Increasing incidence of *Escherichia coli* bacteraemia is driven by an increase in antibiotic-resistant isolates: electronic database study in Oxfordshire 1999–2011

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**Objectives:** To investigate trends in *Escherichia coli* resistance, bacteraemia rates and post-bacteraemia outcomes over time.

**Methods:** Trends in *E. coli* bacteraemia incidence were monitored from January 1999 to June 2011 using an infection surveillance database including microbiological, clinical risk factor, infection severity and outcome data in Oxfordshire, UK, with imported temperature/rainfall data.

**Results:** A total of 2240 *E. coli* (from 2080 patients) were studied, of which 1728 (77%) were susceptible to co-amoxiclav, cefotaxime, ciprofloxacin and gentamicin. *E. coli* bacteraemia incidence increased from 3.4/10000 bedstays in 1999 to 5.7/10000 bedstays in 2011. The increase was fastest around 2006, and was essentially confined to organisms resistant to ciprofloxacin, co-amoxiclav, cefotaxime and/or aminoglycosides. Resistant *E. coli* isolation rates increased similarly in those with and without recent hospital contact. The sharp increase also occurred in urinary isolates, with similar timing. In addition to these long-term trends, increases in ambient temperature, but not rainfall, were associated with increased *E. coli* bacteraemia rates. It is unclear whether resistant *E. coli* bacteraemia rates are currently still increasing [incidence rate ratio = 1.07 per annum (95% CI = 0.99–1.16), *P* = 0.07], whereas current susceptible *E. coli* bacteraemia rates are not changing significantly [incidence rate ratio = 1.01 (95% CI = 0.99–1.02)]. However, neither mortality nor biomarkers associated with mortality (blood creatinine, urea/albumin concentrations, neutrophil counts) changed during the study.

**Conclusions:** *E. coli* bacteraemia rates have risen due to rising rates of resistant organisms; little change occurred in susceptible *E. coli*. Although the severity of resistant infections, and their outcome, appear similar to susceptible *E. coli* in the setting studied, the increasing burden of highly resistant organisms is alarming and merits on-going surveillance.

**Keywords:** surveillance, extended-spectrum β-lactamases, aminoglycosides, multiresistant

**Introduction**

*Escherichia coli* is one of the most common pathogens implicated in bacteraemia of both community and nosocomial origin, with a mortality of up to 40% in the absence of effective antibiotic treatment.¹-³ Voluntary national surveillance has previously identified *E. coli* as an increasingly reported cause of bacteraemia in the UK, with a 33% increase between 2004 and 2008; in 2008 *E. coli* accounted for slightly more than 20% of all bacteraemias and a third of cases in those aged >75 years.⁶

The emergence of multidrug resistance in *E. coli* in Europe over the last decade is highlighted by the European Antimicrobial Resistance Surveillance Network (EARS-Net) showing the number of invasive *E. coli* resistant to third-generation cephalosporins, aminoglycosides and fluoroquinolones rose markedly between 2006 and 2009.⁷ EARS-Net also noted a 70% increase in the total number of invasive *E. coli*, although this could be due to a number of factors, including increased ascertainment and/or reporting. One interesting possibility is that genuine increases might be associated with rising European temperatures,⁸ as an
excess of cases in the warmer summer months have been described in several studies.6,9-11

The fluctuating clinical importance of different microorganisms has been demonstrated in various settings. In some situations, the introduction of pathogens into a susceptible general population can cause a large outbreak, provided conditions are permissive.12 In other situations, particular antimicrobial-resistant strains become prevalent predominantly in vulnerable healthcare-exposed populations, but not outside those settings.13 At present our understanding of the epidemiology of E. coli bacteraemia (EC-B) in the UK and whether it represents either of these scenarios is limited, with data from voluntary surveillance being sensitive to bias from under-ascertainment, and restricted by limited clinical information.6,14

Consequently we have examined a UK region (Oxfordshire) in which an increase in the proportion of E. coli with extended-spectrum β-lactamase mechanisms has recently been noted.15 We used a comprehensive integrated surveillance database16 to investigate whether an increase in EC-B incidence was linked to resistance phenotype, resistance in E. coli urinary isolates, climatic factors, or to either illness severity at presentation or outcome. Further, we investigated whether exposure to the healthcare environment is a major risk factor for EC-B.

