Infection Control & Hospital Epidemiology (2019), **40**, 705–709
doi:10.1017/ice.2019.59

Concise Communication

Increasing burden of *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterococcus faecium* in hospital-acquired bloodstream infections (2000–2014): A national dynamic cohort study

Koen Blot MD[1], Naïma Hammami MD[2], Stijn Blot PhD[1,3], Dirk Vogelaers MD[1,4] and Marie-Laurence Lambert MD[2]

[1]Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium, [2]Healthcare-Associated Infections and Antimicrobial Resistance, Public Health and Surveillance Department, Scientific Institute of Public Health, Brussels, Belgium, [3]Burns, Trauma and Critical Care Research Centre, University of Queensland Centre for Clinical Research, Faculty of Medicine, The University of Queensland, Brisbane, Queensland, Australia and [4]General Internal Medicine, Ghent University Hospital, Ghent, Belgium

Abstract

The epidemiology of hospital-acquired bloodstream infections (HABSIs) based on the Belgian national surveillance program was analyzed (2000–2014). Our mixed-effects regression analysis identified increased rates of *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterococcus faecium*. HABSI incidence and resistance patterns should be further monitored because of their impact on proper empiric antibiotic therapy.

(Received 20 November 2018; accepted 15 February 2019)

Hospital-acquired bloodstream infections (HABSIs) are an important cause of increased morbidity, mortality, length of stay, and costs.[1–3] Although surveillance of blood cultures may not fully represent the epidemiology of all underlying infections, namely those without bacteremia, the clinical relevance of these invasive isolates is indisputable.[4] The Belgian institution Sciensano, previously WIV-ISP, has headed the national "Surveillance of Bloodstream Infections in Hospitals" program. This surveillance program has encouraged hospitals to participate and to collect hospital-wide HABSI case-based data since 1992. Identifying incidence rates, origins, microorganisms, and their trends is essential to characterizing the burden of hospital-acquired infections. In this study, we aimed to analyze HABSI incidence trends (2000–2014) with subgroup analyses for microorganism, origin of infection, and according to setting (ie, intensive care unit (ICU) or university hospital).

Methods

Study design and setting

A national dynamic cohort study of HABSI epidemiology was performed based on the Belgian "Surveillance Data of BSI in Hospitals" program from January 2000 to December 2014.[5]

Participants

Participation requires case-based recording of all HABSI for a minimum of 3 consecutive months annually. Participation became mandatory from 2014 onward; eligible hospitals were all acute- and chronic-care hospitals with >150 beds. Hospitals included in this cohort study reported both HABSI (numerator) and patient day (denominator) data for at least 1 trimester during at least 5 years.

Case definitions and variables

HABSI is defined as BSI with onset 2 or more days after hospital admission, not present upon admission (Appendix 1 online). A BSI requires at least 2 separate cultures with clinical symptoms if the causal microorganism is a skin commensal or with 1 culture of a recognized pathogen. HABSI origins are classified as central-line associated, secondary, or unknown.[6] CLABSI was defined as BSI with concomitant catheter culture or a central venous catheter (CVC) in place within 2 days of BSI onset, unrelated to another infectious site. CDC CLABSI surveillance definitions were applied post hoc to HABSI of unknown origin with a CVC in place in the previous 48 hours.[7] Collected data include HABSI onset date, probable infectious origin, causal microorganism(s), setting (hospital ward or ICU), and hospital type [(university-affiliated or acute-care versus chronic-care [ie, >14-day average length of stay]). Denominator data included number of hospital-wide and ICU patient days per trimester. HABSI incidence was reported as a mean rate per 10,000 patient days hospital-wide and mean rate per 1000 ICU patient days. Antibiotic resistance data collection was mandatory from 2013 to 2014 for *Staphylococcus aureus* (oxacillin, vancomycin), *Enterococcus* spp (vancomycin), Enterobacteriaceae (third-generation cephalosporin, carbapenem), *Pseudomonas aeruginosa* (carbapenem), and *Acinetobacter* spp (carbapenem).

