ORIGINAL ARTICLE

A Toolkit for Monitoring Hospital-Acquired Bloodstream Infection in Neonatal Intensive Care

Pamela Leighton, PhD;[1] Mario Cortina-Borja, PhD;[1] Michael Millar, MD;[2] Stephen Kempley, FRCPCH;[3] Ruth Gilbert, MD[1]

OBJECTIVE. In neonatal intensive care units (NICUs), monitoring hospital-acquired bloodstream infection (BSI) is critical to alert clinicians to variations in the incidence of infection between units and over time. We demonstrate a toolkit of monitoring techniques that account for case mix and could be implemented using routinely available clinical data. This toolkit could enable quality of care comparisons between hospitals to facilitate the sharing of improved practices.

DESIGN. Prospective study over 4 years.

SETTING AND PATIENTS. Babies admitted to 2 tertiary London NICUs.

METHODS. We derived expected numbers of BSI episodes using a Poisson regression risk model adjusting for variations in birth weight, transfers to the NICU from other hospitals, postnatal age, and days spent at each National Health Service level of care. We compared observed and expected numbers of BSI episodes using 2 monitoring techniques: standardized infection ratios (SIRs) and the sequential probability ratio test (SPRT).

RESULTS. Using the SIR method, observed BSI incidence increased over expected incidence in 2002 at both NICUs, but this increase did not reach statistical significance at the 1% level. Using the SPRT method, neither unit showed a clinically important increase or decrease, defined as a 30% deviation from expected incidence.

CONCLUSIONS. Risk-adjusted BSI monitoring can be performed using routine hospital data. NICUs could use SIRs for an annual look back at infection incidence and SPRTs for prospective, quarterly monitoring. The SIR and the SPRT methods have different strengths, and both could help clinicians improve infection control and patient care in NICUs.

Infect Control Hosp Epidemiol 2012;33(8):831-836

Improving control of hospital-acquired infection is a major concern for neonatal intensive care units (NICUs). Between 2% and 10% of babies admitted to NICUs experience at least 1 episode of bloodstream infection (BSI),[1] which can lead to death, neurodevelopmental impairment, and other serious adverse outcomes.[2]

Prospective monitoring could be used to detect variations in BSI incidence between units and over time, which could be due to differences in the quality of care received. Quality of care comparisons and sharing of improved practices may reduce infection incidence.[3-6] Prematurity, morbidity, length of NICU stay, and the intensity of invasive medical procedures can also influence BSI rates.[7] These factors should be adjusted for when making comparisons between units and over time.[8] In previous analyses of routine National Health Service (NHS) data from 2 tertiary London NICUs, we determined that NHS level of care (special care, high dependency care, intensive care),[9] birth weight, postnatal age, and transfer to the NICU from another hospital (outborn status) were strong predictors for hospital-acquired BSI. These factors could be used to adjust estimates of infection incidence.[10-12]

We build on our previous work by demonstrating 2 approaches that could be used in NICUs for risk-adjusted monitoring of BSI incidence: the standardized infection ratio (SIR) and the sequential probability ratio test (SPRT). Our objective was to demonstrate a toolkit of monitoring techniques that could enable quality of care comparisons between hospitals. We apply our approaches to routinely collected hospital data, because in contrast to dedicated data collection, the use of routine data could minimize staff workload in monitoring.[13,14]

METHODS

Patients

Our study population consisted of babies admitted from May 2001 and discharged before March 2005 at 2 inner London

Affiliations: 1. Medical Research Council Centre of Epidemiology for Child Health, University College London Institute of Child Health, London, United Kingdom; 2. Department of Medical Microbiology, Barts and the London National Health Service Trust, Whitechapel, London, United Kingdom; 3. Centre for Paediatrics, Institute of Cell and Molecular Science, Barts and the London School of Medicine and Dentistry, Whitechapel, London, United Kingdom.

Received July 31, 2011; accepted March 13, 2012; electronically published June 12, 2012.

