High prevalence of antibiotic resistance in commensal *Escherichia coli* from healthy human sources in community settings

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Supplementary Table 1. Details of the search strategy used for the different databases.

Database	Search words	Articles
PubMed	(((((((Escherichia coli[MeSH Terms]) OR E. coli[Title/Abstract]) OR Enterobacteriaceae[Title/Abstract])) AND (((((((((Prevalence[MeSH Terms]) OR prevalence[Title/Abstract]) OR incidence[Title/Abstract]) OR morbidity[Title/Abstract]) OR odd ratio[Title/Abstract]) OR confidence interval[Title/Abstract]) OR risk ratio[Title/Abstract]) OR rate[Title/Abstract]) OR p value[Title/Abstract])) AND (((((((antibiotic resistance[MeSH Terms]) OR antibiotic resistance[Title/Abstract]) OR antimicrobial resistance[MeSH Terms]) OR antimicrobial resistance[Title/Abstract]) OR "drug resistance"[MeSH Terms]) OR "drug resistance"[Title/Abstract]) AND English[lang]))	3634
EMBASE + MEDLINE	(*'escherichia coli'*:ab,ti OR *'e. coli'*:ab,ti 'enterobacteriaceae':ab,ti) AND ('antibiotic resistance':ab,ti OR 'antimicrobial resistance':ab,ti OR 'drug resistance':ab,ti) AND ('prevalence':ab,ti OR 'incidence':ab,ti OR 'morbidity':ab,ti OR 'odd ratio':ab,ti OR'risk ratio':ab,ti OR 'confidence interval':ab,ti OR 'p value':ab,ti OR 'rate':ab,ti)	2107
WEB OF SCIENCE	(*E. coli* OR *Escherichia coli* OR Enterobacteriaceae) *AND* **TOPIC:** (Antibiotic resistance OR antimicrobial resistance OR drug resistance) *AND* **TOPIC:** (Prevalence OR Incidence OR Morbidity OR Odd ratio OR Risk ratio OR Confidence interval OR P value OR rate) *AND* **TOPIC:** (HUMAN* OR INFANT* OR CHILD* OR ADOLESCEN* OR MALE* OR FEMALE)	3616
CINAHL	TI (*E. coli* OR *Escherichia coli* OR Enterobacteriaceae) OR AB (*E. coli* OR *Escherichia coli* OR Enterobacteriaceae) AND TI (Antibiotic resistance OR antimicrobial resistance OR drug resistance) OR AB (Antibiotic resistance OR antimicrobial resistance OR drug resistance) AND TI (Prevalence OR Incidence OR Morbidity OR Odd ratio OR Risk ratio OR Confidence interval OR P value OR rate) OR AB (Prevalence OR Incidence OR Morbidity OR Odd ratio OR Risk ratio OR Confidence interval OR P value OR rate).	290
COCHRANE LIBRARY	*E. coli* OR *Escherichia coli* OR Enterobacteriaceae in Title, Abstract, Keywords and Antibiotic resistance OR antimicrobial resistance OR drug resistance in Title, Abstract, Keywords and Prevalence OR Incidence OR Morbidity OR Odd ratio OR Risk ratio OR Confidence interval OR P value OR rate in Title, Abstract, Keywords and HUMAN*	289

Supplementary Table 2. Key information extracted from the studies.

General information	Study characteristics	Participant characteristics	Measurement tools/methods used in the study	Outcome of interest
First author	Study design	Age	Method used to control bias	Prevalence of antibiotic resistance (%)
Year of publication	Study duration	Gender	Method used to detect *E. coli* species	Factors associated with the carriage of resistance (OR, RR, rate, 95% CI, p-value
Journal	Number of isolates	Geographical location	Methods used to detect resistance	
Country of origin	Sample size	Ethnicity		
PubMed ID		Socio-economic status		

Supplementary Table 3. Reference scale used for accessing the quality of evidence of the selected studies.[1,2] **Polymerase chain reaction (PCR), plasmid transfer assay (PTA), pulsed field gel electrophoresis (PFGE), nucleic acid sequencing, and mass spectrometry, detects the presence of resistant genes while disc diffusion/synergy test determines the expression of resistant genes.**

Grade		Criteria
High	Method	Disc diffusion/synergy test and PCR Disc diffusion/synergy test and PTA Disc diffusion/synergy test and PFGE Disc diffusion/synergy test and nucleic acid sequencing/mass spectrometry
	Sample size	>15
	Analysis	Data set completely analysed
Medium		Combination of criteria from high and low (e.g., sample size <15 but uses Disc diffusion/synergy test and PCR)
Low	Method	Disc diffusion/synergy test
	Sample size	<15
	Analysis	Data set partly analysed