Statistical methods

Mixed-effects negative binomial regression analysis was used to calculated adjusted incidence rate ratios (IRRs) with 95% confidence interval (CI) to determine the annual change in total HABSI rate (Appendix 2 online). Fixed confounding factors were

Author for correspondence: Koen Blot, Email: koen.blot@ugent.be

Cite this article: Blot K, *et al.* (2019). Increasing burden of *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterococcus faecium* in hospital-acquired bloodstream infections (2000–2014): A national dynamic cohort study. *Infection Control & Hospital Epidemiology*, 40: 705–709, https://doi.org/10.1017/ice.2019.59

Table 1. Hospital Characteristics and Hospital-Acquired Bloodstream Infection Incidence

Variable	Surveillance Year, No.					Total
	2000–2002	2003–2005	2006–2008	2009–2011	2012–2014	
Hospital-wide						
Hospitals	82	90	101	87	94	110
Total HABSI	10,371	12,283	13,997	10,682	12,608	59,941
CLABSI	2,293	3,004	3,410	2,540	3,265	14,512
Patient-days	12,626,277	14,325,252	16,118,362	13,539,573	15,804,997	72,414,464
Intensive care						
ICUs	78	81	87	77	87	105
Total HABSI	2,067	2,715	2,581	1,821	2,441	11,625
CLABSI	589	772	775	595	827	3,578
Patient-days	390,207	502,807	552,109	401,660	548,153	2,394,936
Hospital type						
University	4	6	6	6	6	6
Chronic care	0	1	4	4	4	5

Note. HABSI, hospital-acquired bloodstream infection; CLABSI, central line-associated bloodstream infection.

university hospital status, chronic care facility, and risk exposure (patient days per trimester). Mixed effects were applied to adjust for varying hospital participation and characteristics. This analysis was applied for total, gram-negative, and gram-positive HABSI rates. Subgroup analyses were performed for ICUs, university hospitals, and the most common microorganisms. In the regression analysis, we calculated both relative (incidence rate ratio) and absolute infection rate changes (per 10,000 patient days). Antibiotic resistance data were classified as sensitive or resistant (intermediate or complete resistance).

In our sensitivity analysis, we evaluated selection bias by repeating the analyses of HABSI rates with 3 different hospital cohorts with varying levels of participation: ≥1 trimester for ≥3 years, ≥1 trimester for ≥10 years, or 4 trimesters for ≥3 years. Statistical analyses were performed using Stata version 14 software (StataCorp, College Station, TX). $P \leq .05$ was considered statistically significant.

Results

In total, 110 hospitals participated for at least 1 trimester for 5 years. This cohort included 56 450 patients with 59,941 HABSIs from 66,610 microorganisms. Table 1 presents the included hospital characteristics. Missing quarterly patient day data led to the exclusion of 91 HABSI hospital-wide (0.2%) and 1,265 from the ICU (9.8%). We detected a 6-fold higher infection rate in ICUs (4.4 HABSIs per 1,000 patient days; IQR, 2.8–7.2) versus hospital-wide (6.8 HABSIs per 1,000 patient days; IQR, 4.6–9.4). The CLABSI rates were 1.6 HABSIs per 1,000 patient days (IQR 0.9–2.8) hospital-wide and 1.8 HABSIs per 1,000 patient days (IQR, 0.9–2.7) in the ICUs.

HABSIs were primarily central-line associated (24.2%) or were of urinary tract (14.9%) or pulmonary origin (9.7%). An important proportion of HABSIs (27.8%) were of unknown origin. The most common microorganisms were coagulase-negative staphylococci (CNS, 18.6%), *E. coli* (18.0%), and *S. aureus* (11.6%), followed by *Enterococcus* (7.8%), *Klebsiella* (7.1%), *Enterobacter* (6.1%), *Candida* (5.7%), and *Pseudomonas* spp (5.6%). Approximately 10% of HABSIs were polymicrobial (9.7%).

Our mixed-effects regression analysis identified a decrease in total HABSI rates (IRR, −0.5%; 95% CI, −0.8 to −0.1; $P = .006$). However, this effect size was small and the incidence trend demonstrated cyclical, fluctuating rates (Appendix 3 online). This trend was nonsignificant within the subgroup of university hospitals (IRR, −0.6%; 95% CI, −1.3 to −0.1; $P = .08$). CLABSI rates did not decrease either hospital-wide (IRR, +0.1%; 95% CI, −0.6 to 0.8; $P = .73$) or in intensive care (IRR, −0.6%; −1.7 to 0.6; $P = .32$). The rate of HABSIs of unknown origin decreased over the year (IRR, −5.8%; 95% CI, −6.6 to −5.1; $P < .001$) with concomitant increases in HABSIs of all secondary origins.

