive care					
≥7	78/13,085	(5.96)	2.68	(1.52, 4.73)	<0.001
4-6	5/1362	(3.67)	1.59	(0.57, 4.41)	0.374
1-3	8/2980	(2.68)	1.15	(0.48, 2.74)	0.753
0	14/5772	(2.43)		1	
Number of days treated with:					
Ventilation					
≥7	78/12,737	(6.12)	2.24	(1.36, 3.70)	0.002
4-6	5/1276	(3.92)	1.39	(0.52, 3.73)	0.510
1-3	3/2781	(1.08)	0.38	(0.11, 1.27)	0.116
0	19/6405	(2.97)		1	
Total parenteral nutrition					
≥7	79/10,965	(7.20)	4.64	(2.75, 7.83)	<0.001
4-6	7/1331	(5.26)	3.34	(1.39, 8.06)	0.007
1-3	2/686	(2.92)	1.85	(0.43, 8.01)	0.410
0	17/10,217	(1.66)		1	
Surgery					
Yes	37/5507	(6.72)	1.82	(1.22, 2.72)	0.003
No	68/17,692	(3.84)		1	

Table 5.24 Poisson regression models for the effect of procedure-related factors on non-CONS BSI, for NICU 2

Potential risk factors	Non-CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
No of blood samples taken					
≥7	16/5683	(2.82)	3.11	(1.49, 6.46)	0.002
4-6	12/4028	(2.98)	3.26	(1.49, 7.14)	0.003
0-3	13/13,488	(0.96)		1	
Number of days spent in:					
Special care					
≥7	19/17,088	(1.11)	0.25	(0.13, 0.49)	<0.001
4-6	3/1220	(2.46)	0.50	(0.15, 1.70)	0.265
1-3	2/992	(2.02)	0.38	(0.09, 1.63)	0.190
0	17/3899	(4.36)		1	
High dependency care					
≥7	6/2382	(2.52)	1.48	(0.61, 3.55)	0.383
4-6	0/865	(0.00)		-	
1-3	5/2894	(1.73)	0.99	(0.38, 2.54)	0.977
0	30/17,058	(1.76)		1	
Intensive care					
≥7	28/13,085	(2.14)	2.24	(0.93, 5.42)	0.072
4-6	1/1362	(0.73)	0.74	(0.09, 6.16)	0.782
1-3	6/2980	(2.01)	2.01	(0.65, 6.24)	0.226
0	6/5772	(1.04)		1	
Number of days treated with:					
Ventilation					
≥7	28/12,737	(2.20)	1.53	(0.74, 3.15)	0.248
4-6	1/1276	(0.78)	0.53	(0.07, 4.13)	0.544
1-3	2/2781	(0.72)	0.48	(0.10, 2.18)	0.339
0	10/6405	(1.56)		1	
Total parenteral nutrition					
≥7	27/10,965	(2.46)	2.69	(1.30, 5.57)	0.007
4-6	2/1331	(1.50)	1.62	(0.36, 7.41)	0.532
1-3	2/686	(2.92)	3.15	(0.69, 14.36)	0.139
0	10/10,217	(0.98)		1	
Surgery					
Yes	16/5507	(2.91)	2.15	(1.15, 4.02)	0.017
No	25/17,692	(1.41)		1	

Table 5.25 Poisson regression models for the effect of procedure-related factors on total BSI, for NICU 3

Potential risk factors	BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
No of blood samples taken					
≥7	41/2947	(13.91)	10.76	(5.66, 20.48)	<0.001
4-6	23/2750	(8.36)	6.35	(3.16, 12.76)	<0.001
0-3	12/8802	(1.36)		1	
Number of days spent in:					
Special care					
≥7	50/11,866	(4.21)	0.30	(0.19, 0.49)	<0.001
4-6	0/451	(0.00)		-	
1-3	1/437	(2.29)	0.13	(0.02, 0.98)	0.047
0	25/1745	(14.33)		1	
High dependency care					
≥7	21/2727	(7.70)	1.51	(0.90, 2.54)	0.119
4-6	10/1533	(6.52)	1.27	(0.64, 2.52)	0.494
1-3	1/1914	(0.52)	0.10	(0.01, 0.71)	0.021
0	44/8325	(5.29)		1	
Intensive care					
≥7	61/6173	(9.88)	11.42	(4.59, 28.42)	<0.001
4-6	4/953	(4.20)	4.71	(1.26, 17.53)	0.021
1-3	6/1955	(3.07)	3.39	(1.03, 11.11)	0.044
0	5/5418	(0.92)		1	
Number of days treated with:					
Ventilation					
≥7	42/3594	(11.69)	6.82	(3.72, 12.48)	<0.001
4-6	5/705	(7.09)	4.08	(1.47, 11.32)	0.007
1-3	15/2509	(5.98)	3.42	(1.65, 7.08)	<0.001
0	14/7691	(1.82)		1	
Total parenteral nutrition					
≥7	62/5512	(11.25)	8.32	(4.49, 15.44)	<0.001
4-6	0/441	(0.00)		-	
1-3	2/130	(15.38)	10.79	(2.41, 48.21)	0.002
0	12/8416	(1.43)		1	
Nasal continuous positive airway pressure					
≥7	45/5126	(8.78)	2.90	(1.73, 4.87)	<0.001
4-6	3/743	(4.04)	1.31	(0.39, 4.40)	0.660
1-3	7/2089	(3.35)	1.06	(0.45, 2.50)	0.890
0	21/6541	(3.21)		1	
Long line					
≥7	56/5230	(10.71)	7.43	(4.07, 13.59)	<0.001
4-6	3/445	(6.74)	4.58	(1.30, 16.06)	0.018
1-3	4/271	(14.76)	10.12	(3.30, 31.03)	<0.001
0	13/8553	(1.52)		1	
Umbilical arterial catheter					
≥7	22/1555	(14.15)	4.26	(2.51, 7.21)	<0.001
4-6	10/1243	(8.05)	2.42	(1.21, 4.87)	0.013
1-3	7/1060	(6.60)	1.97	(0.88, 4.41)	0.101
0	37/10,641	(3.48)		1	

Umbilical venous catheter					
≥7	19/1828	(10.39)	3.55	(2.01, 6.26)	<0.001
4-6	13/708	(18.36)	6.22	(3.26, 11.85)	<0.001
1-3	12/1554	(7.72)	2.60	(1.34, 5.05)	0.005
0	32/10,409	(3.07)		1	

Table 5.26 Poisson regression models for the effect of procedure-related factors on CONS BSI, for NICU 3

Potential risk factors	CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
No of blood samples taken					
≥7	33/2947	(11.20)	11.55	(5.53, 24.15)	<0.001
4-6	22/2750	(8.00)	8.10	(3.73, 17.58)	<0.001
0-3	9/8802	(1.02)		1	
Number of days spent in:					
Special care					
≥7	44/11,866	(3.71)	0.35	(0.21, 0.60)	<0.001
4-6	0/451	(0.00)		-	
1-3	1/437	(2.29)	0.17	(0.02, 1.30)	0.089
0	19/1745	(10.89)		1	
High dependency care					
≥7	17/2727	(6.23)	1.46	(0.82, 2.58)	0.200
4-6	9/1533	(5.87)	1.36	(0.66, 2.82)	0.408
1-3	1/1914	(0.52)	0.12	(0.02, 0.84)	0.033
0	37/8325	(4.44)		1	
Intensive care					
≥7	51/6173	(8.26)	9.55	(3.81, 23.92)	<0.001
4-6	3/953	(3.15)	3.53	(0.84, 14.77)	0.084
1-3	5/1955	(2.56)	2.83	(0.82, 9.76)	0.100
0	5/5418	(0.92)		1	
Number of days treated with:					
Ventilation					
≥7	33/3594	(9.18)	5.77	(3.04, 10.96)	<0.001
4-6	5/705	(7.09)	4.39	(1.57, 12.32)	0.005
1-3	13/2509	(5.18)	3.19	(1.48, 6.88)	0.003
0	13/7691	(1.69)		1	
Total parenteral nutrition					
≥7	50/5512	(9.07)	6.71	(3.58, 12.60)	<0.001
4-6	0/441	(0.00)		-	
1-3	2/130	(15.38)	10.79	(2.41, 48.21)	<0.001
0	12/8416	(1.43)		1	
Nasal continuous positive airway pressure					
≥7	37/5126	(7.22)	2.79	(1.59, 4.89)	<0.001
4-6	3/743	(4.04)	1.53	(0.45, 5.20)	0.495
1-3	6/2089	(2.87)	1.06	(0.42, 2.68)	0.898
0	18/6541	(2.75)		1	
Long line					
≥7	44/5230	(8.41)	5.84	(3.15, 10.84)	<0.001
4-6	3/445	(6.74)	4.58	(1.30, 16.06)	0.018
1-3	4/271	(14.76)	10.12	(3.30, 31.03)	<0.001
0	13/8553	(1.52)		1	
Umbilical arterial catheter					
≥7	16/1555	(10.29)	3.58	(1.96, 6.52)	<0.001
4-6	9/1243	(7.24)	2.52	(1.20, 5.28)	0.014
1-3	7/1060	(6.60)	2.28	(1.00, 5.16)	0.049
0	32/10,641	(3.01)		1	

