The changing aetiology of paediatric bacteraemia in England and Wales, 1998–2007

Katherine L. Henderson,¹ Alan P. Johnson,¹ Berit Muller-Pebody,¹ André Charlett,² Ruth Gilbert³ and Mike Sharland⁴

Correspondence

Katherine L. Henderson
Katherine.Henderson@hpa.org.uk

¹Department of Healthcare-Associated Infection and Antimicrobial Resistance, Health Protection Agency Centre for Infections, London, UK

²Department of Statistics, Modelling and Bioinformatics, Health Protection Agency Centre for Infections, London, UK

³MRC Centre of Epidemiology for Child Health, UCL Institute for Child Health, London, UK

⁴Paediatric Infectious Disease Unit, St George's Hospital Medical School, University of London, London, UK

Bacteraemia in children is a potentially life-threatening condition. The objective of this study was to determine trends in the aetiology of bacteraemia in children aged 1 month–15 years in England and Wales by collecting data voluntarily reported by National Health Service hospital microbiology laboratories. Over the 10-year period 1998–2007, a total of 51 788 bacteraemia cases involving 105 genera/species of bacteria were reported. Total annual reports of bacteraemia increased from 4125 to 6916, with a mean increase of 6.5 % per year (95 % CI: 1.3–12.1 %). In 2007, just over half the cases were accounted for by four groups of organisms: coagulase-negative staphylococci (28 %), *Staphylococcus aureus* (10 %), non-pyogenic streptococci (9 %) and *Streptococcus pneumoniae* (7 %). These organisms along with a further 13 species/genera accounted for 90 % of the cases. The commonest Gram-negative organisms were *Neisseria meningitidis* and *Escherichia coli*, which each accounted for 5 % of total bacteraemia reports in 2007. There was a significant decrease in reports of bacteraemia due to the three vaccine-preventable pathogens *Haemophilus influenzae*, *N. meningitidis* and *Strep. pneumoniae*, following the introduction of each vaccine programme or catch-up campaign. This study identified the commonest causes of bacteraemia in children in England and Wales, and highlighted the shifts in trends observed over time.

Received 14 August 2009

Accepted 8 October 2009

INTRODUCTION

Bacteraemia in children is a potentially life-threatening condition which requires immediate and effective antimicrobial treatment (Sharland, 2007). The surveillance of paediatric bacteraemia is central to monitoring the changing epidemiology, which in turn guides the choice of empirical therapy (Paediatric Formulary Committee, 2008; Watson *et al.*, 2003). Such data can also be used to monitor the effect of current vaccine programmes and inform strategies aimed at preventing and reducing invasive infections in children, such as developing new vaccines and antimicrobial treatments.

Three of the most important influences on bacteraemia incidence are age, vaccination coverage and exposure to invasive procedures. Firstly, the reported rates of bacter-

aemias are higher in younger children, which may reflect the relative immaturity of their immune system, as well as their degree of contact with siblings, and associated exposure to pathogens (Posfay-Barbe *et al.*, 2008). The US study from Watson *et al.* (2003) revealed age-related diversity in incidence rates, with the highest rate in infants aged 1–11 months (156/100 000 population) compared with those aged 5–9 years (22/100 000 population) and 10–14 years (20/100 000 population).

Secondly, vaccine coverage has changed. In the UK, *Haemophilus influenzae* type B (Hib) has been offered since 1992 as part of the routine immunization of infants aged 2, 3 and 4 months, with a booster at 12 months, followed by a catch-up campaign in 2003 (NHS, 2008). The meningococcal C vaccine was introduced in 1999 and originally given to children at 2, 3 and 4 months, with a catch-up for those aged <25 years. Since 2006, the primary immunization programme has changed to deliver the vaccine at 3 and 4 months, with a booster dose combined

Abbreviations: CI, confidence intervals; CoNS, coagulase-negative staphylococci; HPA, Health Protection Agency; IRR, incidence rate ratio; MRSA, methicillin-resistant *Staphylococcus aureus*.

with the Hib vaccine at around 12 months (National Health Service, 2008). The 7-valent conjugate pneumococcal vaccine has been offered to children at 2, 4 and 13 months from 2006 onwards (Department of Health, 2006). Thirdly, changing nosocomial infection may result from more invasive procedures used in hospitals and in intensive care units, such as intravenous catheters (Elward & Fraser, 2006; Watson *et al.*, 2003).