 0899-823X/2012/3308-0010$15.00. DOI: 10.1086/666635

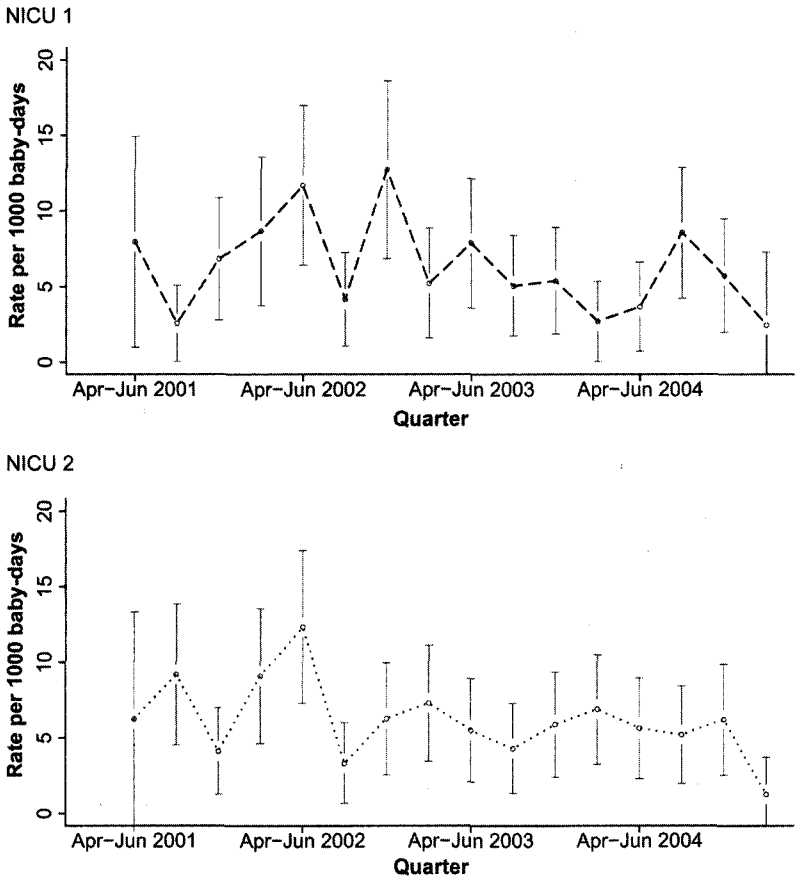

FIGURE 1. Observed quarterly rates of bloodstream infection episodes, with 95% confidence intervals. NICU, neonatal intensive care unit.

tertiary NICUs, which admit approximately 260 (NICU 1) and 430 (NICU 2) babies each year.

Step-by-Step Guide for Monitoring NICU-Acquired BSI

Step 1: preparing the data. We prepared a data set that could be derived from any system that records a daily record for all babies in NICUs and includes their blood culture results. Daily record databases are now standard in NICUs in the United Kingdom, for example, the Standardised Electronic Neonatal Database (SEND).[15] Because our data predated SEND, we created a daily record database by linking data from the patient administration system with results of positive blood cultures obtained from microbiology laboratories. Data linkage was performed using patient identifiers.

Each record contained the following information for the baby and day in question: date, NICU, NHS level of care, age (days), birth weight, and inborn/outborn status. NICU, birth weight, and inborn/outborn status remained the same over each baby's stay.

Step 2: case definition. Investigators can vary the case definition for BSI depending on the organism and clinical indicators available, provided that the number of BSI episodes is sufficient to be informative. We defined BSI as any positive blood culture. A baby could have further BSI episodes if he or she had a different organism cultured at any time or the same organism cultured after an interval of more than 7 days. We restricted analyses to hospital-acquired infections by excluding maternally transmitted infections, defined as all BSI occurring in the first 2 days of life, on the basis of a previously derived empirical threshold.

