Global antibiotic resistance prevalence in paediatric Escherichia coli urinary tract infections and associations with routine use of primary care antibiotics: a systematic review and meta-analysis

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Global antibiotic resistance prevalence in paediatric *Escherichia coli* urinary tract infections and associations with routine use of primary care antibiotics: a systematic review and meta-analysis

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Keywords: urinary tract infection, antimicrobial resistance, *E. coli*, paediatrics, primary care

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ABSTRACT

Objectives

To systematically review studies investigating prevalence of antibiotic resistance in *Escherichia coli* urinary tract infections (UTIs) in children and, where appropriate, meta-analyse the relationship between previous primary care prescribed antibiotics and resistance.

Design and data analysis

Systematic review and meta-analysis. Pooled percentage prevalence of resistance to the most commonly used primary care antibiotics in children, stratified by study country Organisation for Economic Co-operation and Development (OECD) status. Random-effects meta-analysis to quantify the association between previous primary care antibiotic exposure and resistance.

Data Sources

Observational and experimental studies identified through Medline, Embase, Cochrane and ISI Web of Knowledge databases, searched for articles published up to June 2014.

Eligibility criteria for selecting studies

Studies were eligible if they investigated and reported resistance in community-acquired UTI in children aged between 0 to 17 years presenting to primary care. Electronic searches using MeSH terms and text words identified 3015 papers. Two independent reviewers assessed study quality and performed data extraction.

Results

We found 54 observational studies investigating 72,988 *E. coli* urinary isolates. In OECD country studies, the pooled resistance prevalence to ampicillin was 51.4% (95% CI: 47.8-54.9%); trimethoprim 25.8% (21.3-30.4%); co-amoxiclav 9.8% (8.6-10.9%); ciprofloxacin 3.6% (2.6-4.5%); nitrofurantoin was the lowest at 1.6% (1.2-2.1%). Resistance in non-OECD country studies was significantly higher: ampicillin 75.3% (67.2-83.4%); co-amoxiclav 64.1% (42.7-85.5%); ciprofloxacin 25.2% (13.5-36.9%); and nitrofurantoin 12.3% (7.8-16.4%). We found strong evidence of an association between primary care prescribed antibiotics and resistance, which may persist for up to 12 months (OR 2.18; 95% CI: 1.76-2.71).

Conclusions

Prevalence of resistance to commonly prescribed primary care antibiotics in *E. coli* UTIs in children is high, particularly in non-OECD countries, where one possible explanation is over-the-counter antibiotic availability. This could render some antibiotics ineffective as first-line UTI treatments. Routine primary care use of antibiotics contributes to antimicrobial resistance in children, which may persist for up to 12 months post-antibiotic prescription.

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WHAT IS ALREADY KNOWN ON THIS TOPIC
Children are high recipients of primary care prescribed antibiotics worldwide.
Routine primary care use of antibiotics has been shown to increase the probability of antibiotic resistance in adults with urinary tract infections.
Substantial variations in antibiotic use exist globally, with over-the-counter availability common in many countries.
WHAT THIS STUDY ADDS
Prevalence of resistance in *E. coli* causing UTI in children is high, including to some first-line UTI treatments, such as trimethoprim.
Several antibiotics commonly used in primary care for children, including ampicillin and trimethoprim, could be ineffective first-line treatment options.
Routine use of antibiotics for children in primary care increases bacterial resistance in UTI, which may persist for up to 12 months. Clinicians should take account of resistance when considering the need for, and selection of, antibiotics for subsequent infections.

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INTRODUCTION

Antimicrobial resistance is an internationally recognised health threat. The contribution of primary health care is particularly important, as this is where almost 80% of all health service antibiotics are prescribed.[1] Antibiotic resistant bacterial infections can limit the availability of effective treatment options, rendering some commonly encountered bacterial infections difficult to treat, including urinary tract infections (UTI). Antibiotic resistant infections are also twice as likely to be associated with greater morbidity and mortality, and associated with increased healthcare costs.[2] In low-income countries, affordability of second-line drugs and reduced access to healthcare may restrict the use of stronger antibiotics, resulting in growing concerns for increased morbidity and mortality due to antibiotic resistant infections in these countries.[3]

Children are high frequency recipients of primary health care services, and as such receive a disproportionately high number of antibiotics compared with middle-age populations.[4] Children are also key drivers of infection within communities and can contribute to the person-to-person spread of bacteria. Despite this, very little research has been published describing the prevalence of bacterial resistance in children, or the risk factors which may be important in this group. Costelloe *et al* (2010) conducted a systematic review in 2010 which reported strong associations between previous exposure to routinely prescribed primary care antibiotics and antimicrobial resistance persisting for up to 12 months. [5] However, most of the contributing studies were conducted in adults.

UTIs are one of the most common bacterial infections seen in primary care.[6] Empiric antibiotic treatment while awaiting culture and sensitivity testing is the most common management strategy when children are suspected of having a UTI. Young children are more vulnerable to immediate and long-term complications of UTI, including renal scarring and renal failure,[7] and therefore require prompt, appropriate treatment. *E. coli* is responsible for over 80% of all UTIs,[8] and is also the most common cause of bacteraemia, foodbourne infections, and a cause of meningitis in neonates.[9]

We conducted a systematic review aimed to investigate the prevalence of resistance in community-acquired *E. coli* UTI to the most commonly prescribed primary care antibiotics to children, and quantify the relationship between previous exposure to primary care antibiotics and bacterial resistance. We stratified results by study country Organisation for Economic Co-operation and Development (OECD) status as antibiotics tend to be used differently in these groups; in OECD countries antibiotics are obtained mostly by prescription only, whereas in non-OECD countries many antibiotics, including those commonly used to treat UTI, can be obtained over-the-counter (OTC), without the need for a prescription.[10-14]

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METHODS

Search strategy and selection criteria

We searched Medline, Embase and Cochrane for articles published in any language between 1955 and June 2014. MeSH terms for these databases included “drug resistance”, “antimicrobial resistance”, “bacterial resistance”, “primary health care”, “urinary tract infections” and “children”. MeSH terms were combined with text word searches which included “antibiotic(s)”, “primary care”, “family practice”, “ambulatory care”, “community”, “UTI” and “urinary bacteria”. Grey and unpublished literature was searched for using ISI Web of Knowledge software and included journal articles, patents, websites, conference proceedings and open access material. Reference lists of selected key papers were screened and authors who appeared multiple times were contacted to request details of further published and unpublished work. All full-text papers were subject to citation searches. See Appendix 1 for full search strategy. Our review protocol was published on PROSPERO (http://www.crd.york.ac.uk/PROSPERO/).

Two independent reviewers (AB and HT) screened all titles and abstracts independently for eligibility. Studies were eligible for inclusion if they met the following criteria: investigated and reported patterns of resistance in *E. coli*-positive UTI isolates from the community or primary care setting, or investigated associations between previous antibiotic exposure and bacterial resistance; and study participants were children aged 0 to 17 years presenting to primary care with symptoms of UTI and had a urine sample taken. We included hospital-based studies where it was clear thatinvestigation was for community-acquired UTI, which we defined as laboratory-diagnosed UTI from urine samples taken within 48 hours of admission.

Data extraction and quality assessment

Full-text papers for all eligible studies were obtained and three reviewers (AB, CC and IL) extracted data independently using a purpose-built spreadsheet. The following information was extracted from each paper, where provided: author, journal, year of publication, study design, study country, economic status, participants and recruitment location, recruitment time period, age range, method of urine sample collection and testing, method of antimicrobial sensitivity testing, bacteria cultured and reported antibiotic sensitivities, previously prescribed antibiotics and time between antibiotic exposure and urine sample collection. Economic status was measured using the OECD status of the country the study was conducted in.[15] For antimicrobial exposure, time was generally recorded as a period of days, weeks or months prior to the urine sample being taken and resistance being measured using standard local laboratory methods. Where any information was unclear in the paper, authors were contacted for clarification.

We reported resistance to antibiotics commonly prescribed to children in primary care, either for urinary tract infection or other indications including respiratory and skin infections. Resistance data was extracted and reported for the following antibiotics: ampicillin, co-amoxiclav (amoxicillin-clavulanic acid), co-trimoxazole (trimethoprim-sulfamethoxazole), trimethoprim, nitrofurantoin, ciprofloxacin and ceftazidime. Ampicillin was reported in place of amoxicillin due to more frequent reporting and its equivalence in spectrum of antimicrobial activity.[16]

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Included papers were assessed for quality using a checklist based on Cochrane collaboration's 'risk of bias' tool,[17] and the Critical Appraisal Skills Programme (CASP) checklist for cohort and case-control studies (www.casp-uk.net). Quality assessment charts were produced based on a traffic-light system of 'good', 'adequate' and 'poor' reporting (see Appendix 2). Our key quality criteria for eligible studies were: (1) a reliable measure of antibiotic resistance; (2) clear reporting of bacterial resistance in children aged up to 17 years; and (3) clear reporting of urinary bacteria isolated as community-acquired. For papers which included information on previous antibiotic exposure, the same key quality indicators applied, with the addition of adjustment for confounders including age, sex, previous hospitalisation and comorbidities.

