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Invasive fungal infection in very low birth weight infants: National prospective surveillance study

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Abstract

Objective: To describe the epidemiology of invasive fungal infection in very low birth weight (VLBW: <1500 g) infants in the United Kingdom (UK).

Design: National prospective surveillance study between February 2003 and February 2004 using the British Paediatric Surveillance Unit (BPSU) reporting system reconciled with cases identified through routine laboratory reporting to the Health Protection Agency (England, Wales, and Northern Ireland), the Scottish Centre for Infection and Environmental Health, and the UK Mycology Reference Laboratory.

Results: We identified 94 confirmed cases of invasive fungal infection during the surveillance period giving an estimated annual incidence of 10.0 (95% confidence interval (CI) 8.0 to 12.0) cases per 1000 VLBW live births. 81 (86%) of the infants were of extremely low birth weight (ELBW: <1000 g); estimated incidence 21.1 (95% CI 16.5 to 25.7) per 1000 ELBW live births. *Candida* species, predominantly *C. albicans* and *C. parapsilosis*, were isolated in 93% of cases. Most organisms were isolated from the bloodstream and urinary tract. 41% of infected infants died before 37 weeks' post-conceptional age.

Conclusions: The incidence of invasive fungal infection in VLBW and ELBW infants in the UK is lower than reported in previous studies from tertiary centres in North America and elsewhere. The associated late neonatal and post-neonatal mortality rates are substantially higher than expected in infants without invasive fungal infection. These data may inform decisions about the evaluation and use of anti-fungal infection control strategies.

Background

Invasive fungal infection is an important cause of morbidity and mortality in very low birth weight (VLBW: <1500 g) infants.[1,2] The previously reported estimates of incidence of invasive fungal infection in VLBW infants are between 3% and 6%.[3-8] Mortality rates of 25% to 40% are higher than those associated with invasive bacterial infection. However, these estimates are from studies in tertiary centres and may overstate the true disease burden due to referral and ascertainment biases.

The clinical presentation of invasive fungal and bacterial infection is similar and this may cause diagnostic delay.[6] Diagnosis and treatment may be further delayed due to difficulty in culturing the organisms from blood, cerebro-spinal fluid (CSF), or urine.[9] A high index of suspicion and the use of additional laboratory and clinical tests may be needed to confirm the suspected diagnosis.

Given the high mortality and the difficulty in establishing an early diagnosis, recent research attention has focussed on the effect of strategies to prevent invasive fungal infection in VLBW infants.[10] Evidence exists from Cochrane systematic reviews that prophylactic anti-fungal therapy reduces the risk of invasive fungal infection in VLBW infants.[11,12] However, in some of the randomised trials included in these reviews the incidence of invasive fungal infection in the control group was extremely high.[13,14] The applicability of these findings to settings with lower incidence rates has been questioned as very many more infants than suggested from the trial data would need to receive prophylaxis to prevent a single extra case of infection. In addition, there is concern that widespread prophylactic use of anti-fungal agents, particularly fluconazole, may drive the emergence of anti-fungal resistant *Candida* species.

We have undertaken a national prospective surveillance study to describe the clinical epidemiology of invasive fungal infection in VLBW infants in the UK. These data may be used to inform the future evaluation and use of anti-fungal prophylaxis and other strategies to prevent invasive fungal infection in VLBW infants.

Methods

We identified cases of invasive fungal infection in VLBW infants through independent prospective national surveillance schemes.

1. Notifications to the British Paediatric Surveillance Unit (BPSU). Each month between February 2003 and February 2004 we asked all consultant paediatricians in the UK to report whether or not they had seen any new cases (Table 1. Case definition).

2. Reports of deep fungal infections in infants aged less than three months from microbiology laboratories to the Communicable Disease Surveillance Centre, Health Protection Agency (England, Wales and Northern Ireland) and the Scottish Centre for Infection and Environmental Health.

3. Fungal isolates from deep infections in infants aged less than three months referred to the UK Mycology Reference Laboratory for characterisation and/or susceptibility testing.

We sought demographic, clinical, and microbiological details of cases and resolved any discrepancies in case-definition with the reporting clinicians. We pooled and reconciled cases using the infant's date of birth, sex, and hospital of care to avoid duplication.