Compared with other hospitals, university hospitals demonstrated higher infection rates for hospital-wide total HABSIs (IRR, 2.3; 95% CI, 1.7–3.2; $P < .001$), CLABSIs (IRR, 3.4; 95% CI, 2.0–5.9; $P < .001$), and total ICU HABSIs (IRR, 1.4; 95% CI, 1.0–1.96; $P = .04$). ICU CLABSIs were not significantly higher among university hospitals (IRR, 1.6; 95% CI, 0.95–2.6; $P = .08$).

Although the total rate exhibited minimal change, HABSI rates changed significantly in opposite directions for gram-positive and gram-negative bacteria. Gram-negative infections increased (IRR, +1.0%; 95% CI, 0.6–1.4; $P < .001$), whereas gram-positive HABSIs decreased (IRR, −1.8; 95% CI, −2.2 to −1.3; $P < .001$) (Appendix 4 online). This finding corresponds with an increase in the gram-negative proportion from 42.7% to 54.1%. The largest incidence rate changes were increases in *E. coli* (IRR, +2.8%; 95% CI, 2.2–3.3; $P < .001$) and decreases in CNS (IRR, −4.5%; 95% CI, −5.2 to −3.8; $P < .001$) (Fig. 1A). Although the absolute increase was less prominent, *Klebsiella pneumoniae* (IRR, +4.4%; 95% CI, 3.4–5.4; $P < .001$) and *Enterococcus faecium* (IRR, +10.9%; 95% CI, 9.0–12.8; $P < .001$) demonstrated relative rate increases that were large compared to their baseline rate. Notably, *E. faecium* displayed a nearly 10-fold increase among university hospitals (0.11–0.96 per 10,000 patient days). The low rates of *Enterobacter aerogenes* decreased further over the study period (IRR, −6.1%; 95% CI, −7.4 to −4.7; $P < .001$). Although statistically significant,

https://doi.org/10.1017/ice.2019.59 Published online by Cambridge University Press