Step 3: calculating observed numbers of BSI episodes and baby-days. For each NICU, BSI episodes and baby-days of NICU stay were summed by calendar quarter and by year. We divided BSI episodes by baby-days to give crude quarterly rates of BSI with 95% confidence intervals (CIs; Figure 1).[12]

Step 4: calculating expected numbers of BSI episodes, adjusted for risk factors. Expected rates can be derived from various sources, including external benchmarks or standards. We used the overall risk-adjusted BSI rate of our 2 NICUs for the 4-year study period. We adjusted for previously identified risk factors: NHS level of care (special care, high dependency care, intensive care), birth weight (<700 g, 700 to <1200 g, ≥1200 g) inborn/outborn status, and postnatal age (3 to <20 days, ≥20 days).[12]

The risk-adjusted expected rate was calculated using a Poisson generalized linear model with logarithmic link, with the

https://doi.org/10.1086/666635 Published online by Cambridge University Press

risk factors fitted as covariates. The model's estimated parameters were used to calculate the expected BSI rate in each of the 36 strata defined by the 4 risk factors ($3 \times 3 \times 2 \times 2 = 36$ combinations).

All NICU baby-days were summed for each of the 36 strata for each quarter and for each year. The stratified expected rates of BSI were multiplied by the stratified numbers of baby-days for each hospital and year (for SIRs) 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 in each risk stratum.

Step 5: calculating yearly standardized infection ratios. Following the SIR method, for each hospital and year, we divided the observed number of BSI episodes by the expected number.[16] The CIs for the SIR show whether the observed number of BSI episodes deviated significantly (at the 1% level) from the expected number.

Step 6: calculating quarterly sequential probability ratio tests.[17-19] The SPRT allows repeated assessments of whether the observed number of BSI episodes has differed from the expected number beyond a predefined limit. We chose our predefined limit as a 30% increase or decrease. This figure was chosen because Kilbride et al[4] considered a 30% change in BSI incidence to be an important indicator of infection control practices within the Vermont Oxford Network of NICUs.

We calculated SPRT plots for the following comparisons: (1) observed numbers of BSI episodes against risk-adjusted expected numbers, with an important change defined as a 30% increase above expected numbers; (2) as above, with an important change defined as a 30% decrease below expected numbers.

The SPRT carries out a test of a null hypothesis H_0 versus an alternative hypothesis H_1, with H_0 defined as no change in observed numbers of BSI episodes over expected numbers and H_1 defined as an important change in observed numbers over expected numbers (defined as a 30% change in this study).

The SPRT involves plotting a test statistic for each quarter. Values of the test statistic lie between lower and upper thresholds a and b. When the statistic exceeds b, the hypothesis of a 30% change (H_1) is accepted over the hypothesis of no change (H_0), and when it is less than a, no change (H_0) is accepted over a 30% change (H_1).

The thresholds form horizontal lines, defined by α, the probability of eventually rejecting the hypothesis of no change (H_0) when it is true (Type I error), and β, the probability of eventually rejecting the hypothesis of a 30% change (H_1) when it is true (Type II error)

Several values can be chosen for α and β to denote degrees of urgency. Following convention, equal values for α and β were chosen: 0.01 for alert and 0.001 for alarm. Thus, if the test statistic crosses the lower alert threshold a, we can assume that a 30% change has not occurred. The probability of erroneously drawing this conclusion when a 30% change had occurred would be only 1%.

The SPRT test statistic involves plotting for each annual quarter t, numbered sequentially for the whole time period, the sequence $\{X_t = X_{t-1} + W_t\}$, with initial value $X_0 = 0$. For each t, the observed number of BSI episodes, Y_t, occurs with a probability proportional to the log likelihood ratio, defined as $W_t = \log(L_{1t}/L_{0t})$, where L_{0t} and L_{1t} are the model's likelihood contributions under H_0 and H_1. The observed numbers of BSI episodes follow a Poisson distribution, so W_t can be calculated as $W_t = Y_t \log(R_1) - \lambda_0(R_1 - 1)$, where λ_0 is the expected number of BSI episodes and R_1 denotes the change to be measured; that is, $R_1 = \lambda_1\lambda_0 = 1.3$ for a 30% increase, and $\lambda_1\lambda_0 = 0.7$ for a 30% decrease.