Methods

Patients and identification of E. coli bacteraemia

The study was conducted using the Infections in Oxfordshire Research Database (IORD),16 which contains anonymized, linked data from hospital microbiology, biochemical and haematology laboratories, and patient administration systems for hospitals in Oxfordshire. It does not contain data on antimicrobial exposure.

We identified all inpatients with a positive E. coli blood culture result while admitted to the Oxford-based hospitals in the Oxford University Hospitals NHS Trust between 1 January 1999 and 15 June 2011, excluding positive tests within 14 days of a previous positive as duplicates. For some analyses, we only included the first isolate for each patient within the period of study.

The start and end dates were based on the availability of current and previous admission data. For each case, associated demographic information, date of admission, prior hospital admissions and previous EC-B were identified, together with information on the date of death (routinely updated in the underlying databases through the NHS Spine). Twenty-eight-day mortality (in and out of hospital) was available for all cases. To minimize the impact of changing medical practice over time (e.g. changing oncological protocols) we excluded patients with neutropenia (neutrophil counts <1×10⁹/L). Processing of blood cultures used a Bactec system (Becton Dickinson), and antibiotic susceptibility testing was performed essentially as described previously.17,18 The isolates were deemed susceptible if susceptible to all of co-amoxiclav, cefotaxime, ciprofloxacin and gentamicin, otherwise they were considered resistant for the purposes of this analysis. Susceptibility tests for these antibiotics were available for all isolates. The bacteraemia was considered nosocomial if the first sample with a positive result was taken >48 h after admission. In addition, the bacteraemia was deemed hospital-associated if it was either nosocomial or the patient had had a hospital admission in the preceding year.

We defined polymicrobial bacteraemia as the isolation of E. coli from blood cultures together with organisms other than those commonly associated with contamination by skin flora (coagulase-negative staphylococci, Corynebacterium spp. and Propionibacterium spp.).

For haematological and biochemical parameters, we identified the laboratory blood test results closest to the E. coli-positive blood culture sample, within a ±48 h window. Blood test results were used to investigate possible changes in EC-B severity over time (see below): to reduce the impact of atypical patients with extreme values who are likely to have chronic co-morbidities (e.g. renal, liver failure) and not be representative of the wider population with EC-B, values below the 1st and above the 99th percentile were excluded from the severity analysis for urea, creatinine and albumin concentrations.

Details of ethical approval

Extraction and analysis of data from the IORD was approved by the Oxford Research Ethics Committee (09/H0606/85) and the National Information Governance Board [5-07(a)/2009]. These approvals permitted processing and analysis of data (for defined infection-related purposes) without individual patient consent.

E. coli urinary isolation and overall sampling rates

In a secondary analysis, we defined E. coli urinary isolation as the isolation of a pure culture of E. coli from urine. The patient population studied was the same as for bacteraemias (i.e. inpatients); outpatient samples were not considered in either analysis. Samples were taken on clinical grounds, but detailed indications were not available. Culture, identification and susceptibility testing was performed essentially as described previously.19 De-duplication and exclusion was applied as for blood cultures. Overall rates of blood and urine cultures were estimated using the same criteria.

Statistical methods

We used negative binomial regression modelling (with log link function) to identify incidence trends in quarterly EC-B, with the log of the total overnight hospital bedstays (NHS KH03 statistic) as the offset. KH03 statistics were computed from the data held in IORD. The negative binomial model was chosen to account for possible over-dispersion relative to Poisson models.20

To identify changes in incidence over calendar time, we used a grid search algorithm,21 which models incidence as a series of straight lines. Here the study period was split into quarter-year intervals and all possible models with between zero and four join points (changes in trend), with the minimal distance between two consecutive join points being set to 12 months, were considered. The best fitting model was chosen on the basis of the Bayesian Information Criterion (BIC).22

The dependence of incidence on environmental factors (daily air temperature, soil temperature at 10 cm and rainfall) was assessed using weekly counts and mean weekly data from 1999 to 2011 from Oxfordshire obtained from the UK Meteorological Office.23 To assess changes in the severity of EC-B over time, we investigated secular trends in biomarkers known to reflect sepsis severity. Average values over time were assessed using locally weighted scatterpoint smoothing, a technique known as loess.24 To assess statistical significance, we fitted linear regression models on the biomarker data, transformed to achieve normality as described previously.25

The R language (2.11 for Windows) was used for data visualization (ggplot2 package) and incidence (glm.nb, in MASS package) and severity modelling (glm, in R base).