A previous report of national paediatric bacteraemia surveillance in England focused on children aged under 5 years, and indicated a rise in the proportion of Gram-positive pathogens from 50 % to 75 % compared to Gram-negative pathogens between 1992 and 2005 (Sharland, 2007). Other reports across the whole child age range have targeted specific pathogens, such as our studies of paediatric *Staphylococcus aureus* bacteraemia (Khairulddin *et al.*, 2004; Johnson *et al.*, 2009). At the hospital level, one study identified over 50 % of isolates as coagulase-negative staphylococci (CoNS), *Staph. aureus* and *Enterococcus* species (Gray, 2004).

Paediatricians need to be informed of the current burden and aetiology of paediatric bacteraemia. This paper describes trends in the incidence of bacteraemia in England and Wales and documents the commonest species/genera in children aged 1 month–15 years. Neonatal bacteraemias are reported in a separate analysis describing a different age-specific pathogen range.

METHODS

Case ascertainment. Cases of bacteraemia have been electronically reported to the Health Protection Agency (HPA) database (LabBase2) on a voluntary basis by hospital microbiology laboratories in England and Wales since the early 1990s (Pearson *et al.*, 2009; Reacher *et al.*, 2000). Records containing microbiological data (organism identification to genus or species level, but not including serotype) and demographic data on paediatric bacteraemia cases occurring in patients 1 month–15 years old between 1998 and 2007 were extracted from LabBase2 and analysed. There were no data to specify whether the cases were community-associated or nosocomial in origin.

De-duplication was performed by merging records for the same case and pathogen when specimen dates were less than 14 days apart (Pearson *et al.*, 2009). Blood cultures yielding more than one pathogen were included as separate episodes. Manual cross-checking for duplicates was also undertaken by matching for specimen identifiers, specimen date, date of birth, patient initials and sex. Patients were categorized into the following age groups: 1–11 months, 1–4 years old (pre-school age) and 5–15 years old (school age). Incidence rates between 1998 and 2007 were determined by using the LabBase2 data as the numerator and taking the Office of National Statistics mid-year population rates for England and Wales for each of the three age groups as the denominator. As no monthly data were available for the youngest age group, the 1–11 months mid-year population estimate was calculated by taking an 11 month mean of the 12 month mid-year population data (Office of National Statistics, 2008). To determine the proportion of meticillin-resistant *Staph. aureus* (MRSA) to meticillin-sensitive *Staph. aureus* reports, meticillin susceptibility data for *Staph. aureus* isolates were extracted.

Analysis. The dataset was analysed in STATA, version 10.1 (StataCorp, 2008), using negative binomial regression analysis, with the outputs of the model showing the coefficient as incidence rate ratios (IRRs). In preference to logistic or Poisson regression, negative binomial regression was used to account for the overdispersion/abnormal distribution of the dataset (Hilbe, 2008).

To assess the number of bacteraemia report trends over time by organism, the year 1998 was taken as an index value in the regression analysis and adjusted for regional variation. The index value acted as the comparison year for the subsequent years of data in order to calculate the proportionate increase in the IRR changes over time, and to determine *P*-values and confidence intervals (CI). To explore the relationships between the three age groups and numbers of organisms reported over time, the youngest age group was taken as the index value. The resulting coefficients illustrated the association between the two older age groups in comparison to the youngest age group's reporting over time. However, to produce individual linear slope trends for each of the three age groups based on their own respective 1998 index values, instead of solely using the index value of the youngest age group, linear trends adjusted for by age group were calculated. The calculated results were reported as IRRs.

RESULTS

Incidence of reported bacteraemia cases

A total of 51 788 cases of bacteraemia in children aged between 1 month and 15 years were reported to LabBase2 between 1998 and 2007. The number of annual reports increased from 4125 to 6916, the mean annual increase being 6.5 % per year (95 % CI: 1.3–12.1 %). The proportions of bacteraemia cases in 2007 for children aged 1–11 months, 1–4 years and 5–15 years were 32 %, 37 % and 31 %, respectively, and had remained relatively consistent throughout the 10-year period. The corresponding incidence rates (reported cases per 100 000 population) in 2007 showed a 10-fold greater burden of bacteraemia in the youngest (362/100 000 population) compared to the oldest (36/100 000 population) age group. Bacteraemia was consistently more commonly reported in males (56.1 %) than in females (42.7 %) over time (IRR: 1.31; *P*=0.003), with 1.2 % of records lacking data on gender.

