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

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Running title: prevalence of antibiotic resistance among children

Sir,

Recently, Bryce *et al.* showed in a prospective study that the prevalence of resistance to antibiotics in urinary *Escherichia coli* isolates obtained from children aged <5 years of age was high.[1] For example, the prevalences of resistance to amoxicillin and trimethoprim, two antibiotics recommended for the treatment of lower urinary tract infection 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 urinary tract infections (UTIs) in adults.[2,4] However, they 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]

Public Health England's national laboratory surveillance system (Second Generation Surveillance System [SGSS]) captures data supplied electronically by approximately 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 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 year, 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 leukocyte 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 those of of Bryce *et al.*[1] We restricted our analysis to one financial year (April 2014 – March 2015) (as compared to 2010 - 2013 in Bryce *et al.*[1]) and only included samples received from general practices (as compared to 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 as Bryce *et al.*,[1] but with much narrower confidence intervals due to the much larger sample size (Table 1). Our results confirm that the prevalence of trimethoprim resistance is indeed high with approximately 30% of *E. coli* isolates from urinary samples from children aged <5 years old being resistant to trimethoprim. Among children <3 years old, where overestimation of the prevalence was less likely, the trimethoprim 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 resistance levels 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 BNF list price for liquid nitrofurantoin is £446.95 compared to £1.48 for cephalexin).

The comparable results between the prospective study from Bryce *et al*[1] and our results 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, Public Health England will publish regional resistance prevalence data for children <5 years of age by clinical commission group (CCG). These data will be soon available through Fingertips, a publicly available accessible web tool (https://fingertips.phe.org.uk/profile/amr-local-indicators).[7]

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This study was carried out as part of our routine work

Transparency declarations

None to declare

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Table 1.

Prevalence of resistances to antibiotics among urinary *E. coli* samples from female and all children aged<5y

Antibiotic	Female (n=9133),[a] % (95% CI)[b]	Male (n=1393),[a] % (95% CI)[b]	All (n=10526),[a] % (95% CI)[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)	16.51 (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)

[a] Not all urinary E. coli samples included susceptibility test results: trimethoprim (99%), nitrofurantoin (99%), co-amoxiclav (93%), ciprofloxacin (82%), cefalexin (82%) and amoxicillin (77%)

[b] Laboratories usually do not report isolates cultured at $<10^4$ cfu/mL as per Standards for Microbiology Investigations[8]

[c] Results from Bryce et al.[1] Confidence intervals are calculated based on the values from Table 2 from that paper

[d] *E. coli* isolates cultured at >10^5 cfu/mL

[e] *E. coli* isolates cultured at 10^3 – 10^5 cfu/mL