Data synthesis and analysis

All statistical analyses were conducted using STATA version 13 software, and all methods undertaken according to PRISMA guidelines.[18]

We calculated pooled prevalence of resistance estimates by generating a Forest plot for each antibiotic, stratified by OECD status. Forest plots illustrated proportion of resistant *E. coli* for each study, along with 95% confidence intervals (CI), and the pooled prevalence of resistance per antibiotic per economic country group (OECD vs. non-OECD). Pooled prevalence estimates were generated for children of all age groups (0 to 17 years) and children aged 0 to 5 years, for comparison. An I^2 of 25%, 50% and 75% were used to signify low-level, moderate-level and high-level heterogeneity, in line with Cochrane recommendations.[17] Forest plots were generated to present the pooled prevalence of resistance to individual antibiotics in OECD and non-OECD countries.

For studies investigating the association between previous antibiotic exposure and bacterial resistance, the outcome measure was the odds ratio (OR) of bacterial resistance in children previously exposed to antibiotics compared to those children previously unexposed. The crude estimates from these studies were grouped according to the reported preceding exposure time period (0 to 1 month, 0 to 3 months, 0 to 6 months and 0 to 12 months). A random-effects meta-analysis was conducted and a pooled OR was generated for each exposure time period measured. These were compared to adjusted OR for each time period, where reported. We assessed heterogeneity using the I^2 statistic, and the null hypothesis of no heterogeneity was tested using the Q statistic generated from the χ^2 test. Meta-regression was used to investigate differences in the OR between antibiotic exposure and resistance across different time periods. Finally, funnel plots were generated to explore the possibility of small study effects, which can be caused by publication bias.

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RESULTS

Study characteristics

Databases searches identified 4146 articles. Of these, 3015 non-duplicated papers were assessed and 2419 excluded on basis of title (Figure 1). This left 529 papers which were assessed for eligibility by abstract screening; 517 did not meet our eligibility criteria. Seventy-nine full-text papers were obtained and assessed, with 25 papers not meeting our eligibility criteria for the following reasons: 11 had no primary care data, 11 did not report antibiotic susceptibilities for *E. coli* UTI bacteria, two were adult studies and one paper reported duplicate data from another included paper. A total of 54 papers were included in the review, of which five papers (all OECD) reported information of previous antibiotic exposure and were included in our meta-analysis.

Table 1 summarises the characteristics of the 54 studies included in the review. Thirty-one studies were included from OECD countries reporting resistance in 68,766 *E. coli* isolates from the same number of children (see also
Figure 2). All were observational; 23 retrospective, six prospective, and two case-control. Twenty-eight of these studies reported information on prevalence of resistance in *E. coli* UTI isolates, with the remaining three reporting the association between previous antibiotic exposure and *E. coli* resistance only.[19-21] Table 1 also summarises the 23 studies included from non-OECD studies (see also
Figure 2), reporting bacterial resistance in 4188 *E. coli* isolates from the same number of children. All were observational; nine retrospective, 11 prospective, one case-control and two cross-sectional. All 23 non-OECD studies reported information on prevalence of resistance in urinary *E. coli*, with no non-OECD studies reporting information on previous antibiotic exposure. Figure 2 details the number of studies per country included in the review, which generally shows that for both OECD and non-OECD countries, only a few studies from each country were included.

Twenty-eight (19 OECD vs. 9 non-OECD) studies used mixed urine collection methods including clean-catch, catheter or suprapubic aspiration. Antimicrobial sensitivity testing was carried out using standard disk diffusion methods in 41 studies, which were interpreted and reported according to either The British Standard for Antimicrobial Chemotherapy (BSAC) or Clinical and Laboratory Standards Institute (CLSI) guidelines.[22 23] All children had presented to a primary care facility with symptoms of a UTI, with some children sent to a secondary or tertiary care hospital for urine tests.

The quality assessment 'traffic-light' charts for the included studies show that, for the five studies reporting antibiotic exposure information, reporting was generally good for all studies, and good for our all our key quality indicators (see Appendix 2 for charts). For studies reporting prevalence of resistance only, quality overall was good with the exception of controlling for confounding – this was not necessarily an issue as studies which did not control for confounding simply reported numbers of resistant and sensitive urine isolates only and therefore this did not impact on the results.

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Figure 1. Data search and extraction

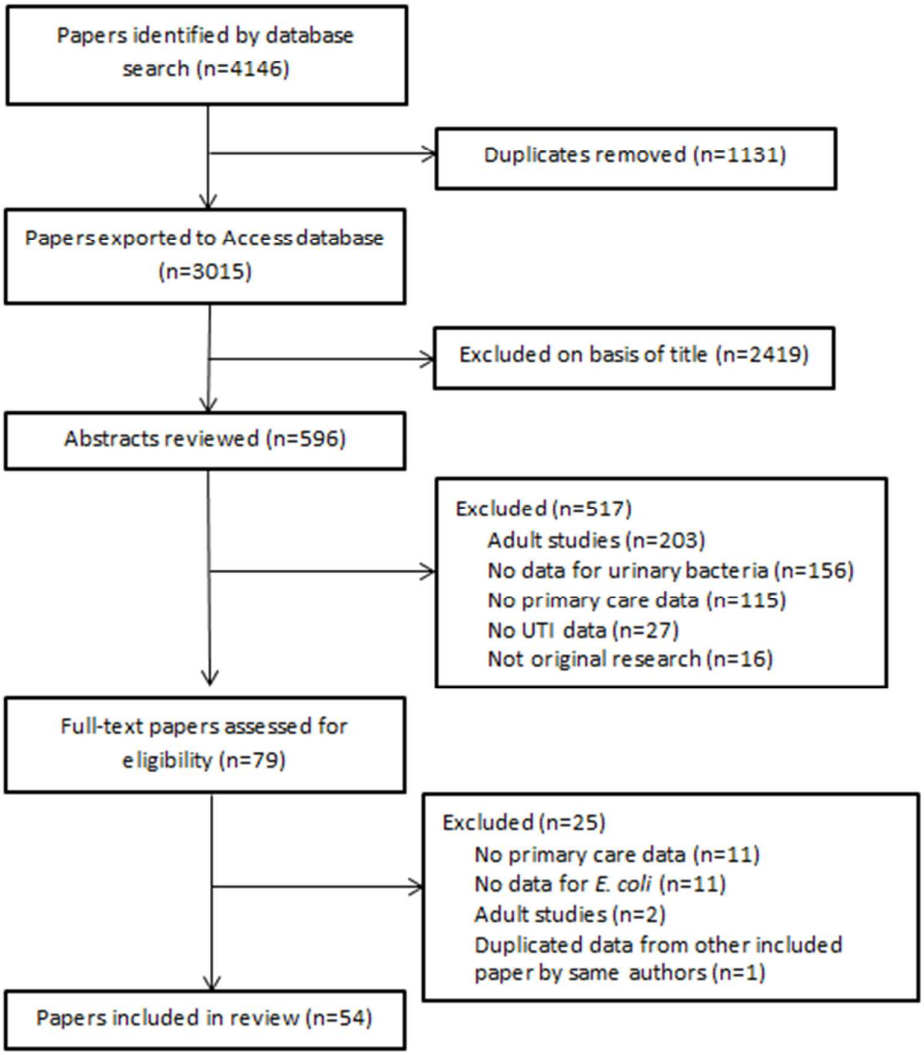

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Table 1. Study characteristics of included papers by OECD status

Study Characteristics	OECD (n=31)		Non-OECD (n=23)	
	Number of papers	Reference number	Number of papers	Reference number
Study Design:				
Retrospective observational	23	8 19 20 24-43 53-58	9	44-52 59-69
Prospective observational	6	21 70	11	71
Case-control	2		1	72 73
Cross-sectional	0		2	
Number of children in study:				
0-100	2	38 42	6	48 52 59 61 63-65 74
101-500	12	20 26 28 32 35 39 53-58	12	45-47 50 52 62 66 68 69 71-73
501-1000	5	31 33 36 41 70	2	44 49
1001-10,000	6	21 25 27 30 34 40	2	51 67
10,001+	6	8 19 24 29 37 43	1	60
Method of urine sampling:				
At least one of: clean-catch, catheter or suprapubic aspiration	19	19-21 26 28 30-38 41 53 55 56 58	9	45 46 60 62 64 69 72-74
Clean-catch only	3	29 42 43 54	4	51 61 67 71
Catheter only	1		0	
Suprapubic aspiration only	0		3	52 59 66
Not reported	8	8 24 25 27 39 40 57 70	7	44 47-49 63 65 68
Method of antimicrobial sensitivity testing:				
Disk diffusion	21	21 24-26 28 30 32 34-36 38-43 53 54 56-58	20	44-46 48-52 60 62-69 71-73
Minimum inhibitory concentration	2	8 37	0	
Vitek	3	29 31 70	0	
Not reported	5	19 20 27 33 55	3	47 59 61
Child age range[a]:				
0-5 years	8	8 32 34 36 37 39 54 70	5	59 62 66 72 73
6-17 years	5	8 34 37 39 70	0	
0-17 years	29	8 19-21 24-31 33 35-43 53 55-58 70	18	44-52 60 61 63-65 67-69 71
Previous antibiotic exposure information[b]	5	19-21 27 70	0	

[a] Age 0-5 years: papers which report data specifically for this age group, 6-17 years: papers which report data specifically for this age group; 0-17 years: papers which report data for the children within 0-17 years, and do not fit into the previous reported age groups. Papers may appear more than once depending on how they have reported their results.

[b] No studies from non-OECD countries collected previous antibiotic exposure data and were not included in the meta-analysis.