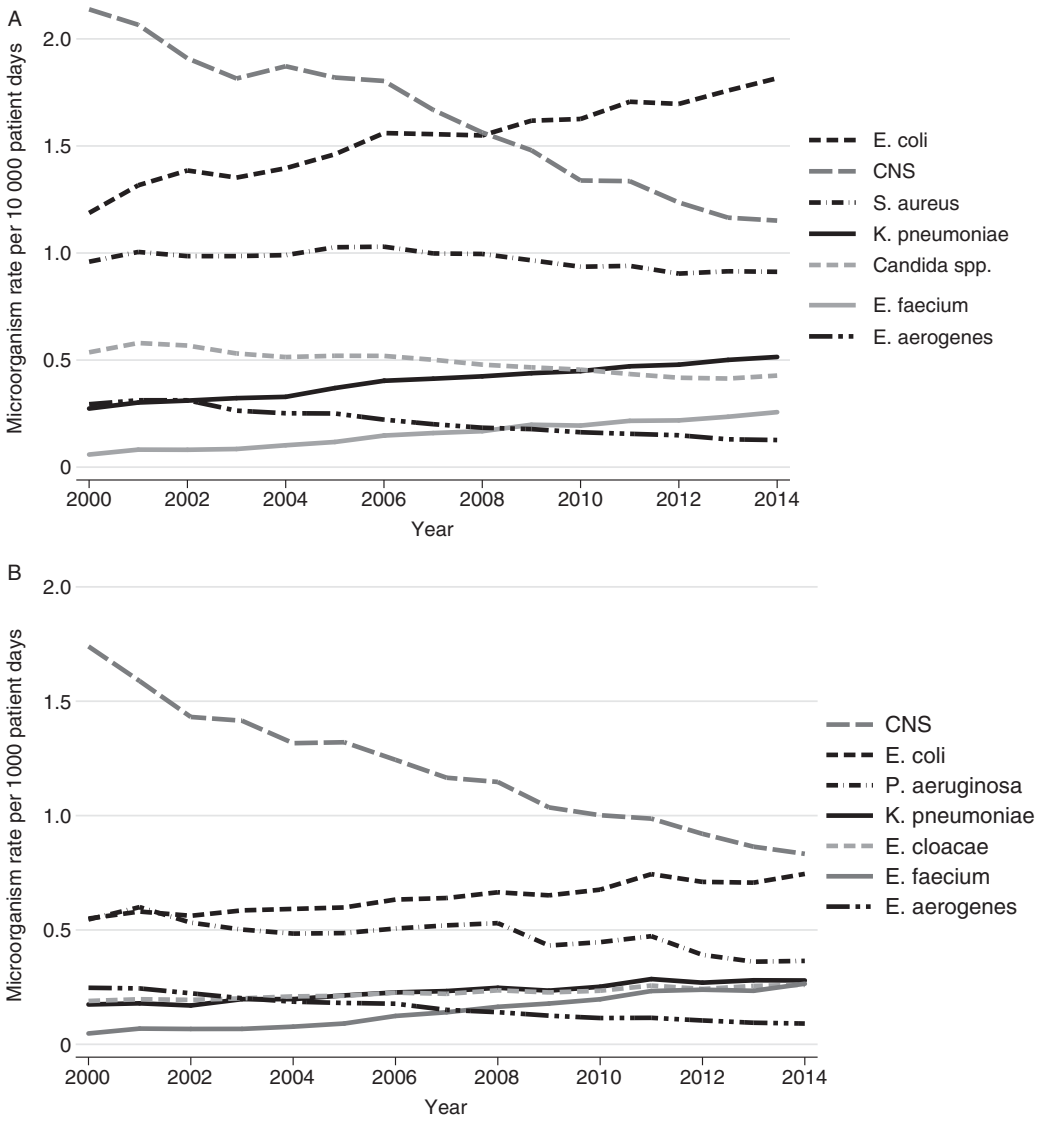

Fig. 1. A. Hospital-wide hospital-acquired bloodstream infection incidence, per microorganism (2000–2014). Incidence of hospital-wide bloodstream infections for microorganisms that demonstrated significant annual incidence rate ratio changes over the years (see online appendix 4). Note. CNS, coagulase-negative staphylococci. **B.** Intensive care hospital-acquired bloodstream infection incidence, per microorganism (2000–2014). Incidence of intensive care bloodstream infections for microorganisms that demonstrated significant annual incidence rate ratio changes over the years (see online appendix 4). Note. CNS, coagulase-negative staphylococci.

the incidence rates of *S. aureus* (IRR, −0.8%; 95% CI, −1.5 to −0.2; $P = .02$) and *Candida* spp (IRR, −1.3%; 95% CI, −2.2 to −0.4; $P = .004$) did not exhibit a large absolute decrease. Hospital-wide trends of *Klebsiella oxytoca*, *Enterobacter cloacae*, *P. aeruginosa*, *Bacteroides* spp and *Candida glabrata* remained stable.

Among ICUs, the CNS rate demonstrated a similar decrease, whereas gram-negative and *Candida* rates remained stable. However, *E. coli*, *K. pneumoniae, E. cloacae*, and *E. faecium* increased, whereas *P. aeruginosa* and *Enterobacter aerogenes* decreased (Fig. 1B).

Methicillin-resistant *S. aureus* accounted for 19.0% of isolates. Vancomycin-resistant *Enterococcus* was uncommon (2.7%). Third-generation cephalosporin resistance was common among *E. coli* (16.2%), *Klebsiella* spp (24.8%), *Enterobacter* spp (48.2%) and *P. aeruginosa* (14.6%). Carbapenem resistance was present among *P. aeruginosa* (18.2%) and *Acinetobacter* (8.1%) but was uncommon among Enterobacteriaceae (<2.5%).

