

- 2 Hombach M, Böttger EC, Roos M. The critical influence of the intermediate category on interpretation errors in revised EUCAST and CLSI antimicrobial susceptibility testing. *Clin Microbiol Infect* 2012; **19**: 59–71.
- 3 Blöchliger N, Keller PM, Böttger EC *et al*. MASTER: a model to improve and standardize clinical breakpoints for antimicrobial susceptibility testing using forecast probabilities. *J Antimicrob Chemother* 2017; **72**: 3864–9.
- 4 EUCAST. Breakpoint Tables for Interpretation of MICs and Zone Diameters, Version 8.0, 2018. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_8.0_Breakpoint_Tables.pdf.
- 5 Hombach M, Maurer FP, Pffner T *et al*. Standardization of operator-dependent variables affecting precision and accuracy of the disk diffusion method for antibiotic susceptibility testing. *J Clin Microbiol* 2015; **53**: 2553–61.
- 6 Leclercq R, Cantón R, Brown DFJ *et al*. EUCAST expert rules in antimicrobial susceptibility testing. *Clin Microbiol Infect* 2013; **19**: 141–60.
- 7 Jacobs MR, Bajaksouzian S, Palavecino-Fasola EL *et al*. Determination of penicillin MICs for *Streptococcus pneumoniae* by using a two- or three-disk diffusion procedure. *J Clin Microbiol* 1998; **36**: 179–83.
- 8 Bruin JP, Diederer BMW, Ijzerman PF *et al*. Correlation of MIC value and disk inhibition zone diameters in clinical *Legionella pneumophila* serogroup 1 isolates. *Diagn Microbiol Infect Dis* 2013; **76**: 339–42.

J Antimicrob Chemother 2018; **73**: 2268–2269
doi:10.1093/jac/dky159
Advance Access publication 2 May 2018

Prevalence of resistance to antibiotics in children's urinary *Escherichia coli* isolates estimated using national surveillance data

K. B. Pouwels^{1,2*}, J. V. Robotham¹, C. A. M. McNulty³,
B. Muller-Pebody⁴ and S. Hopkins^{4,5}

¹Modelling and Economics Unit, National Infection Service, Public Health England, London NW9 5EQ, UK; ²Department of Health Sciences, Global Health, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands; ³Primary Care Unit, Public Health England, Gloucester Royal Hospital, Gloucester, UK; ⁴Healthcare-Associated Infection and Antimicrobial Resistance Department, National Infection Service, Public Health England, London, UK; ⁵Directorate of Infection, Royal Free London NHS Foundation Trust, London, UK

*Corresponding author. Tel: +44-(0)20-8327-6377;
E-mail: k.b.pouwels@gmail.com orcid.org/0000-0001-7097-8950

Sir,
Recently, Bryce *et al.*¹ showed in a prospective study that the prevalence of resistance to antibiotics in urinary *Escherichia coli* isolates obtained from children <5 years of age was high. For example, the prevalences of resistance to amoxicillin and trimethoprim, two antibiotics recommended for the treatment of lower urinary tract infection (UTI) in children,² were approximately 50% and 28%, respectively (Table 1).^{1,3} In contrast, all isolates were susceptible to nitrofurantoin.^{1,2} To improve the certainty on the actual prevalence of resistance in England, a larger sample size is needed. In response to the relatively high prevalence of trimethoprim resistance in isolates from adults, guidelines have been revised recently and now recommend nitrofurantoin be used over trimethoprim as a first-line treatment for uncomplicated UTIs in adults.^{2,4} However, Bryce *et al.*¹ speculated that the same recommendation has not been made for children due to the absence of resistance data for this age group in the UK. NICE are currently reviewing the antibiotic treatment recommendations for children and adults.⁵