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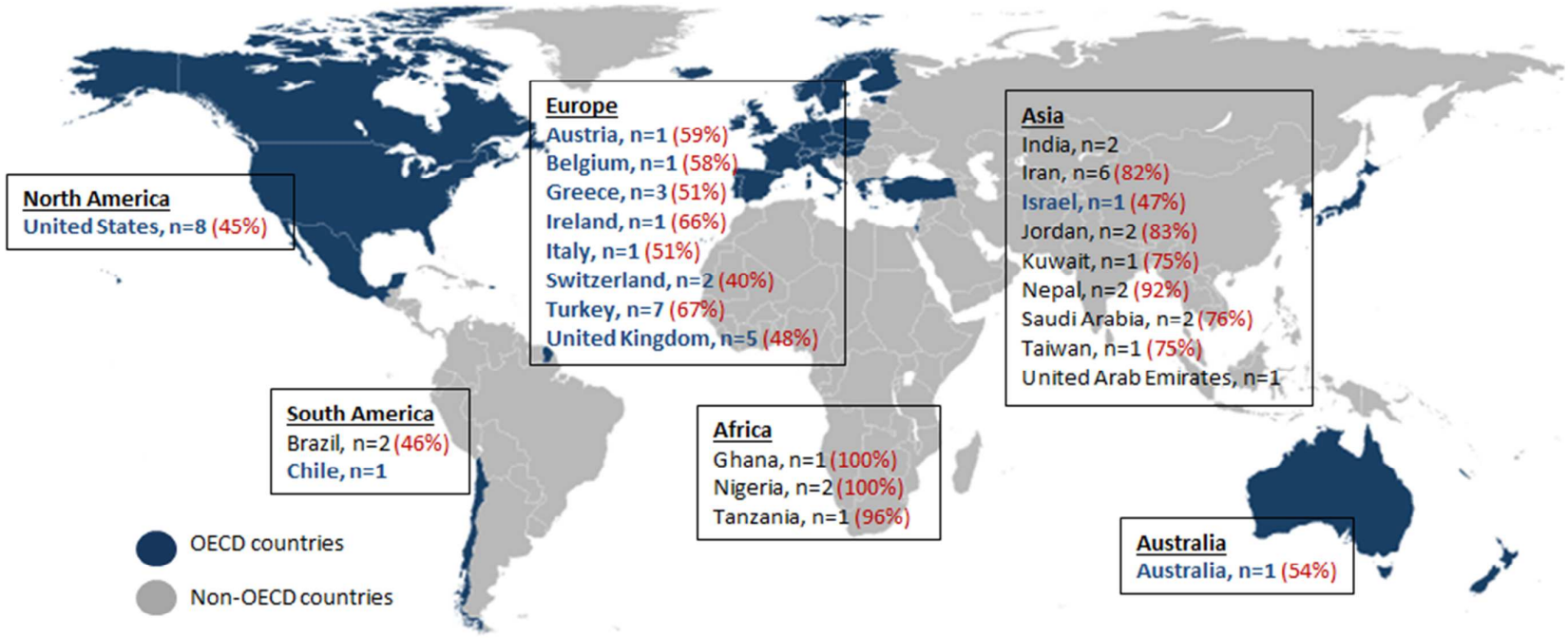
Figure 2. Geographical distribution of urinary *E. coli* resistance prevalence (shown in red) to ampicillin by OECD and non-OECD country,[15] number of included studies per country shown in blue.



Prevalence of resistance in urinary *E. coli*s higher in non-OECD countries, with ciprofloxacin resistance in excess of 20%.

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Table 2 shows the prevalence of E. coli urinary isolate resistance to antibiotics. These data were obtained from Forest plots generated for each antibiotic, which can be found in Appendices 3-9.

Prevalence of antibiotic resistance was higher in non-OECD than OECD countries for all antibiotics tested. Ampicillin resistance was highest for both OECD and non-OECD countries. Figure 2 shows the pooled prevalence (or single-study reported prevalence if n=1) of ampicillin resistance for country. Switzerland had the lowest prevalence of ampicillin resistance at 40%, with Ghana and Nigeria highest at 100%.

Pooled prevalence of resistance to co-trimoxazole and trimethoprim resistance were high in OECD countries, with co-trimoxazole resistance above 30%. Resistance to co-trimoxazole was almost three times higher in non-OECD compared to OECD countries. Trimethoprim resistance was only reported in one non-OECD study conducted by Al-Mugeiren *et al* (1996) which reported 67% resistance from 596 *E. coli* urinary isolates from the same number of children.[67] Nitrofurantoin resistance was lowest for both OECD and non-OECD countries of all reported antibiotics in this review.

Pooled prevalence of resistance to ciprofloxacin and ceftazidime in children's *E. coli* urinary isolates were both below 5% in OECD countries; however, resistance to both antibiotics were over four times higher in non-OECD countries, with ciprofloxacin resistance in excess of 20%.

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Table 2. Pooled percentage prevalence (95% CI) of resistance to primary care antibiotics in urinary *E. coli* from children (see Appendices 3-9 for corresponding Forest plots and paper references)

Antibiotics	OECD				Non-OECD			
	Pooled prevalence	Number of isolates tested	p-value	I^2	Pooled prevalence	Number of isolates tested	p-value	I^2
Ampicillin	**51.4%** (47.8-54.9%)	66,503	0.034	32.4%	**75.3%** (67.2-83.4%)	2265	0.573	0%
Co-amoxiclav	**9.8%** (8.6-10.9%)	65,076	<0.001	85.1%	**64.1%** (42.7-85.5%)	1256	0.715	0%
Co-trimoxazole	**32.0%** (26.2-37.9%)	50,230	0.790	0%	**62.2%** (52.3-72.1%)	2590	0.619	0%
Trimethoprim	**25.8%** (21.3-30.4%)	18,977	0.310	11.8%	Too few data[a]	596	Too few data[a]	Too few data[a]
Nitrofurantoin	**1.6%** (1.2-2.1%)	50,994	<0.001	67.3%	**12.3%** (7.8-16.4%)	3020	0.032	41.9%
Ciprofloxacin	**3.6%** (2.6-4.5%)	52,209	<0.001	58.9%	**25.2%** (13.5-36.9%)	1723	0.131	34.6%
Ceftazidime	**4.1%** (2.7-5.4%)	25,805	<0.001	79.2%	**18.8%** (11.2-26.5%)	1136	0.034	53.8%

[a] Only one study from non-OECD countries

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Prevalence of resistance in children aged 0 to 5 years

Twelve studies reported resistance in urinary *E. coli* specifically for children aged 0 to 5 years, seven from OECD countries and five from non-OECD countries (Table 3). As with all children, the prevalence of antibiotic resistance in children aged 0 to 5 years was higher in non-OECD than OECD countries. The pooled prevalence of resistance in urinary *E. coli* was higher in OECD countries for children aged 0 to 5 years against ampicillin and ceftazidime; and lower for co-amoxiclav, co-trimoxazole and nitrofurantoin, when compared to all children (s higher in non-OECD countries, with ciprofloxacin resistance in excess of 20%.

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Table 2). In non-OECD countries, resistance was higher for children aged 0 to 5 years against all reported antibiotics, compared to all children.

Table 3. Pooled prevalence (%) of resistance to primary care antibiotics in urinary *E. coli* from children aged 0 to 5 years

Antibiotics	OECD					Non-OECD				
	Pooled prevalence (%)	No. isolates tested	p-value	I^2	Reference number	Pooled prevalence (%)	No. isolates tested	p-value	I^2	Reference number
Ampicillin	**55.2%** (95% CI: 48.8-61.5%)	5273	0.354	9.8%	[8 32 34 36 37]	**79.1%** (95% CI: 66.0-92.3%)	176	0.427	0%	[62 66 72]
Co-amoxiclav	**9.3%** (95% CI: 6.2-12.4%)	5273	0.046	51.1%	[8 32 34 36 37]	**72.1%** (95% CI: 40.8-100%)	89	0.370	0%	[59 66 72]
Co-trimoxazole	**28.9%** (95% CI: 21.3-36.4%)	5405	0.097	39.2%	[8 32 34 36 37 39 54]	**69.8%** (95% CI: 32.2-100%)	257	0.553	0%	[62 66 72 73]
Trimethoprim	Too few data[a]	188		Too few data[a]	[36]	No data[b]	0	-	-	-
Nitrofurantoin	**0.6%** (95% CI: 0.4-1.7%)	1706	0.317	0%	[8 36]	**36.4%** (95% CI: 24.3-48.5%)	96	0.975	0%	[66 73]
Ciprofloxacin	**3.6%** (95% CI: 1.0-6.1%)	2864	0.203	32.8%	[8 34 54]	Too few data[c]	49		Too few data[c]	[59]
Ceftazidime	**5.9%** (95% CI: 1.2-10.7%)	1358	0.244	27.9%	[34 36 54]	**42.3%** (95% CI: 7.8-76.8%)	130	0.317	0%	[59 73]

[a] Only one study from OECD countries
[b] No studies from non-OECD countries reported resistance to trimethoprim in children aged 0-5 years
[c] Only one study from non-OECD countries

