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-thecounter 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.

### **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.<sup>1</sup> 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.<sup>2</sup> 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.<sup>3</sup>

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.<sup>4</sup> 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. <sup>5</sup> However, most of the contributing studies were conducted in adults.

UTIs are one of the most common bacterial infections seen in primary care.<sup>6</sup> 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,<sup>7</sup> and therefore require prompt, appropriate treatment. *E. coli* is responsible for over 80% of all UTIs,<sup>8</sup> and is also the most common cause of bacteraemia, foodbourne infections, and a cause of meningitis in neonates.<sup>9</sup>

We conducted a systematic review aimed to investigate the prevalence of resistance in communityacquired *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.<sup>10-14</sup>

## **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.<sup>15</sup> 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 (amoxicillinclavulanic 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.<sup>16</sup>

Included papers were assessed for quality using a checklist based on Cochrane collaboration's 'risk of bias' tool,<sup>17</sup> and the Critical Appraisal Skills Programme (CASP) checklist for cohort and case-control studies (<u>www.casp-uk.net</u>). 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.<sup>18</sup>

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<sup>2</sup> of 25%, 50% and 75% were used to signify low-level, moderate-level and high-level heterogeneity, in line with Cochrane recommendations.<sup>17</sup> 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  $\chi^2$  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.

## 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

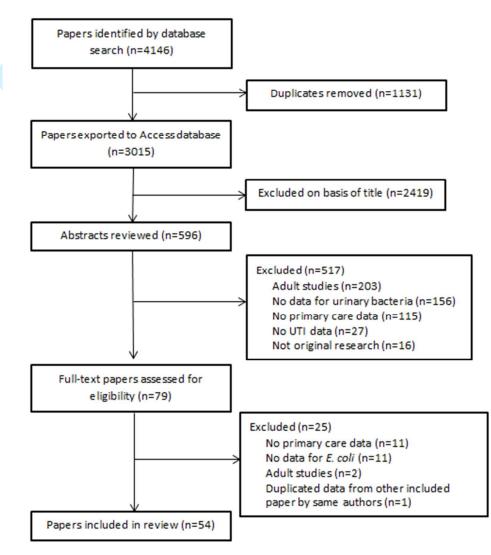
Figure 2). All were observational; 23 retrospective, six prospective, and two case-control. Twentyeight of these studies reported information on prevalence of resistance in *E. coli* UTI isolates, with the remaining three reporting the association between previous antibiotic exposure and *E. coli* resistance only.<sup>19-21</sup> 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.<sup>22 23</sup> 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.

#### Figure 1. Data search and extraction



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Study Characteristics		OECD (n=31)	No	on-OECD (n=23)
	Number		Number	
	of		of	
	papers	Reference number	papers	Reference number
Study Design:				
Retrospective observational	23	8 19 20 24-43	9	44-52
Prospective observational	6	53-58	11	59-69
Case-control	2	21 70	1	71
Cross-sectional	0		2	72 73
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
10,0014	0		Ĩ	
Method of urine sampling:				
At least one of: clean-catch, catheter	19	19-21 26 28 30-38 41 53 55 56 58	9	45 46 60 62 64 69 72-74
or suprapubic aspiration				
Clean-catch only	3	29 42 43	4	51 61 67 71
Catheter only	1	54	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	20	44-46 48-52 60 62-69 71-73
		53 54 56-58		
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 <sup>a</sup> :				
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	18	44-52 60 61 63-65 67-69 71
		70		
Previous antibiotic exposure	5	19-21 27 70	0	
information <sup>b</sup>	5			

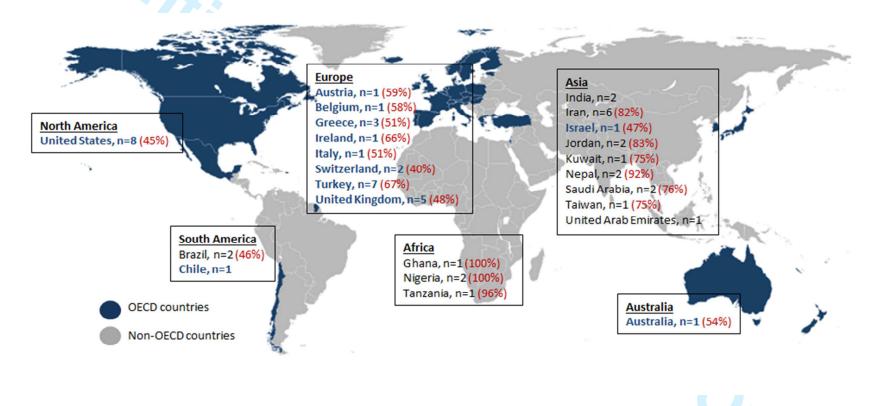
Table 1. Study characteristics of included papers by OECD status

<sup>a</sup> 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. <sup>b</sup> No studies from non-OECD countries collected previous antibiotic exposure data and were not included in the meta-

analysis.

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

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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.<sup>67</sup> Nitrofurantoin resistance was lowest for both OECD and non-OECD countries of all reported antibiotics in this review.

.a. d ceftazidi. n resistance in exce. 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%.

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

### 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

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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.

Antibiotics	OECD					Non-OECD				
	Pooled prevalence (%)	No. isolates tested	p-value	l <sup>2</sup>	Reference number	Pooled prevalence (%)	No. isolates tested	p-value	l <sup>2</sup>	Reference number
Ampicillin	<b>55.2%</b> (95% CI: 48.8-61.5%)	5273	0.354	9.8%	8 32 34 36 37	<b>79.1%</b> (95% Cl: 66.0-92.3%)	176	0.427	0%	62 66 72
Co-amoxiclav	<b>9.3%</b> (95% CI: 6.2-12.4%)	5273	0.046	51.1%	8 32 34 36 37	<b>72.1%</b> (95% Cl: 40.8-100%)	89	0.370	0%	59 66 72
Co-trimoxazole	<b>28.9%</b> (95% CI: 21.3-36.4%)	5405	0.097	39.2%	8 32 34 36 37 39 54	<b>69.8%</b> (95% Cl: 32.2-100%)	257	0.553	0%	62 66 72 73
Trimethoprim	Too few data <sup>a</sup>	188		Too few data <sup>a</sup>	36	No data <sup>b</sup>	0	-	-	-
Nitrofurantoin	<b>0.6%</b> (95% Cl: 0.4-1.7%)	1706	0.317	0%	8 36	<b>36.4%</b> (95% Cl: 24.3-48.5%)	96	0.975	0%	66 73
Ciprofloxacin	<b>3.6%</b> (95% CI: 1.0-6.1%)	2864	0.203	32.8%	8 34 54	Too few data <sup>c</sup>	49		Too few data <sup>c</sup>	59
Ceftazidime	<b>5.9%</b> (95% CI: 1.2-10.7%)	1358	0.244	27.9%	34 36 54	<b>42.3%</b> (95% CI: 7.8-76.8%)	130	0.317	0%	59 73
<sup>b</sup> No studies from	rom OECD countries non-OECD countries repo rom non-OECD countries	rted resistar	nce to trime	ethoprim in	children aged 0	-5 years				

## 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  $\beta$  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

Author	exposure	Resistant to			OR (95% CI)
0 to 1 month					
Duffy et al (2012)	Trimethoprim	Trimethoprim		-	2.32 (1.70, 3.15)
McLoughlin et al (2003)	Any antibiotic	Any antibiotic			9.33 (2.04, 42.66)
Conway et al (2007)	Any antibiotic	Any antibiotic			7.50 (1.60, 35.17)
McLoughlin et al (2003)	Any antibiotic	Co-trimoxazole		•	2.00 (0.20, 20.17)
Subtotal (I-squared = 41.4	%, p = 0.163)			$\langle \rangle$	3.66 (1.65, 8.10)
0 to 3 months					
Duffy et al (2012)	Trimethoprim	Trimethoprim		+	2.63 (2.05, 3.38)
Topaloglu et al (2010)	Any antibiotic	3rd gen Cephalosporin			3.38 (2.05, 5.55)
Subtotal (I-squared = 0.0%	%, p = 0.378)			$\diamond$	2.77 (2.21, 3.46)
0 to 6 months					
Duffy et al (2012)	Trimethoprim	Trimethoprim		+	2.56 (2.04, 3.21)
Allen et al (1999)	Any antibiotic	Co-trimoxazole			13.23 (7.84, 22.31)
Subtotal (I-squared = 96.9	9%, p = 0.000)			$\langle \rangle$	5.72 (1.12, 29.08)
0 to 12 months					
Duffy et al (2012)	Trimethoprim	Trimethoprim		+	1.96 (1.58, 2.41)
Duffy et al (2012)	Trimethoprim	Trimethoprim		-	2.44 (1.97, 3.02)
Subtotal (I-squared = 52.2	2%, p = 0.148)			$\diamond$	2.18 (1.76, 2.71)
		.0	1.1	<b>1</b> 10	100

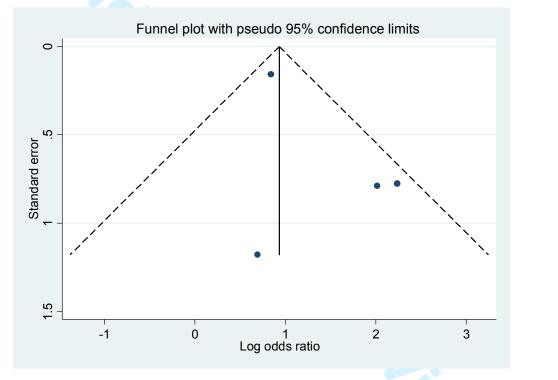
The Forest plot shows pooled OR (log scale) for resistance in children's urinary bacteria and previous exposure to any antibiotic. Studies grouped according to time period during which exposure was measured and ordered within each time period by increasing standard error.

#### **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.

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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



## **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,<sup>75</sup> which this systematic review fills. Our review was rigorously conducted according to the Cochrane guidelines for Systematic Reviews.<sup>17</sup> We chose to stratify our results by OECD status to reflect both national development and likely OTC antibiotic availability.<sup>3 76</sup>

We are aware of several limitations. First, antibiotics are used very differently within OECD and non-OECD countries,<sup>77 78-80</sup> and OTC antibiotic use is difficult to measure. A 2011 systematic review reported high non-prescription antibiotic variability across countries worldwide,<sup>76</sup> 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 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.<sup>8182</sup> 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%.<sup>83</sup> Additionally, Farrell *et al* (2003) reported 27% resistance in *E. coli* urinary isolates from all age groups.<sup>84</sup> 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.<sup>85-87</sup> 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.<sup>88</sup> A study conducted in France found that children under seven years old consumed three times more antibiotics compared to older populations.<sup>89</sup> 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

explored the effect of antibiotic prescribing in primary care on the development of resistance in individual patients of all ages.<sup>5</sup> 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;<sup>90</sup> 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 upto-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 guarter 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 firstline treatments could put pressure on clinicians to prescribe stronger second-line antibiotics, such as co-amoxiclay, 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.<sup>91</sup> Our findings also support other evidence for the continued availability of nitrofurantoin as an effective treatment for uncomplicated UTI's in primary care.<sup>86 92</sup>

#### 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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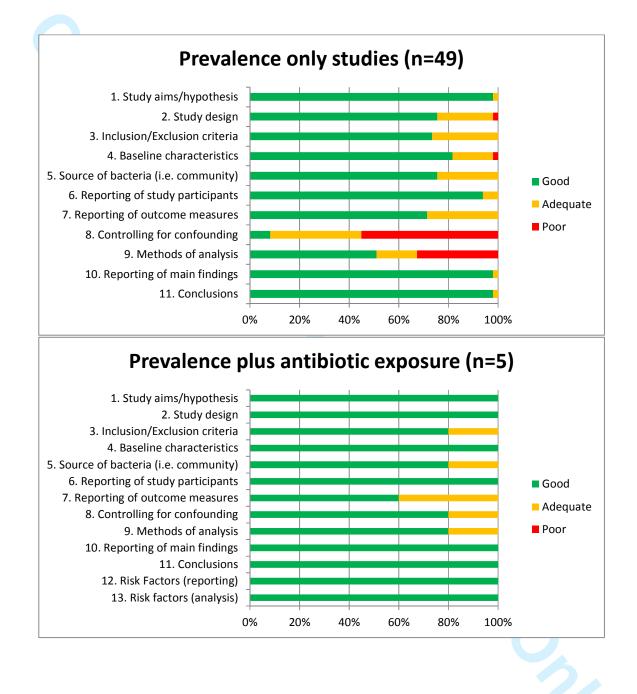
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ME	DLINE and EMBASE search strategy	
1.	exp Drug Resistance, Microbial	21. Exp. Urinary Tract Infections/ Transmissi
2.	Anti-bacterial Agents/ Therapeutic use	22. Exp. Urinary Tract Infections/ Microbiolo
3.	Antibiotic\$.tw	23. Escherichia coli Infections/ 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/	29. urinary.tw
	Microbiology	
10.	Exp. Community-acquired Infections/	30. 18 or 19 or 20 or 21 or 22 or 23 or 24 or
	Transmission	26 or 27 or 28 or 29
11.	Exp. Community-acquired Infections/	31. Exp. Child
	Epidemiology	
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	37. p?ediatri\$.tw
	16	
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	

36. children.tw f 15 or 37. p?ediatri\$.tw sis 38. 31 or 32 or 33 or 34 or 35 or 36 or 37 hiology 39. 7 and 17 and 30 and 38 tion