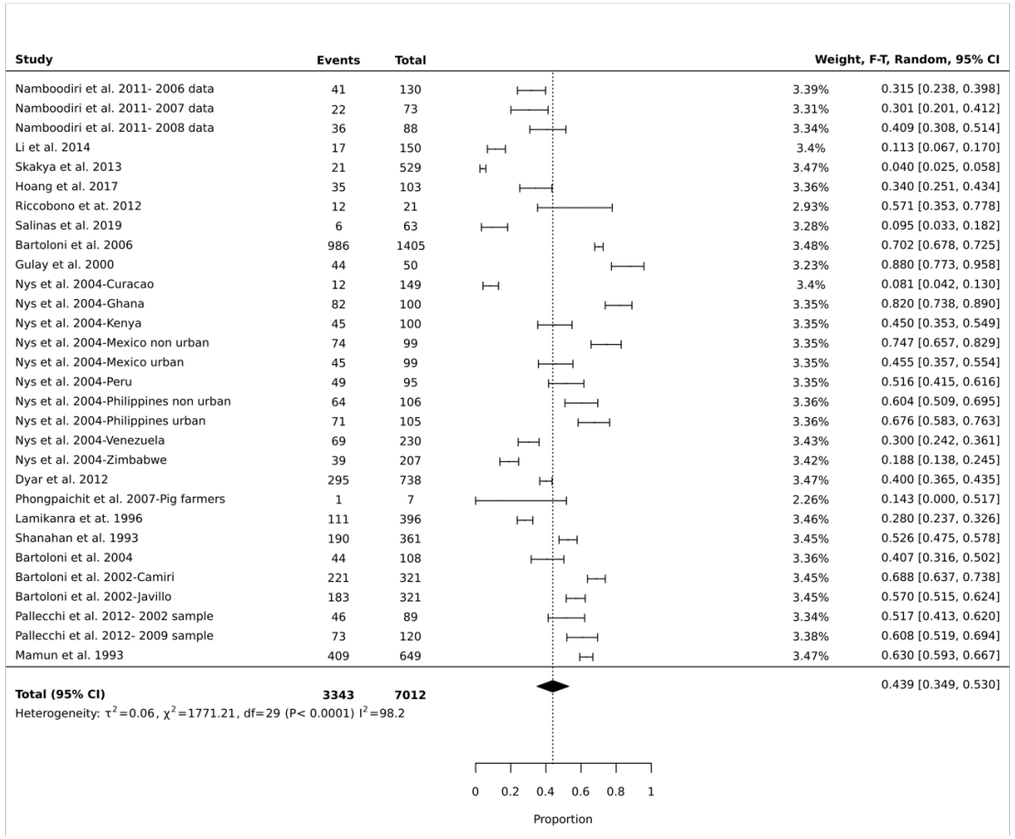
Supplementary Table 4. Prevalence of antibiotic resistance in commensal *E. coli* isolated from human sources in community settings in low- and middle-income countries.

Antibiotics	Mechanism of inhibition	Study number	Total number of isolates	Number of resistant isolates	Pooled prevalence (%)	Lower bound 95% CI	Upper bound 95% CI	Quality of the evidence (study number)	Reference
Amikacin	Protein synthesis	12	6849	254	4	1	7	High (7), medium (5), low (0)	3–13
Amoxicilin	Protein synthesis	1	161	69	43	35	50	High (0), medium (1), low (0)	14
Amoxicillin/clavulanic acid	Cell wall synthesis	4	900	222	13	1	32	High (3), medium (1), low (0)	30,38,40,51
Ampicillin/sulbactam	Cell wall synthesis	2	427	136	30	26	34	High (1), medium (1), low (0)	3,8
Apramycin	Protein synthesis	1	161	0	0	0	1	High (0), medium (1), low (0)	14
Azithromycin	Protein synthesis	1	87	10	11	5	19	High (0), medium (1), low (0)	17
Aztreonam	Cell wall synthesis	2	258	8	3	1	6	High (2), medium (0), low (0)	3,7
Carbenicillin	Cell wall synthesis	1	108	22	20	14	29	High (1), medium (0), low (0)	7
Cefazolin	Cell wall synthesis	3	1490	141	8	4	14	High (1), medium (2), low (0)	3,5,18
Cefepime	Cell wall synthesis	3	5443	2017	17	1	43	High (1), medium (2), low (0)	3,4,9
Cefixime	Cell wall synthesis	1	277	166	60	54	66	High (0), medium (1), low (0)	8
Cefoxitin	Cell wall synthesis	6	1371	528	18	0	62	High (4), medium (2), low (0)	18,30,35,43,50,51
Ceftazidime	Cell wall synthesis	11	6445	3070	28	12	48	High (7), medium (4), low (0)	3–5,7,9,13,19–22
Ceftiofur	Cell wall synthesis	1	7	0	0	0	35	High (1), medium (0), low (0)	12
Ceftriaxone	Cell wall synthesis	7	1951	587	25	3	56	High (3), medium (4), low (0)	30,33,36,41–43,53
Cefuroxime	Cell wall synthesis	3	535	185	31	8	61	High (2), medium (1), low (0)	3,7,8