Umbilical venous catheter					
≥7	15/1828	(8.21)	3.32	(1.77, 6.24)	<0.001
4-6	11/708	(15.54)	6.24	(3.09, 12.57)	<0.001
1-3	11/1554	(7.08)	2.82	(1.40, 5.69)	0.004
0	27/10,409	(2.59)		1	

Table 5.27 Poisson regression models for the effect of procedure-related factors on non-CONS BSI, for NICU 3

Potential risk factors	Non-CONS BSI episodes/baby-days (Rate per 1000 baby-days)		Crude rate ratios (95% CI) *p*-value		
No of blood samples taken					
≥7	8/2947	(2.71)	8.40	(2.23, 31.67)	0.002
4-6	1/2750	(0.36)	1.10	(0.11, 10.61)	0.932
0-3	3/8802	(0.34)		1	
Number of days spent in:					
Special care					
≥7	6/11,866	(0.51)	0.15	(0.05, 0.47)	0.001
4-6	0/451	(0.00)		-	
1-3	0/437	(0.00)		-	
0	6/1745	(3.44)		1	
High dependency care					
≥7	4/2727	(1.47)	1.81	(0.53, 6.18)	0.344
4-6	1/1533	(0.65)	0.80	(0.10, 6.49)	0.833
1-3	0/1914	(0.00)		-	
0	7/8325	(0.84)		1	
Intensive care					
≥7	10/6173	(1.62)		-	
4-6	1/953	(1.05)		-	
1-3	1/1955	(0.51)		-	
0	0/5418	(0.00)		-	
Number of days treated with:					
Ventilation					
≥7	9/3594	(2.50)	20.45	(2.59, 161.41)	0.004
4-6	0/705	(0.00)		-	
1-3	2/2509	(0.80)	6.38	(5.78, 70.34)	0.130
0	1/7691	(0.13)		1	
Total parenteral nutrition					
≥7	12/5512	(2.18)		-	
4-6	0/441	(0.00)		-	
1-3	0/130	(0.00)		-	
0	0/8416	(0.00)		-	
Nasal continuous positive airway pressure					
≥7	8/5126	(1.56)	3.61	(0.96, 13.62)	0.058
4-6	0/743	(0.00)		-	
1-3	1/2089	(0.48)	1.06	(0.11, 10.21)	0.958
0	3/6541	(0.46)		1	
Long line					
≥7	12/5230	(2.29)		-	
4-6	0/445	(0.00)		-	
1-3	0/271	(0.00)		-	
0	0/8553	(0.00)		-	
Umbilical arterial					

catheter					
≥7	6/1555	(3.86)	8.59	(2.62, 28.14)	<0.001
4-6	1/1243	(0.80)	1.79	(0.21, 15.35)	0.594
1-3	0/1060	(0.00)		-	
0	5/10,641	(0.47)		1	
Umbilical venous catheter					
≥7	4/1828	(2.19)	4.78	(1.28, 17.80)	0.020
4-6	2/708	(2.82)	6.12	(1.19, 31.56)	0.030
1-3	1/1554	(0.64)	1.39	(0.16, 11.87)	0.765
0	5/10,409	(0.48)		1	

Appendix to Chapter 7

Table 7.5 Case control study, control selection strategy 2. Results for NICU 1 and NICU 2 combined

Potential risk factor	Number of cases	Number of controls	Crude odds ratios (95% CI) *p*-value			Adjusted odds ratios (95% CI) *p*-value		
Highest level of care[c]								
Intensive care	138	155	5.63	(3.71, 8.54)	<0.001	3.15	(1.88, 5.30)	<0.001
High dependency care	47	41	7.59	(4.26, 13.49)	<0.001	7.84	(4.23, 14.52)	<0.001
Special care	36	266		1			1	
Other[d]	15	10						
Gestational age (weeks)								
<26	72	54	3.53	(2.05, 6.07)	<0.001			
26-<28	35	43	2.00	(1.09, 3.69)	0.026			
28-<32	53	127	1.01	(0.61, 1.68)	0.957			
32-<37	30	144	0.46	(0.27, 0.79)	0.005			
≥37	46	104		1				
Missing[e]	0	0						
Birth weight (g)								
<700g	62	33	6.68	(3.98, 11.23)	<0.001	4.42	(2.25, 8.66)	<0.001
700g-<1200g	78	121	2.41	(1.61, 3.60)	<0.001	1.61	(0.96, 2.70)	0.071
≥1200g	96	318		1			1	
Missing[e]	0	0						
Inborn status								
No	80	86	2.43	(1.67, 3.52)	<0.001	1.67	(1.04, 2.68)	0.033
Yes	154	384		1			1	
Missing[e]	2	2						
Hospital								
NICU 2	129	263	0.96	(0.70, 1.31)	0.791			
NICU 1	107	209		1				
Sex								
Male	130	239	1.20	(0.87, 1.64)	0.262			

Female	106	233		1	
Delivery method					
Emergency CS[f]	92	184	0.94	(0.67, 1.33)	0.736
Elective CS[f]	33	76	0.82	(0.52, 1.31)	0.410
Vaginal	110	210		1	
Missing[e]	1	2			
Number of blood samples taken[c]					
≥2	2	3	1.24	(0.20, 7.50)	0.816
1	27	63	0.83	(0.50, 1.38)	0.468
0	207	406		1	
Surgery[c]					
Yes	5	7	1.43	(0.45, 4.50)	0.542
No	231	465		1	

Table 7.6 Case control study, control selection strategy 2. Results for NICU 1[h]

Potential risk factor	Number of cases	Number of controls	Crude odds ratios (95% CI) *p*-value			Adjusted odds ratios (95% CI) *p*-value		
Highest level of care[c]								
Intensive care	60	75	4.84	(2.54, 9.23)	<0.001	4.69	(2.26, 9.72)	<0.001
High dependency care	28	27	5.99	(2.81, 12.75)	<0.001	6.80	(2.99, 15.48)	<0.001
Special care	16	108	1			1		
Other[d]	3	4						
Gestational age (weeks)								
<26	33	33	2.24	(0.95, 5.26)	0.064			
26-<28	17	28	1.44	(0.58, 3.56)	0.434			
28-<32	28	59	0.96	(0.42, 2.20)	0.926			
32-<37	10	57	0.33	(0.13, 0.82)	0.018			
≥37	19	37		1				
Missing[e]	0	0						
Birth weight (g)								
≤ 700g	24	20	4.28	(1.99, 9.23)	<0.001			
700g-<1200g	42	75	1.93	(1.07, 3.48)	0.028			
≥1200g	41	119		1				
Missing[e]	0	0						
Inborn status								
No	50	56	2.69	(1.58, 4.56)	<0.001	1.56	(0.83, 2.93)	0.167
Yes	55	157		1		1		
Missing[e]	2	1						
Sex								
Male	58	114	1.04	(0.66, 1.63)	0.877			
Female	49	100		1				
Delivery method								
Emergency CS[f]	46	92	0.99	(0.61, 1.62)	0.970			
Elective CS[f]	8	19	0.84	(0.35, 1.98)	0.688			
Vaginal	52	103		1				
Missing[e]	1	0						

Number of blood samples taken[c]					
≥2	1	1	1.83	(0.11, 31.04)	0.677
1	13	29	0.88	(0.40, 1.97)	0.763
0	93	184		1	
Surgery[c]					
Yes	2	4	1	(0.18, 5.46)	1.00
No	105	210		1	

Table 7.7 Case control study, control selection strategy 2. Results for NICU 2

Potential risk factor	Number of cases	Number of controls	Crude odds ratios (95% CI) *p*-value			Adjusted odds ratios incorporating level of care (95% CI) p-value AIC= 172.12			Adjusted odds ratios incorporating total parenteral nutrition (95% CI) p-value AIC= 201.57		
Highest level of care[c]											
Intensive care	78	79	7.08	(3.84, 13.06)	<0.001	2.67	(1.28, 5.59)	0.009			
High dependency care	19	18	9.24	(3.73, 22.91)	<0.001	9.30	(3.54, 24.46)	<0.001			
Special care	20	152		1			1				
Other[d]	12	9									
Gestational age (weeks)											
<26	39	20	7.77	(3.36, 18.00)	<0.001				1.86	(0.69, 5.05)	0.221
26-<28	18	11	7.09	(2.56, 19.64)	<0.001				2.39	(0.78, 7.30)	0.128
28-<32	25	54	1.74	(0.83, 3.64)	0.141				0.66	(0.27, 1.60)	0.363
32-<37	20	100	0.58	(0.29, 1.17)	0.130				0.42	(0.20, 0.91)	0.028
≥37	27	73		1						1	
Missing[e]	0	0									
Birth weight (g)											
≤ 700g	38	15	10.79	(4.96, 23.51)	<0.001	8.26	(3.13, 21.82)	<0.001			
700g-<1200g	36	36	4.31	(2.26, 8.20)	<0.001	3.99	(1.77, 9.00)	0.001			
≥1200g	55	207		1			1				
Missing[e]	0	0									
Inborn status											
No	30	37	1.92	(1.09, 3.39)	0.025						
Yes	99	221		1							
Missing[e]	0	0									
Sex											
Male	72	140	1.06	(0.70, 1.60)	0.779						
Female	57	118		1							
Delivery method											
Emergency CS[f]	46	89	0.98	(0.60, 1.58)	0.919						
Elective CS[f]	25	60	0.79	(0.45, 1.36)	0.387						