Overall aetiology of bacteraemia in children

A total of 105 bacterial species/genera were reported over the 10-year period, although there was marked variation in their relative frequencies. For example, in 2007, just over half the cases were accounted for by four organisms or organism groups (CoNS, *Staph. aureus*, non-pyogenic streptococcus, *Strep. pneumoniae*); these organisms along with a further 13 species/genera accounted for 90 % of the cases that year (Table 1). The range of species/genera seen over the 10-year period varied by age group, with a larger number being seen in the older age groups (98 and 93 in children aged 5–15 years and 1–4 years, respectively), compared to 77 different organisms in children aged 1–11 months.

There were shifts in the overall ranking of the pathogens causing bacteraemia between 1998 and 2007. Negative

Table 1. Aetiology of bacteraemia by age group in 2007

Organism	No. (%) of isolates				
	1–11 months	1–4 years	5–15 years	Total	cum.%
Coagulase-negative staphylococcus*	643 (29 %)	681 (27 %)	615 (28 %)	1939 (28 %)	28 %
<i>Staphylococcus aureus</i>	240 (11 %)	192 (8 %)	263 (12 %)	695 (10 %)	38 %
Non-pyogenic streptococcus†	154 (7 %)	276 (11 %)	191 (9 %)	621 (9 %)	47 %
<i>Streptococcus pneumoniae</i>	116 (5 %)	219 (9 %)	165 (8 %)	500 (7 %)	54 %
<i>Enterococcus</i> spp.	218 (10 %)	156 (6 %)	87 (4 %)	461 (7 %)	61 %
<i>Neisseria meningitidis</i>	124 (6 %)	156 (6 %)	65 (3 %)	345 (5 %)	66 %
<i>Escherichia coli</i>	180 (8 %)	85 (3 %)	78 (4 %)	343 (5 %)	71 %
<i>Klebsiella</i> spp.	116 (5 %)	79 (3 %)	50 (2 %)	245 (4 %)	75 %
<i>Enterobacter</i> spp.	72 (3 %)	71 (3 %)	43 (2 %)	186 (3 %)	78 %
<i>Micrococcus</i> spp.	33 (1 %)	68 (3 %)	56 (3 %)	157 (2 %)	80 %
<i>Acinetobacter</i> spp.	25 (1 %)	48 (2 %)	66 (3 %)	139 (2 %)	82 %
<i>Pseudomonas aeruginosa</i>	30 (1 %)	50 (2 %)	48 (2 %)	128 (2 %)	84 %
<i>Streptococcus pyogenes</i> (group A streptococcus)	24 (1 %)	62 (2 %)	41 (2 %)	127 (2 %)	86 %
<i>Streptococcus agalactiae</i> (group B streptococcus)	99 (4 %)	2 (0 %)	1 (0 %)	102 (1 %)	87 %
<i>Bacillus</i> spp.	14 (1 %)	40 (2 %)	43 (2 %)	97 (1 %)	88 %
<i>Salmonella</i> spp.	8 (0 %)	29 (1 %)	54 (3 %)	91 (1 %)	89 %
<i>Haemophilus influenzae</i>	22 (1 %)	29 (1 %)	16 (1 %)	67 (1 %)	90 %
Other‡	122 (5 %)	274 (11 %)	277 (13 %)	672 (10 %)	100 %
Total	2240 (100 %)	2517 (100 %)	2159 (100 %)	6916 (100 %)	100 %

*Coagulase-negative staphylococcus, *S. epidermidis*, *S. saccharolyticus*, *Staphylococcus* spp.

†*S. mitis* group, *S. viridans*, *S. oralis*, *S. sanguinis* group, *S. salivarius*, beta-haemolytic streptococci, *S. parasanguinis*, *S. milleri* group, *Aerococcus viridans*, non-haemolytic streptococci, *S. anginosus*, *S. acidominimus*, *S. intermedius*, other streptococci.