Table 1. Case-definition of invasive fungal infection in VLBW infants

One or more of the following:

- culture of fungus from a sterile site:
  - blood (peripheral site, not via an in-dwelling catheter)
  - central intra-vascular catheter ("long-line") tip
  - urine (supra-pubic aspirate or aseptic "in-out" urinary catheter sample)
  - cerebro-spinal fluid
  - bone or joint
  - peritoneal or pleural space
- pathognomonic findings on ophthalmological or renal ultrasound examination
- infants with an autopsy diagnosis of invasive fungal infection

Denominator data

We used data from the Office of National Statistics (England and Wales), Information Statistics Division (Scotland), and Government Health Statistics (Northern Ireland) to estimate the number of VLBW infants live born in the UK during the study period. Complete figures were available from Northern Ireland for the study time period. For Scotland and England and Wales, we estimated the number of live births from the data that were available for January to December 2003.

Research Ethics Committee approval

The Scottish Multi-centre Research Ethics Committee and the Ethics Committee of the Health Protection Agency approved the study.

Results

The response rate of UK consultant paediatricians to BPSU surveillance requests during 2003 was 92% (http://bpsu.inopsu.com/). We received reports of cases from paediatricians in 56 neonatal units. These identified 86 confirmed cases. 36 of these were also identified via microbiological surveillance reports to the Communicable Disease Surveillance Centre and the UK Mycology Reference Laboratory. Eight cases that were not reported to the BPSU were identified via microbiological surveillance by these agencies. Therefore, 94 cases were identified in total.

About 9425 VLBW infants were live born in the UK during the study period. The estimated incidence of invasive fungal infection is therefore 10.0 (95% confidence interval (CI) 8.0 to 12.0) cases per 1000 live born VLBW infants.

The median gestational age at birth of cases was 25 weeks' (range 23 to 32: Figure 1a). The median birth weight was 720 grams (range 420 to 1460: Figure 1b). 81 (86%) of the cases were of extremely low birth weight (ELBW: <1000g). About 3837 ELBW infants were live born in the UK during the study period giving an estimated annual incidence of 21.1 (95% CI 16.5 to 25.7) per 1000 live born ELBW infants.

Incidence adjusted for early neonatal mortality

Early neonatal mortality (before 7 days after birth) reported by the Office for National Statistics for 2002 was 132 per 1000 live births for VLBW infants and 280 per 1000 live births for ELBW infants. Using as a denominator the estimated number of infants who survive beyond the first week after birth, and as the numerator only those cases identified more than six days after birth, the adjusted estimates of incidence are 10.0 (95% CI 7.9 to 12.1) per 1000 VLBW infants and 25.7 (95% CI 19.7 to 31.7) per 1000 ELBW infants.

The median age at diagnosis was 14 days (range 0 to 106 days: Figure 2). Two cases had evidence of early onset (congenital) infection with fungal sepsis identified within three days of birth. Other clinical features of the population, including exposure to putative risk factors for invasive fungal infection, are detailed in table 2.

Table 2. Clinical exposures of cases

Exposure	**Number of cases**
Parenteral nutrition	91
Central vascular access	89
Mechanical ventilation	90
Any antibiotics	92
• aminoglycosides	80
• vancomycin/teicoplanin	75
• cephalosporins	64
Post-natal steroids	18
H_2 receptor antagonists	16
Peritoneal dialysis	3

Table 3 details the organ involvement and sites of isolation of fungi during the clinical course.

Table 3. Organ and system involvement and sites of isolation of fungus

Site of infection or site of isolation of organism	Number of cases
peripheral blood	67
urine	26
x-ray evidence of pneumonia*	26
umbilical line tip	21
percutaneous central line tip	17
skin abscess	17
ultrasound finding of renal "fungal balls"	9
meningitis**	7
peritonitis	7
osteomyelitis	2
endocarditis	3
ophthalmitis	2
post mortem diagnosis only	3

* In addition to the 26 infants with chest x-ray evidence of pneumonia reporting clinicians were unable to attribute chest x-ray changes to infection as opposed to respiratory distress in a further 11 infants.
** 34 infants did not have CSF examination.