Vaginal	58	108		1				
Missing[e]	0	1						
Number of blood samples taken[c]								
≥2	1	2	0.62	(0.05, 7.45)	0.708			
1	14	45	0.50	(0.24, 1.05)	0.067			
0	114	211		1				
Surgery[c]								
Yes	3	7	0.86	(0.22, 3.31)	0.823			
No	126	251		1				
Total parenteral nutrition[c]								
Yes	72	35	10.05	(5.29, 19.11)	<0.001	7.42	(3.45, 15.97)	<0.001
No	57	223		1			1	
Ventilation[c]								
Yes	75	68	3.59	(2.29, 5.64)	<0.001			
No	54	190		1				

Table 7.8 Case control study, control selection strategy 3. Results for NICU 1 and NICU 2 combined

Potential risk factor	Number of cases	Number of controls	Crude odds ratios (95% CI) *p*-value			Adjusted odds ratios (95% CI) *p*-value		
Highest level of care[c]								
Intensive care	138	168	5.73	(3.60, 9.13)	<0.001	3.29	(1.87, 5.78)	<0.001
High dependency care	47	58	5.10	(2.96, 8.78)	<0.001	4.89	(2.81, 8.49)	<0.001
Special care	36	225		1			1	
Other[d]	15	21						
Gestational age (weeks)								
<26	72	56	3.32	(1.95, 5.65)	<0.001	2.26	(1.07, 4.78)	0.032
26-<28	35	56	1.63	(0.90, 2.94)	0.106	1.39	(0.65, 2.99)	0.397
28-<32	53	126	0.99	(0.61, 1.63)	0.981	0.98	(0.54, 1.80)	0.958
32-<37	30	130	0.52	(0.30, 0.88)	0.016	0.75	(0.41, 1.39)	0.363
≥37	46	103		1			1	
Missing[e]	0	1						
Birth weight (g)								
≤ 700g	62	52	3.95	(2.50, 6.25)	<0.001			
700g-<1200g	78	129	2.17	(1.45, 3.25)	<0.001			
≥1200g	96	290		1				
Missing[e]	0	1						
Inborn status								
No	80	95	2.04	(1.43, 2.92)	<0.001	1.36	(0.87, 2.10)	0.173
Yes	154	374		1			1	
Missing[e]	2	3						
Hospital								
NICU 2	129	243	1.16	(0.83, 1.62)	0.393			
NICU 1	107	229		1				
Sex								
Male	130	256	1.03	(0.76, 1.41)	0.832			
Female	106	216		1				
Delivery method								
Emergency CS[f]	92	185	0.97	(0.69, 1.37)	0.860			

Elective CS[f]	33	74	0.87	(0.55, 1.37)	0.542
Vaginal	110	212		1	
Missing[e]	1	1			
Number of blood samples taken[c]					
≥2	2	5	0.63	(0.11, 3.67)	0.610
1	27	75	0.62	(0.36, 1.05)	0.074
0	207	392		1	
Surgery[c]					
Yes	5	12	0.82	(0.28, 2.41)	0.724
No	231	460		1	

Table 7.9 Case control study, control selection strategy 3. Results for NICU 1

Potential risk factor	Number of cases	Number of controls	Crude odds ratios (95% CI) *p*-value			Adjusted odds ratios (95% CI) *p*-value		
Highest level of care[c]								
Intensive care	60	65	5.34	(2.88, 9.91)	<0.001	4.83	(2.45, 9.54)	<0.001
High dependency care	28	36	5.10	(2.42, 10.73)	<0.001	5.37	(2.40, 11.97)	<0.001
Special care	16	109		1			1	
Other[d]	3	4						
Gestational age (weeks)								
<26	33	28	4.11	(0.84, 9.22)	0.001			
26-<28	17	28	2.02	(0.85, 4.82)	0.112			
28-<32	28	57	1.57	(0.74, 3.33)	0.235			
32-<37	10	47	0.57	(0.23, 1.42)	0.227			
≥37	19	54		1				
Missing[e]	0	0						
Birth weight (g)								
≤700g	24	19	4.88	(2.22, 10.70)	<0.001			
700g-<1200g	42	66	2.19	(1.25, 3.85)	0.006			
≥1200g	41	129		1				
Missing[e]	0	0						
Inborn status								
No	50	50	2.93	(1.75, 4.92)	<0.001	1.94	(1.08, 3.49)	0.026
Yes	55	161		1			1	
Missing[e]	2	3						
Sex								
Male	58	117	0.98	(0.62, 1.56)	0.937			
Female	49	97		1				
Delivery method								
Emergency CS[f]	46	79	1.23	(0.75, 2.00)	0.409			
Elective CS[f]	8	24	0.69	(0.28, 1.68)	0.414			
Vaginal	52	110		1				
Missing[e]	1	1						

Number of blood samples taken[c]					
≥2	1	2	1.04	(0.09, 11.49)	0.976
1	13	22	1.23	(0.57, 2.67)	0.593
0	93	190		1	
Surgery[c]					
Yes	2	3	1.33	(0.22, 7.98)	0.753
No	105	211		1	

Table 7.10 Case control study, control selection strategy 3. Results for NICU 2

Potential risk factor	Number of cases	Number of controls	Crude odds ratios (95% CI) *p*-value			Adjusted odds ratios incorporating level of care (95% CI) *p*-value AIC= 192.13			Adjusted odds ratios incorporating total parenteral nutrition (95% CI) *p*-value AIC= 226.57		
Highest level of care[c]											
Intensive care	78	92	4.63	(2.70, 17.94)	<0.001	1.81	(0.90, 3.64)	0.095			
High dependency care	19	16	6.83	(2.92, 15.96)	<0.001	8.81	(3.56, 21.81)	<0.001			
Special care	20	134		1			1				
Other[d]	12	16									
Gestational age (weeks)											
<26	39	25	4.68	(2.17, 10.10)	<0.001				1.99	(0.84, 4.71)	0.116
26-<28	18	17	2.63	(1.12, 6.20)	0.027				1.08	(0.41, 2.86)	0.873
28-<32	25	57	1.16	(0.57, 2.34)	0.679				0.69	(0.32, 1.52)	0.361
32-<37	20	93	0.49	(0.24, 1.00)	0.052				0.39	(0.18, 0.83)	0.015
≥37	27	66		1						1	
Missing[e]	0	0									
Birth weight (g)											
≤ 700g	38	25	5.31	(2.86, 9.86)	<0.001	5.71	(2.30, 14.16)	<0.001			
700g-<1200g	36	45	2.85	(1.64, 4.97)	<0.001	3.37	(1.61, 7.06)	0.001			
≥1200g	55	188		1			1				
Missing[e]	0	0									
Inborn status											
No	30	36	1.89	(1.09, 3.28)	0.023						
Yes	99	222		1							
Missing[e]	0	0									
Sex											
Male	72	150	0.91	(0.60, 1.39)	0.667						
Female	57	108		1							
Delivery method											
Emergency CS[f]	46	91	0.95	(0.58, 1.54)	0.823						
Elective CS[f]	25	56	0.85	(0.48, 1.49)	0.570						

Vaginal	58	110		1				
Missing[e]	0	1						
Number of blood samples taken[c]								
≥2	1	5	0.31	(0.03, 2.69)	0.286			
1	14	48	0.45	(0.22, 0.91)	0.027			
0	114	205		1				
Surgery[c]								
Yes	3	9	0.64	(0.17, 2.50)	0.525			
No	126	249		1				
Total parenteral nutrition[c]								
Yes	72	51	5.19	(3.12, 8.63)	<0.001	4.08	(2.26, 7.36)	<0.001
No	57	207		1			1	
Ventilation[c]								
Yes	75	80	2.74	(1.80, 4.16)	<0.001			
No	54	178		1				

c - In the three days prior to the censoring age
d - 'Other' indicates that for the three days prior to the censoring age, the baby was outside the NICU. For example at another hospital or undergoing surgery.
e - Babies with missing variables were few and represented few episodes of BSI. For this reason I considered it acceptable to remove them from the analyses.
f - CS- Caesarean section
g - For cases with higher ages (in days) at BSI, the number of controls available for selection became scarce. For control selection strategy 1 at NICU 1, two cases with ages at BSI of 111 and 132 days had to share controls with other cases.
h - For control selection strategy 2 at NICU 1, one case with age at BSI of 132 days had to share controls with another case.