Cephalothin	Cell wall synthesis	4	404	69	26	22	31	High (1), medium (1), low (0)	[11,15]
Colistin	Cell wall synthesis	2	4764	91	2	1	2	High (1), medium (1), low (0)	[9,13]
Doxycycline	Protein synthesis	1	54	22	41	28	54	High (0), medium (1), low (0)	[23]
Enrofloxacin	Nucleic acid synthesis	1	54	10	18	9	30	High (0), medium (1), low (0)	[23]
Flumequine	Nucleic acid synthesis	1	161	0	0	0	1	High (0), medium (1), low (0)	[14]
Fosfomycin	Cell wall synthesis	2	157	27	25	2	60	High (1), medium (1), low (0)	[21,23]
Gentamicin	Protein synthesis	16	8380	515	9	6	13	High (10), medium (6), low (0)	[4–7,9–13,15,18,20–22,27,28]
Imipenem	Cell wall synthesis	8	5747	317	1	0	4	High (4), medium (4), low (0)	[3–5,7,9,15,20,29]
Kanamycin	Protein synthesis	6	389	48	16	7	27	High (6), medium (0), low (0)	[3,6,10,12,21,28]
Meropenem	Cell wall synthesis	1	4764	434	9	8	10	High (0), medium (1), low (0)	[9]
Neomycin	Protein synthesis	1	161	6	4	1	7	High (0), medium (1), low (0)	[14]
Nitrofurantoin	Nucleic acid synthesis	4	5301	279	3	1	6	High (3), medium (2), low (0)	[7,9–11,13]
Norfloxacin	Nucleic acid synthesis	3	1047	295	36	15	60	High (0), medium (3), low (0)	[4,8,24]
Penicillin	Cell wall synthesis	1	87	41	47	37	57	High (0), medium (1), low (0)	[17]
Piperacillin	Cell wall synthesis	2	850	343	40	27	53	High (0), medium (2), low (0)	[4,11]
Piperacillin/tazobactam	Cell wall synthesis	2	637	13	2	1	7	High (1), medium (1), low (0)	[4,7]
Spectinomycin	Protein synthesis	3	430	176	2	1	4	High (1), medium (1), low (1)	[6,30,31]
Sulfamethoxazole	Folate synthesis	6	5715	2609	53	45	60	High (2), medium (3), low (1)	[9,12,14,23,25,30]

Sulphonamide class	Folate synthesis	4	1399	858	63	56	70	High (3), medium (1), low (0)	[15,31–33]
Tigecycline	Protein synthesis	1	4764	24	0	0	1	High (0), medium (1), low (0)	[9]
Tobramycin	Protein synthesis	1	158	20	8	4	13	High (1), medium (0), low (0)	[10]