‡*Pseudomonas* spp., *Stenotrophomonas* spp., *Corynebacterium*, diphtheroids, *Moraxella* spp., *Streptococcus* group C, D, F and G, *Citrobacter* spp., *Serratia* spp., *Neisseria* spp., *Propionibacterium*, *Gemella* spp., *Haemophilus* spp., *Borrelia* spp., *Ochrobactrum*, *Proteus* spp., *Sphingomonas* spp., *Agrobacterium*, *Lactococcus*, *Brevundimonas*, *Mycobacterium*, *Fusobacterium*, *Pantoea*, *Bordetella*, *Bacteroides*, *Alcaligenes*, *Burkholderia*, *Leuconostoc*, *Rhodococcus*, *Achromobacter*, *Brevibacterium*, *Campylobacter*, *Chryseobacterium*, *Clostridium* spp., *Kingella*, *Lactobacillus*, *Pasteurella*, *Escherichia* spp., *Flavimonas* spp., *Leptospira* spp., *Neisseria gonorrhoeae*, *Peptostreptococcus*, *Ralstonia*, *Veillonella* spp., *Branhamella* spp., *Brucella* spp., *Capnocytophaga* spp., *Kluyvera* spp., *Morganella* spp., *Plesiomonas* spp., *Providencia* spp., *Roseomonas* spp., *Rothia* spp., *Sphingobacterium* spp., *Yersinia* spp.

binomial regression showed a significant decrease in bacteraemia due to the three vaccine-preventable pathogens *H. influenzae*, *Neisseria meningitidis* and *Strep. pneumoniae*, following the introduction of each vaccine programme and catch-up campaign (Figs 1 and 2). The overall reported incidence of *H. influenzae* nearly decreased by half from the pre-vaccine campaign in 2002 to the post-campaign in 2007 (–42 % CI: –18 % to –59 %), while the overall incidence of *N. meningitidis*, which was the most common pathogen in 1998, decreased by 45 % (95 % CI: 37–52 %) by 2007. From 1998 onwards, the incidence of pneumococcal cases increased and peaked in 2003, then subsequently decreased by 25 % (95 % CI: 16–33 %) between 2006 and 2007.

CoNS had the largest annual IRR increase, averaging 16 % per year (95 % CI: 13–19 %). This increase reflected in large part a marked increase in reports from a small number of hospitals from London in the latter years. Other organisms showing increased incidence over time included *Staph. aureus*, enterococci and non-pyogenic streptococci. The increase per year in the IRR of *Staph. aureus* was 4 % (95 %

CI: 2–6 %) between 1998 and 2007. Among the total cases of *Staph. aureus* bacteraemia, the proportion due to MRSA increased from 6.7 % in 1998 to 11.5 % in 2002 but subsequently decreased to 7.8 % by 2007. Between 1998 and 2007, the overall incidence of enterococcal bacteraemia rose by 234 % (95 % CI: 198–277 %), while bacteraemia due to non-pyogenic streptococci increased by 230 % (95 % CI: 199–265 %). *Escherichia coli* reports increased by a total of 34 % (95 % CI: 15–57 %) between 1998 and 2007.

Aetiology of bacteraemia in different age groups

The incidence of bacteraemia caused by the different pathogens varied markedly in children of different ages. To compare these differences by age group, the results are presented in terms of the most commonly reported pathogens distinguishing between the Gram-positive (Fig. 1a–c) and Gram-negative (Fig. 2a–c) pathogens.

Gram-positive bacteria. CoNS were responsible for the highest number of isolate reports in all age groups with a dramatic increase over time, especially in the final 2 years

Fig. 1. Incidence rates (per 100 000 population) for the main Gram-positive pathogens from 1998 to 2007 in children aged: (a) 1–11 months; (b) 1–4 years; (c) 5–15 years.

(Fig. 1a–c). Group B streptococci remained a persistent burden in children aged 1–11 months. In this age group, *Staph. aureus* showed the steepest slope gradient IRR (5.3%; 95% CI: 3.2–7.4%) (Fig. 1a), whereas *Staph. aureus* reports decreased in the other two age groups in 2007. Of the cases of *Staph. aureus* bacteraemia reported in 2007 in children aged 1–11 months, 1–4 years and 5–15 years, MRSA was responsible for 8.6%, 6.5% and 8.0% of cases, respectively.