Appendix to Chapter 8

Table 8.2 Stratified BSI episodes and baby-days (BSI rate per 1000 baby-days) for 2001 [b, c]

NICU 1 Birth weight	<700g		700g-<1200g		≥1200g	
	Inborn	Outborn	Inborn	Outborn	Inborn	Outborn
Level of care						
Special care	0/77 (0)	1/60 (16.67)	1/560 (1.79)	0/235 (0)	1/1074 (0.93)	0/113 (0)
High dependency care	1/33 (30.30)	0/25 (0)	0/34 (0)	1/26 (38.46)	0/175 (0)	0/8 (0)
Intensive care	1/113 (8.85)	8/414 (19.32)	1/307 (3.26)	3/397 (7.56)	1/126 (7.94)	1/20 (50.00)

NICU 2 Birth weight	<700g		700g-<1200g		≥1200g	
	Inborn	Outborn	Inborn	Outborn	Inborn	Outborn
Level of care						
Special care	0/108 (0)	0/42 (0)	1/287 (3.48)	1/98 (10.20)	6/1346 (4.46)	0/217 (0)
High dependency care	0/1 (0)	0/9 (0)	0/37 (0)	0/15 (0)	2/123 (16.26)	0/13 (0)
Intensive care	7/699 (10.01)	2/94 (21.28)	3/395 (7.59)	1/324 (3.09)	3/224 (13.39)	0/18 (0)

Table 8.3 Stratified BSI episodes and baby-days (BSI rate per 1000 baby-days) for 2002 [b, c]

NICU 1 Birth weight	<700g		700g-<1200g		≥1200g	
	Inborn	Outborn	Inborn	Outborn	Inborn	Outborn
Level of care						
Special care	0/165 (0)	0/101 (0)	0/613 (0)	1/268 (3.73)	5/1845 (2.71)	0/349 (0)
High dependency care	2/42 (47.62)	0/9 (0)	1/78 (12.82)	5/170 (29.41)	8/361 (22.16)	5/85 (58.82)
Intensive care	8/356 (22.47)	3/145 (20.69)	5/342 (14.62)	10/877 (11.40)	3/237 (12.66)	0/61 (0)

NICU 2 Birth weight	<700g		700g-<1200g		≥1200g	
	Inborn	Outborn	Inborn	Outborn	Inborn	Outborn
Level of care						
Special care	0/151 (0)	0/7 (0)	1/371 (2.70)	1/184 (5.43)	11/2987 (3.68)	0/150 (0)
High dependency care	1/28 (35.71)	0/0 (0)	0/77 (0)	1/20 (50.00)	3/215 (13.95)	1/54 (18.52)
Intensive care	8/537 (14.90)	8/655 (12.21)	8/843 (9.49)	10/478 (20.92)	2/363 (5.51)	1/53 (18.87)

Table 8.4 Stratified BSI episodes and baby-days (BSI rate per 1000 baby-days) for 2003 [b]

NICU 1 Birth weight	<700g		700g-<1200g		≥1200g	
	Inborn	Outborn	Inborn	Outborn	Inborn	Outborn
Level of care						
Special care	0/230 (0)	0/12 (0)	2/736 (2.72)	0/113 (0)	5/2333 (2.14)	1/129 (7.75)
High dependency care	0/47 (0)	0/10 (0)	3/219 (13.70)	1/177 (5.65)	3/486 (6.17)	2/235 (8.51)
Intensive care	2/162 (12.35)	2/193 (10.36)	5/433 (11.55)	9/689 (13.06)	1/289 (3.46)	3/139 (21.58)

NICU 2 Birth weight	<700g		700g-<1200g		≥1200g	
	Inborn	Outborn	Inborn	Outborn	Inborn	Outborn
Level of care						
Special care	0/27 (0)	0/0 (0)	0/797 (0)	0/187 (0)	4/2959 (1.35)	0/187 (0)
High dependency care	0/0 (0)	0/0 (0)	0/46 (0)	0/1 (0)	2/119 (16.81)	1/19 (52.63)
Intensive care	12/737 (16.28)	5/424 (11.79)	12/1221 (9.83)	1/83 (12.05)	5/615 (8.13)	1/34 (29.41)

Table 8.5 Stratified BSI episodes and baby-days (BSI rate per 1000 baby-days) for 2004 [b]

NICU 1 Birth weight	<700g		700g-<1200g		≥1200g	
	Inborn	Outborn	Inborn	Outborn	Inborn	Outborn
Level of care						
Special care	0/0 (0)	0/17 (0)	1/1156 (0.87)	0/92 (0)	2/1867 (1.07)	1/156 (6.41)
High dependency care	0/0 (0)	3/127 (23.62)	1/158 (6.33)	0/15 (0)	3/424 (7.08)	0/35 (0)
Intensive care	1/94 (10.64)	9/655 (13.74)	9/789 (11.41)	0/376 (0)	4/381 (10.50)	0/92 (0)

NICU 2 Birth weight	<700g		700g-<1200g		≥1200g	
	Inborn	Outborn	Inborn	Outborn	Inborn	Outborn
Level of care						
Special care	0/54 (0)	0/114 (0)	0/437 (0)	0/160 (0)	9/2986 (3.01)	1/241 (4.15)
High dependency care	0/5 (0)	0/0 (0)	1/48 (20.83)	0/6 (0)	4/365 (10.96)	0/7 (0)
Intensive care	12/793 (15.13)	6/431 (13.92)	7/1135 (6.17)	2/306 (6.54)	4/552 (7.25)	0/32 (0)

Table 8.6 Stratified BSI episodes and baby-days (BSI rate per 1000 baby-days) for 2005 [b, c]

NICU 1 Birth weight	<700g		700g-<1200g		≥1200g	
	Inborn	Outborn	Inborn	Outborn	Inborn	Outborn
Level of care						
Special care	0/0 (0)	0/0 (0)	0/56 (0)	0/0 (0)	0/205 (0)	0/0 (0)
High dependency care	0/0 (0)	0/0 (0)	0/0 (0)	0/0 (0)	0/42 (0)	0/0 (0)
Intensive care	0/0 (0)	1/80 (12.5)	0/10 (0)	0/9 (0)	0/5 (0)	0/0 (0)

NICU 2 Birth weight	<700g		700g-<1200g		≥1200g	
	Inborn	Outborn	Inborn	Outborn	Inborn	Outborn
Level of care						
Special care	0/57 (0)	0/0 (0)	0/52 (0)	0/0 (0)	0/386 (0)	0/69 (0)
High dependency care	0/0 (0)	0/0 (0)	0/3 (0)	0/0 (0)	0/2 (0)	0/0 (0)
Intensive care	0/42 (0)	0/0 (0)	0/69 (0)	0/27 (0)	0/54 (0)	1/31 (32.26)

b - Figures are not shown stratified for postnatal age, due to small numbers in some strata

c - As the study period ran from May 2001 to February 2005 inclusive, 2001 and 2005 do not contain the full twelve months of data

Appendix to Chapter 9

HAI surveillance criteria recommended by the ARHAI Surveillance Subgroup

Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI) Surveillance Subgroup (2010) Report on HCAI Surveillance Priorities – Recommendations for HCAI surveillance in England. Permission to reproduce this information was confirmed by the ARHAI in January 2011. http://www.dh.gov.uk/ab/ARHAI/index.htm. Accessed July 2010

Criteria	Factors to be considered
1. Clearly defined and agreed with outcome-related objectives	
• Involve infections where the outcome results in significant mortality and/or morbidity • The costs of the surveillance are justified by its potential impact • Involve conditions associated with a significant economic burden to the health service, to patients or to society • Link to relevant aspects of antimicrobial resistance • Provide performance measures for intra-organisational, national and, where relevant, international, extra-organisational comparisons • Resources are allocated to produce the optimal balance between local and others' needs • Surveillance data informs regular audit cycles • Link with systems that ensure effective implementation of changes to practice that emerge from the surveillance/audit processes • Incorporate arrangements that allow assessment of organisational outcomes	
2. Accurate and timely data with reproducibility consistent with defined objectives	
• Data collection methodology provides accurate data • Takes account of lengths of patient stay • Takes account of variations over time • The methodology ensures appropriate sensitivity for the condition being surveyed • Effective validation systems are in place • Adequate post-discharge follow-up	

3. Data collection utilises informatics systems effectively
• Utilise routine patient management systems • Incorporate efficient, reliable and accurate IT systems (e.g. internet, intranet, personal digital assistants, scanned forms)
4. Programme integrated with other data management systems
• ’Piggy-backs’ onto existing data collection systems • Avoids duplication in relation to data collection • Utilises existing surveillance initiatives, e.g. National Vascular Database, ICNARC
5. Data informs local services, commissioners, relevant government departments, Royal Colleges, professional organisations, general public and the media
• Processes are in place to make results available early in formats that are informative and comprehensible to the target audience • The information is utilised for related professional issues e.g. consultant appraisal, revalidation • Processes exist to provide epidemiology and statistics training for relevant groups

Publications Appendix

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REVIEW

Risk-adjusted surveillance of hospital-acquired infections in neonatal intensive care units: a systematic review

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Bacteraemia;
Systematic review

Summary Comparisons of bacteraemia incidence between neonatal intensive care units (NICUs) can identify centres with effective infection control, whose practices can be shared with other units. For fair comparisons, infection incidence must be risk-adjusted to control for differences between centres in the vulnerability of babies and the intensity of invasive procedures which can introduce infection. We reviewed risk adjustment methods for between-NICU comparisons of bacteraemia incidence, both in the published literature and in regional and national NICU infection monitoring systems. PubMed and Embase were searched for studies reporting risk-adjusted bacteraemia incidence in more than one NICU. An internet search found NICU infection monitoring systems in Western industrialised countries. In all nine studies that met the inclusion criteria, risk adjustment reduced but did not eliminate variation in bacteraemia incidence between NICUs. In both the studies and the regional monitoring systems, adjustment for baby susceptibility generally involved stratification by factors measured at birth. Adjustment for length of stay and invasive procedures involved reporting incidence by days with a device, such as central venous catheter days. Methods for NICU infection monitoring lack consistency. Adjustment for factors measured at birth fails to capture changes in susceptibility throughout admission and adjustment for device days

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does not adequately reflect risk to babies not treated with the device. Further research should address variation in risk for all babies throughout their NICU stay.