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



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

DeCD         UK         avxisterate it al (1975)         UK           Structure (1975)         UK         avxisterate it al (1991)         israel           Jahan (184) (2003)         UK         avxisterate it al (2005)         USA           Stapariet al (2005)         USA         GS (201, 0, 48)           Stapariet al (2005)         USA         GS (201, 0, 28)           Stapariet al (2007)         USA         GS (201, 0, 28)           Stapariet al (2007)         USA         GS (201, 0, 28)           Stapariet al (2007)         USA         GS (201, 0, 28)           Stapariet al (2006)         Austra         OS (201, 0, 28)           Stapariet al (2007)         UKA         Papeid el (2003)         Austra           Stapariet al (2007)         Turkey         GS (201, 0, 28)         GS (201, 0, 28)           Staporiet al (2010)	author	country		ES (95% CI)
Addressing is all (1991)       Israel         Addressing is all (1991)       USA         Lixinani di all (2003)       USA         Separate ial (2005)       Switzestand         Separate ial (2005)       Switzestand         Separate ial (2005)       Switzestand         Separate ial (2005)       Switzestand         Separate ial (2005)       USA         Separate ial (2005)       Switzestand         Separate ial (2005)       USA         Separate ial (2005)       Switzestand         Separate ial (2005)       Switzestand         Separate ial (2005)       Austra is         Separate ial (2005)       Switzestand         Separate ial (2005)       Switzestand         Separate ial (2006)       Turkey         Separate ial (2007)       Turkey         Separate ial (2006)       Turkey         Separate ial (2010)       Turkey         Separate ial (2010)       Turkey         Semel et	OECD			
Nike net al (000)         USA         0.4 (0.4, 0.5)           Stapparte 14 (000)         Austra Bi         0.5 (0.4, 0.5)           Stapparte 14 (000)         USA         0.5 (0.4, 0.5)           Stapparte 14 (000)         USA         0.4 (0.30, 0.9)           Stapparte 11 (000)         USA         0.4 (0.30, 0.9)           Stapparte 11 (000)         USA         0.5 (0.4, 0.4)           Stapparte 11 (000)         USA         0.5 (0.5, 0.7)           Stapparte 11 (000)         UK         0.5 (0.5, 0.7)           Pretog 41 (000)         Turkey         0.5 (0.5, 0.7)           Stare 14 (000)         Turkey         0.5 (0.4, 0.5)	Grunberget al (1975)	UK		0.11 (0.00, 0.21)
Adhami al (2003)         UK         Adhami al (2004)         Adhami al (2005)         USA           Sappariet al (2005)         USA         Odd (2004, 0.50)         Odd (2004, 0.50)           Sappariet al (2005)         USA         Odd (2004, 0.50)         Odd (2004, 0.50)           Sappariet al (2005)         USA         Odd (2004, 0.50)         Odd (2004, 0.50)           Sappariet al (2005)         USA         Odd (2004, 0.50)         Odd (2004, 0.50)           Sappariet al (2005)         USA         Odd (0004, 0.50)         Odd (2004, 0.50)           Sappariet al (2005)         USA         Odd (0004, 0.50)         Odd (0004, 0.50)           Sappariet al (2005)         USA         Odd (0004, 0.50)         Odd (0004, 0.50)           Sappariet al (2005)         Austra         Odd (0005, 0.50)         Odd (0004, 0.50)           Sappariet al (2005)         Austra         Odd (0005, 0.50)         Odd (0004, 0.50)           Sappariet al (2005)         Austra         Odd (0004, 0.50)         Odd (0004, 0.50)           Sappariet al (2005)         Turkey         Odd (0004, 0.50)         Odd (0004, 0.50)           Sappariet al (2010)         Turkey         Odd (0004, 0.50)         Odd (0004, 0.50)           Samel et al (2010)         Turkey         Odd (0004, 0.50)         Odd (0004, 0	Ashkenazi et al (1991)	Israel		0.47 (0.36, 0.57)
Ner et al (2001)         Austita la separite la (2005)         USA         0.54 (0.58, 0.59)           Basparite la (2005)         USA         0.48 (0.46, 0.49)           Basparite la (2005)         USA         0.35 (0.25, 0.59)           Basparite la (2005)         USA         0.35 (0.25, 0.59)           Basparite la (2005)         USA         0.35 (0.24, 0.39)           Basparite la (2005)         Switzetiand         0.35 (0.24, 0.39)           Basparite la (2005)         USA         0.35 (0.24, 0.49)           Basparite la (2005)         USA         0.35 (0.24, 0.47)           Basparite la (2005)         USA         0.48 (0.46, 0.47)           Basparite la (2005)         USA         0.48 (0.46, 0.47)           Basparite la (2005)         USA         0.48 (0.46, 0.47)           Basparite la (2005)         Austita         0.48 (0.46, 0.47)           Pelog et al (2005)         Austita         0.48 (0.46, 0.47)           Pelog et al (2006)         Turkey         0.48 (0.46, 0.47)           Parate at (2006)         Turkey         0.48 (0.46, 0.47)           Parate at (2010)         Turkey         0.48 (0.40, 0.52)           Parate at (2010)         Turkey         0.46 (0.40, 0.52)           Barel et al (2010)         Turkey <t< td=""><td>Allen et al (1999)</td><td>USA</td><td>•</td><td>0.45 (0.41, 0.49)</td></t<>	Allen et al (1999)	USA	•	0.45 (0.41, 0.49)
Separate at (2006)       USA       0.4 (0.35, 0.59)         Sapartet at (2005)       USA       0.4 (0.45, 0.45)         Sapartet at (2005)       USA       0.35 (0.34, 0.39)         Sapartet at (2005)       USA       0.35 (0.34, 0.39)         Sapartet at (2005)       USA       0.35 (0.34, 0.39)         Sapartet at (2005)       Switzenand       0.35 (0.34, 0.39)         Sapartet at (2005)       USA       0.35 (0.34, 0.39)         Sapartet at (2005)       USA       0.38 (0.34, 0.39)         Sapartet at (2005)       USA       0.38 (0.34, 0.39)         Sapartet at (2005)       USA       0.48 (0.44, 0.47)         Sapartet at (2007)       USA       0.48 (0.44, 0.47)         Sapartet at (2007)       USA       0.48 (0.46, 0.66)         Preog et at (2003)       Austra       0.48 (0.40, 0.52)         Sapartet at (2006)       Turkey       0.49 (0.40, 0.52)         Sapartet at (2007)       UKA       0.48 (0.47, 0.42)         Sapartet at (2010)       UK       0.48 (0.47, 0.42)         Sapartet at (2010)       UK       0.48 (0.47, 0.42)         Sapartet at (2011)       Turkey       0.56 (0.47, 0.62)         Sapartet at (2011)       USA       0.56 (0.46, 0.72)         Samet et	Ladhani et al (2003)	UK	•	0.51 (0.48, 0.54)
Saparter at (2005)       USA       0.54 (0.56.0.59)         Saparter at (2005)       USA       0.35 (0.25.0.40)         Saparter at (2005)       USA       0.35 (0.25.0.40)         Saparter at (2005)       USA       0.35 (0.25.0.40)         Saparter at (2005)       USA       0.35 (0.26.0.40)         Saparter at (2005)       USA       0.45 (0.46.0.65)         Probig et at (2005)       Austria       0.45 (0.46.0.40)         Probig et at (2005)       Austria       0.45 (0.46.0.65)         Saparter at (2006)       UKK       0.39 (0.27.0.51)         Saparter at (2010)       Turkey       0.45 (0.44.0.42)         Senel et at (2010)       Turkey       0.45 (0.44.0.62)         Senel et at (2010)       Turkey       0.57 (0.56.0.77)         Senel et at (2010)       Turkey       0.57 (0.56.0.72)         Senel et at (2011)       Turkey       0.58 (0.47.0.66)         Satorer et at (2013)       Turkey       0.58 (0.47.0.66)         Satorer e	Mehret al (2004)	Austra la	- <u>-</u>	0.54 (0.39, 0.70)
Saperiet al (2005)         USA           Saperiet al (2006)         Greece           Peolog et al (2006)         Turkey           Saperiet al (2010)         UK           Saperiet al (2010)         UK           Saperiet al (2010)         UK           Samel et al (2011)         Turkey           Samel et al (2011)         Turkey           Samel et al (2011)         Greece           Sameret al (2012)	Gasparlet al (2005)	USA		0.49 (0.39, 0.59)
Sapartet al (2005)       USA         Prosche tal (2005)       Switzerland         Sapartet al (2005)       Switzerland         Sapartet al (2005)       USA         Sapartet al (2005)       USA         Sapartet al (2006)       USA         Sapartet al (2006)       USA         Sapartet al (2006)       USA         Sapartet al (2006)       USA         Vantolicitik et al (2007)       Greece         Pelog et al (2008)       Austra         Synoe tal (2008)       Switzerland         Palages et al (2008)       Switzerland         Palages et al (2008)       Turkey         Spoe tal (2010)       Turkey         Senel et al (2011)       Turkey         Senel et al (2011)       Turkey         Senel et al (2011)       Turkey         Senel et al (2013)       Turkey         Senel et al (2011)       Turkey         Senel et al (2013)       Turkey         Subortal       Subortal         Subortal       Subortal         Subort et al (2020)       Subort et al (2020) <t< td=""><td>Gasparlet al (2005)</td><td>USA</td><td>٠</td><td>0.54 (0.50, 0.58)</td></t<>	Gasparlet al (2005)	USA	٠	0.54 (0.50, 0.58)
Tresche et al (2005)         Switzetland         0.33 (225, 0.41)           Gasparitet al (2005)         USA         0.53 (0.40, 0.53)           Gasparitet al (2005)         USA         0.39 (0.35, 0.41)           Gasparitet al (2005)         USA         0.46 (0.44, 0.47)           Gasparitet al (2006)         USA         0.46 (0.44, 0.47)           Gasparitet al (2007)         USA         0.46 (0.44, 0.47)           Gasparitet al (2007)         Greece         0.55 (0.46, 0.65)           Pelog et al (2003)         Austifa         0.49 (0.40, 0.39)           Pelog et al (2006)         Turkey         0.39 (0.27, 0.51)           Sanarit et al (2006)         Turkey         0.39 (0.27, 0.51)           Sanarit et al (2006)         Turkey         0.39 (0.27, 0.51)           Sanarit et al (2010)         Turkey         0.39 (0.27, 0.55)           Senel et al (2010)         Turkey         0.56 (0.64, 0.57)           Senel et al (2010)         Turkey         0.56 (0.64, 0.57)           Senel et al (2011)         Turkey         0.56 (0.64, 0.57)           Senel et al (2013)         Turkey         0.56 (0.64, 0.57)           Senel et al (2013)         Turkey         0.56 (0.64, 0.57)           Subtotal         Vor-OECD         0.65 (0.64, 0.57)	Gasparlet al (2005)	USA	۲	0.48 (0.46, 0.49)
Pfizsche et al (2005)         Switzetiand         052 (14.0.05)           Gaspariet al (2006)         USA         039 (035.0.41)           Gaspariet al (2006)         USA         034 (04.0.40)           Gaspariet al (2006)         USA         046 (044.0.47)           Gaspariet al (2006)         USA         046 (044.0.47)           Gaspariet al (2006)         USA         045 (04.0.05)           Perlog et al (2006)         Austifia         045 (04.0.05)           Perlog et al (2003)         Austifia         045 (04.0.05)           Perlog et al (2006)         Turkey         039 (025.0.52)           Catal et al (2006)         Turkey         039 (025.0.52)           Samel et al (2010)         UK         Paschke et al (2010)         UK           Senel et al (2010)         Turkey         059 (061.0.70)           Senel et al (2011)         Turkey         059 (061.0.70)           Senel et al (2011)         Turkey         059 (061.0.70)           Senel et al (2011)         Turkey         059 (061.0.73)           Senel et al (2011)         Turkey         059 (061.0.73)           Senel et al (2011)         Turkey         059 (061.0.73)           Subtotal         005 (042.0.55)         059 (042.0.55)           Non-O	Gasparlet al (2005)	USA	۲	
Saspariet al (2006)       USA         Saspariet al (2006)       USA         Saspariet al (2006)       USA         Saspariet al (2007)       USA         Saspariet al (2007)       USA         Verbiog et al (2003)       Austra         Peolog et al (2003)       Austra         Peolog et al (2006)       USA         Saspariet al (2006)       USA         Saspariet al (2006)       Austra         Peolog et al (2006)       Turkey         Saspariet al (2008)       Greece         Call et al (2010)       UK         Saspariet al (2010)       UK         Saspariet al (2010)       UK         Saspariet al (2010)       Turkey         Sasperiet al (2010)       Turkey         Sasperiet al (2011)       Turkey         Sasperiet al (2011)       Turkey         Samel et al (2011)       Turkey         Samel et al (2011)       Turkey         Samel et al (2013)       Gre (0.44, 0.45)	Fritzsche et al (2005)	Switzerland		0.33 (0.25, 0.41)
Saspariet al (2005)       USA         Saspariet al (2006)       USA         Saspariet al (2007)       Greece         Peolog et al (2003)       Austria         Senstrat et al (2007)       Greece         Peolog et al (2003)       Austria         Senstrat et al (2006)       Austria         Senstrat et al (2006)       Austria         Senstrat et al (2006)       Austria         Senstrat et al (2003)       Greece         Calal et al (2003)       Greece         Calal et al (2006)       Turkey         Senel et al (2010)       UK         Senel et al (2010)       UK         Senel et al (2010)       Turkey         Senel et al (2010)       Turkey         Senel et al (2010)       Turkey         Senel et al (2011)       Turkey         Senel et al (2011)       Turkey         Senel et al (2011)       Turkey         Subtotal       Osfs (04.7, 0.65)         Non-OECD       Saudon et al (2013)         Hean (1636)       Kuw att         Atharden et al (1996)       Saudi Arab b         Subon et al (2010)       Tara         Samari et al (2011)       Tara         Saubon et al (2003)       Brezul	Fritzsche et al (2005)	Swtzerland	-	0.52 (0.40, 0.63)
Gasparlet al (2006)       USA       0.48 (044, 0.45)         Gasparlet al (2007)       Greece       0.48 (044, 0.45)         Prelog el al (2003)       Austina       0.48 (044, 0.45)         Prelog el al (2003)       Austina       0.49 (038, 0.57)         Donasi el al (2003)       Sutzetiand       0.39 (027, 0.51)         Pagas el al (2005)       Turkey       0.39 (027, 0.51)         Staparlet al (2003)       Greece       0.46 (043, 0.46)         Catal et al (2010)       Turkey       0.39 (027, 0.51)         Senel et al (2010)       UK       0.46 (043, 0.46)         Pachet al (2010)       Turkey       0.71 (0.65, 0.77)         Senel et al (2010)       Turkey       0.56 (0.67, 1.02)         Senel et al (2011)       Turkey       0.56 (0.47, 0.65)         Senel et al (2011)       Turkey       0.56 (0.41, 0.45)         Senel et al (2011)       Turkey       0.56 (0.41, 0.45)         Subortal       0.58 (0.47, 0.69)       0.56 (0.41, 0.45)         Non-OECD       Heln (1985)       Kuwait       0.56 (0.41, 0.45)         Addig et al (2013)       Turkey       0.56 (0.42, 0.55)         Subortal       Cors (0.56, 0.57)       0.56 (0.56, 0.57)         Subortal       Cors (0.56, 0.57)       0	Gasparlet al (2006)	USA	۲	0.39 (0.36, 0.41)
Gasparte tal (2006)       USA         Anabilictaki et al (2007)       Greece         Anabilictaki et al (2008)       Austria         Sensart et al (2008)       Austria         Sensart et al (2008)       Switzestand         Falegas et al (2008)       Greece         Catal et al (2009)       Turkey         Catal et al (2009)       Turkey         Catal et al (2010)       UK         Senel et al (2010)       UK         Senel et al (2010)       Turkey         Senel et al (2011)       Turkey         Senel et al (2011)       Turkey         Senel et al (2011)       Turkey         Senel et al (2013)       Turkey         Solo of al (2011)       Turkey         Solo of al (2013)       USA         Oxfo (044, 0.45)       Oxfo (045, 0.57)         Solo of al (2013)       USA         Oxfo (045, 0.57)       Oxfo (045, 0.57)         Solo of al (2013)       USA         Oxfo (045, 0.57)       Oxfo (045, 0.	Gasparlet al (2005)	USA	•	0.46 (0.44, 0.47)
Ausinitizati et al (2007)       Greece         Prelog et al (2008)       Austitia         Prelog et al (2008)       Austitia         Balgas et al (2008)       SW Izzetand         Palagas et al (2009)       Turkey         Stati et al (2009)       Turkey         Stati et al (2009)       Turkey         Speciet al (2010)       UK         Pasentet al (2010)       UK         Senel et al (2010)       UK         Senel et al (2010)       Turkey         Senel et al (2011)       Turkey         Senel et al (2013)       Urkey         Subotal       OS6 (04.6.05)         Non-OECD       Sudonal et al (2020)       Jordan         Parmad et al (2010)       Iran         Subotal       OS6 (04.6.0.50)         Sharma et al (2010)       Iran         Parmad et al (2010)       Iran<	Gasparlet al (2005)	USA		0.48 (0.45, 0.51)
Prebog et al (2005)       Austria         Prebog et al (2005)       Austria         Somari et al (2005)       Austria         General et al (2006)       Switzziand         Graigas et al (2006)       Turkey         Catal et al (2006)       Turkey         Catal et al (2006)       Turkey         Senel et al (2010)       UK         Benel et al (2010)       UK         Senel et al (2010)       Turkey         Senel et al (2010)       Turkey         Senel et al (2010)       Turkey         Senel et al (2011)       Generee         Subrat et al (2011)       Belgum         Non-OECD       Hein (1986)         Hein (1986)       Saudi Arabia         Subrotal       Soudi Arabia         Galob et al (2023)       Brazil         Gubon et al (2030)       Brazil	Gasparlet al (2006)	USA	+	0.48 (0.41, 0.56)
Perbog et al (2005)         Austria           Prebog et al (2005)         Austria           Obstrait et al (2005)         Austria           Strope et al (2006)         Switzziand           Prebog et al (2006)         Switzziand           Pratages et al (2007)         Turkey           Catal et al (2009)         Turkey           Catal et al (2010)         UK           Benel et al (2010)         UK           Senel et al (2010)         Turkey           Senel et al (2010)         Turkey           Senel et al (2010)         Turkey           Senel et al (2011)         Belgum           Martadakk et al (2011)         Belgum           Martadakk et al (2011)         Geg (026, 0.73)           Subtotal         Obs (041, 0.62)           Non-OECD		Greece		
Prebg al (2005) Borsarl et al (2008) Switzeriand Stalig et al (2008) Switzeriand Stalig et al (2009) Turkey Strope et al (2010) UK Paschkeet al (2010) UK Paschkeet al (2010) Turkey Senel et al (2011) Turkey Senel et al (2011) Turkey Suborn et al (2013) Suborn et al (2003) Nigeria Suborn et al (2003) Suborn et al (2012) Turkey Suborn et al (2010) Suborn et al (2012) Turkey Suborn et al (2012) Turkey		Austria		
Borsair et al (2003)         Switzertand         0.39 (027, 0.51)           Palagas et al (2003)         Greece         0.49 (0.40, 0.58)           Catal et al (2009)         Turkey         0.39 (027, 0.51)           Porce et al (2010)         UK         0.46 (0.43, 0.48)           Paschke et al (2010)         UK         0.46 (0.43, 0.49)           Paschke et al (2010)         Turkey         0.49 (0.4, 0.52)           Senel et al (2010)         Turkey         0.69 (0.5, 0.72)           Senel et al (2010)         Turkey         0.67 (0.13, 1.00)           Senel et al (2011)         Turkey         0.57 (0.13, 1.00)           Senel et al (2011)         Turkey         0.58 (0.47, 0.69)           Senel et al (2011)         Greece         0.59 (0.43, 0.55)           Senel et al (2011)         Greece         0.59 (0.43, 0.55)           Senel et al (2013)         Urkey         0.58 (0.47, 0.69)           Subtdal         0.55 (0.47, 0.69)         0.58 (0.47, 0.69)           Non-OECD         Kiwait         0.44 (0.44, 0.46)           Hahn (198e)         Kiwait         0.49 (0.44, 0.45)           Addie et al (2003)         Brazil         0.56 (0.47, 0.59)           Guboni et al (2003)         Brazil         0.56 (0.47, 0.59)	-			