PHE's national laboratory surveillance system, Second Generation Surveillance System (SGSS), captures data supplied electronically by ~98% of hospital microbiology laboratories in England. SGSS records contain results for all antimicrobials tested (including results suppressed from clinical reports) for isolates from all clinical specimen types as well as demographic patient information such as age and gender.⁶ A limitation of using urine specimens recorded in SGSS is that samples may be more likely to be tested if a patient has risk factors for antibiotic resistance, potentially leading to overestimation of resistance prevalence. However, among infants and children <3 years of age the prevalence should not be systematically overestimated as national guidance recommends to always send a sample in case of symptoms suggestive of UTI.² For children aged ≥3 years, the prevalence might be overestimated to a certain extent as current NICE guidance recommends sending a sample for culture only if the patient is at risk of serious illness and/or has a history of recurrent UTI, if both leucocyte esterase and nitrite are positive.²

Here we evaluated whether, when using these national data, the estimated prevalence of resistance to antibiotics in urinary *E. coli* isolates obtained from children <5 years of age was concordant with the results of Bryce *et al.*¹ We restricted our analysis to one financial year (April 2014 to March 2015) (as compared with 2010 to 2013 in Bryce *et al.*¹) and only included samples received from general practices (as compared with primary care and emergency department presentations in Bryce *et al.*¹). Repeat specimen reports received from the same patient with matching causative agents were excluded if the specimen dates were within 90 days. We focused on antibiotics recommended for treatment of UTI in children and for which at least 75% of the urinary *E. coli* samples included susceptibility test results: trimethoprim (99%), nitrofurantoin (99%), co-amoxiclav (93%), ciprofloxacin (82%), cefalexin (82%) and amoxicillin (77%). We observed similar prevalences of resistance to Bryce

Table 1. Prevalence of resistance to antibiotics among urinary *E. coli* samples from children aged <5 years

Antibiotic	Female (n = 9133), % (95% CI) ^{a,b}	Male (n = 1393), % (95% CI) ^{a,b}	All (n = 10 526), % (95% CI) ^{a,b}	Pathogens (n = 79), % (95% CI) ^{c,d}	Contaminants (n = 745), % (95% CI) ^{c,e}
Nitrofurantoin	1.35 (1.13–1.61)	1.96 (1.35–2.83)	1.43 (1.22–1.68)	0.00 (0.00–4.64)	0.00 (0.00–0.51)
Trimethoprim	30.72 (29.78–31.68)	31.77 (29.37–34.27)	30.86 (29.98–31.75)	27.85 (19.17–38.58)	16.52 (14.02–19.35)
Amoxicillin	52.56 (51.40–53.73)	64.92 (62.07–67.68)	54.25 (53.16–55.33)	49.37 (38.63–60.16)	37.32 (33.92–40.85)
Co-amoxiclav	13.71 (12.99–14.46)	19.33 (17.28–21.58)	14.46 (13.77–15.17)	16.46 (9.88–26.15)	21.48 (18.68–24.57)
Ciprofloxacin	6.17 (5.65–6.74)	7.19 (5.84–8.83)	6.31 (5.81–6.84)	3.80 (1.30–10.58)	3.62 (2.50–5.22)
Cefalexin	7.20 (6.64–7.81)	10.64 (8.98–12.57)	7.66 (7.11–8.24)	1.27 (0.22–6.83)	4.03 (2.84–5.69)

^aNot all urinary *E. coli* samples included susceptibility test results: trimethoprim (99%), nitrofurantoin (99%), co-amoxiclav (93%), ciprofloxacin (82%), cefalexin (82%) and amoxicillin (77%).

^bLaboratories usually do not report isolates cultured at <10⁴ cfu/mL, as per UK Standards for Microbiology Investigations.⁸

^cResults from Bryce *et al.*¹ CIs are calculated based on the values from Table 2 of that paper.

^d*E. coli* isolates cultured at ≥10⁵ cfu/mL.