Introduction

Between 2% and 10% of babies admitted to neonatal intensive care units (NICUs) experience at least one episode of bacteraemia, which can lead to death and other serious adverse outcomes.[1–3] The majority of bacteraemia episodes are hospital-acquired, and often preventable through improvements in hygiene practices and infection control.[4–6]

Suggestions that bacteraemia monitoring itself might decrease infection rates[7] are supported by evidence from a systematic review of >100 randomised controlled trials showing that audit and feedback alone produce small to moderate improvements in clinical practice.[8,9] When comparative monitoring has been used to trigger sharing of improved practices between units, substantial reductions in infection incidence appear to have been achieved.[10–12]

Comparisons are complicated by the fact that some of the variation observed between NICUs is attributable to factors other than quality of care, such as case mix, babies' length of stay and the invasive medical procedures carried out, all of which can influence hospital-acquired infection.[13] To make fair and meaningful comparisons between hospitals, a multicentre monitoring system must adjust for these factors. Any residual variation may be explained, at least in part, by factors amenable to change, such as hygiene practices. To formulate a method for risk adjustment, factors must be identified which are both associated with infection and reliably recorded. These factors can then be used to stratify infection incidence, or can be included in a statistical risk adjustment model.

We performed a systematic review to determine methods used for risk adjustment in studies that compared infection incidence between NICUs, and to determine how much infection incidence varied before and after risk adjustment. We also determined the extent to which these approaches for risk adjustment are being used by regional surveillance systems for NICU-acquired infection around the world. We discuss different approaches for risk adjustment and suggest ways to improve robustness of comparisons and consistency of reporting.

Methods

Systematic review of studies reporting risk adjustment

Studies were included if they reported any measure of the frequency of bacteraemia at more than one NICU and comparative results that were risk-adjusted. We accepted any approach for risk adjustment, including stratification for risk factors, for example reporting infections as rates per catheter days, as well as the inclusion of risk factors in a statistical risk adjustment model. We accepted any definition for hospital-acquired bacteraemia, but excluded studies concentrating on delivery-associated bacteraemia in the first few days of life.

We combined three sets of search synonyms relating to NICU, bacteraemia, and monitoring or risk adjustment to search PubMed and Embase databases (with Embase thesaurus mapping) in any language until October 2007 (search strategy available from the authors). One person (P.P.) reviewed all titles and abstracts for potentially eligible articles. Studies meeting the inclusion criteria were reviewed by two reviewers (P.P. and R.G.). We also searched reference lists and 'related articles' of all included studies (using PubMed). Abstracts from relevant conferences were reviewed from 2005 to 2007.

Review of regional monitoring systems

As both infections and organisational structures vary greatly among NICUs in developing countries, we included only monitoring systems from Europe, North America and Australasia to ensure generalisability. The search was performed in Google using short phrases and the region of interest.

Results

Systematic review of studies reporting risk adjustment

Quality of literature

Nine studies met our inclusion criteria (Figure 1) (Table I).[1,14–21] Case definitions for bacteraemia

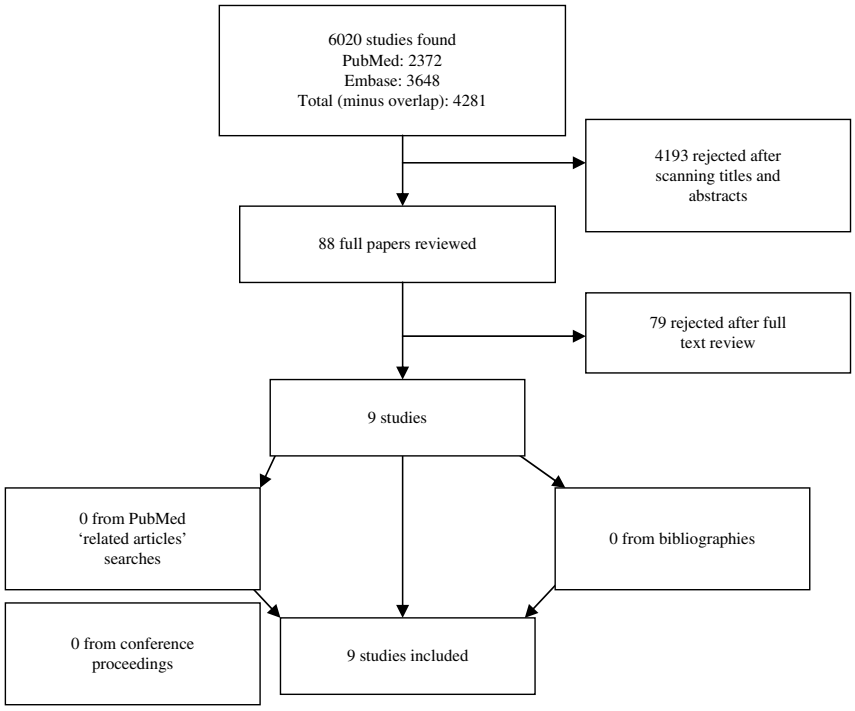

Figure 1 Flow diagram of the process and results of the systematic literature review.

varied in complexity from a first positive blood culture,[1,21] to hospital-acquired bacteraemia defined by US Centers for Disease Control and Prevention (CDC) criteria.[17,18,20,22] Two studies excluded bacteraemia acquired before NICU admission by including only diagnostic blood cultures taken at least 48 h after admission.[14,16] CDC criteria state that 'there must be no evidence that the infection was present or incubating at the time of hospital admission', but give no time threshold.[22] All but two studies distinguished hospital-acquired from delivery-associated bacteraemia, using thresholds ranging from 48 to 72 h after birth.[18,20]

Risk adjustment

Table I shows that most studies took into account the duration of exposure, by reporting incidence per baby days of stay or per central venous catheter (CVC) days, sometimes with Cox regression or Kaplan–Meier analyses of time to infection.[16,17] Four studies did not take into account length of stay, and reported only one or more infections per baby.[1,14,19,21]

Adjustment for baby susceptibility and organisational factors was performed by stratifying bacteraemia incidence by birthweight, or by including baby susceptibility factors in a risk adjustment model.[14,18,20] Adjustment for medical procedures was performed by reporting bacteraemia per days with a CVC. Other studies included medical procedures in a risk adjustment model: some factors were included as binary variables (e.g. CVC: yes/no), some as durations censored at the onset of bacteraemia or removal of the CVC or ventilator, and others as time-dependent variables updated continuously during a baby's stay.[16,17]

Two studies addressed the possibility that differences in blood sampling frequency between hospitals could influence comparisons, as the more samples taken the greater the risk of detecting asymptomatic bacteraemia or a contaminated

Table I Studies comparing risk-adjusted bacteraemia incidence between NICUs

Authors and setting (study period)	Population	Outcome measure	Outcome measures adjusted for:		
			Baby susceptibility factors	Procedure-related factors	Organisational factors
Canadian Neonatal Network, 2002, 2005 17 Canadian NICUs (1996–1997)	(1) 19 507 babies[15]	(1) Incidence per CVC days	(1) Gestational age, outborn status, SNAP II	(1) Duration of CVC (by CVC type)	(1) No
	(2) 16 497 babies[14]	(2) Proportion of babies with ≥1 bacteraemia	(2) Birthweight, gestational age, outborn status, SNAP II	(2) No	(2) No
Brodie *et al.*, 2000[16] 6 US NICUs (1994–1996, 1996–1997)	1354 babies birthweight <1500 g	Time to first bacteraemia after admission	Birthweight, SGA	Duration of Broviac catheter parenteral nutrition (time-dependent variables)	No
Carrieri *et al.*, 2003[17] 21 Italian NICUs (1996–1997)	2160 babies with birthweight ≤1750 g	(1) Time to first bacteraemia after admission	(1) 3–10 day model: birthweight, sex, Apgar score, respiratory distress syndrome, patent ductus arteriosus, intraventricular haemorrhage	(1) 3–10 days: CVC ventilation (yes/no variables)	(1) No
	Babies with 15 defined 'minor' conditions excluded	(2) Time to first bacteraemia after admission	(2) 10–35 day model: birthweight, maximum base excess, NEC	(2) 10–35 days: Duration of CVC ventilation (censored at onset of bacteraemia)	(2) No
Gaynes *et al.*, 1991[18] 35 US NICUs (1986–1990)	24 480 babies	Incidence per CVC days	Birthweight	Duration of CVC	No
National Institute of Child Health and Human Development Neonatal Research Network[19] (NICHD), 2002 15 US NICUs (1998–2000)	6215 babies with birthweight 401–1500 g	Proportion of babies ≥1 bacteraemia	Birthweight, gestational age, sex, ethnicity	No	No
Stover *et al.*, 2001[20] 41 US NICUS (1997)	No number given	Incidence per CVC days	Birthweight	Duration of CVC	No
UK Neonatal Staffing Study Group, 2002, 2005 54 UK NICUs (1998–1999)	13 334 babies <1 month old corrected for gestation	(1) Proportion of babies ≥1 bacteraemia[21]	(1) Gestational age, SGA, sex, mode of delivery, diagnostic category, antenatal steroids	(1) No	(1) Provision of handwash basins and infection control nurse