Falagas et al (2005)       Greece       0.49 (0.40, 0.52)         Cztal et al (2006)       Turkey       0.39 (0.26, 0.25)         Spoe et al (2010)       UK       0.46 (0.40, 0.52)         Senel et al (2010)       Turkey       0.46 (0.40, 0.52)         Senel et al (2010)       Turkey       0.67 (0.57, 0.55)         Senel et al (2010)       Turkey       0.67 (0.57, 0.55)         Senel et al (2011)       Turkey       0.67 (0.57, 0.55)         Senel et al (2011)       Turkey       0.67 (0.57, 0.55)         Senel et al (2011)       Turkey       0.65 (0.57, 0.55)         Senel et al (2011)       Turkey       0.58 (0.47, 0.62)         Senel et al (2011)       Turkey       0.58 (0.47, 0.62)         Senel et al (2011)       Turkey       0.58 (0.47, 0.55)         Subortet al (2012)       Turkey       0.56 (0.43, 0.55)         Subortal       Von-OECD       0.58 (0.47, 0.48)         Veal (1966)       Kuwalt       0.55 (0.38, 0.71)         Adglet al (2001)       Grana       0.55 (0.38, 0.71)         Subortet al (2005)       Brazil       0.56 (0.54, 0.55)         Subortet al (2006)       Jordan       0.56 (0.58, 1.36)         Faranad et al (2011)       Iran       0.58 (0.46, 0.55)	-	Swtzerland		
Casali et al (2016)       Turkey         Casali et al (2016)       Turkey         Depose et al (2010)       UK         Paschke et al (2010)       UK         Paschke et al (2010)       Turkey         Senel et al (2011)       Gast (0.41, 0.62)         Subto at al (2013)       USA         Cube net al (2013)       USA         Cube net al (2013)       USA         Cube net al (2003)       Nigerta         AtM/ugerten et al (2003)       Berzali         Suboni et al (2004)       Gana         Suboni et al (2012)       Tran         Parshad et al (2011)       Iran         Suboni et al (2012)       Tan         Parshad et al (2011)       Iran         Suboni et al (2012)       Tan         Nu et al (2012)       Tan		Greece		
Catal et al (2009)       Turkeý       0.70 (05.4, 0.85)         Stype et al (2010)       UK         Senel et al (2010)       Turkey         Senel et al (2010)       Turkey         Senel et al (2010)       Turkey         Senel et al (2011)       Turkey         Sunta dask et al (2011)       Gelg Um         Warta dask et al (2011)       Gelg Um         Von-OECD       Heln (1986)         Saudi Arab b       Saudi Arab b         Sown et al (2003)       Brazil         Subontet al (2003)       Brazil         Subontet al (2003)       Brazil         Subontet al (2010)       Iran         Paraba et al (2011)       Iran         Subontet al (2009)       Jordan         Paraba et al (2011)       Iran         Nue et al (2011)       Iran         Nue et al (2011)       Iran	-			
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Senel et al (2010)       Turkey         Senel et al (2011)       Turkey         ismall et al (2011)       Turkey         ismall et al (2011)       Turkey         ismall et al (2011)       Belgum         Guner et al (2012)       Turkey         Suner et al (2013)       USA         Cullen et al (2013)       USA         Non-OECD       Heln (1986)         Heln (1986)       Kowalt         Adjel et al (2003)       Nyeria         Adjel et al (2003)       Nyeria         Adjel et al (2004)       Ghana         Gutoni et al (2003)       Brazili         Advardeni et al (2011)       Iran         Parina det al (2011)       Iran         Sharma et al (2011)       Iran         Sharma et al (2011)       Iran         Nue tal (2012)       Tanken         Parina det al (2011)       Iran         Sharma et al (2011)       Nepal         Alkohar et al (2012)       Tanken         Sharma et al (2011)       Saudi-Arabia         <			+	
Senel et al (2010)       Turkey         Senel et al (2010)       Turkey         Senel et al (2010)       Turkey         Catacobb et al (2011)       Italy         Isall et al (2011)       Italy         Wantdockis et al (2011)       Belglum         Mantdockis et al (2011)       Greece         Sun et al (2013)       USA         Cullen et al (2013)       USA         Cullen et al (2013)       USA         Non-OECD       Helm (1986)         Helm (1986)       Kuw alt         AMAugeten et al (2003)       Brezil         Guitoni et al (2003)       Nigeria         Soutoni et al (2003)       Brezil         Guitoni et al (2003)       Brezil         Guitoni et al (2003)       Brezil         Guitoni et al (2010)       Iran         Farshad et al (2011)       Iran         Parishad et al (2011)       Iran         Parishad et al (2011)       Iran         Parishad et al (2012)       Iran         Parishad et al (2012)       Tana         Parishad et al (2012)       Tana         Nu et al (2012)       Tana         Rubrai et al (2012)       Tana         Subtotal       Or5 (0.65, 0.55)      <		Turkey		
Senel et al (2010)       Turkey         Senel et al (2010)       Turkey         Case octo et al (2011)       Italy         pek et al (2011)       Turkey         small et al (2011)       Turkey         small et al (2011)       Gerece         Suner et al (2013)       USA         cullen et al (2013)       Turkey         subotal       0.51 (0.44, 0.45)         Non-OECD       0.51 (0.48, 0.55)         Heiln (1986)       Kowalt         AVMardeni et al (2004)       Ghana         Subotal       0.51 (0.48, 0.55)         Subotal       0.51 (0.48, 0.55)         Subotal       0.52 (0.54, 0.95)         Subotal       0.55 (0.37, 0.60)         Subotal       0.51 (0.48, 0.55)         Non-OECD       0.56 (0.53, 0.30)         Heid (1986)       Kowalt         Subotal et al (2004)       Ghana         Subotal et al (2010)       Iran         Parina det al (2010)       Iran         Parina d			+	
Senel et al (2010)       Turkey         Caracobb et al (2011)       Italy         pek et al (2011)       Turkey         small et al (2011)       Belgum         Wantadxis et al (2011)       Greece         Suner et al (2012)       Turkey         Collen et al (2013)       USA         Cullen et al (2013)       Ireland         Volta et al (2013)       USA         Cullen et al (2013)       Turkey         Subtotal       0.51 (0.44, 0.65)         Non-OECD       0.65 (0.64, 0.57)         Helm (1986)       Kuwalt         AvAdugeten et al (1996)       Saudi Arab b         Srown et al (2003)       Brazili         Subtotal       0.55 (0.64, 0.55)         Suboni et al (2004)       Ghana         Suboni et al (2003)       Brazili         Suboni et al (2010)       Iran         Farshad et al (2011)       Iran         Farshad et al (2011)       Iran         Farshad et al (2011)       Varian         Khatra (2011)       Jordan         Farshad et al (2012)       Talwan         Wartat (2012)       Talwan         Wartat (2012)       Talwan         Subtotal       0.75 (0.67, 0.83)		-	•	
Catacobb èt al (2011) Italy pek et al (2011) Turkey small et al (2011) Belglum Vantadakis et al (2011) Greece Suner et al (2012) Turkey Collen et al (2013) USA Collen et al (2013) Turkey Subtotal Non-OECD Heln (1996) Kowalt Non-OECD Heln (1996) Saudi Arab b Sown et al (2003) Ngerba Adgle et al (2003) Brazil Subtotal Non-OECD Heln (1996) Saudi Arab b Sown et al (2003) Brazil Subtotal (2003) Brazil Subtotal (2003) Brazil Subtotal (2003) Brazil Subtotal (2003) Brazil Subtotal (2010) Iran Farshad et al (2010) Iran Farshad et al (2011) Nepal Nu et al (2012) Talwan Nu et al (2012) Talwan Nu et al (2012) Talwan Subtotal		-		
pek et al (2011)       Turkey       0.84 (0.67, 1.02)         ismall et al (2011)       Belgum         Mantadakis et al (2011)       Greece         Guner et al (2012)       Turkey         Edlin et al (2013)       USA         Culen et al (2013)       USA         Subtotal       0.45 (0.44, 0.46)         Non-OECD       0.65 (0.64, 0.67)         Hein (1996)       Saudi Arab is         Snon et al (2003)       Nigeria         Addition et al (2003)       Nigeria         Guidoni et al (2003)       Brazil         Guidoni et al (2003)       Brazil         Guidoni et al (2011)       Iran         Farrhad et al (2011)       Iran         Parthad et al (2011)       Iran         Namal et al (2012)       Tahwan         Manal et al (2012)       Tahwan         Manal et al (2013)       Tanzan Ia         Subtotal       0.96 (0.58, 1.34)         Or 50 (0.58, 0.35)       0.96 (0.58, 1.34)         Or 50 (0.58, 0.35)       0.96 (0.58, 1.34)         Or 50 (0.58, 0.35)       0.96 (0.58, 1.34) <td></td> <td></td> <td></td> <td></td>				
small et al (2011)       Belgum         Wantacki is et al (2011)       Greece         Guner et al (2012)       Turkey         Solin et al (2013)       USA         Culen et al (2013)       Ireland         Yorbas et al (2013)       Turkey         Subtotal       0.56 (0.47, 0.69)         Non-OECD       0.66 (0.64, 0.67)         Heln (1986)       Kuwalt         AMMugehen et al (1996)       Saudi Arabia         Brown et al (2003)       Nigeria         Adjel et al (2004)       Ghana         Suidont et al (2005)       Brazili         Suidont et al (2005)       Brazili         Suidont et al (2006)       Brazili         Suidont et al (2007)       Jordan         Faraha et al (2011)       Iran         Shama et al (2011)       Iran         Shama et al (2012)       Taiwan         Wu et al (2012)       Taiwan         Wu et al (2012)       Taiwan         Subtotal       0.75 (0.65, 0.78)				
Wartadakis et al (2011)       Greece         Guner et al (2012)       Turkey         Ediln et al (2013)       USA         Culen et al (2013)       Ireland         Yobas et al (2013)       Turkey         Subtotal       0.56 (0.64, 0.67)         Non-OECD       0.51 (0.48, 0.55)         Heln (1986)       Kuwalt         AM-Mugehen et al (1996)       Saudi Arabia         Brown et al (2003)       Nigeria         Adjel et al (2003)       Brazil         Guidoni et al (2003)       Brazil         Advigerta et al (2011)       Iran         Farshad et al (2011)       Iran         Sharma et al (2011)       Iran         Sharma et al (2012)       Iran         Wuetal (2012)       Talwan         Waalt et al (2012)       Talwan         Maal et al (2013)       Tanzania         Subtotal       0.96 (0.56, 0.50)         Or5 (0.66, 0.90)       0.75 (0.67, 0.83)         Official et al (2012)       Talwan         Maal et al (2013)       Tanzania         Subtotal       0.96 (0.56, 0	small et al (2011)	Belgum		
Guner et al (2012)       Turkey         Ediln et al (2013)       USA         Cullen et al (2013)       Ireland         Yolbas et al (2013)       Turkey         Subtotal       0.66 (0.64, 0.67)         Non-OECD       0.51 (0.48, 0.55)         Helm (1986)       Kuw alt         Addle et al (2003)       Nigeria         Adjel et al (2004)       Ghana         Guidoni et al (2003)       Brazili         Guidoni et al (2003)       Brazili         Advalerat et al (2009)       Jordan         Farshad et al (2010)       Iran         Farshad et al (2011)       Iran         Farshad et al (2012)       Talwan         Wu et al (2012)       Talwan         Wu et al (2013)       Tanzania         Subtotal       0.75 (0.67, 0.83)				
Edlin et al (2013)       USA         Cutien et al (2013)       Ireland         Yobas et al (2013)       Turkey         Subtotal       0.55 (0.44, 0.46)         Non-OECD       0.84 (0.55)         Helin (1985)       Kowalt         AdMugehen et al (1996)       Saudi Arabia         Brown et al (2003)       Nigeria         Adjel et al (2004)       Ghana         Guidoni et al (2005)       Brazili         Guidoni et al (2006)       Brazili         Guidoni et al (2009)       Jordan         Farinad et al (2011)       Iran         Farinad et al (2011)       Iran         Farinad et al (2012)       Ian         Wu et al (2012)       Talwan         Manal et al (2012)       Saudi-Arabia         Fredrick et al (2013)       Tanzania		Turkey	•	
Cullen et al (2013)       Ireland         Yolbas et al (2013)       Turkey         Subtotal       0.66 (0.54, 0.57)         Non-OECD       Heln (1986)         Heln (1996)       Saudi Arab is         Brown et al (2003)       Nigeria         Adjel et al (2003)       Nigeria         Adjel et al (2004)       Ghana         Guidoni et al (2003)       Brazili         Guidoni et al (2003)       Brazili         Guidoni et al (2003)       Brazili         Guidoni et al (2009)       Jordan         Farahad et al (2011)       Iran         Parshad et al (2011)       Iran         Parshad et al (2012)       Tahvan         Wuetal (2012)       Tahvan         Manal et al (2013)       Tanzania         Subtotal       0.56 (0.58, 1.34)	Edlin et al (2013)	USA	•	
Yolbas et al (2013)       Turkey       0.84 (0.59, 1.10)         Subtotal       0.51 (0.48, 0.55)         Non-OECD       Heln (1986)       Kuwalt         AH-Mugehen et al (1996)       Saudi Arab is         Brown et al (2003)       Nigeria         Adglei et al (2004)       Ghana         Suidoni et al (2003)       Brazili         Suidoni et al (2010)       Iran         Farshad et al (2011)       Iran         Sharma et al (2011)       Nepai         Akshara (2011)       Jordan         Farshad et al (2012)       Taiwan         Watal (2012)       Taiwan         Watal (2013)       Tanzania         Subtotal       0.96 (0.58, 1.34)         Subtotal       0.95 (0.67, 0.83)			•	
Subtotal		Turkey		
Heln (1985) Kuwalt Al-Mugeten et al (1996) Saudi Arab b Brown et al (2003) Nigerla Adgle et al (2004) Ghana Guidoni et al (2003) Brazili Guidoni et al (2003) Brazili Guidoni et al (2003) Brazili Al-Mardeni et al (2009) Jordan Farshad et al (2010) Iran Sharma et al (2011) Iran Sharma et al (2011) Nepal Alesara (2011) Jordan Farshad et al (2012) Iran Wu et al (2012) Talwan Manal et al (2013) Tanzan la Subiotal Alesara (2013) Tanzan la	Subtotal		٥	0.51 (0.48, 0.55)
AHMugehen et al (1996)       Saudi Arabia         Brown et al (2003)       Nigerla         Adjel et al (2004)       Ghana         Suidoni et al (2008)       Brazili         Suidoni et al (2009)       Jordan         Farshad et al (2010)       Iran         Shama et al (2011)       Iran         Akharac (2011)       Jordan         Farshad et al (2012)       Iran         Akharac (2012)       Iran         Akhara et al (2012)       Iran         Sudi Akhara (2012)       Iran         Sudi Akhara (2012)       Iran         Subotal       0.82 (0.73, 0.90)         Ogel (0.52, 0.56)       0.88 (0.71)         Jordan       0.80 (0.62, 0.98)         Rarshad et al (2011)       Jordan         Farshad et al (2012)       Iran         Wu et al (2012)       Tahwan         Vu et al (2012)       Tahwan         Subtotal       0.96 (0.58, 1.34)         O.75 (0.67, 0.83)       0.75 (0.67, 0.83)				
Brown et al (2003)       Nigerla         Adjel et al (2004)       Ghana         Suldoni et al (2003)       Brazili         Judiconi et al (2008)       Brazili         Addata et al (2009)       Jordan         Farshad et al (2010)       Iran         Shama et al (2011)       Iran         Alshara (2011)       Jordan         Farshad et al (2012)       Iran         Wu et al (2012)       Talwan         Vu et al (2012)       Saudi-Arabia         Firedrick et al (2013)       Tanzania         Subtotal       0.75 (0.67, 0.83)				
Adjel et al (2004)       Ghana         Suldoni et al (2003)       Brazili         Suldoni et al (2003)       Brazili         Administration et al (2009)       Jordan         Farshad et al (2010)       Iran         Farshad et al (2011)       Iran         Shama et al (2011)       Jordan         Farshad et al (2011)       Iran         Parshad et al (2012)       Iran         Nu et al (2012)       Iran         Wu et al (2012)       Talwan         Vu et al (2013)       Tanzan la         Subtotal       0.95 (0.58, 1.34)			+	
Suidoni et al (2008)         Brazili           Suidoni et al (2008)         Brazili           Al-Mardeni et al (2009)         Jordan           Farina det al (2010)         Iran           Farina det al (2011)         Iran           Stanta et al (2012)         Iran           Vue tal (2012)         Talwan           Wanal et al (2013)         Tanzan la           Subtotal         0.55 (0.58, 1.34)				
Guidoni et al (2003)         Brazili         0.55 (0.38, 0.71)           AHMardeni et al (2009)         Jordan         0.82 (0.73, 0.90)           Farshad et al (2010)         Iran         0.86 (0.66, 1.06)           Sharma et al (2011)         Iran         0.86 (0.66, 1.06)           Sharma et al (2011)         Jordan         0.86 (0.66, 1.06)           Nama et al (2011)         Jordan         0.86 (0.66, 1.06)           Alshara (2011)         Jordan         0.80 (0.62, 0.98)           Alshara (2011)         Jordan         0.80 (0.62, 0.98)           Nu et al (2012)         Iran         0.80 (0.62, 0.98)           Wu et al (2012)         Tahwan         0.80 (0.62, 0.90)           Wanal et al (2012)         Saudi-Arabia         0.75 (0.66, 0.90)           Firedrick et al (2013)         Tanzan la         0.96 (0.58, 1.34)           Subtotal         0.75 (0.67, 0.83)         0.75 (0.67, 0.83)				
Al-Mardeni et al (2009)       Jordan         Farshad et al (2010)       Iran         Farshad et al (2011)       Iran         Shama et al (2011)       Nepal         Akharar (2011)       Jordan         Shama et al (2011)       Jordan         Vu et al (2012)       Iran         Wu et al (2012)       Talwan         Vanal et al (2012)       Saudi-Arabia         Fredrick et al (2013)       Tanzan Ia         Subtotal       0.96 (0.58, 1.34)				
Farshad et al (2010)       Iran         Farshad et al (2011)       Iran         Shama et al (2011)       Iran         Alshara (2011)       Jordan         Farshad et al (2012)       Iran         Alshara (2012)       Iran         Wu et al (2012)       Talwan         Vu et al (2012)       Saudi-Arabia         Firedrick et al (2013)       Tanzanta         Subtotal       0.96 (0.58, 1.34)				
Farshad et al (2011)       Iran       0.86 (0.66, 1.06)         Shama et al (2011)       Nepal       0.92 (0.37, 1.46)         Alshara (2011)       Jordan       0.84 (0.74, 0.94)         Farshad et al (2012)       Iran       0.84 (0.74, 0.94)         Wu et al (2012)       Talwan       0.75 (0.60, 0.90)         Wanal et al (2012)       Saudi-Arabia       0.73 (0.60, 0.85)         Fedrick et al (2013)       Tanzan Ia       0.96 (0.58, 1.34)         Subtotal       0.75 (0.67, 0.83)       0.75 (0.67, 0.83)				
Sharma et al (2011)         Nepal           Alshara (2011)         Jordan           Alshara (2011)         Jordan           Farshad et al (2012)         Iran           Wu et al (2012)         Talwan           Wanal et al (2012)         Saudi-Arabia           Fiedrick et al (2013)         Tanzan la           Subtotal         0.95 (0.67, 0.83)				
Alshara (2011) Jordan Farshad et al (2012) Iran Wu et al (2012) Talwan Wanal et al (2012) Saudi-Atabla Firedrick et al (2013) Tanzan la Subtotal 0.75 (0.67, 0.83)				
Farshad et al (2012)         Iran           Wu et al (2012)         Talwan           Wu et al (2012)         Talwan           Vanal et al (2012)         Saudi-Arabia           Fiedrick et al (2013)         Tanzan la           Subtotal         0.96 (0.58, 1.34)           0.75 (0.67, 0.83)				
Wu et al (2012)         Talwan         0.75 (0.60, 0.90)           Wanal et al (2012)         Saudi-Arabia         0.73 (0.60, 0.85)           Fiedrick et al (2013)         Tanzanta         0.96 (0.58, 1.34)           Subtotal         0.75 (0.67, 0.83)         0.75 (0.67, 0.83)	Alshara (2011)	Jordan		
Wanal et al (2012)         Saudi-Atabla           Fedrick et al (2013)         Tanzan la           Subtotal         0.73 (0.50, 0.85)           0.96 (0.58, 1.34)         0.75 (0.57, 0.83)				
Fiedrick et al (2013)         Tanzan la           Subtotal         0.96 (0.58, 1.34)           \$\scilon\$ 0.75 (0.67, 0.83)				
Subtotal 0.75 (0.67, 0.83)			•	
		Tanzan la		
	Subtotal			0.75 (0.67, 0.83)
0 2 .4 .6 .8 1			0 .2 .4 .6 .8 1	