The 1–11 months age group showed the largest decrease (43%; 95% CI: 29–55%) in incidence of bacteraemia due to *Strep. pneumoniae* from 2006 to 2007, followed by children aged 1–4 years showing a 26% reduction (95% CI: 16–41%). However, the incidence of pneumococcal bacteraemia in children aged 5–15 years continued to rise in 2007. Non-pyogenic streptococci infections at least doubled in incidence over time in all age groups, where they were the second most commonly reported isolates in

Fig. 2. Incidence rates (per 100 000 population) for the main Gram-negative pathogens from 1998 to 2007 in children aged: (a) 1–11 months; (b) 1–4 years; (c) 5–15 years.

children aged 1–4 years in 2007 (Fig. 1b), showing the highest rate of increased reporting, averaging at 13.6 % per year (95 % CI: 10.9–16.4 %).

Gram-negative bacteria. The incidence of the Gram-negative pathogens was found to be substantially lower than that of the Gram-positive pathogens across all three age groups. Reports of *N. meningitidis* reduced significantly after 1999 across all age groups, although it still remained

the most frequently isolated Gram-negative pathogen in children aged 1–4 years, whereas *E. coli* was the commonest Gram-negative species in the other two age groups (Fig. 2a, c). *E. coli* comprised a larger proportion of the cases in children aged 1–11 months (Fig. 2a) compared to the other two age groups (Fig. 2b, c), and this was the only age group with a significant increase over the 10-year period, averaging at 6 % per year (6 %; 95 % CI: 3–9 %). For all children, *Enterobacter* species and *Klebsiella* species

also increased significantly over time, with the youngest age group having the highest percentage of annual change. An increase in *Pseudomonas aeruginosa* was seen only in the youngest and oldest age groups and no statistically significant change was detected for *Salmonella* species (Fig. 2a–c). The incidence of bacteraemia due to *H. influenzae* remained low across all three age groups, with an observed decrease after 2003.

DISCUSSION

This study identifies the changing aetiology of bacteraemia in children in England and Wales. Following a previous bacteraemia trend analysis that was conducted across all age groups in England and Wales from 1990 to 1998 (Reacher *et al.*, 2000), we identified a continued increase in the absolute numbers of paediatric isolates reported from 1998 to 2007. This may be due to a combination of significant changes in causative organisms, increases in the number of blood cultures taken, increases in central venous catheter insertions (a risk factor for bacteraemia) or improved electronic data capture with associated reporting bias. As an example of the latter, in 2006 the Automated Pathology Interface for Cosurv and Amsurv (API A) project was introduced into the England and Wales electronic laboratory reporting system to improve the efficiency and increase the number of laboratories reporting to the HPA. This electronic reporting will have been a contributing factor to the increase in total reported isolates (Health Protection Agency, 2008a; Pearson *et al.*, 2009).

One of the main purposes of this study was to identify the most commonly isolated species/genera and the differences in their reporting by age group. Large differences were found, with younger children infected by a narrower range of pathogens, but with considerably higher incidence rates compared to older children. Two main findings were that Gram-positive bacteria continued to outweigh Gram-negative bacteria as a cause of paediatric bacteraemia, and that there was a marked decline in vaccine-preventable infections. Other studies of paediatric bacteraemia have reported similar findings (Gray, 2004; Lyytikäinen *et al.*, 2002; Sharland, 2007), although a study, in Southern Israel, identified a higher proportion of Gram-negative than Gram-positive pathogens (Frank *et al.*, 2005).

The decline in vaccine-preventable infections was seen especially for *N. meningitidis*. Although serotype data were not available in the present study, it is likely that the reduction reflects immunization with the meningitis C vaccine, for which there has been 90% or greater national vaccine coverage of children by their first birthday (Health and Social Care Information Centre, 2009). The continued dominance of meningococci in the 1–4 year age group probably reflects both lack of a booster dose at 12 months prior to 2006 (National Health Service, 2008), and the occurrence of meningococci belonging to other serotypes. In addition, the introduction of PVC7 in 2006 saw a

reduction in reported pneumococcal infections in children aged <5 years. Given the large reductions seen in pneumococcal bacteraemia in other countries such as Canada, further positive effects of the pneumococcal vaccine are likely to be observed in England and Wales in the coming years (Laupland *et al.*, 2009). The relatively low occurrence of bacteraemia due to *H. influenzae* probably reflects the efficacy of the Hib vaccine introduced in 1992. Moreover, the introduction of a catch-up campaign in 2003 was followed by a decrease in reports of bacteraemia due to *H. influenzae* in the 1–4 years age group.