The calculation of the test statistic was restarted (by bringing the cumulative calculation back to 0) when it crossed the "accept no change (H_0)" boundary a. This avoided the buildup of credit, where increases in infection rates are masked by previous decreases, or vice versa.

The thresholds for the SPRT are calculated as $a = \log[\beta(1-\alpha)]$ and $b = \log[(1-\beta)\alpha]$. If $\alpha = \beta = 0.01$, then the boundaries for alert are $a = -4.6$ and $b = 4.6$; for $\alpha = \beta = 0.001$, the boundaries for alarm are $a = -6.91$ and $b = 6.91$.

Analyses were carried out using Microsoft Excel 2003[20] and Stata 10.0.[21] Research ethics approval was received from the National Hospital for Neurology and Neurosurgery and the University College London Institute of Neurology Joint Research Ethics Committee.

RESULTS

Data from 2,230 babies were analyzed (901 from NICU 1 and 1,329 from NICU 2), after 15 babies with missing birth weights and/or missing inborn/outborn status were excluded; 322 episodes of BSI were included, of which 232 were coagulase-negative staphylococcus (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.

Figure 1 shows crude observed quarterly rates of BSI for both hospitals. Because the study period ran from May 2001 to February 2005, the first and last quarters did not contain the full 3 months of data.

TABLE 1. Risk-Adjusted Standardized Infection Ratios (99% Confidence Intervals) by Neonatal Intensive Care Unit (NICU) and Year

Year	NICU 1	NICU 2
2001	.79 (.41–1.37)	.96 (.55–1.56)
2002	1.43 (.98–2.00)	1.22 (.84–1.71)
2003	.91 (.58–1.36)	.98 (.64–1.43)
2004	.77 (.47–1.19)	.96 (.64–1.39)
2005	.41 (.00–3.08)	.28 (.00–2.08)

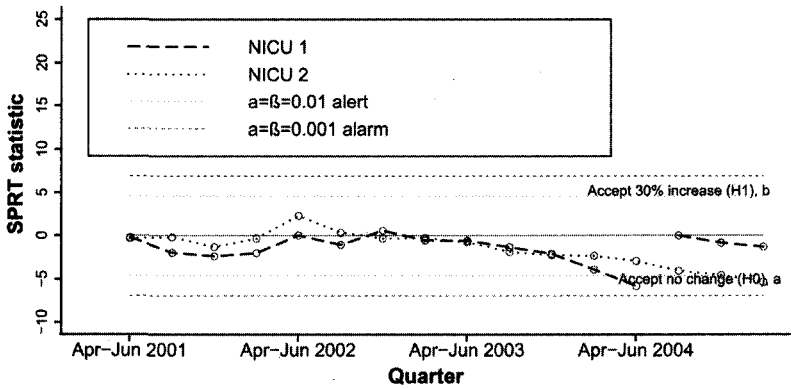

FIGURE 2. Risk-adjusted sequential probability ratio tests (SPRTs) to detect a 30% increase in bloodstream infection episodes. NICU, neonatal intensive care unit.

Yearly Standardized Infection Ratios

Table 1 shows SIRs for each hospital and year. The ratios were mostly close to 1, indicating no statistically significant difference between observed numbers of BSI episodes and risk-adjusted expected numbers. In 2002, both NICUs had more BSI episodes than expected, but this difference was not statistically significant (NICU 1: 56 observed, 39.26 expected; SIR, 1.43 [99% CI, 0.98–2.00]; NICU 2: 56 observed, 45.78 expected; SIR, 1.22 [99% CI, 0.84–1.71]).