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

author	country		ES (95% CI)
OECD Ladhani et al (2003) Fritzsche et al (2005) Gaspari et al (2006) Gaspari et al (2006) Anatoliotaki et al (2007) Falagas et al (2008) Prelog et al (2008) Prelog et al (2008) Rokeni et al (2010) Senel et al (2010) Senel et al (2010) Senel et al (2010) Bryce et al (2010) Bryce et al (2011) Ismaili et al (2011) Guner et al (2012) Yolbas et al (2013) Cullen et al (2013) Subtotal	UK Switzerland Switzerland USA USA USA USA USA USA USA USA USA USA		0.04 (0.03, 0.04) 0.15 (0.09, 0.20) 0.11 (0.06, 0.17) 0.06 (0.03, 0.10) 0.05 (0.05, 0.06) 0.04 (0.03, 0.05) 0.06 (0.04, 0.09) 0.06 (0.04, 0.09) 0.06 (0.05, 0.07) 0.05 (0.05, 0.06) 0.04 (0.03, 0.05) 0.15 (0.10, 0.21) 0.07 (0.04, 0.11) 0.07 (0.04, 0.11) 0.07 (0.04, 0.11) 0.07 (0.04, 0.10) 0.04 (0.01, 0.07) 0.50 (0.37, 0.64) 0.21 (0.18, 0.25) 0.19 (0.15, 0.23) 0.17 (0.13, 0.21) 0.17 (0.13, 0.21) 0.17 (0.13, 0.17) 0.73 (0.56, 0.89) 0.15 (0.11, 0.18) 0.08 (0.04, 0.13) 0.08 (0.04, 0.13) 0.08 (0.04, 0.12) 0.13 (0.11, 0.14) 0.60 (0.43, 0.76) 0.05 (0.05, 0.05) 0.10 (0.09, 0.11)
Non-OECD Al-Mugeiren et al (1996) Brown et al (2003) Adjei et al (2004) Narchi et al (2008) Alshara (2011) Fredrick et al (2013) Sharan et al (2013) Subtotal	Saudi Arabia Nigeria Ghana UAE Jordan Tanzania India		0.31 (0.27, 0.36) 0.76 (0.35, 1.18) 0.40 (0.08, 0.72) 0.62 (0.51, 0.73) 0.75 (0.65, 0.84) 0.88 (0.51, 1.25) 0.88 (0.62, 1.14) 0.64 (0.43, 0.85)
		0.2.4.6.81	
		Prevalence of resista	nce