The high incidence of bacteraemia due to *Staph. aureus* was striking, especially in the youngest age group, as *Staph. aureus* can cause serious morbidity and mortality, and can often be difficult to treat, due to resistance to multiple antibiotics (Khairulddin *et al.*, 2004; Livermore, 2000). Equally, the steady increase in Gram-negative pathogens is notable, especially for *E. coli*, which was the commonest Gram-negative pathogen throughout all age groups, aside from *N. meningitidis* in children aged 1–4 years. This needs to be closely monitored as *E. coli* has been reported as a growing reservoir for extended-spectrum β -lactamases, which mediate cephalosporin resistance that inhibits successful antibiotic treatment (Viagappan & Kelsey, 1995). The general rise in all the Gram-negative species/genera observed in this study may represent a trend towards increased nosocomial or healthcare-associated infections.

Our results may be affected by reporting bias. Although the HPA reporting guidelines indicate that clinically significant infections should be reported (Health Protection Agency, 2008b), the possibility that some reporting laboratories produce data outputs that include contaminants cannot be excluded. This is particularly relevant to reports of bacteraemia due to CoNS, which were the most frequently isolated organisms by 2007. Although there were no clinical correlates reported for the CoNS in this study, a number of studies have reported similar findings and there is a growing recognition of CoNS as a cause of bacteraemia, particularly in association with indwelling appliances (Frank *et al.*, 2005; Huebner & Goldmann, 1999; Lyytikäinen *et al.*, 2002; Raymond & Aujard, 2000).

Within the study, a constraint of the LabBase2 dataset is the absence of clinical data, which limits the ability to distinguish between community-acquired and nosocomial infection. A further source of bias is that as reporting of bacteraemia to the HPA in England and Wales is voluntary, it is likely that there was underascertainment of cases. Although the HPA undertakes enhanced surveillance of some specific pathogens, it would be invalid to compare incidence data generated using different methodologies. Thus, while the incidence rates reported here may underestimate the true incidence of bacteraemia, the overall changes in the proportions of different organisms should nonetheless give an indication of the trends in aetiology.

Despite these caveats, our study showed that surveillance of paediatric bacteraemia gives important insight into its current complex and dynamic aetiology, and reporting should continue to be encouraged to increase case ascertainment. The importance of population-level surveillance has been highlighted by the decline in the vaccine-preventable pathogens, and should be maintained to guide future evaluation of vaccination programmes. In the future, the empiric treatment of the septic child may become more complex as the major vaccine-preventable pathogens continue to decline. This will need to be balanced with the maintenance of narrow-spectrum antibiotic prescribing to avoid driving future resistance in an era of very limited antibiotic options. Further delineation of the absolute risks of specific serious bacterial infections will become ever more important.

ACKNOWLEDGEMENTS

We would like to thank all the microbiology laboratory staff in England and Wales for reporting isolates to the HPA surveillance system, and Ruth Blackburn and Catherine Goodall for their useful advice.