Quarterly Sequential Probability Ratio Tests

Figure 2 shows the risk-adjusted SPRTs to detect increases in BSI incidence. The test statistic increased slightly with BSI incidence in 2002, then it decreased and crossed the lower threshold, *a*, during April to June 2004 for NICU 1 and during January to February 2005 for NICU 2. This indicated that a 30% increase in observed numbers of BSI episodes over expected numbers had not occurred, in other words, an acceptance of H_0 over H_1.

Figure 3 shows the SPRTs to detect decreases in BSI incidence. The test statistic crossed the lower threshold during April to June 2002 for both hospitals. This indicated that a 30% decrease in observed numbers of BSI episodes below expected numbers had not occurred.

DISCUSSION

We found no evidence of a clinically important increase or decrease in BSI incidence at either NICU. We demonstrated 2 approaches for BSI monitoring, since each method has different strengths. NICUs could use SIRs for an annual look back at infection incidence and SPRTs for the prospective, quarterly monitoring of infection incidence. In addition, clinicians should be presented with simple plots of yearly or quarterly observed rates of BSI with CIs (as in Figure 1).

Advantages of SIRs are that they provide a straightforward method for comparing incidence over time and can be included in annual reports. Disadvantages are that they do not take account of the fact that, with multiple hospitals and time points, it is likely that a significantly increased ratio ($P <$ .01) will occur simply by chance. Monitoring systems should

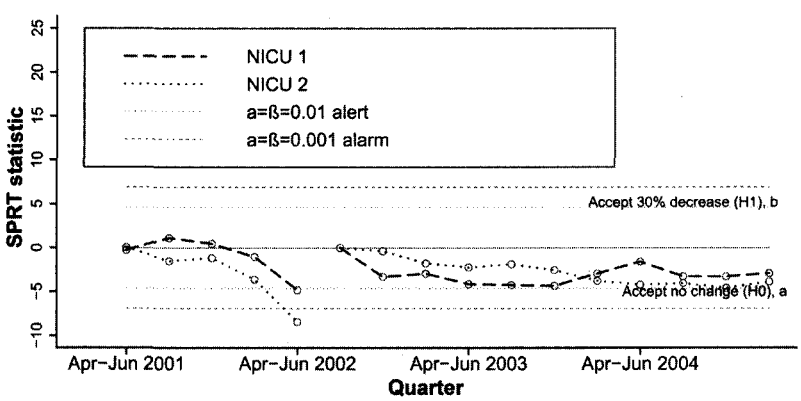

FIGURE 3. Risk-adjusted sequential probability ratio tests (SPRTs) to detect a 30% decrease in bloodstream infection episodes. NICU, neonatal intensive care unit.

https://doi.org/10.1086/666635 Published online by Cambridge University Press

be aware of this problem to avoid unfairly penalizing units with single high ratios.

The SPRT is better suited for continuous monitoring over shorter intervals—for example, quarterly—because it takes multiple time points into account. Another advantage of the SPRT over the SIR is that a clinically significant change in BSI incidence can be prespecified, which prevents NICUs from overreacting to small changes. By calendar quarter of 2002, the slight increase in observed BSI incidence did not exceed expected incidence by more than 30%, so it did not trigger an alert on the SPRT plots. We specified the arbitrary threshold of a 30% change in BSI incidence, but this could be modified according to the needs of the monitoring system. For example, a lower threshold could be chosen (a 15% or 20% change) to increase sensitivity to variations. The SPRT can be used to detect decreases in BSI incidence following infection control interventions; in this case, the threshold could be set to detect a 30% or 40% decrease to define an ambitious target for change.

A disadvantage of the SPRT is that it is more complicated to produce and interpret than the SIR. In addition, the SPRT test statistic is affected by previous BSI incidence, so increases can be masked by previous decreases and vice versa. However, this effect is mitigated by bringing the test statistic back to 0 (as described in step 6 in "Methods"). Use of the SPRT has not been reported previously for infection monitoring in NICUs. As in other areas of quality of care monitoring, multiple methods should be used to interpret variation.[22] The SIR and the SPRT could complement each other in infection monitoring initiatives.