BMJ

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

CGCD       Alter et al (1969)       USA         Alter et al (1969)       USA       0.24 (0.24), 0.67)         Burman et al (2003)       USA       0.24 (0.24), 0.67)         Burman et al (2003)       USA       0.24 (0.24), 0.67)         Burman et al (2005)       Switzenind       0.24 (0.22, 0.27)         Geopart et al (2005)       USA       0.24 (0.24, 0.67)         Geopart et al (2005)       USA       0.24 (0.24, 0.25)         Geopart et al (2005)       Turkey       0.24 (0.24, 0.25)	author	country	ES (95% CI)
Advertage (19(91))       Israel       0.38 (27, 0.40)         Burman et al (2003)       USA       0.38 (27, 0.40)         Burman et al (2005)       USA       0.37 (200, 0.15)         Burman et al (2005)       USA       0.37 (200, 0.15)         Gaspari et al (2005)       USA       0.38 (27, 0.40)         Gaspari et al (2005)       USA       0.37 (200, 0.15)         Gaspari et al (2005)       USA       0.34 (0.10, 0.22)         Gaspari et al (2005)       Austin       0.36 (0.27, 0.43)         Denati et al (2005)       Austin       0.36 (0.27, 0.43)         Denati et al (2005)       Austin       0.36 (0.27, 0.43)	OECD		
Alen et al (1999)       USA       USA         Burman et al (2003)       USA       USA         Burman et al (2003)       USA       044 (0.21, 0.67)         Burman et al (2005)       USA       047 (0.00, 0.16)         Frizzoh et al (2005)       USA       024 (0.22, 0.22)         Gaspari et al (2005)       USA       024 (0.22, 0.27)         Gaspari et al (2005)       USA       024 (0.22, 0.25)         Gaspari et al (2005)       Autoria       024 (0.22, 0.25)         Gatal et al (2005)	Ashkenazi et al (1991)	Israel	0.36 (0.27, 0.46)
Burnan et al (200)         USA           Burnan et al (2003)         USA           Burnan et al (2003)         USA           Fitzach et al (2005)         USA           Gapari et al (2005) </td <td></td> <td></td> <td></td>			
Burnan et al (2003) USA	. ,		
Burman et al (2003)         USA         0.07 (000, 016)           Fritzache et al (2005)         USA         0.07 (000, 016)           Grappit et al (2005)         Austin         0.07 (000, 016)           Grappit e	. ,		
Fitzsche stal (2006)       Switzerland       0.2 6 (0.7, 0.33)         Gespari et al (2005)       USA       0.2 6 (0.7, 0.33)         Fitzsche stal (2005)       USA       0.2 6 (0.7, 0.33)         Gespari et al (2005)       USA       0.2 6 (0.7, 0.33)         Gespari et al (2005)       USA       0.1 6 (0.0, 0.21)         Gespari et al (2005)       USA       0.1 6 (0.0, 0.21)         Gespari et al (2005)       USA       0.2 6 (0.7, 0.33)         Gespari et al (2005)       USA       0.2 1 (0.0, 0.21)         Gespari et al (2005)       USA       0.2 1 (0.0, 0.17)         Anatolicable et al (2006)       USA       0.3 10 (0.0, 0.7)         Anatolicable et al (2007)       Greece       0.3 3 (0.27, 0.43)         Freidg et al (2008)       Austria       0.3 0 (0.27, 0.43)         Sonart et al (2010)       Turkey       0.2 1 (0.14, 0.27)         Catal et al (2010)       Turkey       0.2 0 (0.14, 0.27)         Sonart et al (2010)       Turkey       0.5 0 (0.44, 0.76)         Sonart et al (2010)       Turkey       0.5 0 (0.44, 0.76)         Sonart et al (2010)       Turkey       0.5 0 (0.44, 0.76)         Sonart et al (2010)       Turkey       0.5 0 (0.44, 0.76)         Sonal et al (2010)       Turkey			
Gaspari et al (2005)         USA         22 (0.22, 0.27)           Gaspari et al (2005)         Sutternand         0.16 (0.10, 0.21)           Gaspari et al (2005)         USA         0.16 (0.10, 0.21)           Gaspari et al (2005)         USA         0.24 (0.22, 0.26)           Gaspari et al (2005)         Greece         0.27 (0.20, 0.25)           Prelog et al (2005)         Greece         0.27 (0.20, 0.25)           Boran et al (2005)         Greece         0.27 (0.20, 0.35)           Boran et al (2005)         Turkey         0.26 (0.04, 0.27)           Catal et al (2005)         Turkey         0.26 (0.05, 0.67)           Senel et al (2011)         Turkey         0.26 (0.05, 0.67)           Senel et al (2011)         Turkey         0.26 (0.05, 0.67)           Senel et al (2011)         Turkey         0.26 (0.05, 0.67)           Garaccine et al (2011)         Turkey         0.26 (0.02, 0.52)			
Gaspari et al (2005)       USA       0.21 (0.20.0.22)         Gaspari et al (2005)       USA       0.16 (0.10.0.21)         Gaspari et al (2005)       USA       0.14 (0.12.0.15)         Gaspari et al (2005)       USA       0.21 (0.20.22)         Gaspari et al (2005)       USA       0.21 (0.10.0.17)         Arathridekh et al (2005)       USA       0.21 (0.10.0.17)         Arathridekh et al (2005)       USA       0.21 (0.10.2.0.15)         Gaspari et al (2006)       Austria       0.21 (0.10.2.0.15)         Gaspari et al (2006)       Turkey       0.24 (0.01.0.17)         Frends et al (2006)       Turkey       0.24 (0.01.0.26)         Senet et al (2010)       Turkey       0.24 (0.01.0.26)         Senet et al (2011)       Turkey       0.24 (0.02.0.22)         Senet et al (2011)       Turkey       0.24 (0.02.0.26)         Gala et al (2010)       Turkey       0.24 (0.02.0.26)         Gala et al (2002)       Brazal       0.24 (0.22.0.25) <t< td=""><td></td><td></td><td>• 0.25 (0.17, 0.33)</td></t<>			• 0.25 (0.17, 0.33)
Fr2sche et al (2005)       USA       0.1 (0 (0.1 0.21)         Gaspari et al (2005)       USA       0.1 (0 (0.1 0.21)         Gaspari et al (2005)       USA       0.2 (0 (0.2 c) (5)         Gaspari et al (2005)       USA       0.2 (0 (0.2 c) (5)         Gaspari et al (2005)       USA       0.2 (0 (0.2 c) (5)         Gaspari et al (2005)       USA       0.2 (0 (0.2 c) (5)         Gaspari et al (2005)       USA       0.3 (0 (0.2 c) (2)         Gaspari et al (2005)       USA       0.3 (0 (0.2 c) (2)         Gaspari et al (2006)       Austria       0.3 (0 (0.2 c) (2)         Fraigas et al (2006)       Austria       0.2 (0 (1.2 c) (2)         Gatal et al (2006)       Austria       0.2 (0 (1.2 c)         Catal et al (2006)       Turkey       0.6 (0 (0.4 (-76)         Semel et al (2010)       Turkey       0.6 (0 (0.4 (-76)         Semel et al (2010)       Turkey       0.6 (0 (0.4 (-76)         Semel et al (2010)       Turkey       0.5 (0 (0.4 (-76)         Semel et al (2010)       Turkey       0.5 (0 (0.4 (-76)         Semel et al (2010)       Turkey       0.5 (0 (0.4 (-76)         Garacice al (2011)       Turkey       0.5 (0 (0.4 (-76)         Garacice al (2011)       Turkey       0.5 (0 (0.4	Gaspari et al (2005)	USA	• 0.24 (0.22, 0.27)
Gaspari et al (2005)         USA         0.14 (0.12, 0.15)           Gaspari et al (2005)         USA         0.23 (0.02, 0.23)           Gaspari et al (2005)         USA         0.21 (0.02, 0.22)           Gaspari et al (2005)         USA         0.21 (0.02, 0.22)           Gaspari et al (2005)         USA         0.21 (0.02, 0.22)           Gaspari et al (2005)         USA         0.31 (0.01, 0.17)           Antolicidant at (2007)         Greece         0.22 (0.22, 0.26)           Felog et al (2008)         Austria         0.20 (0.22, 0.24)           Stand et al (2005)         Turkey         0.26 (0.22, 0.43)           Felog et al (2005)         Turkey         0.26 (0.22, 0.43)           Stand et al (2010)         Turkey         0.26 (0.25, 0.61)           Catal et al (2010)         Turkey         0.26 (0.50, 0.61)           Stand et al (2011)         Turkey         0.26 (0.50, 0.61)           Stand et al (2011)         Turkey         0.26 (0.50, 0.61)           Stand et al (2011)         Turkey         0.26 (0.50, 0.61)           Gale et al (2011)         Turkey         0.26 (0.52, 0.62)           Stand et al (2011)         Turkey         0.26 (0.52, 0.62)           Goldrain et al (2020)         Brazil         0.26 (0.62, 0.72)	Gaspari et al (2005)	USA	• 0.21 (0.20, 0.22)
Gaspari et al (2005)         USA         0.14 (0.12, 0.15)           Gaspari et al (2005)         USA         0.23 (0.02, 0.23)           Gaspari et al (2005)         USA         0.21 (0.02, 0.22)           Gaspari et al (2005)         USA         0.21 (0.02, 0.22)           Gaspari et al (2005)         USA         0.21 (0.02, 0.22)           Gaspari et al (2005)         USA         0.31 (0.01, 0.17)           Antolicidant at (2007)         Greece         0.22 (0.22, 0.26)           Felog et al (2008)         Austria         0.20 (0.22, 0.24)           Stand et al (2005)         Turkey         0.26 (0.22, 0.43)           Felog et al (2005)         Turkey         0.26 (0.22, 0.43)           Stand et al (2010)         Turkey         0.26 (0.25, 0.61)           Catal et al (2010)         Turkey         0.26 (0.50, 0.61)           Stand et al (2011)         Turkey         0.26 (0.50, 0.61)           Stand et al (2011)         Turkey         0.26 (0.50, 0.61)           Stand et al (2011)         Turkey         0.26 (0.50, 0.61)           Gale et al (2011)         Turkey         0.26 (0.52, 0.62)           Stand et al (2011)         Turkey         0.26 (0.52, 0.62)           Goldrain et al (2020)         Brazil         0.26 (0.62, 0.72)	Fritzsche et al (2005)	Switzerland	• 0.16 (0.10, 0.21)
Gaspari et al (2006)       USA         Gaspari et al (2007)       Greece         Anabidotati et al (2007)       Greece         Destant et al (2008)       USA         Sassari et al (2008)       USA         Sassari et al (2008)       USA         Sassari et al (2008)       Carece         Destant et al (2008)       Nutzerfand         Prebog et al (2008)       Tunkey         Senel et al (2010)       Tunkey         Senel et al (2011)       Tunkey         Salend et al (2013)       Tunkey         Galagos et al (2013)       Cheece <td></td> <td>USA</td> <td>• 0.14 (0.12, 0.15)</td>		USA	• 0.14 (0.12, 0.15)
Gaspari et al (2006)       USA         Anatolicitài et al (2007)       Greece         Prelog et al (2008)       Austina         Borsari et al (2008)       Suitzerland         Prelog et al (2008)       Austina         Catal et al (2009)       Turkey         Catal et al (2009)       Turkey         Senel et al (2010)       Turkey         Senel et al (2011)       Turkey         Senel et al (2011)       Turkey         Galagas et al (2013)       Turkey         Senel et al (2011)       Turkey         Senel et al (2011)       Turkey         Caracciolo et al (2011)       Turkey         Caracciolo et al (2011)       Turkey         Caracciolo et al (2012)       Turkey         Caracciolo et al (2012)       <			
Gaspari et al (2006)       USA       0.21 (0.20, 0.22)         Gaspari et al (2006)       USA       0.13 (0.10, 0.17)         Anatolotaki et al (2006)       USA       0.27 (0.20, 0.35)         Prolog et al (2006)       Austria       0.27 (0.20, 0.35)         Falaga et al (2006)       Austria       0.38 (0.27, 0.43)         Borant et al (2006)       Austria       0.21 (0.12, 0.30)         Catal et al (2000)       Turkey       0.38 (0.27, 0.43)         Senel et al (2010)       Turkey       0.46 (0.12, 0.50)         Senel et al (2010)       Turkey       0.46 (0.12, 0.50)         Senel et al (2010)       Turkey       0.46 (0.61, 0.83)         Senel et al (2010)       Turkey       0.47 (0.44, 0.59)         Senel et al (2010)       Turkey       0.46 (0.61, 0.83)         Paschke et al (2011)       UseA       0.55 (0.44, 0.52)         Immañ et al (2011)       Turkey       0.46 (0.61, 0.85)         Paschke et al (2011)       UseA       0.56 (0.44, 0.52)         Immañ et al (2012)       Turkey       0.46 (0.42, 0.25)         Garaccób et al (2012)       Turkey       0.46 (0.42, 0.25)         Subtofal       0.56 (0.42, 0.27)       0.56 (0.42, 0.27)         Gidranich et al (2022)       Brazl       0			
Gaspari et al (2006)       USA       0.14 (0:12, 0.15)         Gaspari et al (2006)       USA       0.13 (0:10, 0.17)         Anatoloxik et al (2007)       Greece       0.27 (0:20, 0:25)         Prolog et al (2008)       Austra       0.27 (0:20, 0:25)         Borsan et al (2008)       Sutzerland       0.27 (0:21, 0:23)         Decision et al (2009)       Turkey       0.66 (0:44, 0:76)         Catal et al (2009)       Turkey       0.66 (0:44, 0:76)         Senel et al (2010)       Turkey       0.66 (0:44, 0:76)         Senel et al (2010)       Turkey       0.56 (0:65, 0:67)         Senel et al (2010)       Turkey       0.56 (0:45, 0:52)         Senel et al (2010)       Turkey       0.56 (0:44, 0:57)         Senel et al (2010)       Turkey       0.56 (0:45, 0:52)         Senel et al (2010)       Turkey       0.56 (0:47, 0:45)         Galades et al (2010)       Turkey       0.56 (0:47, 0:45)         Galegas et al (2011)       Belgium       0.56 (0:47, 0:45)         Manatodakis et al (2011)       Turkey       0.29 (0:42, 0:27)         Galegas et al (2013)       Chuke       0.29 (0:42, 0:27)         Galegas et al (2013)       Chuke       0.29 (0:42, 0:27)         Galedas et al (2012)       Berazl <td> ,</td> <td></td> <td></td>	,		
Gaspari et al (2006)         USA         0.13 (0.10, 0.17)           Anabicidasi et al (2007)         Greece         0.38 (0.27, 0.43)           Prelog et al (2008)         Greece         0.38 (0.27, 0.43)           Bosari et al (2009)         Austia         0.21 (0.12, 0.30)           Austia         0.21 (0.12, 0.30)         0.21 (0.14, 0.27)           Call et al (2009)         Turkey         0.43 (0.01, 0.17)           Call et al (2009)         Turkey         0.38 (0.27, 0.43)           Senel et al (2010)         Turkey         0.45 (0.53, 0.58)           Senel et al (2010)         Turkey         0.45 (0.50, 0.51)           Senel et al (2010)         Turkey         0.46 (0.63, 0.52)           Senel et al (2010)         Turkey         0.44 (0.64, 0.52)           Senel et al (2011)         Turkey         0.44 (0.64, 0.52)           Pasche et al (2011)         Turkey         0.44 (0.64, 0.52)           Mandadaks et al (2011)         Turkey         0.49 (0.46, 0.52)           Goldraich et al (2021)         Turkey         0.49 (0.42, 0.27)           Goldraich et al (2021)         Brazil         0.42 (0.23, 0.45)           Goldraich et al (2020)         Brazil         0.49 (0.42, 0.27)           Goldraich et al (2020)         Brazil			
Anatolizational et al (2007)       Greece       0.27 (0.20, 0.35)         Prings et al (2008)       Austria       0.35 (0.27, 0.43)         Prings et al (2009)       Switzerland       0.21 (0.14, 0.27)         Other et al (2009)       Turkey       0.21 (0.14, 0.27)         Catal et al (2009)       Turkey       0.02 (0.63, 0.87)         Scenel et al (2010)       Turkey       0.02 (0.64, 0.75)         Scenel et al (2010)       Turkey       0.05 (0.65, 0.87)         Senel et al (2010)       Turkey       0.56 (0.56, 0.61)         Senel et al (2010)       Turkey       0.56 (0.50, 0.61)         Senel et al (2010)       Turkey       0.56 (0.50, 0.61)         Senel et al (2010)       Turkey       0.56 (0.50, 0.62)         Senel et al (2010)       Turkey       0.56 (0.50, 0.62)         Ismail et al (2011)       Turkey       0.56 (0.50, 0.62)         Ismail et al (2011)       Turkey       0.56 (0.50, 0.62)         Ismail et al (2013)       Greece       0.20 (0.16, 0.25)         Caraciolo et al (2013)       Turkey       0.46 (0.62, 0.25)         Yobas et al (2013)       Turkey       0.46 (0.63, 0.62)         Subtral       0.24 (0.22, 0.25)       0.58 (0.44, 0.72)         Coddrain et al (2002)       Brazal<			
Prelog et al (2006)         Austria         0.38 (0.27, 0.43)           Borsan et al (2008)         Greece         0.38 (0.27, 0.43)           Borsan et al (2008)         Austria         0.21 (0.12, 0.30)           Calat et al (2009)         Turkey         0.21 (0.12, 0.30)           Calat et al (2009)         Turkey         0.45 (0.27, 0.43)           Sensel et al (2010)         Turkey         0.45 (0.33, 0.58)           Sensel et al (2010)         Turkey         0.45 (0.33, 0.58)           Sensel et al (2010)         Turkey         0.46 (0.33, 0.58)           Sensel et al (2010)         Turkey         0.44 (0.01, 0.58)           Sensel et al (2010)         Turkey         0.44 (0.01, 0.58)           Pasche et al (2011)         Turkey         0.44 (0.02, 0.52)           Ismali et al (2011)         Turkey         0.44 (0.02, 0.52)           Ismali et al (2011)         Turkey         0.44 (0.02, 0.52)           Caraccolo et al (2011)         Turkey         0.46 (0.62, 0.52)           Subtral         0.38 (0.27, 0.43)         0.48 (0.42, 0.27)           Coldraich et al (2012)         Turkey         0.48 (0.42, 0.27)           Coldraich et al (2012)         Turkey         0.48 (0.42, 0.27)           Coldraich et al (2020)         Brazal			
Falagase tal (2008)         Greece         0.35 (0.27, 0.43)           Descriat et al (2009)         Austria         0.21 (0.12, 0.30)           Catal et al (2009)         Turkey         0.60 (0.44, 0.76)           Catal et al (2009)         Turkey         0.60 (0.44, 0.76)           Senel et al (2010)         Turkey         0.60 (0.44, 0.76)           Senel et al (2010)         Turkey         0.56 (0.50, 0.61)           Senel et al (2010)         Turkey         0.56 (0.50, 0.61)           Senel et al (2010)         Turkey         0.44 (0.45, 0.52)           Senel et al (2010)         Turkey         0.44 (0.04, 0.52)           Senel et al (2011)         Turkey         0.44 (0.04, 0.52)           Ismaile et al (2011)         Greece         0.20 (0.16, 0.25)           Caracelob et al (2013)         Urkey         0.49 (0.45, 0.52)           Volue et al (2013)         Urkey         0.49 (0.45, 0.52)           Subto et al (2013)         Urkey         0.49 (0.45, 0.52)           Subto et al (2013)         Urkey         0.49 (0.45, 0.52)           Subto et al (2013)         Urkey         0.49 (0.45, 0.52)           Caracelo et al (2013)         Urkey         0.49 (0.45, 0.52)           Caracelo et al (2013)         Descret al (2013)         Des			