Fungi were isolated from multiple sites in 42 (45%) cases. Of the 27 infants who did not have a fungus isolated from blood culture, 13 had a diagnosis based only on another single positive culture or pathognomonic finding as listed in table 4.

Table 4. Cases diagnosed on the basis of a single clinical finding or fungus isolation

Site of infection or site of isolation of organism	Number of cases
urine	6
CSF	2
peritoneum	2
umbilical line tip*	1
ophthalmitis	1
ultrasound finding of renal "fungal balls"	1

* this case also had fungus isolated on two "clean catch" urine specimens

Mycology
Candida species were isolated in 87 (93%) of the cases. Most were identified as *C. albicans* [50 (53%)] or *C. parapsilosis* [23 (24%)]. Three isolates were identified as *C. glabrata* and one each as *C. lusitanaei* and *C. migosa*. We do not know the species of nine *Candida* isolates. The remaining five fungal isolates were: 2 *Malassezia* species, one *Aspergillus* species, 1 *Rhizopus* species, and 1 unidentified yeast. Infants infected with *C. albicans*, *C. parapsilosis*, or other *Candida* species did not differ significantly in median birth weights, gestational age, or age at diagnosis.

Anti-fungal resistance patterns were unknown or not determined in 53 (56%) cases. Of the remainder, only one case involving an anti-fungal resistant organism was reported (*C. glabrata* resistant to fluconazole).

33 (35%) infants had microbiological evidence of surface colonisation with *Candida* species prior to the diagnosis of invasive fungal infection. 36 (38%) cases had received antifungal prophylaxis, most commonly with oral and/or topical nystatin. Nine infants had received fluconazole as prophylaxis.

Anti-fungal therapy
74 (78%) infants were treated with amphotericin B, usually in a lipid-complex formulation. Fluconazole was also commonly prescribed (46%). 47 (50%) infants received more than one drug either simultaneously or sequentially. Flucytosine was never prescribed as mono-therapy but always used in combination with amphotericin B. Anti-fungal therapy was started before confirming the diagnosis in 21 (22%) cases. In seven cases, clinicians ceased drug administration because of suspected drug toxicity, mainly renal toxicity attributed to amphotericin B (both lipid complex and non-lipid complex formulations), and suspected bone marrow or renal toxicity attributed to flucytosine.

Mortality
39 (41%) VLBW infants died before 37 weeks' post-conceptional age. 35 (43%) ELBW infants died. The late neonatal and post-neonatal mortality rates for ELBW infants with invasive fungal infection were much higher than the overall mortality rates for all ELBW infants in 2002 (Figure 3). None of the infants with evidence of fungal meningitis died before 37 weeks' post-conceptional age. The mortality rates between the infants infected with *C. albicans* versus *C. parapsilosis* were not significantly different.

Discussion

This national prospective surveillance study estimated the incidence of invasive fungal infection to be about 1% in VLBW infants and about 2% in ELBW infants in the UK. The vast majority of cases were due to "late-onset" infection acquired in hospital. We identified only two cases of fungal infection diagnosed within the first three days after birth. Although "early-onset" or congenital invasive fungal infection has been described, it is extremely rare.[15,16]

Overall, most live born ELBW or VLBW infants who die do so within the early neonatal period and do not survive to acquire "late-onset" nosocomial infection. We

calculated adjusted incidences allowing for reported rates of early neonatal mortality. After adjustment the incidence of invasive fungal infection was 2.6% in ELBW infants, still substantially lower than the incidences of 5% to 15% reported in other studies.[2-8,14]

Validity of case ascertainment

This population-based prospective surveillance study is less likely to have been affected by referral bias than studies restricted to tertiary centres where the smallest and sickest infants are cared for. We undertook surveillance of the whole UK population of VLBW infants to avoid problems with clustering or temporal variation that may bias estimates of incidence from smaller studies. As our study included all live born VLBW infants born in the UK during the study period we were able to provide a more precise estimate of incidence than previous smaller studies.