(2) Proportion of babies ≥1 bacteraemia[1]	(2) Birth model: Gestational age, SGA, sex, mode of delivery, diagnostic category, antenatal steroids	(2) No	(2) Low birthweight patient volume, provision of consultants and nurses
(3) Proportion of babies ≥1 bacteraemia[1]	(3) 12 h model: admission temperature, blood analysis: most extreme $PaCO_2$, mean appropriate FiO_2 and lowest base excess	(3) No	(3) Low birthweight patient volume, provision of consultants and nurses

SNAP II, Score for Neonatal Acute Physiology II; CVC, central venous catheter; SGA, small for gestational age; NEC, necrotising enterocolitis.

sample. The UK Neonatal Staffing Study Group (2005) found no association between the ratio of positive to all blood cultures and the incidence of bacteraemia or any of their risk adjustment variables. Brodie *et al.* measured a two-fold variation in the frequency of blood sampling among NICUs, but reported that differences in bacteraemia incidence between NICUs remained significant when results for the commonest contaminant, coagulase-negative staphylococcus, were removed from the analysis.[16]

All nine studies showed residual variation in bacteraemia incidence between NICUs after risk adjustment. Five studies reported a reduction in between-NICU variation with risk adjustment (Table II).

Regional monitoring systems

Table III shows the seven regional monitoring systems found.[23–29] Case definitions varied in complexity from a positive bacterial culture (excluding cultures for coagulase-negative staphylococcus) to CDC case definitions, while NEO-KISS (Krankenhaus Infektions Surveillance System) modified the CDC case definition for use in neonates.[24,27,29,30] Four systems exclude bacteraemia acquired before NICU admission by including only diagnostic blood cultures taken at least 48 h after admission, or rejecting infections with evidence that they were acquired elsewhere.[23,24,26,29] Two systems differentiate between delivery-associated and hospital-acquired bacteraemia, using thresholds of 48 or 72 h after birth.[26,28]

Risk adjustment

Five systems provide some adjustment for duration of exposure, by reporting incidence by catheter days, or catheter days and baby days of stay.[23–26,29]

All systems except NeonIN use some methods of risk adjustment. Being based around the original US CDC surveillance system, these are remarkably similar; adjustment for baby susceptibility factors by stratification into birthweight groups, and adjustment for medical procedure-related factors by reporting incidence by catheter days. NEO-CAT incorporates several factors in a multivariable risk adjustment model.

Although most systems do not directly adjust for differences in blood sampling frequency between NICUs, their case definitions attempt to control for differences in blood sample contamination by, for example, requiring that a positive blood culture be associated with clinical symptoms or a CVC.[25] The Vermont Oxford Network goes further in recommending 'potentially better practices' to standardise sampling technique between participating

Table II Variation in bacteraemia incidence between NICUs before and after risk adjustment

Authors	Outcome measure	Between-NICU variation reduced by risk adjustment?	How much residual variation between NICUs?
Canadian Neonatal Network, 2002, 2005	(1) Incidence per CVC days	(1) Yes	(1) Statistically significant variation for all CVC strata
	(2) Proportion of babies with ≥1 bacteraemia	(2) Yes	(2) Statistically significant variation for babies with birthweight <1500 g
Brodie *et al.*, 2000	Time to bacteraemia after admission	Yes	Statistically significant variation between 3/6 NICUs
Carrieri *et al.*, 2003	(1) Time to bacteraemia after admission	(1) Unable to determine: no crude measures provided	(1) Bacteraemia 3—10 days: statistically significant variation
	(2) Time to bacteraemia after admission	(2) Unable to determine: no crude measures provided	(2) Bacteraemia 11—35 days: statistically significant variation
Gaynes *et al.*, 1991	Incidence per CVC days	Unable to determine: no crude measures provided	'Significant between-centre differences', but no risk-adjusted figures provided
NICHD, 2002	Proportion of babies ≥1 bacteraemia	Unable to determine: no risk-adjusted figures provided	'Statistically significant variation', but no risk-adjusted figures provided
Stover *et al.*, 2001	Incidence per CVC days	Yes for babies with birthweight 1501—2500 g	Variation remained, no information concerning statistical significance
UK Neonatal Staffing Study Group, 2002, 2005	(1) Proportion of babies with ≥1 bacteraemia	(1) Yes	(1) Statistically significant variation in odds ratios between NICUs with >1 level 1 cot per handwash basin and NICUs with <1. More handwash basins led to lower outcomes Statistically significant variation in odds ratios between units with an infection control nurse and units without. Presence of an infection control nurse led to lower outcomes.
	(2) Proportion of babies ≥1 bacteraemia	(2) Birth model: Yes	(2) Statistically significant variation for NICUs allocated to different strata of consultant provision. Lower consultant availability led to lower odds ratios.
	(3) Proportion of babies ≥1 bacteraemia	(3) 12 h model: Yes	(3) Statistically significant variation for NICUs allocated to different strata of consultant provision. Lower consultant availability led to lower odds ratios.

CVC, central venous catheter; NICU, neonatal intensive care unit.

NICUs, for example by recommending a minimum blood sample of 1 mL.[11]

Most case definitions combine clinical evidence of infection with blood culture results and consequently require active reporting by clinicians. As data storage generally differs between hospitals, the methods for its collection are usually specific to the NICU. We found no evidence that any system exclusively uses electronic hospital administrative data.

Discussion

Overall, risk adjustment attenuated but did not remove differences in infection incidence between

Table III Risk adjustment in regional monitoring systems

System and setting (year established)	Population	Outcome measure	Outcome measures adjusted for:
Canadian Nosocomial Infection Surveillance Program (CNISP)[23] Canada (2006)	21 hospitals Babies with a CVC inserted	Incidence of bacteraemia per CVC days, days of NICU stay	Birthweight Duration of CVC NICU stay
National Healthcare Safety Network (NHSN), previously the National Nosocomial Infections Surveillance System (NNIS)[24] USA NNIS (1970) NHSN (2005)	140 NICUs Babies with a CVC inserted, or on a ventilator	Incidence per CVC days, days of NICU stay[a]	Birthweight Duration of CVC NICU stay
NEOCAT of CCLIN (Centre de Coordination de la Lutte contre les Infections Nosocomiales)[25] Paris and Western region, France (2006)	9 NICUs Babies with a CVC inserted for >48 h	Incidence per CVC days	Baby susceptibility factors Procedure-related factors[b] Duration of CVC
NEO-KISS (Krankenhaus Infektions Surveillance System)[26] Germany (1997)	66 NICUs Babies with birthweight <1500 g	Incidence per CVC days, peripheral VC days[c,d]	Birthweight Duration of CVC peripheral VC
Neonatal Infection Network (NeonIN) surveillance database[27] UK (2007)	12 NICUs (pending further expansion)	Frequency of bacteraemia episodes[e]	None
Vermont Oxford Network[28] USA, UK (1998)	700 hospitals Babies with birthweight 501–1500 g	Proportion of babies ≥1 bacteraemia[e]	Birthweight
VICNISS Hospital Acquired Infection Surveillance System[29] Victoria, Australia (2002)	29 hospitals	Incidence per CVC days, peripheral VC days	Birthweight Duration of CVC peripheral VC

CVC, central venous catheter; NICU, neonatal intensive care unit; VC, venous catheter.

[a] Incidence of pneumonia also reported per ventilator days and days of NICU stay, and stratified by birthweight.

[b] Risk adjustment factors summarised for brevity.

[c] Peripheral venous catheter days.

[d] Incidence of pneumonia also reported per ventilator days and continuous positive airway pressure days. Incidence of necrotising enterocolitis reported by days of NICU stay.

[e] Outcome measures also reported for bacterial infection in cerebrospinal fluid and urine.

NICUs. Residual variation could indicate residual confounding due to case mix or invasive medical procedures, differences in data quality, or differences in the quality of care. The UK Neonatal Staffing Study Group suggests that residual variation is due to differences in quality of care: measures of risk-adjusted bacteraemia showed statistically significant associations with NICU organisational factors such as the provision of neonatal consultants, hand washbasins and infection control nurses. There is general consensus that risk adjustment is necessary, feasible and effective, but there is no agreement as to the best method for carrying it out.

Our review highlights the need for more consistent outcome measures and risk adjustment methods. A Europe-wide survey of hospital infection control physicians revealed that their strongest consensus research priority is standardisation of surveillance systems for international comparison of hospital-acquired infection incidence.[31] Consistency in the choice of denominator is the minimum requirement; most studies and regional monitoring systems reported incidence by baby or catheter days, controlling for variations between NICUs in duration of exposure to infections, which is recommended in order to avoid bias in comparative studies.[32] Reporting rates also captures recurrent infections within the same baby, which is not possible if reporting consists of a proportion of babies experiencing one or more bacteraemias.