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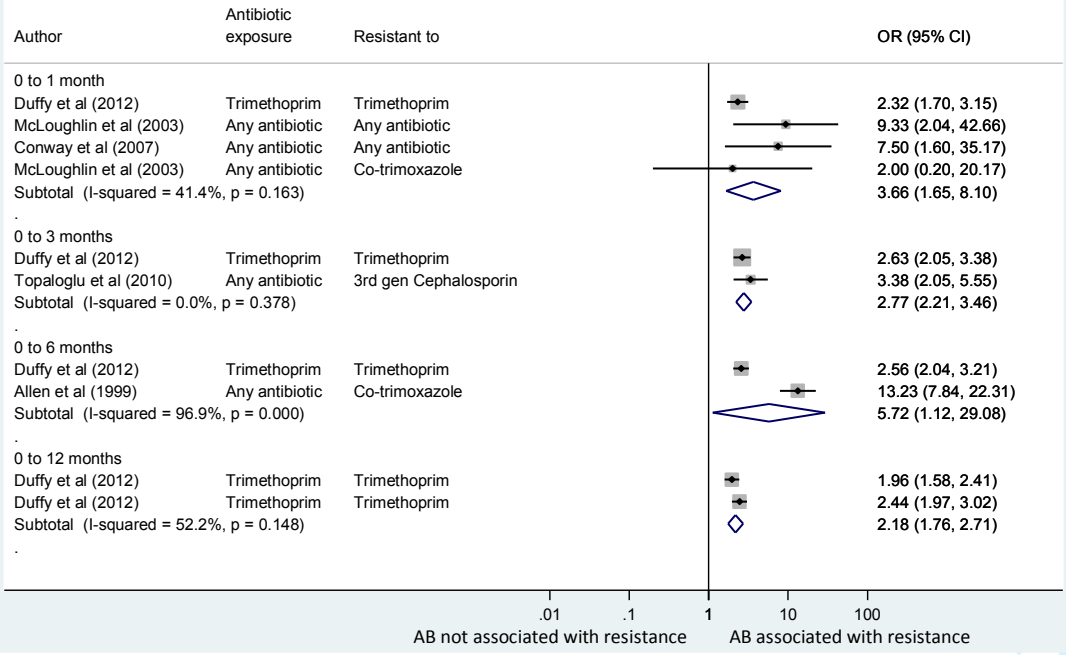
Association between previous antibiotic exposure and bacterial resistance

Figure 3 shows a Forest plot of five studies investigating the relationship between previous exposure to any versus no antibiotics and bacterial resistance. The studies varied in the drug-bug combinations investigated, some reporting resistance to any antibiotic, while others reporting resistance to trimethoprim, co-trimoxazole or third generation cephalosporins.

For all antibiotic exposure time periods the crude odds of resistance were generally greater in children exposed to antibiotics than in those who were unexposed. The effect sizes are reasonably similar for all time periods, with a pooled OR of resistance at 0 to 1 month following prescribing of 3.7 (95% CI: 1.7-8.1), 0 to 3 months 2.8 (2.2-3.5), 0 to 6 months 5.7 (1.1-29.1) and 0 to 12 months 2.2 (1.8-2.7). The β coefficient for each month increase in exposure time period for the unadjusted model was -0.2 (95% CI: -0.6 to 0.3, P=0.474), indicating no evidence of a trend over time.

There was no evidence of within group heterogeneity in the 0-3 month time period, with moderate heterogeneity in the 0-1 month and 0-12 month periods, and high heterogeneity in the 0-6 month period. For those studies which reported adjusted ORs, we compared these results with our crude estimates, although there was sufficient data to do this for exposure at 0-6 months only. The pooled adjusted OR did not differ substantially from our crude pooled estimates (pooled adjusted OR 5.6, 95% CI: 1.6-77.4), compared to the pooled crude OR of 5.7 (1.1-29.1).

Figure 3. Meta-analysis of individual studies examining association between previous primary care antibiotic exposure and resistance

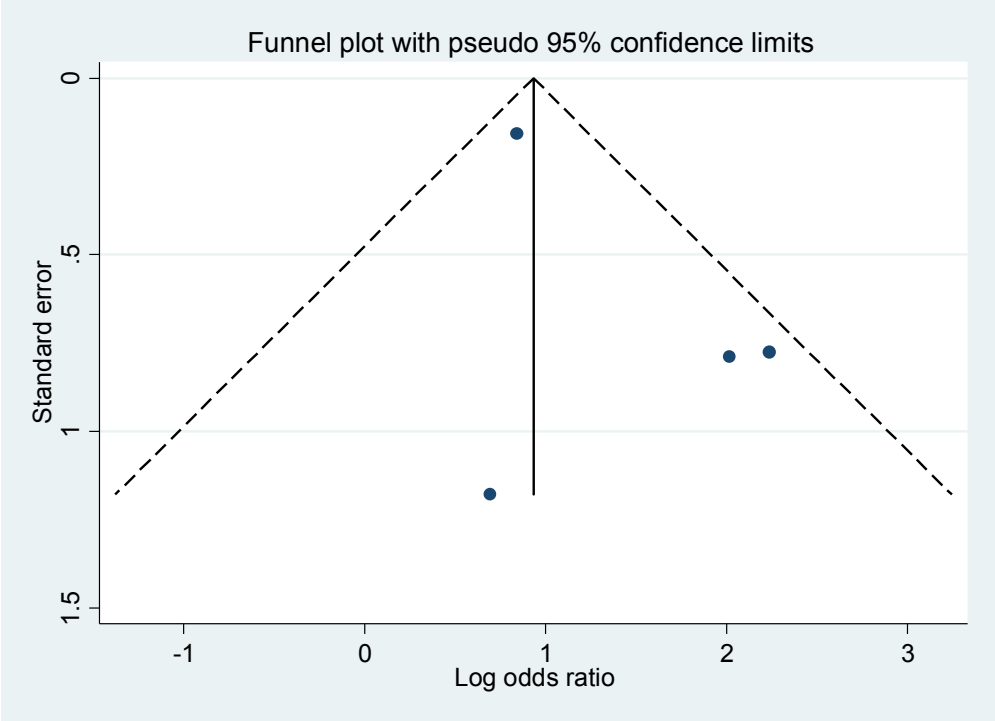


The Forest plot shows pooled OR (log scale) for resistance in children's urinary bacteria and previous exposure to any antibiotic. Studies grouped according to time period during which exposure was measured and ordered within each time period by increasing standard error.

Publication bias

Publication bias was assessed for the studies investigating urinary bacterial resistance in *E. coli* and antibiotic exposure within the previous one month of the urine sample being taken. The Funnel plot shown in Figure 4 did not suggest clear evidence of any publication bias.

Figure 4. Funnel plot with pseudo 95% confidence limits for studies investigating the relationship between antibiotic exposure in the previous one month and urinary bacterial resistance



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DISCUSSION

Principal findings

We identified 54 studies from both OECD and non-OECD countries which provide evidence of high prevalence of bacterial resistance in children's *E. coli* UTI isolates to some of the most commonly prescribed antibiotics in primary care. This was most significant for ampicillin resistance, irrespective of OECD status. Resistance to all reported antibiotics was higher in non-OECD than OECD countries, with resistance to nitrofurantoin relatively low worldwide. High-level resistance may render several antibiotics ineffective first-line treatments in some countries. Routine primary care antibiotic prescribing is an important contributor to bacterial resistance in children, which may persist for up to 12 months post-antibiotic prescription.

Strengths and weaknesses

To our knowledge, ours is the first systematic review and meta-analysis to explore and report global evidence regarding the prevalence of bacterial resistance in children's UTI and associations with the routine use of antibiotics in primary care. The World Health Organisation recently published their 'Global Action Plan' on antimicrobial resistance, which described data relating to the prevalence of resistance, including geographical patterns as a key gap in our current knowledge,[75] which this systematic review fills. Our review was rigorously conducted according to the Cochrane guidelines for Systematic Reviews.[17] We chose to stratify our results by OECD status to reflect both national development and likely OTC antibiotic availability.[3 76]

We are aware of several limitations. First, antibiotics are used very differently within OECD and non-OECD countries,[77 78-80] and OTC antibiotic use is difficult to measure. A 2011 systematic review reported high non-prescription antibiotic variability across countries worldwide,[76] with some evidence of less than 100% agreement between OECD status and OTC antibiotic availability. However, to our knowledge there is no better country-level alternative, and none of the included studies reported or measured OTC antibiotic availability. We also acknowledge that factors other than antibiotic usage and OTC availability can account for differences in resistance prevalence between OECD and non-OECD countries, including; poor sanitation, unstable governance, and lower levels of medicine regulation.

Of the five studies included in our meta-analysis, most reported the association between previous antibiotic exposure and resistance within overlapping time periods. This implies that the associations with longer time periods (*i.e*. 0 to 12 months) could reflect a combination of long and short-term relationships. Our meta-analysis of the association between antibiotic exposure and resistance reported moderate-to-high heterogeneity within some exposure time periods. The overlapping time periods in terms of exposure may have accounted for this, as well as the difficulty in estimating a more accurate point of antibiotic exposure. Heterogeneity was highest in the 0 to 6 month time period, likely to be due to one study which measured exposure to antibiotics for >4 weeks within the previous 6 months,[68] whereas the remaining paper measured exposure to antibiotic prescriptions of any nature. Though we did not find any evidence of publication bias, this should be interpreted with caution, as the meta-analysis for antibiotic exposure within the previous month included only four studies.

Reverse causality and confounding could be important to our meta-analysis. Standard practice in most countries is to treat empirically with an antibiotic when a patient presents to primary care with

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symptoms of a UTI, taking a urine sample if the illness does not respond to first-line antibiotic treatment. For many studies included in this review, the participants are children presenting to primary care with UTI symptoms, therefore retrospective analyses could show spuriously strong associations with previous antibiotic prescribing. This could also apply to our prevalence data, as the children who have provided a urine sample may be more likely to carry a resistant bacterial isolate if they are presenting due to failure of empirical treatment. If only incident cases were included this problem would be avoided, but many studies did not present this information. Reverse causality, and other confounding associations could also have introduced bias to our findings; including previous hospital admission, comorbidities, age and sex. However, all included studies which attempted to adjust for any potential confounding factors seldom demonstrated any substantial difference between crude and adjusted association estimates.