Some clinicians may not have reported cases but this is unlikely to be a major source of under-ascertainment as we were able to identify unreported cases through independent laboratory sources. We may have failed to identify some cases where the diagnosis of invasive fungal infection was not confirmed by the infant's clinician. The diagnostic sensitivity of blood culture for invasive fungal infection is low (about 50%) and may be even lower in infants receiving prophylactic systemic anti-fungal treatment.[9] 30% of the reported cases did not have a fungus isolated from blood culture but had evidence of invasive fungal infection from culture of urine, CSF or a central intra-vascular line tip, or from other findings on clinical examination. It is also possible that cases where an infant died but did not undergo post-mortem examination remained undetected.

We do not think that over-ascertainment is a major problem in this study. We obtained sufficient identifying data to remove duplicate reports. We discussed any discrepancies in the case definition with the reporting clinician and resolved disagreements by consensus. Adhering to the *a priori* case definition reduced the likelihood of false-positive microbiological diagnoses. The case definition did not include diagnoses based on culture of blood drawn from in-dwelling intra-vascular catheters as these may represent contamination rather than true bloodstream infection. Although it is also possible that cases diagnosed solely on the basis of a fungal culture from a removed umbilical or percutaneous central line tip may be due to colonisation rather than true infection, all but one of these infant had other evidence of invasive fungal infection from deep cultures (mainly positive blood cultures from peripheral samples) or from clinical findings.

Implications for anti-fungal prophylaxis

Evidence from Cochrane reviews suggests that prophylactic anti-fungal therapy reduces the incidence of invasive fungal infection in VLBW infants. However, the general applicability of the data has been questioned because of the high incidence of invasive fungal infection in the control or placebo groups of some of the included trials.[13,14] With regard to fluconazole prophylaxis, the Cochrane review estimated that treating eight (95% CI 5 to 20) VLBW infants with prophylactic fluconazole would prevent one extra case of invasive fungal infection.[14] However, based on the incidence estimates in the UK population of infants from this surveillance study, we would need to treat 125 VLBW infants (or 45 ELBW infants) to prevent one extra case of invasive fungal infection.

There is concern that such widespread use may lead to the emergence of anti-fungal resistance. Although we did not find evidence that drug resistance is a common problem in fungal isolates in VLBW infants in the UK at present, changes in practice such as more widespread use of prophylactic anti-fungal therapy might alter this situation. It is essential to maintain microbiological surveillance systems to detect changes in the epidemiology of invasive fungal infection in high-risk groups including VLBW infants.

Mortality

Almost half of the infants diagnosed with invasive fungal infection died before 37 weeks' post-conceptional age. Although the late neonatal and post-neonatal mortality rates in ELBW infants with invasive fungal infection were much higher than would be expected in the absence of invasive fungal infection, we cannot attribute all deaths to infection. In some cases it may be that infants who were receiving maximum intensive care were already critically unwell and likely to die even before acquiring invasive fungal infection. Unexpectedly, none of the infants with confirmed fungal meningitis died prior to 37 weeks' post-conceptional age. However, we cannot be sure that all cases of meningitis were identified as 40% of infected infants did not have CSF examination to exclude meningitis and this group may have included infants with meningitis who were too unwell and clinically unstable to tolerate lumbar puncture.

Anti-fungal treatment

The anti-fungal treatment regimens employed in the UK are similar to those reported from North America.[17] At present there is insufficient evidence to favour one anti-fungal agent over another for treating VLBW infants with invasive fungal infection.[18] Currently the clinical choice of therapy may be affected by concerns about the risk of toxicity associated with the various drugs. In some patient groups, for example cancer patients with neutropaenia, evidence exists that renal toxicity is higher with conventional amphotericin B than with lipid complex formulations or with azole drugs.[19,20] However, there are only limited observational data on the relative risks of toxicity of anti-fungal drugs in VLBW infants.[21,22]

In this study, anti-fungal therapy was administered before the diagnosis was confirmed in less than one-quarter of the cases. Given the difficulty and delay in achieving a definite diagnosis of invasive fungal infection in VLBW infants, and the high mortality rates, it has been proposed that early empirical anti-fungal therapy for suspected invasive infection could improve outcomes for VLBW infants.[23] This strategy has not yet been evaluated prospectively. Although early empirical anti-fungal treatment is part of management algorithms for suspected infection in other immuno-compromised populations, for example cancer patients with neutropaenia, there is only limited evidence that this approach improves clinical outcomes.[24] Continuing efforts to develop better methods for rapid diagnosis of invasive fungal infection may help clinicians to target earlier anti-fungal treatment.