REFERENCES

- Department of Health (2006).** Pneumococcal conjugate vaccine (PCV) for children factsheet. Department of Health. Available at: http://www.immunisation.nhs.uk/publications/275878_Pneumofactsheet.pdf Accessed 29 June 2009.
- Elward, A. M. & Fraser, V. J. (2006).** Risk factors for nosocomial primary bloodstream infection in pediatric intensive care unit patients: a 2-year prospective cohort study. *Infect Control Hosp Epidemiol* **27**, 553–560.
- Frank, M., Gur, E., Givon-Lavi, N., Peled, N., Dagan, R. & Leibovitz, E. (2005).** Nosocomial bloodstream infections in children and adolescents in southern Israel: a 10-year prospective study (1992–2001). *Scand J Infect Dis* **37**, 177–183.
- Gray, J. W. (2004).** A 7-year study of bloodstream infections in an English children's hospital. *Eur J Pediatr* **163**, 530–535.
- Health and Social Care Information Centre (2009).** Immunisation. Available at: <http://www.ic.nhs.uk/statistics-and-data-collections/health-and-lifestyles/immunisation> Accessed 2 October 2009.
- Health Protection Agency (2008a).** APICA Project: Automated Pathology Interface for CoSurv and AmSurv. Available at: <http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1221202928425?p=1221202928425> Accessed 26 June 2009.
- Health Protection Agency (2008b).** Reporting to the HPA: a guide for diagnostic laboratories. Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1194947381307 Accessed 22 September 2009.
- Hilbe, J. M. (2008).** *Negative Binomial Regression*, 2nd edn. Cambridge: Cambridge University Press.
- Huebner, J. & Goldmann, D. A. (1999).** Coagulase-negative staphylococci: role as pathogens. *Annu Rev Med* **50**, 223–236.
- Johnson, A. P., Sharland, M., Goodall, C. M., Blackburn, R., Kearns, A. M., Gilbert, R., Lamagni, T. L., Charlett, A., Ganner, M. & other authors (2009).** Enhanced surveillance of methicillin-resistant *Staphylococcus aureus* (MRSA) bacteraemia in children in the UK and Ireland. *Arch Dis Child* (in press).
- Khairulddin, N., Bishop, L., Lamagni, T. L., Sharland, M. & Duckworth, G. (2004).** Emergence of methicillin resistant *Staphylococcus aureus* (MRSA) bacteraemia among children in England and Wales, 1990–2001. *Arch Dis Child* **89**, 378–379.
- Laupland, K. B., Gregson, D. B., Vanderkooi, O. G., Ross, T. & Kellner, J. D. (2009).** The changing burden of pediatric bloodstream infections in Calgary, Canada, 2000–2006. *Pediatr Infect Dis J* **28**, 114–117.
- Livermore, D. M. (2000).** Antibiotic resistance in staphylococci. *Int J Antimicrob Agents* **16**, S3–S10.
- Lyttikäinen, O., Lumio, J., Sarkkinen, H., Kolho, E., Kostiala, A., Ruutu, P. & Hospital Infection Surveillance Team (2002).** Nosocomial bloodstream infections in Finnish hospitals during 1999–2000. *Clin Infect Dis* **35**, e14–e19.
- National Health Service (2008).** Routine childhood immunisations. Available at: <http://www.immunisation.nhs.uk/Vaccines> Accessed 22 September 2009.
- Office of National Statistics (2008).** Mid-2007 UK, England and Wales, Scotland and Northern Ireland. Available at: <http://www.statistics.gov.uk/statbase/Product.asp?vlnk=15106> Accessed 29 June 2009.
- Paediatric Formulary Committee (2008).** *BNF for Children*. London: BMJ Group, RPS Publishing, RCPCH Publications.
- Pearson, A., Kronias, A. & Murray, M. (2009).** Voluntary and mandatory surveillance for MRSA and MSSA bacteraemia in England. *J Antimicrob Chemother* **64**, i11–i17.
- Posfay-Barbe, K. M., Zerr, D. M. & Pittet, D. (2008).** Infection control in pediatrics. *Lancet Infect Dis* **8**, 19–31.
- Raymond, J. & Aujard, Y. (2000).** Nosocomial infections in paediatric patients: a European, multicenter prospective study. *Infect Control Hosp Epidemiol* **21**, 260–263.
- Reacher, M. H., Shah, A., Livermore, D. M., Wale, M. C. J., Graham, C., Johnson, A. P., Heine, H., Monnickendam, M. A., Barker, K. F. & other authors (2000).** Bacteraemia and antibiotic resistance of its pathogens reported in England and Wales between 1990 and 1998: trend analysis. *BMJ* **320**, 213–216.
- Sharland, M. (2007).** The use of antibacterials in children: a report of the Specialist Advisory Committee on Antimicrobial Resistance (SACAR) Paediatric Subgroup. *J Antimicrob Chemother* **60**, i15–i26.
- StataCorp (2008).** *Stata Statistical Software: Release 10.1*. College Station, TX: Stata Corporation.
- Viagappan, M. & Kelsey, M. C. (1995).** The origin of coagulase-negative staphylococci isolated from blood cultures. *J Hosp Infect* **30**, 217–223.
- Watson, R. S., Carcillo, J. A., Linde-Zwirble, W. T., Clermont, G., Lidicker, J. & Angus, D. C. (2003).** The epidemiology of severe sepsis in children in the United States. *Am J Respir Crit Care Med* **167**, 695–701.