Borsain et al (2006)         Switzerland         021 (0.14, 0.27)           Catal et al (2006)         Austria         041 (0.14, 0.27)           Catal et al (2009)         Turkey         046 (0.33, 0.58)           Scheel et al (2010)         Turkey         046 (0.33, 0.58)           Senel et al (2010)         Turkey         046 (0.44, 0.59)           Senel et al (2010)         Turkey         046 (0.44, 0.59)           Senel et al (2010)         Turkey         046 (0.44, 0.59)           Senel et al (2010)         Turkey         046 (0.46, 0.52)           Senel et al (2010)         Turkey         046 (0.46, 0.52)           Pasztike et al (2011)         Turkey         046 (0.46, 0.52)           Franciscio et al (2011)         Beiglum         0.46 (0.46, 0.52)           Mantidakis et al (2011)         Turkey         0.46 (0.46, 0.52)           Galegos et al (2013)         Turkey         0.49 (0.46, 0.52)           Caracciok et al (2013)         Turkey         0.49 (0.46, 0.52)           Subtotal         0.44 (0.41, 0.24)         0.44 (0.41, 0.24)           Non-OECD         0.49 (0.45, 0.25)         0.49 (0.45, 0.25)           Coldrain et al (2002)         Brazil         0.49 (0.45, 0.25)           Subtotal         0.47 (0.41, 0.34)	Prelog et al (2008)	Austria	• 0.36 (0.29, 0.42)
Borsain et al (2006)         Switzerland         021 (0.14, 0.27)           Catal et al (2006)         Austria         041 (0.14, 0.27)           Catal et al (2009)         Turkey         046 (0.33, 0.58)           Scheel et al (2010)         Turkey         046 (0.33, 0.58)           Senel et al (2010)         Turkey         046 (0.44, 0.59)           Senel et al (2010)         Turkey         046 (0.44, 0.59)           Senel et al (2010)         Turkey         046 (0.44, 0.59)           Senel et al (2010)         Turkey         046 (0.46, 0.52)           Senel et al (2010)         Turkey         046 (0.46, 0.52)           Pasztike et al (2011)         Turkey         046 (0.46, 0.52)           Franciscio et al (2011)         Beiglum         0.46 (0.46, 0.52)           Mantidakis et al (2011)         Turkey         0.46 (0.46, 0.52)           Galegos et al (2013)         Turkey         0.49 (0.46, 0.52)           Caracciok et al (2013)         Turkey         0.49 (0.46, 0.52)           Subtotal         0.44 (0.41, 0.24)         0.44 (0.41, 0.24)           Non-OECD         0.49 (0.45, 0.25)         0.49 (0.45, 0.25)           Coldrain et al (2002)         Brazil         0.49 (0.45, 0.25)           Subtotal         0.47 (0.41, 0.34)	Falagas et al (2008)	Greece	• 0.35 (0.27, 0.43)
Presso et al (2009)         Austria         021 (0.14, 0.27)           Catal et al (2009)         Turkey         060 (0.44, 0.76)           Scheel et al (2010)         Turkey         027 (0.56, 0.87)           Senel et al (2010)         Turkey         027 (0.56, 0.87)           Senel et al (2010)         Turkey         056 (0.55, 0.61)           Senel et al (2010)         Turkey         051 (0.44, 0.59)           Senel et al (2010)         Turkey         051 (0.44, 0.59)           Senel et al (2010)         Turkey         051 (0.44, 0.59)           Senel et al (2010)         Turkey         040 (0.25, 0.25)           Isenal et al (2011)         Turkey         040 (0.25, 0.25)           Isenal et al (2011)         Turkey         040 (0.25, 0.25)           Isenal et al (2011)         Turkey         040 (0.45, 0.25)           Galace et al (2013)         Turkey         058 (0.44, 0.72)           Galace et al (2013)         Turkey         058 (0.44, 0.72)           Subbal         0.16 (0.60, 0.25)         0.58 (0.44, 0.72)           Galace et al (2013)         UsA         0.29 (0.42, 0.77)           Goldraich et al (2002)         Brazil         0.58 (0.44, 0.72)           Galace et al (2003)         Nogreira         0.59 (0.42, 0.77)		Switzerland	
Catal et al (2009)       Turkey       046 (0.43, 0.76)         Catal et al (2010)       Turkey       046 (0.33, 0.56)         Senel et al (2010)       Turkey       0.66 (0.80, 0.61)         Senel et al (2010)       Turkey       0.56 (0.80, 0.61)         Senel et al (2010)       Turkey       0.56 (0.80, 0.61)         Senel et al (2010)       Turkey       0.56 (0.80, 0.61)         Senel et al (2010)       Turkey       0.46 (0.33, 0.56)         Senel et al (2010)       Turkey       0.46 (0.30, 0.61)         Paschke et al (2011)       Turkey       0.49 (0.45, 0.52)         Senel et al (2011)       Turkey       0.49 (0.46, 0.52)         Senel et al (2011)       Turkey       0.49 (0.46, 0.25)         Caraccolo et al (2012)       Turkey       0.49 (0.46, 0.25)         Galegose et al (2013)       Urkey       0.49 (0.46, 0.25)         Caraccolo et al (2013)       UsA       0.29 (0.26, 0.32)         Non-OECD       Coldraich et al (2002)       Brazil       0.59 (0.44, 0.72)         Galegose et al (2013)       Nigeria       0.57 (0.42, 0.73)         Guidoni et al (2002)       Brazil       0.57 (0.42, 0.73)         Goldraich et al (2003)       Nigeria       0.57 (0.42, 0.43)         Galegose et al (2011) <td></td> <td></td> <td></td>			
Catal et al (2009) Turkey Kokenii et al (2010) Turkey Senei et al (2010) Turkey Paschke et al (2011) Turkey D44 (045, 6.52) D44 (046, 6.52) D44 (046, 6.52) D45 (044, 0.72) Caracobo et al (2011) Turkey Caner et al (2012) Turkey Voltas et al (2013) Turkey Subtotal Non-OECD Goldraich et al (2002) Brazil Goldraich et al (2002) Brazil Goldraich et al (2003) Nigeria Adgie et al (2014) Ghana Guidoni et al (2005) Brazil Guidoni et al (2005) Brazil Guidoni et al (2006) UAE Razil Adgie et al (2011) Iran Adgie et al (2011) Iran Adgie et al (2011) Iran Addie et al (2012) Iran Addie et al (2013) Iran Ad			
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Senel et al (2010)Turkey $0.56 (0.50, 0.61)$ Senel et al (2010)TurkeySenel et al (2010)TurkeySenel et al (2011)TurkeyBaschke et al (2011)UtkeyIpaschke et al (2011)TurkeyIsmail et al (2011)TurkeyGalegos et al (2012)TurkeyGalegos et al (2013)TurkeyGalegos et al (2013)TurkeyChile et al (2013)USAGalegos et al (2013)ChileColdraich et al (2002)BrazilGoldraich et al (2002)BrazilGoldraich et al (2002)BrazilGuidoni et al (2003)NigeriaGuidoni et al (2004)GhanaGuidoni et al (2005)BrazilGuidoni et al (2006)HegalAt-Mardeni et al (2011)LaRRait et al (2011)JordanSharma et al (2012)IranAt-Mardeni et al (2012)Iran		-	
Senel et al (2010)       Turkey         Senel et al (2010)       Turkey         Senel et al (2010)       Turkey         Paschke et al (2010)       UsA         Ipek et al (2011)       Turkey         Samali et al (2011)       Belgium         Mantdaxis et al (2011)       Belgium         Caracciols et al (2012)       Turkey         Caracciols et al (2013)       Turkey         Gallegos et al (2013)       Turkey         Subtotal       USA         Non-OCCD       Goldraich et al (2002)         Goldraich et al (2002)       Brazil         Goldraich et al (2002)       Brazil         Goldraich et al (2003)       Nigeria         Adjei et al (2004)       Ghana         Guidoni et al (2008)       Brazil         Guidoni et al (2009)       Jordan         Shama et al (2011)       Iran         Albarae (2011)       Iran         Albarae (2011)       Iran         Albarae (2014)       Ghana         Guidoni et al (2008)       Mezal         Shama et al (2011)       Iran         Albarae (2011)       Jordan         Pourakbari et al (2012)       Iran         Albarae (2011)       Nepal		-	
Senel et al (2010)       Turkey         Senel et al (2010)       Turkey         Paschke et al (2011)       Turkey         Ipsk et al (2011)       Turkey         Ipsk et al (2011)       Belgium         Mantadakis et al (2011)       Greece         Caraccobe et al (2013)       Turkey         Sunder et al (2013)       Turkey         Gallegos et al (2013)       Turkey         Subtet al (2013)       Turkey         Subtet al (2013)       USA         Non-OECD       Other (2012)         Goldraich et al (2002)       Brazil         Goldraich et al (2002)       Brazil         Goldraich et al (2003)       Nigeria         Adjel et al (2014)       Ghama         Guidoni et al (2008)       UAE         Narchi et al (2008)       Brazil         Guidoni et al (2008)       Brazil         Narchi et al (2011)       Jordan         Alberal       Orf (0.05, 0.25)         Jordan       Orf (0.05, 0.25)         Sharma et al (2011)       Brazil         Guidoni et al (2002)       Brazil         Narchi et al (2008)       UAE         Narchi et al (2011)       Jordan         Sharma et al (2011)       Jordan	( )	-	
Sendel ral (2010)       Turkey         Paschke et al (2011)       Turkey         Ismail et al (2011)       Turkey         Ismail et al (2011)       Belgium         Mantadakis et al (2011)       Greece         Caraccobe et al (2011)       Turkey         Gallegos et al (2013)       Turkey         Oblass et al (2013)       Turkey         Gallegos et al (2013)       Turkey         Gallegos et al (2013)       USA         Subtobal       USA         Non-OECD       Goldraich et al (2002)         Goldraich et al (2002)       Brazil         Goldraich et al (2003)       Nigeria         Adjei et al (2003)       Nigeria         Adjei et al (2008)       Brazil         Guidoni et al (2008)       Brazil         Guidoni et al (2008)       Brazil         Guidoni et al (2009)       Jordan         Shara et al (2011)       Iran         Al-Mardeni et al (2012)       Iran         Al-Mardeni et al (2012)       Iran         Al-Mardeni et al (2013)       Jordan         Pourakbari et al (2013)       Taiwan         Manal et al (2013)       Taiwan         Al-Marteni et al (2013)       Taiwan         Manal et al (2013		-	
Paschke et al (2010)       USA       0.15 (0.11, 0.19)         Ipek et al (2011)       Turkey       0.40 (0.28, 0.52)         Ismail et al (2011)       Greece       0.20 (0.16, 0.25)         Caracciole et al (2011)       Italy       0.49 (0.42, 0.52)         Guner et al (2012)       Turkey       0.49 (0.45, 0.52)         Yobs et al (2013)       Turkey       0.49 (0.45, 0.52)         Salegos et al (2013)       Turkey       0.49 (0.45, 0.52)         Subtotal       0.52 (0.22, 0.46)       0.20 (0.6, 0.25)         Non-OECD       0.53 (0.27, 0.46)         Goldraich et al (2002)       Brazil       0.49 (0.45, 0.52)         Goldraich et al (2002)       Brazil       0.59 (0.24, 0.77)         Goldraich et al (2002)       Brazil       0.59 (0.42, 0.77)         Goldraich et al (2003)       Nigeria       0.59 (0.42, 0.77)         Goldraich et al (2003)       Nigeria       0.57 (0.34, 0.43, 0.76)         Sharma et al (2013)       UAE       0.52 (0.52, 0.46)         Narchi et al (2008)       Brazil       0.51 (0.35, 0.67)         Guidoni et al (2009)       Jordan       0.57 (0.34, 0.81)         Asharea (et al (2011)       Iran       0.57 (0.54, 0.81)         Ashardeni et al (2012)       Iran       0.57 (0.54,	Senel et al (2010)	Turkey	• 0.49 (0.45, 0.52)
ipek et al (2011)       Turkey       0.40 (0.28, 0.52)         ismail et al (2011)       Belgium       0.38 (0.27, 0.49)         Mantadakis et al (2011)       Italy       0.20 (0.16, 0.25)         Caracciolo et al (2012)       Turkey       0.49 (0.45, 0.52)         Guler et al (2013)       Turkey       0.49 (0.45, 0.52)         Callegos et al (2013)       Urkey       0.49 (0.45, 0.52)         Galegos et al (2013)       Urkey       0.24 (0.23, 0.46)         Coldraich et al (2002)       Brazil       0.24 (0.23, 0.25)         Subtotal       0.29 (0.26, 0.32)       0.29 (0.26, 0.32)         Non-OECD       Goldraich et al (2002)       Brazil       0.56 (0.44, 0.72)         Goldraich et al (2002)       Brazil       0.56 (0.44, 0.72)         Goldraich et al (2002)       Brazil       0.56 (0.42, 0.77)         Goldraich et al (2002)       Brazil       0.56 (0.42, 0.76)         Guidon et al (2003)       Nigeria       1.00 (0.52, 1.48)         Adjei et al (2004)       Ghana       0.57 (0.47, 0.67)         Guidon et al (2008)       Brazil       0.57 (0.47, 0.67)         Sharma et al (2011)       Iran       0.57 (0.43, 0.61)         Al-Materin et al (2012)       Iran       0.57 (0.43, 0.61)         Farshad	Senel et al (2010)	Turkey	• 0.44 (0.01, 0.88)
Ismalii et al (2011)       Belgium       0.36 (0.27, 0.45)         Mantadakis et al (2011)       Ialy       0.20 (0.16, 0.25)         Caracciole et al (2012)       Turkey       0.49 (0.45, 0.52)         Callegos et al (2013)       Chile       0.38 (0.27, 0.45)         Callegos et al (2013)       Turkey       0.49 (0.45, 0.52)         Callegos et al (2013)       USA       0.24 (0.23, 0.45)         Subtotal       0.29 (0.26, 0.22)       0.24 (0.23, 0.45)         Non-OECD       Brazil       0.59 (0.42, 0.77)         Goldrach et al (2002)       Brazil       0.59 (0.42, 0.77)         Goldrach et al (2002)       Brazil       0.59 (0.42, 0.77)         Goldrach et al (2003)       Nigeria       0.59 (0.42, 0.77)         Goldrach et al (2003)       Brazil       0.59 (0.42, 0.77)         Guidoni et al (2008)       Brazil       0.59 (0.42, 0.77)         Guidoni et al (2008)       Brazil       0.57 (0.40, 0.34)         Guidoni et al (2008)       Brazil       0.57 (0.44, 0.73)         Guidoni et al (2009)       Jordan       0.77 (0.67, 0.87)         Al-Mardeni et al (2011)       Iran       0.57 (0.34, 0.81)         Al-Mardeni et al (2012)       Iran       0.57 (0.34, 0.81)         Farshad et al (2012)       I	Paschke et al (2010)	USA	• 0.15 (0.11, 0.19)
Ismalii et al (2011)       Belgium       0.36 (0.27, 0.45)         Mantadakis et al (2011)       Ialy       0.20 (0.16, 0.25)         Caracciole et al (2012)       Turkey       0.49 (0.45, 0.52)         Callegos et al (2013)       Chile       0.38 (0.27, 0.45)         Callegos et al (2013)       Turkey       0.49 (0.45, 0.52)         Callegos et al (2013)       USA       0.24 (0.23, 0.45)         Subtotal       0.29 (0.26, 0.22)       0.24 (0.23, 0.45)         Non-OECD       Brazil       0.59 (0.42, 0.77)         Goldrach et al (2002)       Brazil       0.59 (0.42, 0.77)         Goldrach et al (2002)       Brazil       0.59 (0.42, 0.77)         Goldrach et al (2003)       Nigeria       0.59 (0.42, 0.77)         Goldrach et al (2003)       Brazil       0.59 (0.42, 0.77)         Guidoni et al (2008)       Brazil       0.59 (0.42, 0.77)         Guidoni et al (2008)       Brazil       0.57 (0.40, 0.34)         Guidoni et al (2008)       Brazil       0.57 (0.44, 0.73)         Guidoni et al (2009)       Jordan       0.77 (0.67, 0.87)         Al-Mardeni et al (2011)       Iran       0.57 (0.34, 0.81)         Al-Mardeni et al (2012)       Iran       0.57 (0.34, 0.81)         Farshad et al (2012)       I	lpek et al (2011)	Turkey	0.40 (0.28, 0.52)
Mantadakis et al (2011)       Greece       0.20 (0.16, 0.25)         Caracciob et al (2011)       Italy       0.18 (0.11, 0.24)         Guner et al (2013)       Turkey       0.58 (0.44, 0.72)         Gallegos et al (2013)       Chile       0.34 (0.23, 0.45)         Edin et al (2013)       USA       0.29 (0.26, 0.32)         Non-OECD       Frazil       0.59 (0.42, 0.77)         Goldraich et al (2002)       Brazil       0.59 (0.42, 0.77)         Goldraich et al (2002)       Brazil       0.59 (0.42, 0.77)         Goldraich et al (2002)       Brazil       0.59 (0.42, 0.77)         Goldraich et al (2003)       Nigeria       0.57 (0.34, 0.81)         Adjei et al (2004)       Ghana       0.57 (0.34, 0.81)         Guidoni et al (2008)       Brazil       0.36 (0.25, 0.46)         Narchi et al (2008)       Brazil       0.37 (0.67, 0.67)         Guidoni et al (2009)       Jordan       0.57 (0.34, 0.81)         Arbardeni et al (2011)       Iran       0.57 (0.34, 0.81)         Arbardeni et al (2012)       Iran       0.77 (0.67, 0.57)         Arbardeni et al (2012)       Iran       0.77 (0.67, 0.56)         Arbarde et al (2011)       Iran       0.57 (0.34, 0.81)         Arbarade et al (2012)       Iran		-	
Caracciolo et al (2011)       Italy       0.18 (0.11, 0.24)         Guner et al (2012)       Turkey         Yolhas et al (2013)       Chile         Gallegos et al (2013)       Chile         Edin et al (2013)       USA         Subtotal       0.24 (0.23, 0.25)         Non-OECD       0.29 (0.26, 0.32)         Goldraich et al (2002)       Brazil         Goldraich et al (2002)       Brazil         Grown et al (2003)       Nigeria         Adjei et al (2003)       Brazil         Guidon iet al (2008)       Brazil         Guidon iet al (2008)       Brazil         Guidon iet al (2008)       Brazil         Sharma et al (2011)       Itan         Albara (2011)       Jordan         Sharma et al (2012)       Itan         Archard et al (2012)       Itan         Farshad et al (2012)       Itan         Afshara (2011)       Jordan         Jordan       O.57 (0.34, 0.81)         Alshara (2011)       Itan         Alshara (2011)       Itan         Jordan       O.57 (0.34, 0.81)         Goldon iet al (2012)       Itan         Arabara       O.57 (0.34, 0.81)         Arabara       O.76 (0.65, 0.7			
Guner et al (2012)       Turkey         Yolbas et al (2013)       Turkey         Gallegos et al (2013)       Chile         Edlin et al (2013)       USA         Subtotal       0.34 (0.23, 0.45)         Non-OECD       0.29 (0.26, 0.32)         Goldraich et al (2002)       Brazil         Goldraich et al (2002)       Brazil         Goldraich et al (2003)       Nigeria         Adjei et al (2004)       Ghana         Guidoni et al (2008)       Brazil         Guidoni et al (2009)       Jordan         Ahardeni et al (2011)       Nepal         Farshad et al (2011)       Jordan         Pourabari et al (2012)       Iran         Afsharpaiman et al (2012)       Iran         Manare et al (2012)       Iran         Yulbari et al (2013)       Iran         Afsharpaiman et al (2012)       Iran         Yulbari et al (2013) <td></td> <td></td> <td></td>			