Results in the context of existing research

Prevalence of urinary bacterial resistance

We believe our resistance prevalence rates are accurate due to their consistency with other data sources. The highest reported resistance to ampicillin in this review was very similar to the reported aminopenicillin group resistance in the European EARS-Net database and US Centre for Disease Dynamics, Economics and Policy (CDDEP) databases.[81 82] Resistance to ampicillin in other studies from the US ranged between 36% and 54%, suggesting that resistance to antibiotics in young children is similar to that of the general population. The similarities observed here could be a result of between age-group transmission of genetic resistance factors such as plasmids; facilitated via frequent interaction between children and adults. Trimethoprim resistance was reported by three studies from the UK all with a large sample size (>1700 isolates); all reported resistance in excess of 20%. These are similar to trimethoprim resistance levels reported by other UK-based studies; Bean *et al* (2008), reported trimethoprim resistance in community-acquired urinary isolates from adults and children at 39%.[83] Additionally, Farrell *et al* (2003) reported 27% resistance in *E. coli* urinary isolates from all age groups.[84] Resistance to nitrofurantoin, an antibiotic used almost exclusively for UTIs, was very low worldwide, supporting its continued effectiveness as a first-line treatment for uncomplicated UTIs. [85-87] Conversely, resistance to co-trimoxazole, a common first-line UTI treatment in many countries outside the UK, was relatively high worldwide, particularly in non-OECD countries at 64%.

For many of the antibiotics reported in this review, the pooled prevalence of resistance was higher in children aged 0-5 years, compared with all children (0-17 years). It has been previously suggested that resistance levels are likely to be higher in those communities with a higher proportion of young children, due to their high consumption of antibiotics.[88] A study conducted in France found that children under seven years old consumed three times more antibiotics compared to older populations.[89] The findings in our review support this theory, as resistance to all commonly prescribed antibiotics worldwide was higher in younger children, when compared to children of predominantly older age. Our findings also suggest there could be a reversible element of antibiotic resistance, whereby reduced use of antibiotics (in older children) reduces selective antibiotic resistance pressure.

Association between previous antibiotic exposure and bacterial resistance

Our meta-analysis showing an association between exposure to antibiotics in the previous 12 months and isolation of resistant urinary isolates is consistent with our previous 2010 review, which

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explored the effect of antibiotic prescribing in primary care on the development of resistance in individual patients of all ages.[5] However, unlike the Costelloe *et al* review, we found no evidence of decreasing resistance for increasing time from antibiotic prescribing.

Clinical and research implications

Our findings detail the global high-level resistance to some of the most commonly prescribed primary care antibiotics in children, which could result in several antibiotics becoming ineffective first-line treatments for many countries. The Infectious Diseases Society of America (IDSA) in collaboration with the European Society for Microbiology and Infectious Diseases (ESCMID) published clinical practice guidelines in 2010 relating to the treatment of uncomplicated UTI;[90] the guidelines recommend that an antibiotic should only be used as a first-line empirical UTI treatment if the local prevalence of resistance is <20%. The findings from our review suggest that, according to these guidelines, ampicillin, co-trimoxazole and trimethoprim may no longer be suitable first-line UTI treatment options in OECD countries. Similarly, in the UK, The National Institute for Health and Care Excellence (NICE) publish prescribing guidelines for the management of UTI in children. The most up-to-date guidelines state that in children three months or older, trimethoprim and amoxicillin are suitable first-line treatments for uncomplicated UTI. The findings from our review suggest that in around 50% of children from OECD countries, including the UK, amoxicillin is ineffective against *E. coli* UTI. Around a quarter of children are also likely to be resistant to trimethoprim. This supports the need for prescribing guidelines to reflect local resistance levels, as failure to do so may encourage inappropriate primary care prescribing. Ruling out certain antibiotics as appropriate first-line treatments could put pressure on clinicians to prescribe stronger second-line antibiotics, such as co-amoxiclav, cephalosporins and quinolones – increased use of such antibiotics as empirical treatment will likely result in the development of a vicious cycle of increasingly powerful antibiotic use and bacterial resistance.

Furthermore, the results indicate that bacterial resistance to antibiotics may persist for up to 12 months following antibiotic exposure in individual children. The best solution is for primary care clinicians to consider the impact of any antibiotic use on antimicrobial resistance, and avoid their unnecessary use by following local and national guidance wherever possible. Where antibiotic treatment is needed, our findings support the need to consider a child's antibiotic use in the past 12 months when selecting further treatment, avoiding the use of broad-spectrum antibiotics wherever possible.[91] Our findings also support other evidence for the continued availability of nitrofurantoin as an effective treatment for uncomplicated UTI's in primary care.[86 92]

Conclusions

Prevalence of resistance to commonly prescribed primary care antibiotics in *E. coli* UTIs in children is high, particularly in non-OECD countries, where one possible explanation is over-the-counter antibiotic availability. This could render some antibiotics ineffective as first-line UTI treatments. Routine primary care use of antibiotics contributes to antimicrobial resistance in children, which may persist for up to 12 months post-antibiotic prescription.

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Appendix 1. Medline and Embase search strategy

MEDLINE and EMBASE search strategy	
1. exp Drug Resistance, Microbial	21. Exp. Urinary Tract Infections/ Transmission
2. Anti-bacterial Agents/ Therapeutic use	22. Exp. Urinary Tract Infections/ Microbiology
3. Antibiotic$.tw	23. Escherichia coli Infections/ Epidemiology
4. Antimicrobial$.tw	24. urinary tract infection.mp
5. antimicrobial resistance.mp	25. UTI.tw
6. resistan$.tw	26. urinary isolate$.tw
7. 1 or 2 or 3 or 4 or 5 or 6	27. uropathoge$.tw
8. Exp. Primary Health Care	28. urine.tw
9. Exp. Community-acquired Infections/ Microbiology	29. urinary.tw
10. Exp. Community-acquired Infections/ Transmission	30. 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
11. Exp. Community-acquired Infections/ Epidemiology	31. Exp. Child
12. Outpatient$.tw	32. Exp. Child/ Preschool
13. Community.tw	33. Exp. Infant
14. Family practice.mp	34. Exp. Adolescent
15. Ambulatory care.mp	35. child.tw
16. Primary care.mp	36. children.tw
17. 8 or 9 or 10 or 11 or 12 or 13 or 14 of 15 or 16	37. p?ediatri$.tw
18. Exp. Urinary Tract Infections/ Diagnosis	38. 31 or 32 or 33 or 34 or 35 or 36 or 37
19. Exp. Urinary Tract Infections/ Epidemiology	39. 7 and 17 and 30 and 38
20. Exp. Urinary Tract Infections/ Prevention and Control	