Meaningful international comparisons also require consistency in the baby susceptibility factors and medical procedures chosen for risk adjustment. Most studies and regional monitoring systems adjust for factors measured at birth, such as birthweight, but this does not adjust for changes in a baby's susceptibility throughout his or her NICU stay. Days with a CVC can provide such a continuous measure, but they exclude the 80% of NICU babies not treated with a CVC, who may have widely differing risks of infection.[15] Holmes *et al.* question the use of CVC days for risk adjustment, as their multivariable analysis found parenteral nutrition to be a stronger predictor of bacteraemia than CVC use alone.[33] Nevertheless, parenteral nutrition is used to treat a minority (24%) of babies in the NICU.[34] Further analyses could investigate the attributable risk of different medical procedures; if a procedure is responsible for the burden of bacteraemia in a unit, it may be an acceptable risk adjustment variable even if it is used to treat a minority of babies. Current estimates suggest that only ~40% of bacteraemia are CVC-related.[15] Otherwise continuous composite risk adjustment variables may be preferable; capturing multiple risk factors and all babies throughout their NICU stay. An example is days of stay at each NICU level of care, which in some countries is updated daily and allocated to all babies according to clinical status.[35]

The only regional monitoring system not performing risk adjustment is NeonIN, which aims to provide simple, rapid determination of the patterns of organisms in NICUs, with data entry by busy clinicians. NeonIN highlights dual requirements for NICU monitoring: rapid data collection and feedback and more time-consuming comparisons of risk-adjusted rates. Both approaches are necessary; the former can alert clinicians to sudden changes, the latter is essential for quality of care benchmarking. For both approaches, the use of routine electronic clinical records would minimise staff workload and accelerate the collection of data, but must be balanced against the use of case definitions that include clinical observations, which can require skilled data collection and stand-alone data systems. It is possible that, with the standardisation of improved blood sampling techniques such as those recommended by the Vermont Oxford Network, blood sample contamination could be reduced and with it the requirement for clinical symptoms to differentiate an episode of bacteraemia from a contaminated sample. More detailed data systems are being developed, such as the Standardised Electronic Neonatal Database in the UK and the Canadian NICU Network, which in the future may support common definitions based on routine electronic data.[34,36]

Risk adjustment is widely recognised as necessary for meaningful comparisons of bacteraemia rates between NICUs. However, there is a lack of consistency in the case definitions, outcome measures and risk adjustment methods used. Case definitions should be developed that allow data extraction from routine electronic data, thereby accelerating data collection and minimising staff workload. Most regional monitoring systems agree that adjustment for duration of exposure is a minimum requirement; further research should investigate the possibility of adjustment for routinely recorded, continuous, composite measures of baby susceptibility and risk from medical procedures. The development of shared, detailed routine electronic clinical record systems has the potential to facilitate all of these improvements.

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Variation in infection incidence between neonatal intensive care units can depend on the measures used

Madam,

Bloodstream infection (BSI) incidence varies between neonatal intensive care units (NICUs).[1] When comparative BSI monitoring is used to trigger sharing of improved practices between units, it can reduce infection rates substantially.[2] We compared the incidence of BSI in two Inner London tertiary NICUs, using two different measures: the proportion of babies developing one or more BSIs; and the rate of BSI per baby-days.

We analysed linked National Health Service laboratory and patient administrative data for admissions over a period of four years (admissions per year: 260 in NICU 1 and 430 in NICU 2). An episode of BSI was defined by one or more blood cultures for the same bacterial organism within seven days. Because ~30% of blood cultures positive for coagulase-negative staphylococcus (CoNS) may reflect blood sample contamination, we performed separate analyses for CoNS and non-CoNS BSI.[3] For each NICU, we calculated the percentage of babies (admissions) developing one or more BSIs, and the rate of BSI by dividing total BSI episodes by total baby-days of NICU stay. We also calculated monthly rates of BSI, median lengths of NICU stay, and percentages of BSI that were recurrent within babies. Differences between NICUs were assessed for statistical significance using two-sample *Z*-tests for proportions, Poisson generalised linear models for rates, and non-parametric *k*-sample tests for medians.

A total of 58 196 baby-days were included in the analyses. Of these, 10.9% of babies developed CoNS BSI in NICU 1 compared with 8.5% in NICU 2 ($P = 0.04$). Rates of CoNS BSI per 1000 baby-days were similar for both units: 5.3 for NICU 1 and 5.2 for NICU 2 [crude rate ratio: 1.0; 95% confidence interval (CI): 0.8–1.2]. The proportion of babies developing non-CONS BSI was similar in both units (3.4% NICU 1 vs 3.5% NICU 2; $P = 0.86$), as were rates of non-CoNS BSI per 1000 baby-days (2.2 NICU 1 vs 2.2 NICU 2; crude rate ratio: 1.0; 95% CI: 0.7–1.4). The median length of stay was significantly longer in NICU 1 (13 days versus 7 days, $P < 0.001$). Slightly more recurrent BSI occurred in NICU 1 compared with NICU 2, but these differences were not statistically significant: 20.8% of CoNS episodes were recurrences in NICU 1 versus 13.3% in NICU 2 ($P = 0.07$); non-CoNS recurrences comprised 1.7% in NICU 1 and 1.3% in NICU 2 ($P = 0.82$).

The findings highlight the importance of taking into account length of stay. Median length of stay in NICU 1 was nearly twice as long as for NICU 2, so although NICU 1 may have had a higher proportion of babies experiencing CoNS BSI, the two units had similar numbers of CoNS BSI episodes per days of stay. Differences in infection incidence must be measured and interpreted with caution. Proportions of babies experiencing one or more infections are used in many studies reporting between-NICU comparisons.[2,4,5] Rates may be preferable as they take into account differences in length of stay and capture recurrent infections. An awareness of length of NICU stay would allow clinicians to investigate BSI in more detail, in order to target infection control more effectively. An increased length of stay may increase the risk of BSI, and may be amenable to reduction. Conversely, it could be the consequence of a higher incidence of BSI, as babies with infections are kept in the NICU for longer. As a minimum, comparisons of BSI incidence between NICUs should be adjusted for differences in length of NICU stay. Figure 1 demonstrates this adjusted comparison by month.

Using appropriate measures is but one element of making fair and meaningful comparisons of infection incidence between units. Analyses should also adjust for differences in case mix and invasive

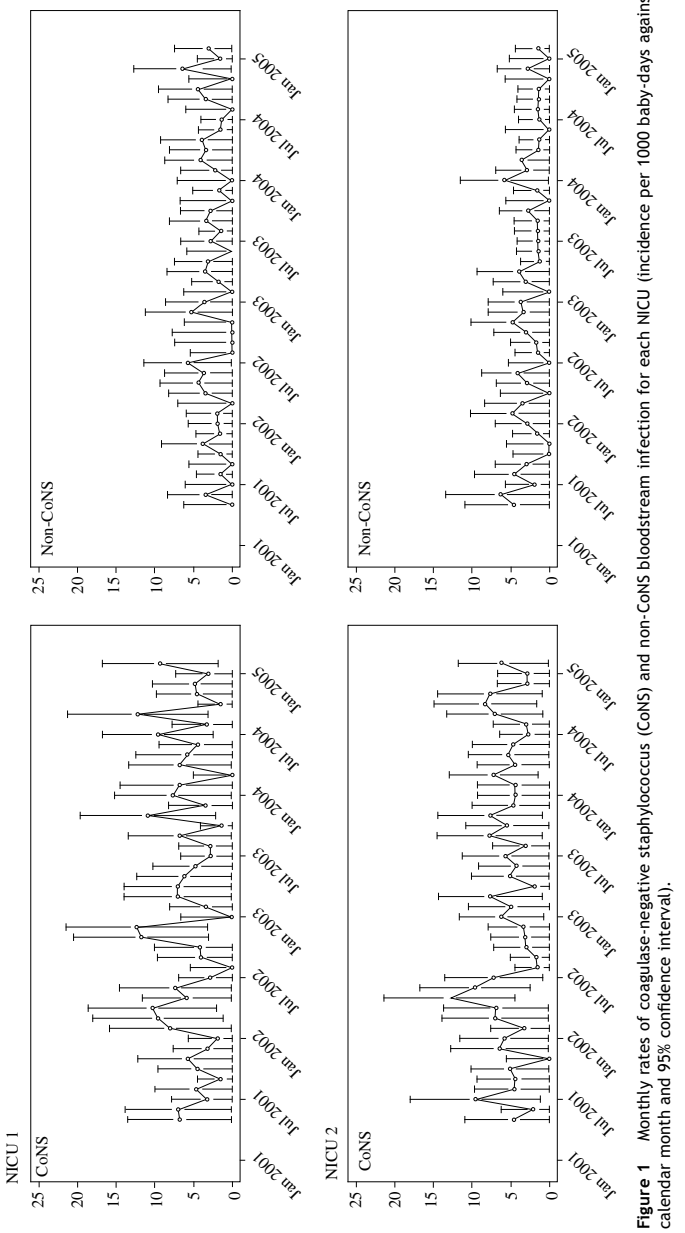

Figure 1 Monthly rates of coagulase-negative staphylococcus (CoNS) and non-CoNS bloodstream infection for each NICU (incidence per 1000 baby-days against calendar month and 95% confidence interval).

medical procedures, which can also affect BSI incidence regardless of quality of care.[1] We previously reported a method of adjusting for these confounding factors.[6] If, as in our analyses, comparisons rely on routine hospital data, the effort and cost involved in data collection is decreased. However, a disadvantage of routine data is that clinical symptoms required to differentiate between true BSI and blood sample contamination are lacking. Reporting rates by organisms, as in this analysis for CoNS and non-CoNS, offers a crude but easy way to differentiate between infections more or less likely to represent contamination. It is also important to monitor CoNS BSI, as even 'false positive' blood cultures result in the increased use of antibiotics and longer lengths of hospital stay. Further research is needed to evaluate appropriate methods of risk adjustment as the availability of reliable data expands.