Both monitoring techniques can be produced in spreadsheet programs, such as Microsoft Excel. Information from NICU data systems such as SEND could be fed in to preprepared spreadsheets on a quarterly basis to provide risk-adjusted monitoring using minimum time and effort. NICUs could consider prospectively linking administrative records with blood culture results, which may be more efficient than retrospective linkage, as carried out for this analysis.

Participation of more NICUs in monitoring would increase the potential to detect variation in BSI incidence. We analyzed only 2 NICUs, which were both in London. Even before risk adjustment, their incidences of infection were similar and changed little over time (Figure 1). This was compounded by the fact that expected rates were based on the overall average for both hospitals over the study period. The consistency found may partly be the result of comparing like with like. A greater number of NICUs and a longer time period would provide more generalizable expected rates based on the overall average. Alternatively, observed rates could be compared with an external benchmark rate.

Because our analyses were based on routinely collected data, we restricted our case definition to any positive blood culture. However, 72% of all BSI episodes were due to CONS, about 45% of which are reported to reflect contamination during blood culture sampling.[23] Our method could be enhanced using case definitions incorporating clinical symptoms if these are routinely collected. However, such definitions differ in sensitivity and specificity, and unless systematized, data quality is likely to suffer.[8,24] If NICUs wish to differentiate between infections more or less likely to represent contamination using routine data, risk adjustment and monitoring can be performed separately for CONS and non-CONS BSIs. We found that the same risk factors predicted non-CONS BSIs and all BSIs.[12] Reporting rates of CONS may help address contamination itself, which can lead to increased antibiotic use and longer durations of hospital stay. We found no evidence that differences in blood sampling frequency affected comparisons of BSI incidence between the 2 NICUs.[12]

Issues such as whether the results of monitoring should be available to stakeholders outside the NICU or the general public are beyond the scope of this article. Consultation will be necessary to avoid the negative connotations associated with the use of monitoring for ranking or penalizing units. Monitoring of the quality of care is of most value to generate questions among clinicians about how their care practices differ or could be improved. Engagement with staff is fundamental to the success of any monitoring system, as highlighted by experience from other infection surveillance systems and quality improvement initiatives.[4,16,25]

ACKNOWLEDGMENTS

Financial support. This work was undertaken at Great Ormond Street Hospital/University College London Institute of Child Health, which received a proportion of funding from the Department of Health's National Institute for Health Research Biomedical Research Centres funding scheme. The Centre for Paediatric Epidemiology and Biostatistics also benefits from funding support from the Medical Research Council (MRC) in its capacity as the MRC Centre of Epidemiology for Child Health. P.L. was funded by a Capacity Building PhD Studentship from the MRC.

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

Address correspondence to Pamela Leighton, Medical Research Council Centre of Epidemiology for Child Health, University College London Institute of Child Health, 30 Guilford Street, London WC1N 1EH, United Kingdom (ph.leighton@gmail.com).

REFERENCES

1. Parry GJ, Tucker JS, Tarnow-Mordi WO. Relationship between probable nosocomial bacteraemia and organisational and structural factors in UK neonatal intensive care units. *Qual Saf Health Care* 2005;14:264–269.
2. Stoll BJ, Hansen NI, Adams-Chapman I, et al. Neurodevelopmental and growth impairment among extremely low-birthweight infants with neonatal infection. *JAMA* 2004;292:2357–2365.
3. Kilbride HW, Powers R, Wirtschafter DD, et al. Evaluation and development of potentially better practices to prevent neonatal nosocomial bacteremia. *Pediatrics* 2003;111:e504–e518.