Results

After 14 day de-duplication, there were 2417 cases of EC-B from 2233 inpatients at the Oxford hospitals between January 1999
and June 2011. After excluding 177 cases with neutropenia, 2240 samples were studied (Table 1). A total of 1728 (77%) were susceptible to co-amoxiclav, cefotaxime (which was used as an indicator of third-generation cephalosporin resistance in in vitro susceptibility testing), ciprofloxacin and gentamicin; every other possible resistance pattern across these drugs was observed in the remaining 512 (23%) cases (Figure 1), with co-amoxiclav mono-resistance being the most common pattern (OR = 1.25, 95% CI 1.02–1.52). There was no independent effect of gender (OR = 1.00, 95% CI 0.87–1.15; for OR see Table 1).

Table 1. Demographics of E. coli bacteraemia cases

<table>
<thead>
<tr>
<th>Factor</th>
<th>Subcategory</th>
<th>n (%) or median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of cases</td>
<td>All isolates, susceptible, resistant, OR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>Age at admission years</td>
<td>2240 (100)</td>
<td>1728 (100)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male (49%)</td>
<td>820 (47)</td>
</tr>
<tr>
<td>Type of infection</td>
<td>Polymicrobial</td>
<td>192 (11)</td>
</tr>
<tr>
<td>Previous E. coli</td>
<td>In the study period</td>
<td>73 (6–82)</td>
</tr>
<tr>
<td>Hospital-associated</td>
<td>Admission, no pha</td>
<td>597 (35)</td>
</tr>
<tr>
<td></td>
<td>Admission, pha &gt;28 days ago</td>
<td>372 (22)</td>
</tr>
<tr>
<td></td>
<td>Admission, pha ≤28 days ago</td>
<td>242 (14)</td>
</tr>
<tr>
<td>Haematological/biochemical</td>
<td>Albumin (× g/L)</td>
<td>36 (30–40)</td>
</tr>
<tr>
<td></td>
<td>Creatinine (× μM/L)</td>
<td>116 (88–180)</td>
</tr>
<tr>
<td></td>
<td>Neutrophils (× 10⁹/L)</td>
<td>11 (7–15)</td>
</tr>
<tr>
<td></td>
<td>Urea (× μM/L)</td>
<td>9 (6–14)</td>
</tr>
<tr>
<td>Missing data</td>
<td>Albumin</td>
<td>82 (5)</td>
</tr>
<tr>
<td></td>
<td>Creatinine</td>
<td>24 (1)</td>
</tr>
<tr>
<td></td>
<td>Neutrophils</td>
<td>64 (4)</td>
</tr>
<tr>
<td></td>
<td>Urea</td>
<td>57 (3)</td>
</tr>
<tr>
<td>Mortality</td>
<td>Within 28 days</td>
<td>301 (17)</td>
</tr>
</tbody>
</table>

Logistic regression was used to calculate univariable ORs (resistant:susceptible for all rows except mortality, where OR is for death within 28 days:alive within 28 days). OR and 95% CI for effects of age at admission and haematological/biochemical parameters were calculated per 10 units higher. The abbreviation ‘pha’ refers to the previous hospital admission within the previous year.

Repeated episodes of EC-B

Most recurrences occurred rapidly; the median time from previous infection was 91 days. Multivariate modelling (as above) of data with at least 1 year follow-up (1 January 2000 onwards) gave essentially identical results to those described above.

Of the 2080 patients with a first EC-B, with median follow-up time of 5.7 years, 124 (6%) had one or more subsequent EC-B: 48 (2%) cases had one or more resistant subsequent culture, while in 76 (4%) all their subsequent EC-B were susceptible. Considering resistance patterns in individuals with earlier episodes of EC-B, 27 (42%) of the 64 resistant cases had previously had a susceptible strain isolated (i.e. potential selection of resistance) and 37 (58%) had previously had a resistant strain isolated (i.e. potential failure to adequately treat resistant infection, or recurrence). In contrast, 87 of 96 (91%) patients with recurrent but susceptible EC-B also had susceptible EC-B at a previous diagnosis.