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Endemic carbapenem-resistant *Acinetobacter baumannii* in a Brazilian intensive care unit

Madam,

In recent years, strains of multidrug-resistant *Acinetobacter baumannii* have emerged as important nosocomial pathogens, causing ventilator-associated pneumonia, bacteraemia, and urinary tract infection.[1,2] Several outbreaks caused by this micro-organism have been reported.[3] However, the endemic situation of this hospital pathogen has been little investigated. In the present study, we evaluated contamination in an intensive care unit (ICU) caused by endemic carbapenem-resistant *Acinetobacter baumannii* (CR-Ab) strains, using environmental and patient cultures.

This prospective study was conducted from January to July 2008, in an eight-bed adult ICU, in a 120-bed Brazilian university hospital. All

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Risk stratification by level of care for comparing bloodstream infection rates in neonatal intensive care units

Madam,

Comparisons of bloodstream infection (BSI) incidence between neonatal intensive care units (NICUs) can identify centres with potentially better practices for infection control, which can be shared with other units.[1] To provide fair comparisons, infection rates must take into account differences between centres in the vulnerability of babies and the intensity of invasive procedures that can introduce infection. Factors associated with infection must be identified, which can be used to stratify infection rates to give meaningful comparisons between hospitals and over time.[2]

To formulate a strategy for monitoring, we examined gestational age at birth and daily National Health Service (NHS) level of care, as factors which could stratify BSI rates, to compare two inner London tertiary NICUs with 260 and 430 admissions each year. Level of care has not previously been evaluated in risk-adjusted analyses; it is a standardised measure of the intensity of care, which is daily and routinely recorded for each baby throughout NHS NICUs.[3]

We used linked NHS laboratory and patient administrative data for admissions over four years, producing daily counts of positive blood cultures and babies at each level of care and gestational age band. An episode of BSI was defined as one or more blood cultures in which the same bacterial organism was isolated within a seven-day period. This method of data collation was chosen to reflect what could easily be carried out by hospital data managers for routine monitoring.

We fitted crude and adjusted Poisson generalised linear models to investigate relationships between the rate of BSI per baby-days of stay and level of care, gestational age, NICU and blood sampling frequency. We investigated blood sampling frequency as this could influence comparisons; the more samples taken the greater the risk of detecting asymptomatic BSI or a contaminated sample.

NHS level of care and gestational age were strongly associated with the rate of BSI, with level of care being the strongest predictor. The best adjusted model, in terms of minimising the Akaike information criterion, included both factors.[4] The rate of BSI was 7.4 per 1000 baby-days and did not differ between NICUs. The rate ratio for BSI, adjusted for gestational age and sampling frequency and relative to the baseline, special care, was 3.37 [95% confidence interval (CI): 2.38, 4.77] in intensive care and 4.40 (95% CI: 3.15, 6.15) in high dependency care.

Level of care is itself a measure of vulnerability, so its relationship with BSI is not surprising. The key implication of this is that stratification by level of care could provide a simple risk adjustment tool for meaningful comparisons of BSI between NICUs. This is illustrated in Figure 1, which shows monthly rates of BSI, by level of care for each NICU. Within

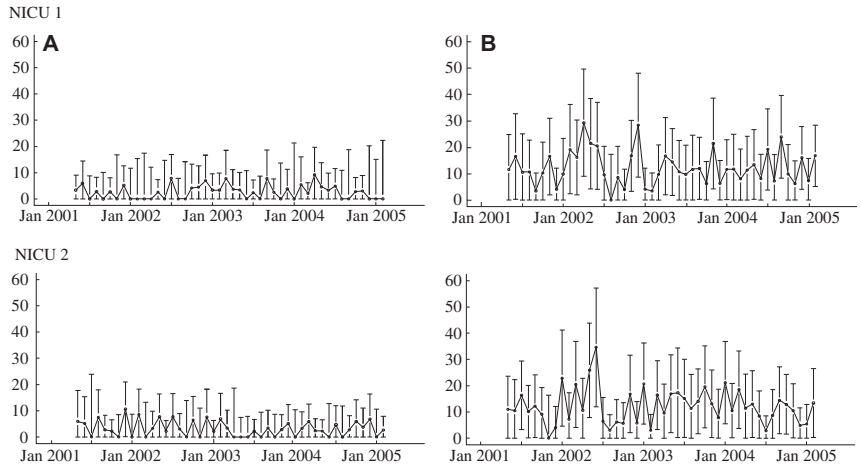

Figure 1 Monthly rates of bloodstream infection, by level of care for each neonatal intensive care unit (NICU) (incidence per 1000 baby-days against calendar month and 95% confidence interval). (a) Special care. (b) High dependency and intensive care.

levels of care different procedures may confer different risks, but this broad stratification provides a consistent approach across the NHS. Aggregation of rates for high dependency and intensive care is appropriate as they encompass similar invasive procedures. However, if numbers allow, differentiation into the three levels would provide more discriminatory power.

A weakness of gestational age as a risk adjustment measure is that it represents susceptibility to infection at birth, without taking into account changes in susceptibility throughout the NICU stay. By contrast, level of care is updated daily, so stratification for level of care incorporates changes in risk throughout the NICU stay. Risk factors used in previous studies include days with a central venous catheter (CVC),[2] or days with parenteral nutrition.[5] Parenteral nutrition may be a stronger predictor of BSI than CVC use alone.[5] Both procedures provide a continuous measure of risk, but are used to treat a minority of babies in the NICU; 20% for CVCs and 24% for parenteral nutrition.[6,7] The remaining babies have widely differing risks for infection. An advantage of level of care is that it reflects risk status for all babies for every day of stay.

In addition, stratification by level of care describes rates by their location and clinical team, which is relevant for targeting infection control measures. Moreover, level of care data are standardised across the NHS, routinely recorded and relatively complete and accurate because they are used for costing purposes. Disadvantages include the fact that clinical symptoms required to differentiate between true BSI and contamination are not routinely collected (although we found no significant association between blood sampling rate and BSI rate in the adjusted analysis, which would be expected if many positive blood cultures represented contamination). In addition, we did not differentiate between BSI which is hospital-acquired and the ~20% of BSI occurring in the first two days of life, which is likely to be maternally transmitted. Such distinction by age at infection is possible, but involves more intensive data management. As the quality of routine neonatal data improves, further research will be needed to evaluate more complex methods of risk adjustment.

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Conflict of interest statement
None declared.

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Survey of gut colonisation with *Stenotrophomonas maltophilia* among neonates

Madam,

Stenotrophomonas maltophilia is a nosocomial pathogen with inherent and mutationally acquired antibiotic resistance.[1] Studies have implicated this organism in bacteraemia and neonatal infections.[1–3] Trimethoprim/sulfamethoxazole remains the therapy of choice for infections with *S. maltophilia* worldwide.[1,4] However, this antibiotic is not usually used in neonates as it increases risk of hyperbilirubinaemia.[5]

In India ~52% of all neonatal deaths are due to sepsis.[6] Sick neonates are admitted to a neonatal intensive care unit (NICU) for treatment. However, the ICU is a focal point for the emergence and spread of antibiotic-resistant pathogens.[7] Antibiotic resistance frequently poses more difficulty in neonates where the options for therapy are limited, especially for *S. maltophilia*, for example, where the antibiotic of choice is generally not empirically given to neonates. *S. maltophilia* is thus a real threat in NICUs.

Surveillance of colonisation by *S. maltophilia* in the NICU may be an effective way of monitoring the carriage and antibiotic resistance pattern of the organism. We therefore evaluated the carriage of *S. maltophilia* as a part of a larger study to understand the colonisation pattern of Gram-negative organisms and their effect in neonates. The gut of hospitalised patients is often colonised with pathogens, and organisms from the gut may be a predictor of nosocomial infections.

The study was carried out in a 20-bedded NICU in a tertiary care centre in Kolkata. Samples were collected over a one-year period. In all, 243 babies were included in the study. Gastric aspirates were collected from the neonates within 4 h of birth (GA1) and also at any time if the babies were clinically diagnosed with sepsis (GA2). An attempt was also made to collect a faecal sample within 24 h of the collection of GA2.

The gastric aspirates were stored at 4 °C and the faecal samples were kept at room temperature and