^e*E. coli* isolates cultured at 10³–10⁵ cfu/mL.

et al.,¹ but with much narrower CIs due to the much larger sample size (Table 1). Our results confirm that the prevalence of trimethoprim resistance is indeed high with ~30% of *E. coli* isolates from urinary samples from children aged <5 years being resistant to trimethoprim. Among children <3 years of age, where overestimation of the prevalence was less likely, the trimethoprim resistance prevalence was 32%. Our much larger sample confirms that nitrofurantoin resistance is low in this age group (1.4%).

Given the relatively high prevalence of resistance to trimethoprim and low levels of resistance to nitrofurantoin, it should be reconsidered whether the guidelines for children should, in line with the recent changes made for UTIs in adults, recommend nitrofurantoin as first-line treatment for uncomplicated lower UTIs (cystitis) in children and reserve trimethoprim for those patients where isolated bacteria have been identified as trimethoprim susceptible. A shift from trimethoprim to nitrofurantoin may result in a decrease in the trimethoprim resistance prevalence,⁶ thereby increasing the effectiveness of trimethoprim in those who are really dependent on this antibiotic for their recovery. However, a switch to nitrofurantoin is not without drawbacks: it is not effective in treating ascending UTI, pyelonephritis or bloodstream infection and is markedly more expensive for the liquid formulation that is required for young children [for example the current British National Formulary (BNF) list price for liquid nitrofurantoin is £446.95 compared with £1.48 for cefalexin].

The comparable results between the prospective study from Bryce *et al.*¹ and our study suggest that SGSS can be reliably used for surveillance in children in this age category. To enable physicians and other stakeholders to assess the local prevalence of resistance in *E. coli* isolates from urinary samples from children, and with this additional cross-validity confirmation, PHE will publish regional resistance prevalence data for children <5 years of age by clinical commission group (CCG). These data will soon be available through Fingertips, a publicly available accessible web tool (<https://fingertips.phe.org.uk/profile/amr-local-indicators>).⁷

Transparency declarations

None to declare.

References

- 1 Bryce A, Costelloe C, Wootton M *et al.* Comparison of risk factors for, and prevalence of, antibiotic resistance in contaminating and pathogenic urinary *Escherichia coli* in children in primary care: prospective cohort study. *J Antimicrob Chemother* 2018; **73**: 1359–67.
- 2 NICE. *Urinary Tract Infection in Under 16s: Diagnosis and Management. Clinical Guideline [CG54]*. Published date: August 2007. Last updated: September 2017. <https://www.nice.org.uk/guidance/cg54>.
- 3 Hay AD, Birnie K, Busby J *et al.* The Diagnosis of Urinary Tract infection in Young children (DUTY): a diagnostic prospective observational study to derive and validate a clinical algorithm for the diagnosis of urinary tract infection in children presenting to primary care with acute illness. *Health Technol Assess* 2016; **20**: 1–294.
- 4 PHE. *Managing Common Infections: Guidance for Primary Care*. 2017. <https://www.gov.uk/government/publications/managing-common-infections-guidance-for-primary-care>.
- 5 NICE. *Managing Common Infections - Antimicrobial Prescribing Guidelines. In Development [GID-NG10050]*. <https://www.nice.org.uk/guidance/indevelopment/gid-ng10050>.
- 6 Pouwels KB, Freeman R, Muller-Pebody B *et al.* Association between use of different antibiotics and trimethoprim resistance: going beyond the obvious crude association. *J Antimicrob Chemother* 2018; **73**: 1700–7.
- 7 Johnson AP, Muller-Pebody B, Budd E *et al.* Improving feedback of surveillance data on antimicrobial consumption, resistance and stewardship in England: putting the data at your Fingertips. *J Antimicrob Chemother* 2018; **72**: 953–6.
- 8 Standards Unit, Microbiology Services, PHE. *UK Standards for Microbiology Investigations: Investigation of Urine*. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/638270/B_41i8.4.pdf.

Funding

This study was carried out as part of our routine work.