4. Kilbride HW, Wirtschafter DD, Powers RJ, et al. Implementation of evidence-based potentially better practices to decrease nosocomial infections. *Pediatrics* 2003;111:e519–e533.
5. Gill AW, Keil AD, Jones C, Aydon L, Biggs S. Tracking neonatal nosocomial infection: the continuous quality improvement cycle. *J Hosp Infect* 2011;78:20–25.
6. Weireter LJ Jr, Collins JN, Britt RC, Reed SF, Novosel TJ, Britt LD. Impact of a monitored program of care on incidence of ventilator-associated pneumonia: results of a longterm performance-improvement project. *J Am Coll Surg* 2009;208:700–704.
7. Couto RC, Pedrosa TM, Tofani CP, Pedroso ER. Risk factors for nosocomial infection in a neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2006;27:571–575.
8. Phillips P, Cortina-Borja M, Millar M, Gilbert R. Risk-adjusted surveillance of hospital-acquired infections in neonatal intensive care units: a systematic review. *J Hosp Infect* 2008;70:203–211.
9. British Association of Perinatal Medicine. *Standards for Hospitals Providing Neonatal Intensive and High Dependency Care (Second Edition) and Categories of Babies Requiring Neonatal Care.* London: British Association of Perinatal Medicine, 2001.
10. Phillips P, Cortina-Borja M, Gilbert R, Millar M, Kempley S. Risk stratification by level of care for comparing bloodstream infection rates in neonatal intensive care units. *J Hosp Infect* 2009;72:181–183.
11. Phillips P, Cortina-Borja M, Millar M, Kempley S, Gilbert R. Variation in infection incidence between neonatal intensive care units can depend on the measures used. *J Hosp Infect* 2009;72:363–365.
12. Leighton P, Cortina-Borja M, Millar M, Kempley S, Gilbert R. Risk-adjusted comparisons of bloodstream infection rates in neonatal intensive-care units. *Clin Microbiol Infect* 2012, doi: 10.1111/j.1469-0691.2011.03733.x.
13. Leal J, Gregson DB, Ross T, Flemons WW, Church DL, Laupland KB. Development of a novel electronic surveillance system for monitoring of bloodstream infections. *Infect Control Hosp Epidemiol* 2010;31:740–747.
14. Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection Surveillance Subgroup. *Report on HCAI Surveillance Priorities: Recommendations for HCAI Surveillance in England.* London: Department of Health, 2010.
15. Neonatal Networks. *Standardised Electronic Neonatal Database.* London: Neonatal Networks, 2006–2011. http://www.neonatal.org.uk/send. Accessed January 2012.
16. Gastmeier P, Sohr D, Just HM, Nassauer A, Daschner F, Ruden H. How to survey nosocomial infections. *Infect Control Hosp Epidemiol* 2000;21:366–370.
17. Wald A. Sequential tests of statistical hypotheses. *Ann Math Stat* 1945;6:117–186.
18. Grigg OA, Farewell VT, Spiegelhalter DJ. Use of risk-adjusted CUSUM and RSPRT charts for monitoring in medical contexts. *Stat Methods Med Res* 2003;12:147–170.
19. Spiegelhalter D, Grigg O, Kinsman R, Treasure T. Risk-adjusted sequential probability ratio tests: applications to Bristol, Shipman and adult cardiac surgery. *Int J Qual Health Care* 2003;15:7–13.
20. Microsoft. *Excel 2003.* Redmond, WA: Microsoft, 2003.
21. StataCorp. *Stata Statistical Software: Release 10.* College Station, TX: StataCorp, 2007.
22. Spiegelhalter DJ. Monitoring clinical performance: a commentary. *J Thorac Cardiovasc Surg* 2004;128:820–822.
23. Huang SY, Tang RB, Chen SJ, Chung RL. Coagulase-negative staphylococcal bacteremia in critically ill children: risk factors and antimicrobial susceptibility. *J Microbiol Immunol Infect* 2003;36:51–55.
24. Lin MY, Hota B, Khan YM, et al. Quality of traditional surveillance for public reporting of nosocomial bloodstream infection rates. *JAMA* 2010;304:2035–2041.
25. Wilkinson J, Powell A, Davies H. *Evidence: Are Clinicians Engaged in Quality Improvement?* London: Health Foundation, 2011.