Yolbas et al (2013)       Turkey       0.58 (0.44, 0.72)         Galegos et al (2013)       Chie         Edin et al (2013)       USA         Subtotal       0.24 (0.23, 0.25)         Non-OECD       0.26 (0.26, 0.32)         Goldraich et al (2002)       Brazil         Goldraich et al (2002)       Brazil         Goldraich et al (2003)       Nigeria         Adjei et al (2004)       Ghana         Guidoni et al (2008)       Brazil         Sharma et al (2011)       Nepal         Alshara (2011)       Jordan         Pourakbari et al (2012)       Iran         Afsharapaiman et al (2012)       Iran         Parshed et al (2012)       Iran         Vue et al (2012)       Taiwan         Marchi et al (2013)       Taiwan         Vue et al (2012)       Taiwan         Vue et al (2012)       Taiwan         Vue et al (2012)       Taiwan         Vue et al		-	
Gallegos et al (2013)       Chile       0.34 (0.23, 0.45)         Edin et al (2013)       USA       0.24 (0.23, 0.25)         Subtotal       0.29 (0.26, 0.32)         Non-OECD       Brazil       0.56 (0.42, 0.77)         Goldraich et al (2002)       Brazil       0.56 (0.42, 0.77)         Goldraich et al (2003)       Nigeria       0.60 (0.43, 0.76)         Adjei et al (2004)       Ghana       0.56 (0.42, 0.77)         Guidoni et al (2008)       Brazil       0.57 (0.43, 0.76)         Guidoni et al (2008)       Brazil       0.51 (0.35, 0.67)         Guidoni et al (2008)       Brazil       0.51 (0.35, 0.67)         Guidoni et al (2009)       Jordan       0.51 (0.35, 0.67)         Sharma et al (2011)       Nepal       0.77 (0.67, 0.67)         Al-Mardeni et al (2011)       Iran       0.57 (0.34, 0.81)         Alshara (2011)       Jordan       0.77 (0.57, 0.69)         Porarkad et al (2012)       Iran       0.56 (0.64, 0.67)         Fredrick et al (2013)       Tanzania       0.56 (0.56, 0.76)         Vul et al (2013)       Iran       0.56 (0.56, 0.76)         Valavi et al (2013)       Iran       0.56 (0.56, 0.76)         Vul et al (2013)       Iran       0.56 (0.56, 0.76)		-	
Edin et al (2013)       USA       0.24 (0.23, 0.25)         Subtotal       0.29 (0.26, 0.32)         Non-OECD       Goldraich et al (2002)       Brazil         Goldraich et al (2002)       Brazil       0.16 (0.06, 0.25)         Goldraich et al (2002)       Brazil       0.59 (0.42, 0.77)         Goldraich et al (2003)       Nigeria       0.67 (0.40, 1.34)         Adjei et al (2004)       Ghana       0.87 (0.40, 1.34)         Guidoni et al (2008)       Brazil       0.51 (0.35, 0.67)         Sudoni et al (2008)       Brazil       0.51 (0.35, 0.67)         Narchi et al (2008)       UAE       0.52 (0.64)         Narchi et al (2010)       Jordan       0.57 (0.34, 0.81)         Sharma et al (2011)       Iran       0.57 (0.34, 0.81)         Farshad et al (2012)       Iran       0.57 (0.34, 0.81)         Farshad et al (2012)       Iran       0.57 (0.34, 0.81)         Farshad et al (2012)       Iran       0.57 (0.57, 0.65)         Farshad et al (2013)       Tanzania       0.56 (0.45, 0.67)         Vu et al (2012)       Tana       0.56 (0.45, 0.67)         Fredrick et al (2013)       Tanzania       0.56 (0.45, 0.76)         Subtotal       0.56 (0.45, 0.76)       0.56 (0.45, 0.76)		-	
Subtotal       0.29 (0.26, 0.32)         Non-OECD       Goldraich et al (2002)       Brazil         Goldraich et al (2002)       Brazil       0.56 (0.42, 0.77)         Goldraich et al (2003)       Nigeria       0.66 (0.06, 0.25)         Adjei et al (2004)       Ghana       0.87 (0.40, 1.34)         Guidrain et al (2008)       Brazil       0.87 (0.40, 1.34)         Guidoni et al (2008)       Brazil       0.87 (0.40, 1.34)         Guidoni et al (2008)       Brazil       0.86 (0.25, 0.46)         Narchi et al (2008)       UAE       0.86 (0.25, 0.46)         Narchi et al (2008)       UAE       0.57 (0.67, 0.87)         Al-Mardeni et al (2009)       Jordan       0.57 (0.28, 0.40)         Sharma et al (2011)       Iran       0.57 (0.24, 0.81)         Pourakbari et al (2012)       Iran       0.57 (0.34, 0.81)         Farshad et al (2012)       Iran       0.56 (0.45, 0.67)         Farshad et al (2013)       Tanzania       0.56 (0.56, 0.76)         Vul et al (2013)       Iran       0.56 (0.56, 0.76)	Gallegos et al (2013)	Chile	0.34 (0.23, 0.45)
Non-OECD       Goldraich et al (2002)       Brazil         Goldraich et al (2003)       Nigeria         Adjei et al (2004)       Ghana         Guidoni et al (2008)       Brazil         Guidoni et al (2008)       Brazil         Guidoni et al (2008)       Brazil         Al-Mardeni et al (2009)       Jordan         Sharma et al (2011)       Iran         Alshara (2011)       Jordan         Pourakbari et al (2012)       Iran         Afsharpaiman et al (2012)       Iran         Anal et al (2012)       Iran         Anal et al (2012)       Taiwan         Manal et al (2013)       Tanzania         Valavi et al (2013)       Tanzania         Valavi et al (2013)       Iran         Subtotal	Edlin et al (2013)	USA	• 0.24 (0.23, 0.25)
Goldraich et al (2002)       Brazil       0.16 (0.06, 0.25)         Goldraich et al (2002)       Brazil         Goldraich et al (2002)       Brazil         Goldraich et al (2003)       Nigeria         Adjei et al (2004)       Ghana         Guidoni et al (2008)       Brazil         Guidoni et al (2008)       Brazil         Guidoni et al (2008)       Brazil         Archi et al (2009)       UAE         Rai et al (2009)       Jordan         Sharma et al (2011)       Iran         Alshara (2011)       Jordan         Pourakbari et al (2012)       Iran         Farshad et al (2012)       Iran         Farshad et al (2012)       Tanan         Yua et al (2013)       Tanzania         Valavi et al (2013)       Tanzania         Valavi et al (2013)       Iran         Subtotal       0.66 (0.56, 0.76)         Subtotal       0.66 (0.56, 0.76)	Subtotal		0.29 (0.26, 0.32)
Goldraich et al (2002)       Brazil       0.16 (0.06, 0.25)         Goldraich et al (2002)       Brazil         Goldraich et al (2002)       Brazil         Goldraich et al (2003)       Nigeria         Adjei et al (2004)       Ghana         Guidoni et al (2008)       Brazil         Guidoni et al (2008)       Brazil         Guidoni et al (2008)       Brazil         Archi et al (2009)       UAE         Rai et al (2009)       Jordan         Sharma et al (2011)       Iran         Alshara (2011)       Jordan         Pourakbari et al (2012)       Iran         Farshad et al (2012)       Iran         Farshad et al (2012)       Tanan         Yua et al (2013)       Tanzania         Valavi et al (2013)       Tanzania         Valavi et al (2013)       Iran         Subtotal       0.66 (0.56, 0.76)         Subtotal       0.66 (0.56, 0.76)	Non-OECD		
Goldraich et al (2002)       Brazil       0.59 (0.42, 0.77)         Goldraich et al (2002)       Brazil       0.60 (0.43, 0.76)         Brown et al (2003)       Nigeria       0.60 (0.43, 0.76)         Adjei et al (2004)       Ghana       0.67 (0.40, 1.34)         Guidoni et al (2008)       Brazil       0.51 (0.35, 0.67)         Guidoni et al (2008)       Brazil       0.62 (0.51, 0.73)         Rai et al (2009)       Jordan       0.77 (0.67, 0.87)         Al-Mardeni et al (2011)       Iran       0.57 (0.24, 0.81)         Alshara (2011)       Jordan       0.77 (0.67, 0.84)         Pourakbari et al (2012)       Iran       0.77 (0.57, 0.96)         Farshad et al (2012)       Iran       0.76 (0.59, 0.93)         Wu et al (2012)       Taiwan       0.56 (0.45, 0.67)         Waard et al (2013)       Tanzania       0.56 (0.45, 0.67)         Yalavi et al (2013)       Iran       0.56 (0.45, 0.67)         Yalavi et al (2013)       Iran       0.56 (0.45, 0.67)         Subtotal       0.62 (0.52, 0.72)       0.66 (0.56, 0.76)		Brazil	0 16 (0 06 0 25)
Goldraich et al (2002)         Brazil         0.60 (0.43, 0.76)           Brown et al (2003)         Nigeria         1.00 (0.52, 1.48)           Adjei et al (2004)         Ghana         0.51 (0.35, 0.67)           Guidoni et al (2008)         Brazil         0.51 (0.35, 0.67)           Guidoni et al (2008)         UAE         0.36 (0.25, 0.46)           Narchi et al (2008)         UAE         0.62 (0.51, 0.73)           Rai et al (2010)         Jordan         0.77 (0.67, 0.87)           Alshara et al (2011)         Iran         0.57 (0.24, 0.81)           Alshara (2011)         Iran         0.57 (0.24, 0.81)           Pourakbari et al (2012)         Iran         0.77 (0.67, 0.80)           Yu et al (2012)         Iran         0.77 (0.57, 0.96)           Farshad et al (2012)         Iran         0.76 (0.59, 0.93)           Wu et al (2012)         Taiwan         0.56 (0.45, 0.67)           Fredrick et al (2013)         Tanzania         0.56 (0.45, 0.76)           Subtotal         0.62 (0.52, 0.72)         0.62 (0.52, 0.72)			
Brown et al (2003)       Nigeria         Adjei et al (2004)       Ghana         Guidoni et al (2008)       Brazil         Ouidoni et al (2008)       Brazil         Narchi et al (2008)       Brazil         Narchi et al (2008)       UAE         Rai et al (2009)       Jordan         Sharma et al (2011)       Iran         Alshara (2011)       Jordan         Pourakbari et al (2012)       Iran         Farshad et al (2012)       Iran         Farshad et al (2012)       Iran         Manal et al (2012)       Iran         Valavi et al (2013)       Tanzania         Valavi et al (2013)       Iran         Subtotal       0.56 (0.576)         Subtotal       0.56 (0.56, 0.76)			
Adjei et al (2004)       Ghana         Guidoni et al (2008)       Brazil         Guidoni et al (2008)       Brazil         Narchi et al (2008)       Brazil         Narchi et al (2008)       UAE         Rai et al (2008)       Nepal         Al-Mardeni et al (2009)       Jordan         Sharma et al (2011)       Nepal         Alshara (2011)       Iran         Alshara (2012)       Iran         Afsharapainan et al (2012)       Iran         Maral et al (2012)       Iran         Manal et al (2013)       Tanzania         Valavi et al (2013)       Iran         Subtotal       0.56 (0.45, 0.67)			
Guidoni et al (2008)       Brazil       0.51 (0.35, 0.67)         Guidoni et al (2008)       Brazil       0.36 (0.25, 0.46)         Narchi et al (2008)       UAE       0.57 (0.57, 0.57)         Al-Mardeni et al (2009)       Jordan       0.72 (0.64, 0.80)         Sharma et al (2011)       Iran       0.67 (0.22, 1.04)         Alshara (2011)       Iran       0.57 (0.34, 0.81)         Alshara (2011)       Jordan       0.77 (0.63, 0.80)         Pourakbari et al (2012)       Iran       0.77 (0.63, 0.80)         Pourakbari et al (2012)       Iran       0.77 (0.57, 0.96)         Farshad et al (2012)       Iran       0.76 (0.59, 0.93)         Wu et al (2012)       Taiwan       0.56 (0.45, 0.67)         Manal et al (2013)       Tanzania       0.56 (0.45, 0.67)         Valavi et al (2013)       Iran       0.66 (0.56, 0.76)         Subtotal       0.62 (0.52, 0.72)       0.62 (0.52, 0.72)		-	
Guidoni et al (2008)         Brazil         0.36 (0.25, 0.46)           Narchi et al (2008)         UAE         0.62 (0.51, 0.73)           Rai et al (2008)         Nepal         0.77 (0.67, 0.87)           Al-Mardeni et al (2009)         Jordan         0.72 (0.64, 0.80)           Sharma et al (2011)         Iran         0.57 (0.29, 1.04)           Alshara et al (2011)         Iran         0.57 (0.24, 0.81)           Alshara et al (2012)         Iran         0.90 (0.64, 1.16)           Afsharpaiman et al (2012)         Iran         0.77 (0.57, 0.96)           Farshad et al (2012)         Iran         0.77 (0.57, 0.96)           Maral et al (2012)         Taiwan         0.76 (0.59, 0.93)           Wu et al (2012)         Tainzania         0.56 (0.45, 0.67)           Fredrick et al (2013)         Tanzania         0.56 (0.45, 0.76)           Subtotal         0.62 (0.52, 0.72)         0.62 (0.52, 0.72)			
Narchi et al (2008)       UAE       0.62 (0.51, 0.73)         Rai et al (2008)       Nepal       0.77 (0.67, 0.67)         Al-Mardeni et al (2009)       Jordan       0.67 (0.29, 1.04)         Farshad et al (2011)       Iran       0.57 (0.29, 1.04)         Pourakbari et al (2012)       Iran       0.57 (0.36, 0.80)         Pourakbari et al (2012)       Iran       0.57 (0.57, 0.96)         Farshad et al (2012)       Iran       0.77 (0.57, 0.96)         Farshad et al (2012)       Iran       0.76 (0.58, 0.93)         Wu et al (2012)       Taiwan       0.76 (0.56, 0.57)         Fredrick et al (2013)       Tanzania       0.56 (0.45, 0.67)         Yeahviet al (2013)       Iran       0.56 (0.45, 0.67)         Subtotal       0.52 (0.52, 0.72)       0.62 (0.52, 0.72)			
Rai et al (2008)       Nepal         Al-Mardeni et al (2009)       Jordan         Sharma et al (2011)       Nepal         Farshad et al (2011)       Iran         Alshara (2011)       Jordan         Pourakbari et al (2012)       Iran         Afsharpaiman et al (2012)       Iran         Afsharbari et al (2012)       Iran         Afsharbari et al (2012)       Iran         Manal et al (2012)       Iran         Manal et al (2012)       Taiwan         Manal et al (2013)       Tanzania         Valvi et al (2013)       Iran         Subtotal       0.56 (0.45, 0.67)         Fredrick et al (2013)       Iran         O.66 (0.56, 0.76)       0.66 (0.56, 0.76)         Subtotal       0.62 (0.52, 0.72)			
Al-Mardeni et al (2009)       Jordan         Sharma et al (2011)       Nepal         Farshad et al (2011)       Iran         Alshara (2011)       Jordan         Pourakbari et al (2012)       Iran         Afsharapainan et al (2012)       Iran         Manal et al (2012)       Iran         Manal et al (2012)       Taiwan         Manal et al (2013)       Tanzania         Yulavi et al (2013)       Iran         Subtotal       0.56 (0.45, 0.67)         Ferdick et al (2013)       Iran         O.66 (0.56, 0.76)       0.66 (0.56, 0.76)         Subtotal       0.66 (0.56, 0.76)	Narchi et al (2008)	UAE	0.62 (0.51, 0.73)
Al-Mardeni et al (2009)       Jordan         Sharma et al (2011)       Nepal         Farshad et al (2011)       Iran         Alshara (2011)       Jordan         Pourakbari et al (2012)       Iran         Afsharapainan et al (2012)       Iran         Manal et al (2012)       Iran         Manal et al (2012)       Taiwan         Manal et al (2013)       Tanzania         Yulavi et al (2013)       Iran         Subtotal       0.56 (0.45, 0.67)         Ferdick et al (2013)       Iran         O.66 (0.56, 0.76)       0.66 (0.56, 0.76)         Subtotal       0.66 (0.56, 0.76)	Rai et al (2008)	Nepal	0.77 (0.67, 0.87)
Sharma et al (2011)         Nepal         0.67 (0.29, 1.04)           Farshad et al (2011)         Iran         0.57 (0.34, 0.81)           Alshara (2011)         Jordan         0.57 (0.34, 0.81)           Pourakbari et al (2012)         Iran         0.90 (0.64, 1.16)           Afsharpaiman et al (2012)         Iran         0.77 (0.57, 0.96)           Farshad et al (2012)         Iran         0.77 (0.57, 0.96)           Wu et al (2012)         Taiwan         0.76 (0.59, 0.93)           Manal et al (2012)         Tanzania         0.56 (0.45, 0.67)           Fredrick et al (2013)         Tanzania         1.00 (0.61, 1.39)           Valavi et al (2013)         Iran         0.66 (0.56, 0.76)           Subtotal         0.52 (0.52, 0.72)         0.52 (0.52, 0.72)			
Farshad et al (2011)       Iran         Alshara (2011)       Jordan         Pourakbari et al (2012)       Iran         Afsharajiman et al (2012)       Iran         Farshad et al (2012)       Iran         Farshad et al (2012)       Iran         Wu et al (2012)       Iran         Manal et al (2012)       Taiwan         Manal et al (2012)       Taiwan         Valavi et al (2013)       Tanzania         Valavi et al (2013)       Iran         Subtotal       0.66 (0.56, 0.76)         Corfe       0.62 (0.52, 0.72)			
Alshara (2011)       Jordan         Pourakbari et al (2012)       Iran         Afsharapaiman et al (2012)       Iran         Farshad et al (2012)       Iran         Wu et al (2012)       Iran         Manal et al (2012)       Taiwan         Manal et al (2012)       Saudi-Arabia         Fredrick et al (2013)       Tanzania         Valavi et al (2013)       Iran         Subtotal       0.66 (0.56, 0.76)         O.62 (0.52, 0.72)			
Pourakbari et al (2012)       Iran         Afsharpaiman et al (2012)       Iran         Farshad et al (2012)       Iran         Wu et al (2012)       Taiwan         Manal et al (2012)       Saudi-Arabia         Fredrick et al (2013)       Tanzania         Valavi et al (2013)       Iran         Subtotal       0.66 (0.56, 0.76)         0.62 (0.52, 0.72)	. ,		
Afsharpaiman et al (2012)       Iran       0.77 (0.57, 0.96)         Farshad et al (2012)       Iran       0.76 (0.59, 0.93)         Wu et al (2012)       Taiwan       0.56 (0.45, 0.67)         Fredrick et al (2013)       Tanzania       0.56 (0.45, 0.67)         Valavi et al (2013)       Iran       0.66 (0.45, 0.67)         Subtotal       0.66 (0.56, 0.76)       0.62 (0.52, 0.72)			
Farshad et al (2012)       Iran         Wu et al (2012)       Taiwan         Manal et al (2012)       Saudi-Arabia         Fredrick et al (2013)       Tanzania         Valavi et al (2013)       Iran         Subtotal       0.66 (0.56, 0.76)         0.62 (0.52, 0.72)			
Wu et al (2012)         Taiwan         0.29 (0.20, 0.38)           Manal et al (2012)         Saudi-Arabia         0.56 (0.45, 0.67)           Fredrick et al (2013)         Tanzania         1.00 (0.61, 1.39)           Valavi et al (2013)         Iran         0.66 (0.56, 0.76)           Subtotal         0.62 (0.52, 0.72)			
Manal et al (2012)         Saudi-Arabia         0.56 (0.45, 0.67)           Fredrick et al (2013)         Tanzania         1.00 (0.61, 1.39)           Valavi et al (2013)         Iran         0.66 (0.56, 0.76)           Subtotal         0.62 (0.52, 0.72)         0.62 (0.52, 0.72)	Farshad et al (2012)	Iran	0.76 (0.59, 0.93)
Manal et al (2012)         Saudi-Arabia           Fredrick et al (2013)         Tanzania           Valavi et al (2013)         Iran           Subtotal         0.66 (0.45, 0.67)	Wu et al (2012)	Taiwan	0.29 (0.20, 0.38)
Fredrick et al (2013)         Tanzania           Valavi et al (2013)         Iran           Subtotal         0.66 (0.56, 0.76)           0.62 (0.52, 0.72)		Saudi-Arabia	
Valavi et al (2013) Iran 0.66 (0.56, 0.76) Subtotal 0.62 (0.52, 0.72)			
Subtotal 0.62 (0.52, 0.72)			
		II all	
	Subiolal		0.62 (0.52, 0.72)
			0.2.4.6.81