Among total HABSI incidence, goodness of fit identified 2 severe regression model outliers. However, removal thereof did not meaningfully affect the results (Appendix 5 online). Sensitivity analysis was performed to assess selection bias associated with varying participation criteria (Appendix 6 online). The hospital-wide rise in gram-negative and decline in gram-positive and fungal rates remained significant among all cohorts, albeit with slightly different effect sizes. Hospitals participating ≥10 years showed attenuation of the increasing gram-negative rate, stronger rate reductions among gram-positive HABSI, and a nonsignificant trend toward lower CLABSI rates (IRR, −0.7%; 95% CI, −1.4 to 0.1; $P = .07$).

Discussion

In this study, we analyzed HABSI trends over 15 years of surveillance (2000–2014) in 110 hospitals. Although the total HABSI rate

https://doi.org/10.1017/ice.2019.59 Published online by Cambridge University Press

was slightly decreasing, there was a clear increase in gram-negative pathogen incidence represented by *E. coli* and *K. pneumoniae*. *Enterococcus faecium* demonstrated important rate increases, most markedly within ICUs and university-affiliated hospitals. Among ICUs the gram-negative HABSI rate remained stable yet the proportions of specific microorganisms changed with increases in *E. coli*, *K. pneumoniae*, and *E. cloacae* and decreases in *P. aeruginosa* and *E. aerogenes*. Notably, within the ICU, the incidence of *E. faecium* rose to the same level as *K. pneumoniae* and *E. cloacae*.

CLABSI rates did not decrease either hospital-wide or in ICUs. University hospitals displayed hospital-wide CLABSI rates triple that of nonuniversity hospitals, yet this difference was not significant among ICUs. This higher infection rate among university hospital wards may reflect an area for improvement through CLABSI prevention initiatives. The subgroup of hospitals participating at least 10 years exhibited a nonsignificant trend toward decreasing CLABSI rates, which aligns with evidence that CLABSI reduction can be achieved through long-term surveillance as part of a quality improvement initiative.[8]

The strengths of this study include the long-term surveillance, hospital-wide data collection, nationwide participation, and mixed-effects modeling to account for confounding factors. Countrywide surveillance programs have been shown to estimate valid BSI incidences when data are collected during random trimesters of the year.[9] In this study, hospitals could choose which trimester to report from, but there was no statistically significant difference in reporting rates between trimesters. Furthermore, the hospital cohort reporting data year-round exhibited similar rate changes compared to cohorts that did not.

The limitations of this study include missing data on confounding factors such as catheter days, blood culturing frequency, and recent ICU admission. No distinction could be made between infections acquired in the ICU versus HABSIs that led to ICU admission. Finally, because it was not mandatory to perform surveillance consecutively across trimesters or years, time-series regression analysis with temporal autocorrelation was not possible without exclusion of most of the data, at the expense of its external validity. Unfortunately, because resistance data were only available during the final 2 surveillance years, resistance trends could not be analyzed in this cohort.

Overall, CNSs comprised the majority of CLABSI and demonstrated rate decreases both in intensive care and hospital-wide, yet CLABSI incidence appeared to remain stable. Although the definition requires at least 2 positive cultures with clinical symptoms, this CNS decline could partially represent an improved recognition of skin contaminants instead of a true incidence decline.

This study identified an increasing HABSI rate for *E. coli*, *K. pneumoniae*, and *E. faecium*, which represents an increased treatment burden and the underlying epidemiology of hospital-acquired infections. This is alarming because of these microorganisms' resistance levels to fluoroquinolones, third-generation cephalosporins, and amoxicillin. *Escherichia coli*, *K. pneumoniae*, *E. cloacae*, and *E. faecium* increases were mirrored in the ICU, reflecting their clinical importance as either representing sepsis requiring critical care admission or infection of susceptible ICU patients.[10–12] Other surveillance studies have likewise identified rises in *E. coli* and *K. pneumoniae*[13–16] and increasing proportions of *E. coli* resistant to third-generation cephalosporins among 12 of 30 European countries.[4] Increasing trends of antimicrobial-resistant microorganisms threatens to complicate proper early and appropriate antibiotic treatment.[17] Empiric antibiotic therapy should be based on local epidemiology, and these changing trends warrant further monitoring of microorganism incidence and resistance patterns.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2019.59

Author ORCIDs. Koen Blot, 0000-0002-0847-0133

Acknowledgments.

Financial support. S.B. holds a research mandate of the Specific Research Fund at Ghent University.