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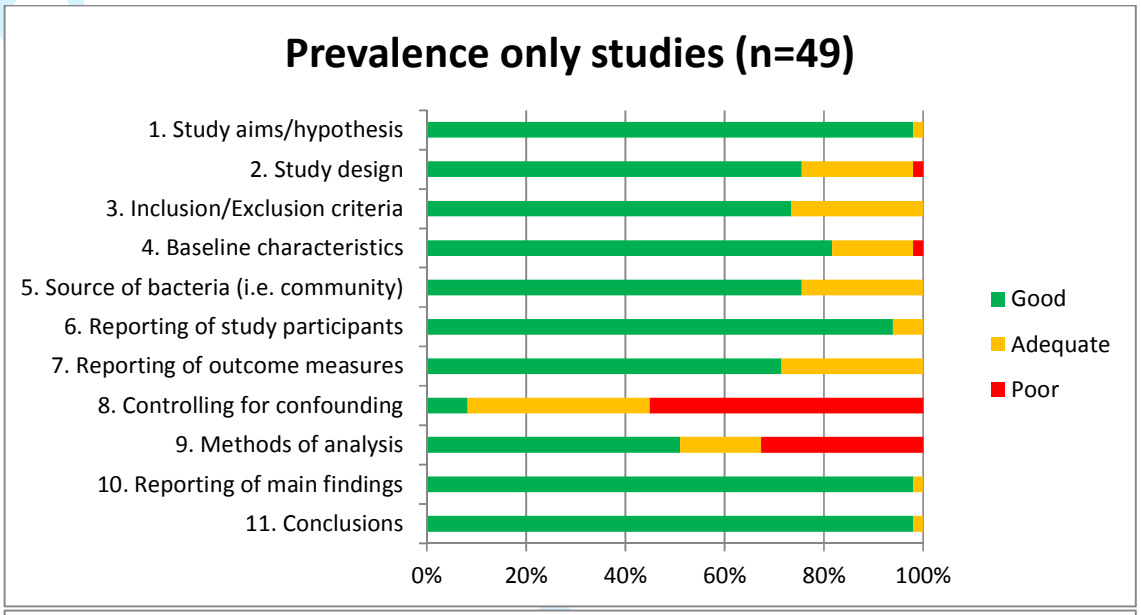
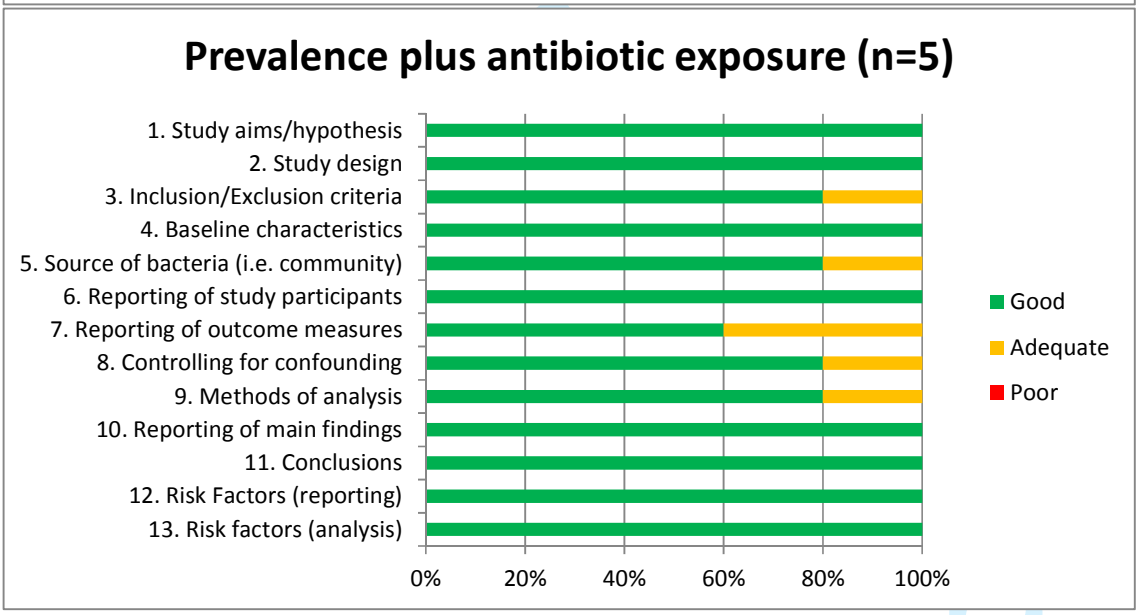
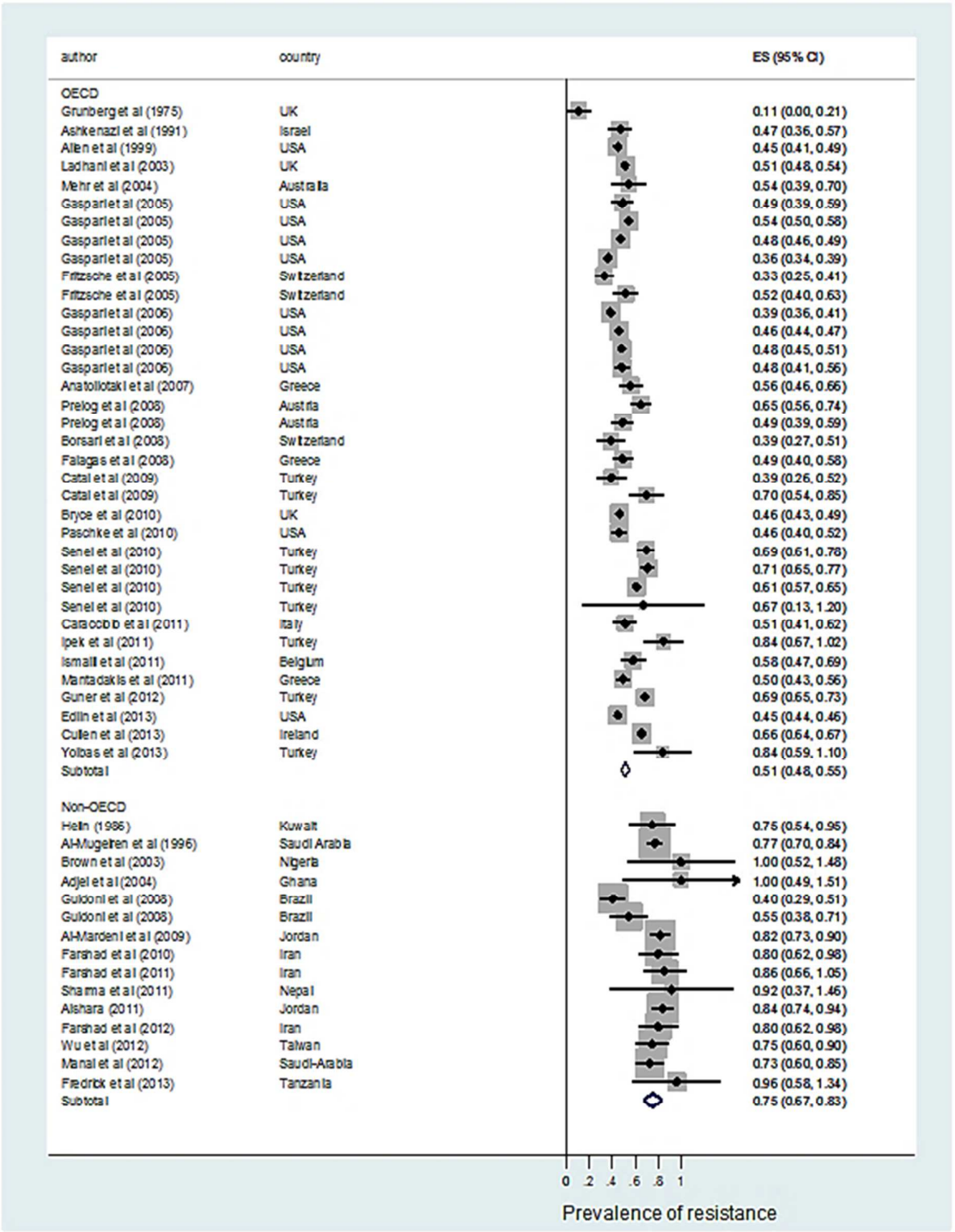
Appendix 2. Data quality charts (split by studies reporting prevalence of resistance only and prevalence plus antibiotic exposure)