Contribution of resistant organisms to EC-B incidence

Current (April–June 2011) quarterly incidence was estimated at 5.7 (3.7 susceptible and 2.0 resistant) cases per 10000 bedstays, compared with 3.4 (3.1 susceptible and 0.3 resistant) in April–June 1999 (see Figure 2 for all timepoints). We used the grid search technique (see the Methods section) to identify trends in total, resistant and susceptible EC-B incidence over calendar time. This technique identifies a range of models that fit the secular trends observed with similar confidence, and gives broadly similar inference to the best grid search model.
This suggests an increase in 2006–07 of about 30% (incidence rate ratio (IRR) per year \(= 1.30 \) (95% CI \(= 1.14–1.48 \)), \(P = 0.001 \)) followed by a constant incidence (IRR \(= 1.01 \) (95% CI \(= 0.95–1.07 \)), \(P = 0.8 \)). The timing of the increase in total EC-B was broadly consistent with an almost 2-fold increase in the resistant subgroup around 2006 (IRR \(= 1.86 \) (95% CI \(= 1.41–2.46 \)) over the year, \(P = 0.001 \)), an increase that subsequently slowed down (from 2007 onwards, IRR per year \(= 1.07 \) (95% CI \(= 0.99–1.16 \)), \(P = 0.07 \)). Restriction of the analysis to cases with their first EC-B gave the same results (Figure 2). Notably, at the end of the study (June 2011) there was no strong evidence for an increasing incidence in the susceptible subgroup (IRR per year \(= 1.01 \) (95% CI \(= 0.99–1.02 \)), \(P = 0.4 \)).

Although there were small fluctuations, no trends of such magnitude were identified in rates of taking blood for cultures over the study period (Figure 2; estimated IRR per year \(= 1.01 \) (95% CI \(= 1.01–1.02 \))), suggesting that changes in EC-B incidence, particularly the difference between trends in the susceptible and resistant subgroup, cannot be fully explained by variation in ascertainment.

Restricting analysis to bacteraemia isolates resistant to co-amoxiclav (Figure 3), comprising 70% of all resistant cases, gave similar secular trends as those for isolates resistant to any of co-amoxiclav, cefotaxime, ciprofloxacin and gentamicin. Results were also qualitatively similar in the smaller number of EC-B isolates resistant to cefotaxime, ciprofloxacin or gentamicin. To assess whether such changes were observed in other E. coli populations, we studied urinary E. coli. Interestingly, a rapid increase in co-amoxiclav resistance in urinary tract E. coli infections (Figure 3) was noted between the last quarter of 2005 and the first half of 2006 concomitant with the increase in bloodstream isolates (\(P < 0.0001 \)).

### Hospital contact and EC-B incidence

If exposure to the hospital environment were a critical determinant of the increase in resistant isolates, the rise in resistance might differ between hospital-naive patients diagnosed on admission and healthcare-associated cases. Defining hospital-associated as being in a hospital for 2 days or more, or having visited a hospital in the last year (see the Methods section), it was notable that similar increases in resistant EC-B were identified in patients both with and without previous hospital contact, suggesting that the increase in resistance is not restricted to the hospital-exposed population (Figure 4). Comparable trends were not apparent in either susceptible EC-B subgroup (Figure 4).

### Severity of EC-B over time

Given the increase in resistant EC-B (Figures 2 and 4), we then explored its possible impact on outcome and infection severity.
There was no difference in 28 day mortality following resistant or susceptible EC-B (OR = 1.0 (95% CI = 0.8–1.3), Table 1; similar results [adjusted OR = 0.8 (95% CI = 0.5–1.2)] were obtained adjusting for other Table 1 characteristics), and there were no secular trends in mortality among all cases, or either subgroup, over time (P > 0.5).

We have recently observed that monitoring mortality can be a relatively insensitive method of monitoring the changing severity of infection, with superior performance achievable by tracking inflammatory biomarkers on diagnosis (I. Schlackow, A. S. Walker and D. H. Wyllie, unpublished data). Elevated age and levels of creatinine, urea and neutrophils, as well as decreased levels of albumin, have been reported to be associated with poorer outcomes following EC-B.26,27 We confirmed these associations within the population studied (Figure 5). However, inspection of smoothed biomarker trends over time did not suggest any rising infection severity on diagnosis concurrent with increases in resistance (Figure 6). There was no significant change in the mean values of (Box–Cox transformed) neutrophils, urea or creatinine using linear regression models (P > 0.1). The levels of albumin on diagnosis have not changed significantly since 2002 (P = 0.06; small increases in 1999–2001 were also seen in other patient groups and likely reflect changing laboratory processes; data not shown). Similar results were obtained for the resistant and susceptible subgroups and for age-adjusted analysis (not shown).