Conflicts of interest. D.V. has received an institutional grant for work under consideration for publication from Pfizer and has been a consultant for Astellas, Pfizer, and Tibotec. All other authors report no potential conflicts.

References

1. Blot SI, Depuydt P, Annemans L, *et al.* Clinical and economic outcomes in critically ill patients with nosocomial catheter-related bloodstream infections. *Clin Infect Dis* 2005;*41*:1591–1598.
2. Vrijens F, Hulstaert F, Van de Sande S, Devriese S, Morales I, Parmentier Y. Hospital-acquired, laboratory-confirmed bloodstream infections: linking national surveillance data to clinical and financial hospital data to estimate increased length of stay and healthcare costs. *J Hosp Infect* 2010;*75*:158–162.
3. Pien BC, Sundaram P, Raoof N, *et al.* The clinical and prognostic importance of positive blood cultures in adults. *Am J Med* 2010;*123*:819–828.
4. European Centre for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2015. *Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net)*. Stockholm: ECDC; 2017.
5. WIV-ISP. *Surveillance nationale des septicémies dans les hôpitaux belges 2017. Sciensano website.* http://www.nsih.be/surv_sep/beschrijving_fr.asp. Published 2017. Accessed March 8, 2019.
6. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988;*16*:128–140.
7. Central line-associated bloodstream infection (CLABSI) event protocol. Center for Disease Control and Prevention website. http://www.cdc.gov/nhsn/PDFs/pscManual/4PSC_CLABScurrent.pdf. Updated January 2019. Accessed March 8, 2019.
8. Blot K, Bergs J, Vogelaers D, Blot S, Vandijck D. Prevention of central line-associated bloodstream infections through quality improvement interventions: a systematic review and meta-analysis. *Clin Infect Dis* 2014;*59*:96–105.
9. Fontela PS, Quach C, Buckeridge D, Pai M, Platt RW. Surveillance length and validity of benchmarks for central line-associated bloodstream infection incidence rates in intensive care units. *PLoS One* 2012;*7*:e36582–6. doi: 10.1371/journal.pone.0036582.
10. Blot SI, Vandewoude KH, Colardyn FA. Evaluation of outcome in critically ill patients with nosocomial enterobacter bacteremia: results of a matched cohort study. *Chest* 2003;*123*:1208–13.
11. Blot SI, Vandewoude KH, Colardyn FA. Clinical impact of nosocomial *Klebsiella* bacteremia in critically ill patients. *Eur J Clin Microbiol Infect Dis* 2002;*21*:471–473.
12. Blot S, Vandewoude K, Hoste E, *et al.* Absence of excess mortality in critically ill patients with nosocomial *Escherichia* coli bacteremia. *Infect Control Hosp Epidemiol* 2003;*24*:912–915.
13. Holmbom M, Giske CG, Fredrikson M, *et al.* 14-Year survey in a Swedish county reveals a pronounced increase in bloodstream infections (BSI). Comorbidity—an independent risk factor for both BSI and mortality. *PLoS One* 2016;*11*:e0166527. doi: 10.1371/journal.pone.0166527.
14. Wilson J, Elgohari S, Livermore DM, *et al.* Trends among pathogens reported as causing bacteraemia in England, 2004–2008. *Clin Microbiol Infect* 2011;*17*:451–458.
15. Buetti N, Marschall J, Atkinson A, Kronenberg A, Swiss Centre for Antibiotic Resistance (ANRESIS). National bloodstream infection

surveillance in Switzerland 2008–2014: different patterns and trends for university and community hospitals. *Infect Control Hosp Epidemiol* 2016;*37*:1060–1067.
16. Søgaard M, Nørgaard M, Dethlefsen C, Schønheyder HC. Temporal changes in the incidence and 30-day mortality associated with bacteremia in hospitalized patients from 1992 through 2006: a population-based cohort study. *Clin Infect Dis* 2011;*52*:61–69.
17. McGregor JC, Rich SE, Harris AD, *et al.* A systematic review of the methods used to assess the association between appropriate antibiotic therapy and mortality in bacteremic patients. *Clin Infect Dis* 2007;*45*:329–337.

https://doi.org/10.1017/ice.2019.59 Published online by Cambridge University Press