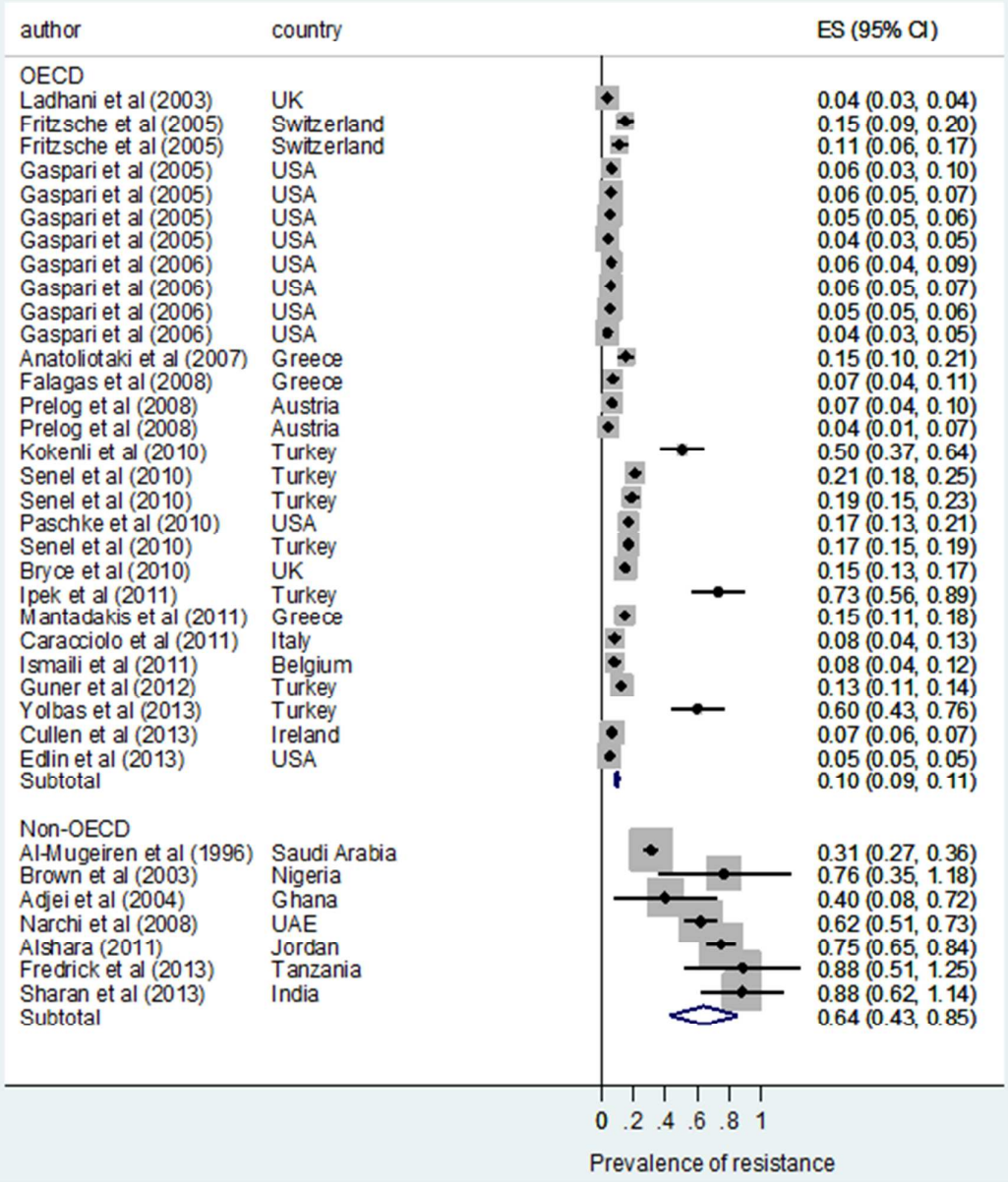




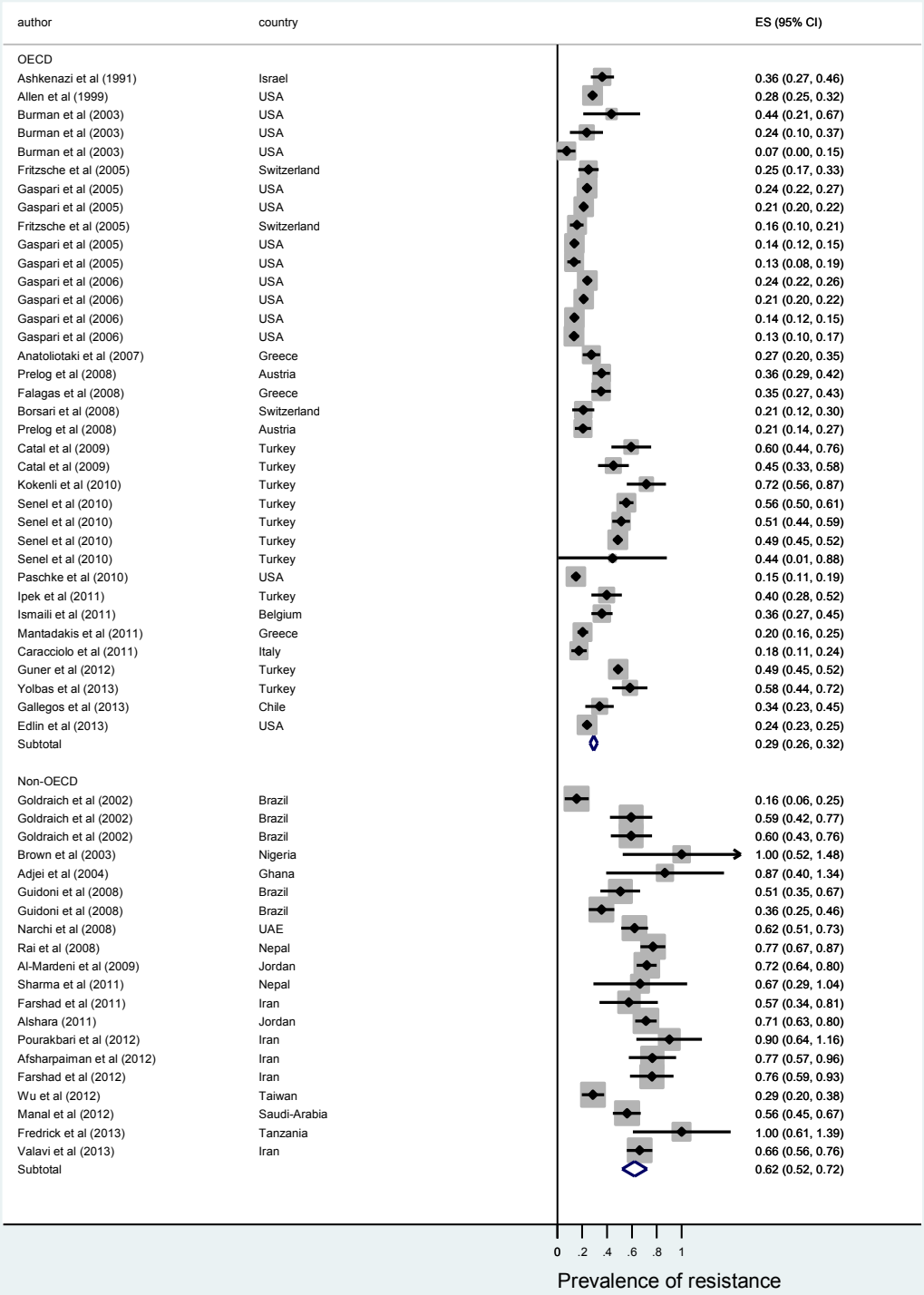
Appendix 3. Ampicillin resistance in *E. coli* urinary isolates from children, by OECD status



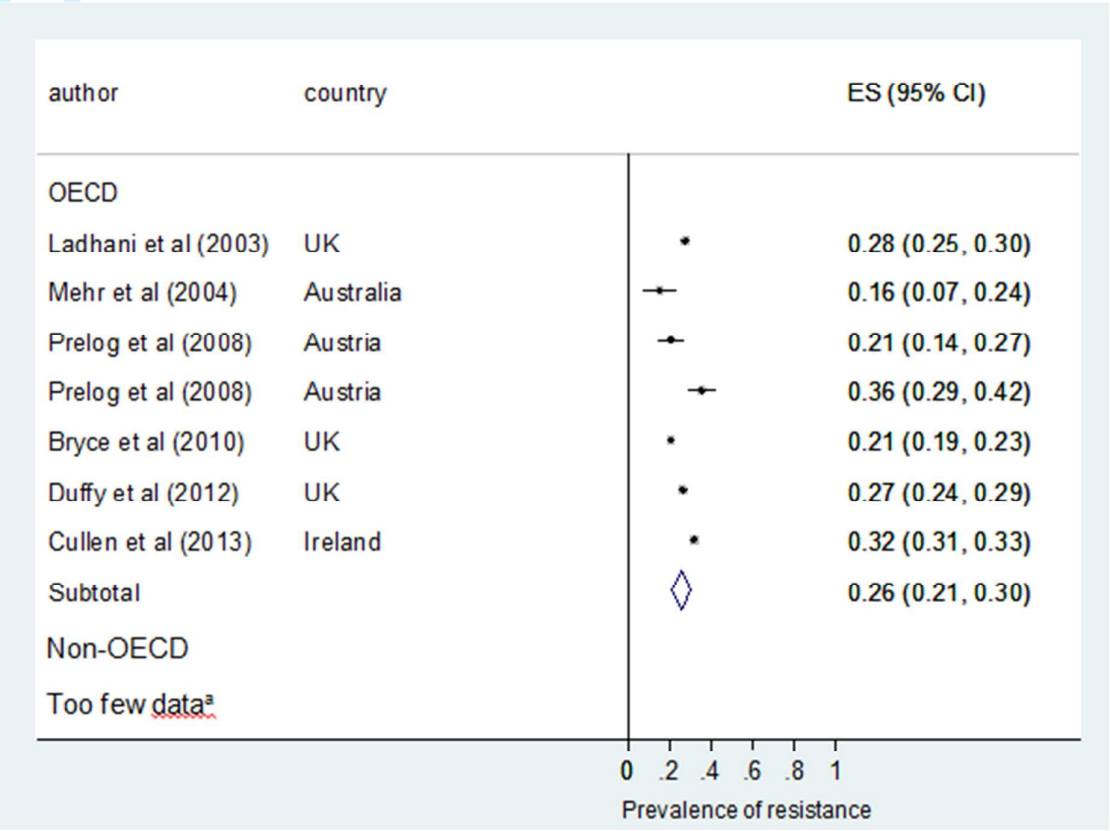
Appendix 4. Co-amoxiclav resistance in *E. coli* urinary isolates from children, by OECD status



Appendix 5. Co-trimoxazole resistance in *E. coli* isolates from children, by OECD status



Appendix 6. Trimethoprim resistance in *E. coli* urinary isolates from children, by OECD status