Thus, neither biomarkers associated with sepsis severity nor 28 day mortality have changed significantly as resistance has emerged.

**Association between E. coli bacteraemia incidence and environmental factors**

In addition to analysing long-term trends in EC-B, we investigated associations with seasonal factors. We confirmed the
reported variation of EC-B incidence with temperature in our study (Figure 7). An increase in mean weekly air temperature of 5°C was associated with a 5% increase in EC-B incidence ([IRR = 1.05 (95% CI = 1.01–1.09), P = 0.03]. The effect size was similar in both susceptible and resistant subgroups, with IRR = 1.05 (95% CI = 1.00–1.10) and 1.04 (95% CI = 0.94–1.15) per 5°C, respectively, although power was lower for the smaller number of resistant organisms. The dependence of incidence on the mean weekly soil temperature at 10 cm was very similar. In contrast, there was no significant association (P > 0.1) between the bacteraemia incidence rate and weekly rainfall (Figure 7).

Figure 3. Changes in co-amoxiclav resistance. Changes in incidence [panels (a) and (b), showing both actual data and modelled trends] and proportion [panels (c) and (d), actual data] of co-amoxiclav-resistant bloodstream [panels (a) and (c)] and urinary [panels (b) and (d)] E. coli infections in 1999–2011.

Figure 4. Changes in EC-B incidence by susceptibility phenotype and exposure to the hospital environment. The best grid search models for total, hospital-associated (HA) and not HA EC-B incidence together with the observed data are shown. Estimates of the current yearly IRRs and 95% CI are presented on the right-hand side.
Expansion of resistant organisms driving rising incidence

The use of an integrated data warehouse allows us to report the largest UK study of EC-B incorporating severity, outcome, and clinical risk factor and climatic data. The incidence of EC-B in Oxfordshire has increased in the last decade, most rapidly around 2006. This increase was due to an increase in antimicrobial-resistant isolates; our modelling suggests that resistant organisms added to a constant burden of disease due to susceptible organisms. The increase in resistant EC-B occurred in both hospital-exposed and hospital-naive individuals, in both admission and nosocomial settings, and was accompanied by increasing resistance in urinary E. coli.

This article expands on a recent publication characterizing an outbreak of CTX-M-15-containing Klebsiella pneumoniae ST490 in Oxford Radcliffe Hospitals,15 which included data to mid-2010. Here we examine E. coli bacteraemia incidence (which was not assessed in the previous report) using data to mid-2011. Although it has been suggested that proportions of E. coli resistant to co-amoxiclav and to other drugs have risen steadily over time,15 tests for homogeneity of the slope over time were not performed to support this suggestion. This analysis of additional de-duplicated data using breakpoint-based regression analysis (Figures 2–4) provides strong statistical evidence this is not the case, with a rapid change in co-amoxiclav resistance evident in both urinary and blood isolates around 2006.

Discussion

Expansion of resistant organisms driving rising incidence

The use of an integrated data warehouse allows us to report the largest UK study of EC-B incorporating severity, outcome, and clinical risk factor and climatic data. The incidence of EC-B in Oxfordshire has increased in the last decade, most rapidly around 2006. This increase was due to an increase in antimicrobial-resistant isolates; our modelling suggests that resistant organisms added to a constant burden of disease due to susceptible organisms. The increase in resistant EC-B occurred in both hospital-exposed and hospital-naive individuals, in both admission and nosocomial settings, and was accompanied by increasing resistance in urinary E. coli.
The reason for this rapid rise is unclear; it appears to have preceded an antibiotic policy switch away from second- and third-generation cephalosporins towards co-amoxiclav with gentamicin as empirical treatment for sepsis, in response to rising *Clostridium difficile* infection rates. This switch occurred in October 2006, and monthly audits showed high compliance with this change in policy (data not shown). No changes in laboratory practice were made that might explain the increase in incidence. Possible hypotheses include the introduction and expansion of a successful clone into the community around that time, or the existence of selection pressures (including community antimicrobial policy) that we were unable to monitor in this study.