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What is already known on this topic

- Invasive fungal infection, mainly due to *Candida* species, is an increasingly common cause of mortality and morbidity in VLBW infants
- The incidence is highest in the lowest birth weight and gestational age categories
- Diagnosis and treatment is often delayed and better methods of prevention are needed

What this study adds

- In the UK, about 1% of VLBW infants and 2% of ELBW infants acquire invasive fungal infection, lower than in previously reported studies from tertiary centres in North America and elsewhere
- The late neonatal and post-neonatal mortality rates are much higher than expected in infants without infection
- Anti-fungal drug resistance in infections in VLBW infants does not appear to be a major problem in the UK at present

Figure legends

Figure 1a and 1b
Gestational age and birth weight distribution of VLBW infants with invasive fungal infection.

Figure 2
Post-natal age (days) at diagnosis of invasive fungal infection in VLBW infants.

Figure 3
Mortality rates (early neonatal, late neonatal, post neonatal) per 1000 for infants with invasive fungal infection compared to all live born ELBW infants (Office for National Statistics 2002).

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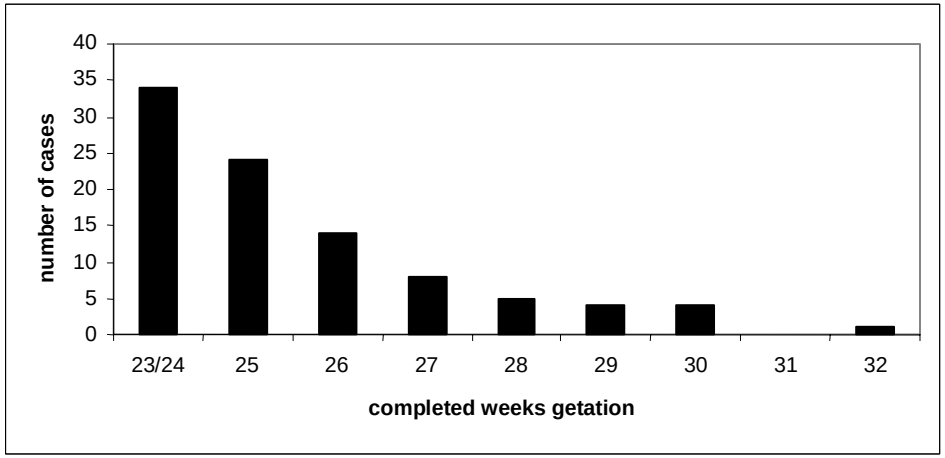
Figure 1a and 1b.

Gestational age and birth weight distribution of VLBW infants with invasive fungal infection.



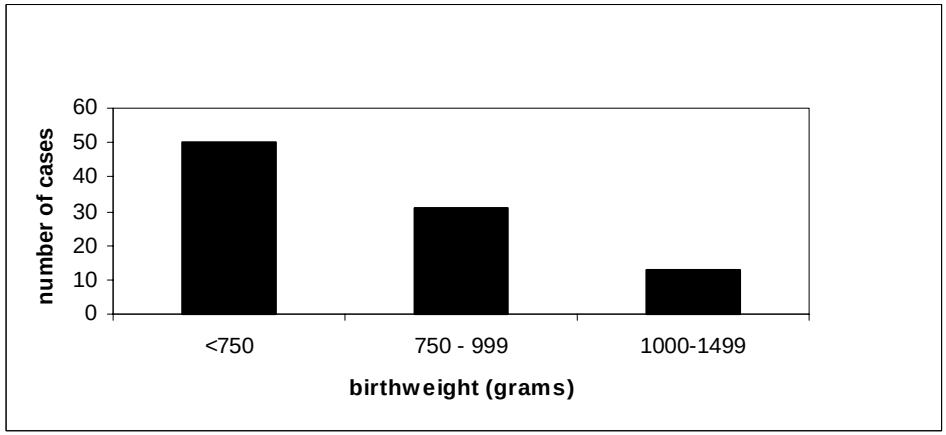


Figure 2.