[a] Only one study from non-OECD countries

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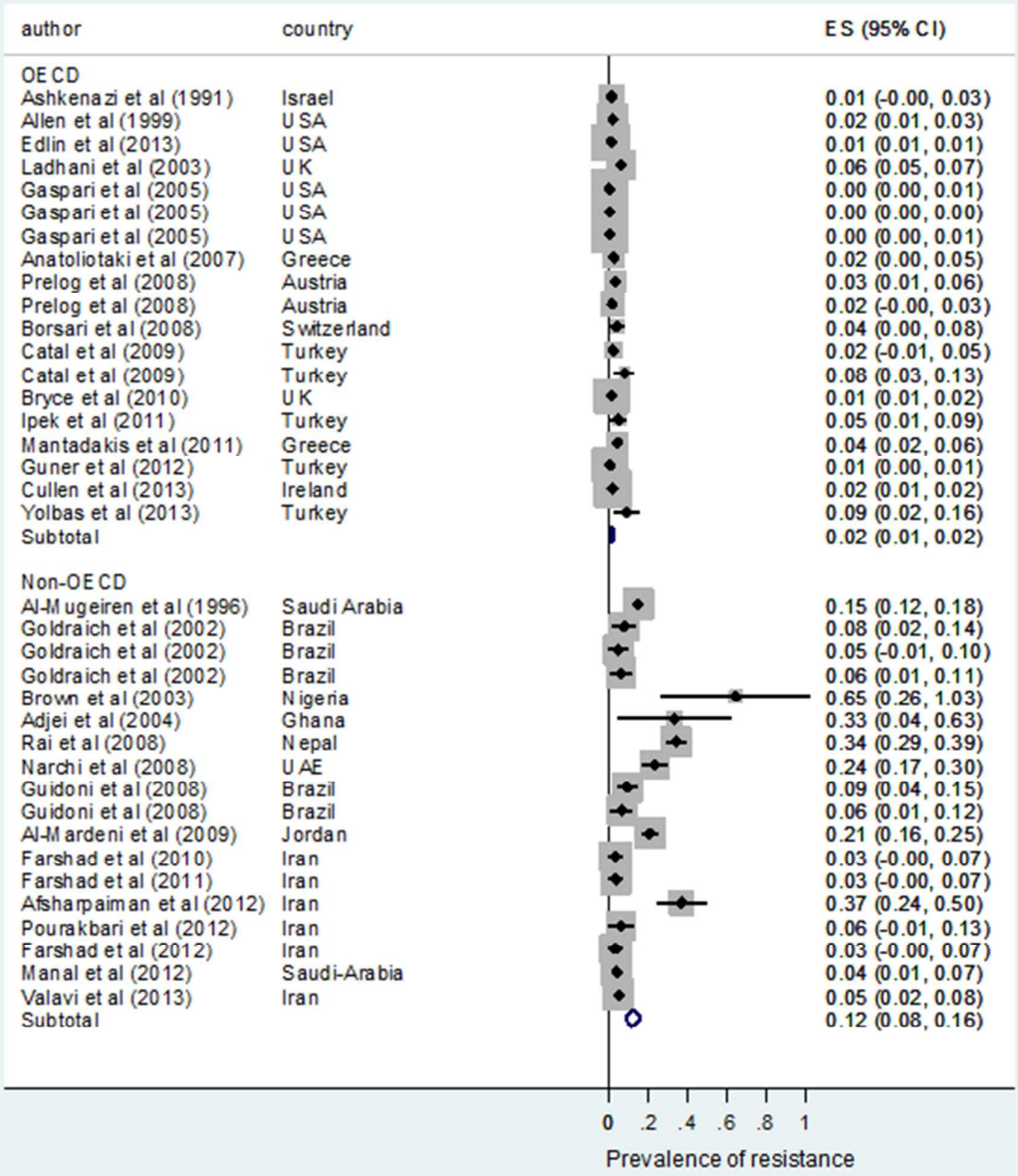
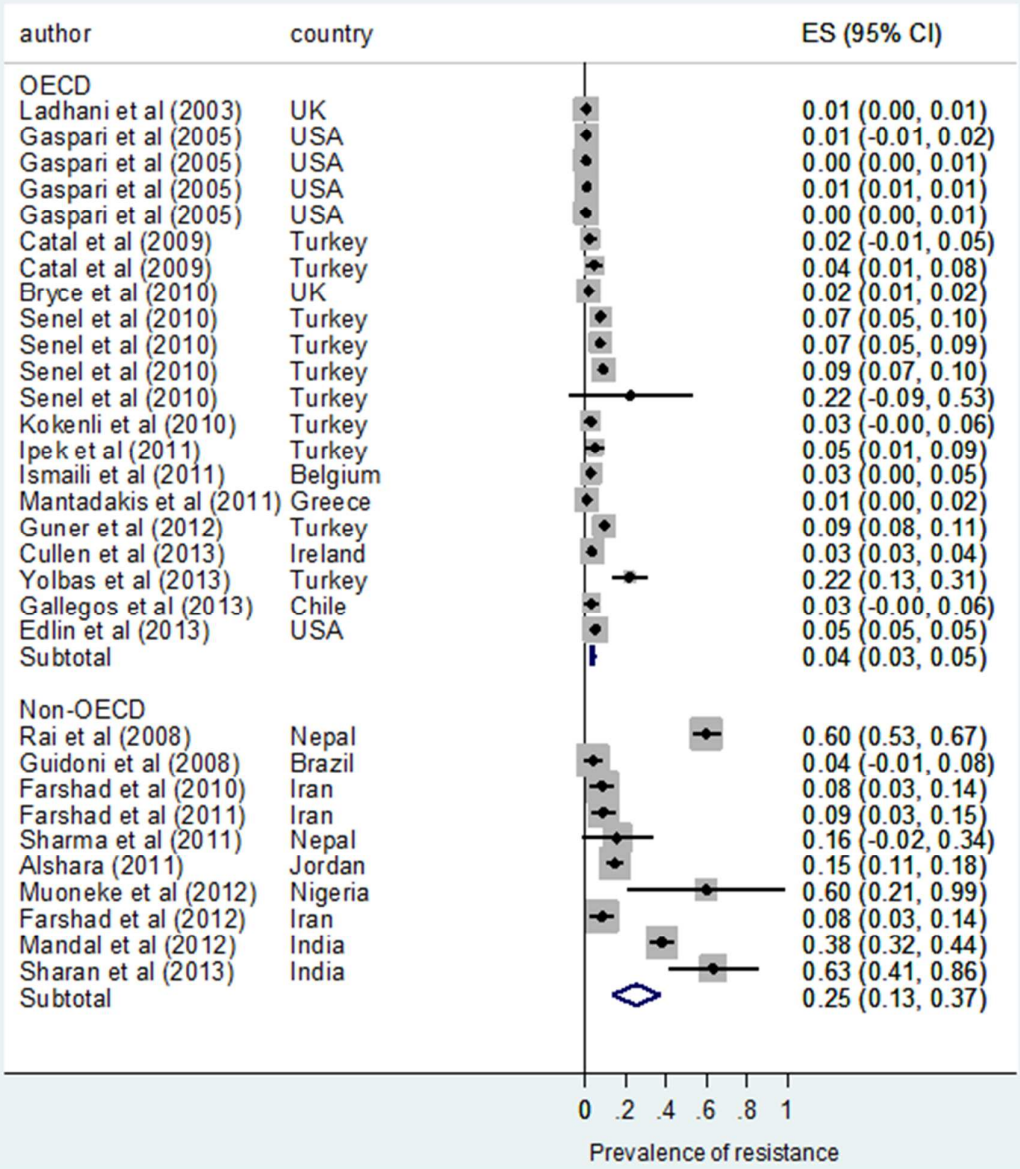
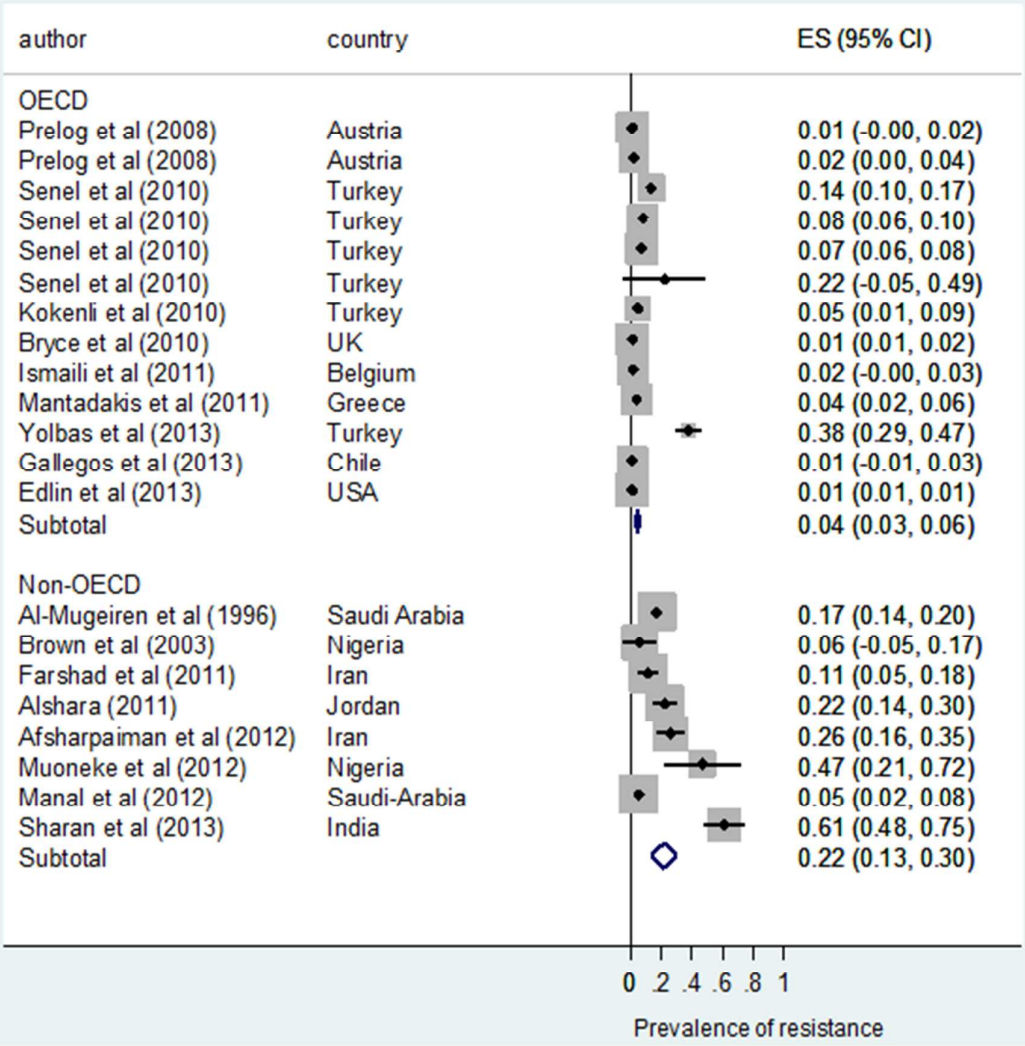
Appendix 7. Nitrofurantoin resistance in *E. coli* isolates from children, by OECD status



Appendix 8. Ciprofloxacin resistance in *E. coli* urinary isolates from children, by OECD status



Appendix 9. Ceftazidime resistance in *E. coli* urinary isolates from children, by OECD status



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