**Current situation**

Resistant EC-B rates may still be increasing. While the rate of change does not reach conventional significance in the region studied ($P=0.07$), we cannot exclude small on-going increases of up to 16% per annum—or that in fact rates are basically stable (lower 95% CI of 1% decrease per year). Detecting such increases with statistical confidence would require larger studies.

**Severity of infection**

We did not observe increases in either markers of host inflammation on diagnosis or in mortality following EC-B over the period studied. Consequently we believe that (at least to date) the strains responsible do not produce particularly severe clinical syndromes, and that the empirical antibiotic therapy administered on diagnosis, which was not recorded at an individual level in this study, is likely either to have been effective or to have been successfully rescued by follow-on therapy once resistance patterns were known. However, this study has not addressed the likelihood of infection given exposure (a classical definition of virulence) or investigated the genotypes of colonizing and disease-causing strains. Additionally we cannot exclude the possibility of smaller subpopulations within the resistant group with particular resistance patterns causing increased mortality. Larger studies will help address this.

**Groups of cases affected**

The risk of having a resistant EC-B in our locality is widely distributed across patient groups, limiting the capacity to differentiate a
resistant from a susceptible infection on the basis of the demographic features studied here. However, we did observe that individuals with prior hospital admission and/or diagnosis > 48 h after admission with EC-B were more likely to have resistant organisms, as were those with a previous EC-B, even if it was susceptible. Overall, the observed epidemiology is compatible with a model in which resistance elements and/or resistant bacterial clones are present in both hospital and community settings, and with either hospital acquisition of resistant organisms or the selection of endogenous resistant flora in hospitals. Such selection may also occur in antibiotic-exposed community-based individuals, but we lack prescription data to investigate this possibility directly.

**Impact of climate**

Temperature is clearly related to EC-B risk (our study, Freeman et al.\(^{11}\) and Perencevich et al.\(^{21}\)). Given global climate trends, our findings suggest *E. coli* may become even more prevalent over the next decades. We considered whether high rainfall, something associated with human exposure to animal *Cryptosporidium* spp.\(^{32}\) might also be a risk factor for EC-B. Interestingly, we did not observe such an association. It would be useful to further characterize the impact of environmental factors on *E. coli* acquisition in future studies.

**Limitations**

There are several limitations to this study. The first is that it is retrospective and based on routine electronic data sources. However, the fact that EC-B is typically severe and that the data collected were recorded during inpatient stays should limit possible bias. The second is that the region covered may not reflect the more general UK epidemiology; we cannot address this, but note that national surveillance suggests our...
rates are typical of the underlying population, and a study of other organisms in the region has yielded generalizable results. Our study was not designed to define transmission mechanisms, but these are clearly of interest. Third, individual antimicrobial exposure is not recorded in the underlying data sources. More work is needed to understand the complex interplay of antibiotic resistance with prevalent disease-causing E. coli and the association of particular resistance genotypes; this could be used to inform antibiotic guidelines and infection control policies and identify novel therapeutic approaches.

**Future prospects: resistant organisms adding to disease burden**

Our data raise several interesting questions not addressed in this study. First, what is driving the increase in resistant organisms and why did rates rise so rapidly in 2006–07? Second, what does the future hold? The UK prevalence of multiresistant E. coli is low relative to some other countries (EARS-Net); in parts of the Far East and India, current prevalences as high as 60%–70% have been reported following annual increases in resistance of about 3%–7% per annum over the last few years. It is therefore of concern that incidence trends in Oxfordshire are compatible with on-going increases of this magnitude. If this conclusion is supported by larger, UK-wide studies, a major impact on UK healthcare is to be expected over the coming decade. Faced with this threat and the uncertainty over future trends, it is reassuring that comprehensive national data are being collected by the UK Health Protection Agency’s (HPA) enhanced mandatory surveillance of EC-B.

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### Members of the IORD Team


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### Transparency declarations

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare the following: I. S. was supported by NIHR grant RP-DG-1108-10125 during the grant and D. H. W. was supported in part by the HPA during the work described. We declare no other financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

### Author contributions

Author contributions were as follows: all authors designed the study; I. S. developed statistical methods with A. S. W.; I. S. and D. H. W. analysed data; I. S., N. S., A. S. W. and D. H. W. wrote the paper; and all authors commented critically on the manuscript and have approved the final version.

### Disclaimer

The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the NIHR or the Department of Health.

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