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author	country		ES (95% CI)
OECD			
Ladhani et al (2003)	UK	•	0.28 (0.25, 0.30)
Mehr et al (2004)	Australia	-	0.16 (0.07, 0.24)
Prelog et al (2008)	Austria	-	0.21 (0.14, 0.27)
Prelog et al (2008)	Austria	-	0.36 (0.29, 0.42)
Bryce et al (2010)	UK	•	0.21 (0.19, 0.23)
Duffy et al (2012)	UK	•	0.27 (0.24, 0.29)
Cullen et al (2013)	Ireland	•	0.32 (0.31, 0.33)
Subtotal			0.26 (0.21, 0.30)
Non-OECD			
Too few data <sup>a</sup>			
		0 .2 .4 .6	.8 1
		Prevalence of r	resistance
ly one study from non-OEC	D countries		

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

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5 6 7	
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13 14 15	
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22 23 24	
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39 40	
41 42 43	
44 45 46	
47 48 49	
50 51 52	
53 54 55	
55 56 57 58	
58 59 60	

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

author	country		ES (95% CI)
OECD			
Ashkenazi et al (1991)	Israel	•	0.01 (-0.00, 0.03
Allen et al (1999)	USA	•	0.02 (0.01, 0.03)
Edlin et al (2013)	USA	•	0.01 (0.01, 0.01)
Ladhani et al (2003)	UK	•	0.06 (0.05, 0.07)
Gaspari et al (2005)	USA	•	0.00 (0.00, 0.01)
Gaspari et al (2005)	USA		0.00 (0.00, 0.00)
Gaspari et al (2005)	USA		0.00 (0.00, 0.01)
Anatoliotaki et al (2007)	Greece		0.02 (0.00, 0.05)
	Austria		
Prelog et al (2008)			0.03 (0.01, 0.06)
Prelog et al (2008)	Austria		0.02 (-0.00, 0.03
Borsari et al (2008)	Switzerland	5	0.04 (0.00, 0.08)
Catal et al (2009)	Turkey		0.02 (-0.01, 0.05
Catal et al (2009)	Turkey	1.4	0.08 (0.03, 0.13)
Bryce et al (2010)	UK	•	0.01 (0.01, 0.02)
Ipek et al (2011)	Turkey	•	0.05 (0.01, 0.09)
Mantadakis et al (2011)	Greece	•	0.04 (0.02, 0.06)
Guner et al (2012)	Turkey	•	0.01 (0.00, 0.01)
Cullen et al (2013)	Ireland	•	0.02 (0.01, 0.02)
Yolbas et al (2013)	Turkey		0.09 (0.02, 0.16)
Subtotal			0.02 (0.01, 0.02)
Non-OECD			
Al-Mugeiren et al (1996)	Saudi Arabia		0.15 (0.12, 0.18)
Goldraich et al (2002)	Brazil	-	0.08 (0.02, 0.14)
Goldraich et al (2002)	Brazil		0.05 (-0.01, 0.10
Goldraich et al (2002)	Brazil		0.06 (0.01, 0.11)
Brown et al (2003)	Nigeria		0.65 (0.26, 1.03)
Adjei et al (2004)	Ghana		0.33 (0.04, 0.63)
Rai et al (2008)	Nepal		0.34 (0.29, 0.39)
Narchi et al (2008)	UAE		0.24 (0.17, 0.30)
Guidoni et al (2008)	Brazil		0.09 (0.04, 0.15)
Guidoni et al (2008)	Brazil		0.06 (0.01, 0.12)
Al-Mardeni et al (2009)	Jordan	1 - E	0.21 (0.16, 0.25)
Farshad et al (2010)	Iran	<b>.</b>	0.03 (-0.00, 0.07
Farshad et al (2011)	Iran	•	0.03 (-0.00, 0.07
Afsharpaiman et al (2012)			0.37 (0.24, 0.50)
Pourakbari et al (2012)	Iran		0.06 (-0.01, 0.13
Farshad et al (2012)	Iran	•	0.03 (-0.00, 0.07
Manal et al (2012)	Saudi-Arabia	•	0.04 (0.01, 0.07)
Valavi et al (2013)	Iran	•	0.05 (0.02, 0.08)
Subtotal		•	0.12 (0.08, 0.16)
		0 .2 .4 .6	.8 1
		Prevalence o	fresistance

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

Rai et al (2008) Nepal Guidoni et al (2008) Brazil ← Farshad et al (2010) Iran ← Farshad et al (2011) Iran ←	$\begin{array}{c} 0.01 \ (0.00, \ 0.01) \\ 0.01 \ (-0.01, \ 0.02) \\ 0.00 \ (0.00, \ 0.01) \\ 0.01 \ (0.01, \ 0.01) \\ 0.01 \ (0.01, \ 0.01) \\ 0.02 \ (-0.01, \ 0.05) \\ 0.04 \ (0.01, \ 0.08) \\ 0.02 \ (0.01, \ 0.02) \\ 0.07 \ (0.05, \ 0.10) \\ 0.07 \ (0.05, \ 0.09) \\ 0.09 \ (0.07, \ 0.10) \\ 0.22 \ (-0.09, \ 0.53) \\ 0.03 \ (-0.00, \ 0.06) \\ 0.05 \ (0.01, \ 0.09) \\ 0.03 \ (0.00, \ 0.05) \\ 0.01 \ (0.00, \ 0.02) \\ 0.09 \ (0.03, \ 0.04) \\ 0.22 \ (0.13, \ 0.31) \\ 0.03 \ (-0.00, \ 0.06) \\ 0.05 \ (0.05, \ 0.05) \\ 0.04 \ (0.03, \ 0.05) \\ \end{array}$
Guidoni et al (2008) Brazil Farshad et al (2010) Iran Farshad et al (2011) Iran	
Alshara (2011) Jordan Muoneke et al (2012) Nigeria Farshad et al (2012) Iran Mandal et al (2012) India Sharan et al (2013) India Subtotal	<ul> <li>0.60 (0.53, 0.67) 0.04 (-0.01, 0.08) 0.08 (0.03, 0.14) 0.09 (0.03, 0.15) 0.16 (-0.02, 0.34) 0.15 (0.11, 0.18)</li> <li>0.60 (0.21, 0.99) 0.08 (0.03, 0.14) 0.38 (0.32, 0.44)</li> <li>0.63 (0.41, 0.86) 0.25 (0.13, 0.37)</li> </ul>
0.2.4.	.6 .8 1
Prevalence	e of resistance

Appendix 9. Ceftazidime resistance in <i>E. coli</i> urinary isolates from children,
by OECD status

author	country	ES (95% CI)	
OECD Prelog et al (2008) Prelog et al (2008) Senel et al (2010) Senel et al (2010) Senel et al (2010) Senel et al (2010) Kokenli et al (2010) Bryce et al (2010) Ismaili et al (2011) Mantadakis et al (2011)	Austria Austria Turkey Turkey Turkey Turkey Turkey UK Belgium Greece	<ul> <li>0.01 (-0.00, 0.02)</li> <li>0.02 (0.00, 0.04)</li> <li>0.14 (0.10, 0.17)</li> <li>0.08 (0.06, 0.10)</li> <li>0.07 (0.06, 0.08)</li> <li>0.22 (-0.05, 0.49)</li> <li>0.05 (0.01, 0.09)</li> <li>0.01 (0.01, 0.02)</li> <li>0.02 (-0.00, 0.03)</li> <li>0.04 (0.02, 0.06)</li> </ul>	
Yolbas et al (2013) Gallegos et al (2013) Edlin et al (2013) Subtotal	Turkey Chile USA	<ul> <li>0.38 (0.29, 0.47)</li> <li>0.01 (-0.01, 0.03)</li> <li>0.01 (0.01, 0.01)</li> <li>0.04 (0.03, 0.06)</li> </ul>	
Non-OECD Al-Mugeiren et al (1996) Brown et al (2003) Farshad et al (2011) Alshara (2011) Afsharpaiman et al (2012) Muoneke et al (2012) Manal et al (2012) Sharan et al (2013) Subtotal	Saudi Arabia Nigeria Iran Jordan Iran Nigeria Saudi-Arabia India	<ul> <li>0.17 (0.14, 0.20)</li> <li>0.06 (-0.05, 0.17)</li> <li>0.11 (0.05, 0.18)</li> <li>0.22 (0.14, 0.30)</li> <li>0.26 (0.16, 0.35)</li> <li>0.47 (0.21, 0.72)</li> <li>0.05 (0.02, 0.08)</li> <li>0.61 (0.48, 0.75)</li> <li>0.22 (0.13, 0.30)</li> </ul>	
		0 .2 .4 .6 .8 1	
		Prevalence of resistance	