Post-natal age (days) at diagnosis of invasive fungal infection in VLBW infants.

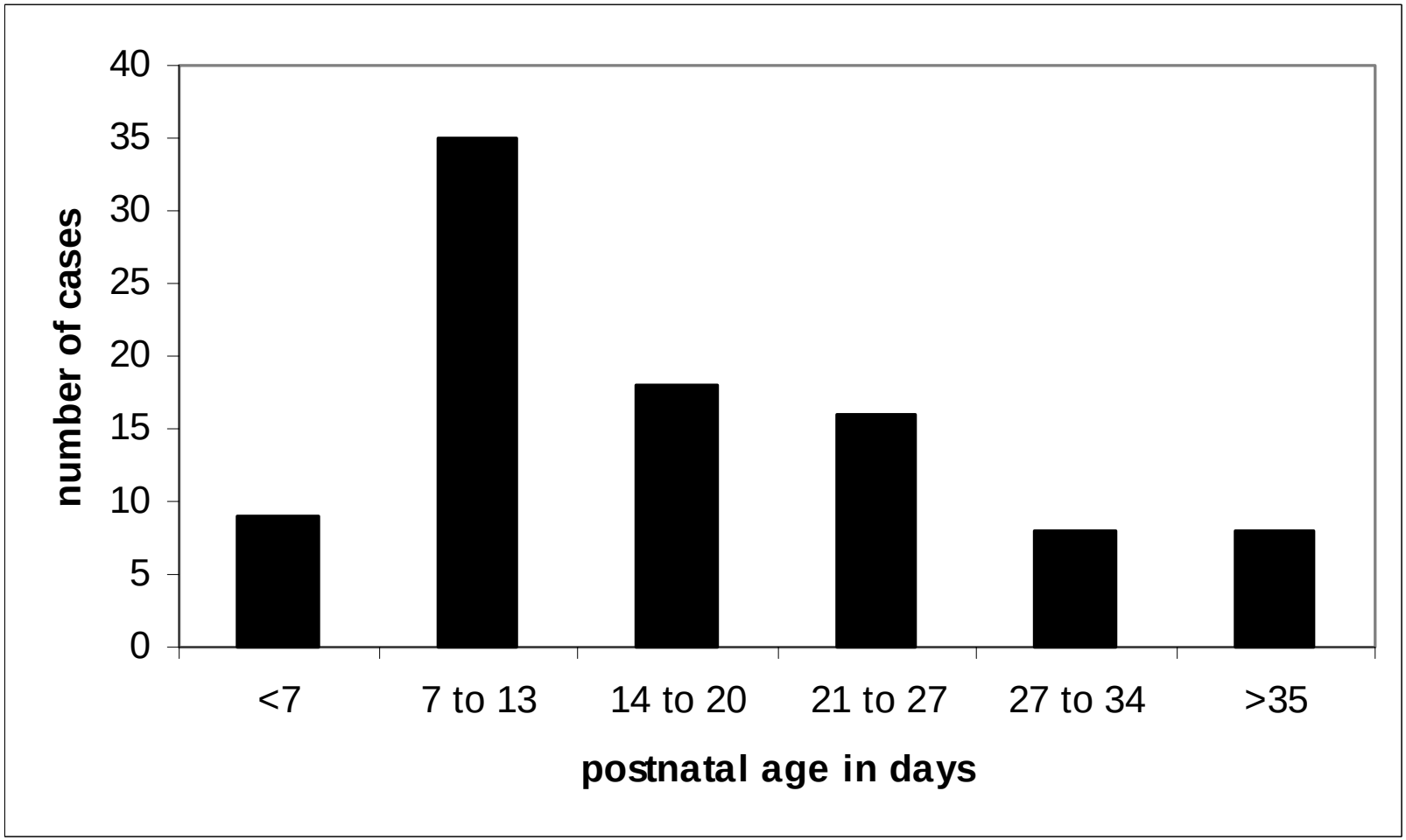


Figure 3.
Mortality rates (early neonatal, late neonatal, post neonatal) per 1000 for infants with invasive fungal infection compared to all live born ELBW infants (Office for National Statistics 2002).