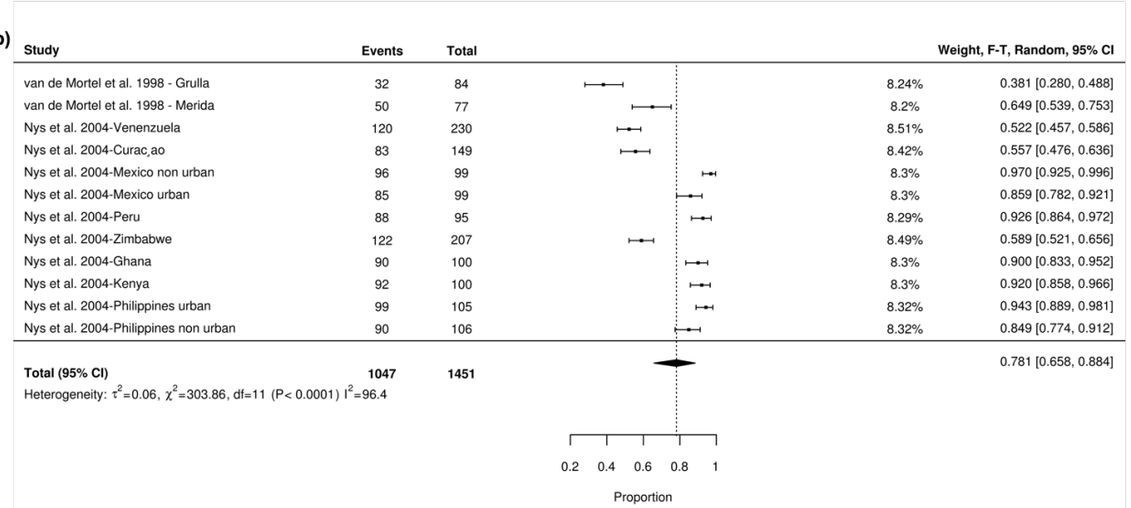
a)



Study	Events	Total	Weight	F-T, Random, 95% CI
Namboodiri et al. 2011- 2006 data	41	130	3.39%	0.315 [0.238, 0.398]
Namboodiri et al. 2011- 2007 data	22	73	3.31%	0.301 [0.201, 0.412]
Namboodiri et al. 2011- 2008 data	36	88	3.34%	0.409 [0.308, 0.514]
Li et al. 2014	17	150	3.4%	0.113 [0.067, 0.170]
Skakya et al. 2013	21	529	3.47%	0.040 [0.025, 0.058]
Hoang et al. 2017	35	103	3.36%	0.340 [0.251, 0.434]
Riccobono et at. 2012	12	21	2.93%	0.571 [0.353, 0.778]
Salinas et al. 2019	6	63	3.28%	0.095 [0.033, 0.182]
Bartoloni et al. 2006	986	1405	3.48%	0.702 [0.678, 0.725]
Gulay et al. 2000	44	50	3.23%	0.880 [0.773, 0.958]
Nys et al. 2004-Curacao	12	149	3.4%	0.081 [0.042, 0.130]
Nys et al. 2004-Ghana	82	100	3.35%	0.820 [0.738, 0.890]
Nys et al. 2004-Kenya	45	100	3.35%	0.450 [0.353, 0.549]
Nys et al. 2004-Mexico non urban	74	99	3.35%	0.747 [0.657, 0.829]
Nys et al. 2004-Mexico urban	45	99	3.35%	0.455 [0.357, 0.554]
Nys et al. 2004-Peru	49	95	3.35%	0.516 [0.415, 0.616]
Nys et al. 2004-Philippines non urban	64	106	3.36%	0.604 [0.509, 0.695]
Nys et al. 2004-Philippines urban	71	105	3.36%	0.676 [0.583, 0.763]
Nys et al. 2004-Venezuela	69	230	3.43%	0.300 [0.242, 0.361]
Nys et al. 2004-Zimbabwe	39	207	3.42%	0.188 [0.138, 0.245]
Dyar et al. 2012	295	738	3.47%	0.400 [0.365, 0.435]
Phongpaichit et al. 2007-Pig farmers	1	7	2.26%	0.143 [0.000, 0.517]
Lamikanra et at. 1996	111	396	3.46%	0.280 [0.237, 0.326]
Shanahan et al. 1993	190	361	3.45%	0.526 [0.475, 0.578]
Bartoloni et al. 2004	44	108	3.36%	0.407 [0.316, 0.502]
Bartoloni et al. 2002-Camiri	221	321	3.45%	0.688 [0.637, 0.738]
Bartoloni et al. 2002-Javillo	183	321	3.45%	0.570 [0.515, 0.624]
Pallecchi et al. 2012- 2002 sample	46	89	3.34%	0.517 [0.413, 0.620]
Pallecchi et al. 2012- 2009 sample	73	120	3.38%	0.608 [0.519, 0.694]
Mamun et al. 1993	409	649	3.47%	0.630 [0.593, 0.667]
Total (95% CI)	**3343**	**7012**		0.439 [0.349, 0.530]

Heterogeneity: τ^2=0.06, χ^2=1771.21, df=29 (P< 0.0001) I^2=98.2

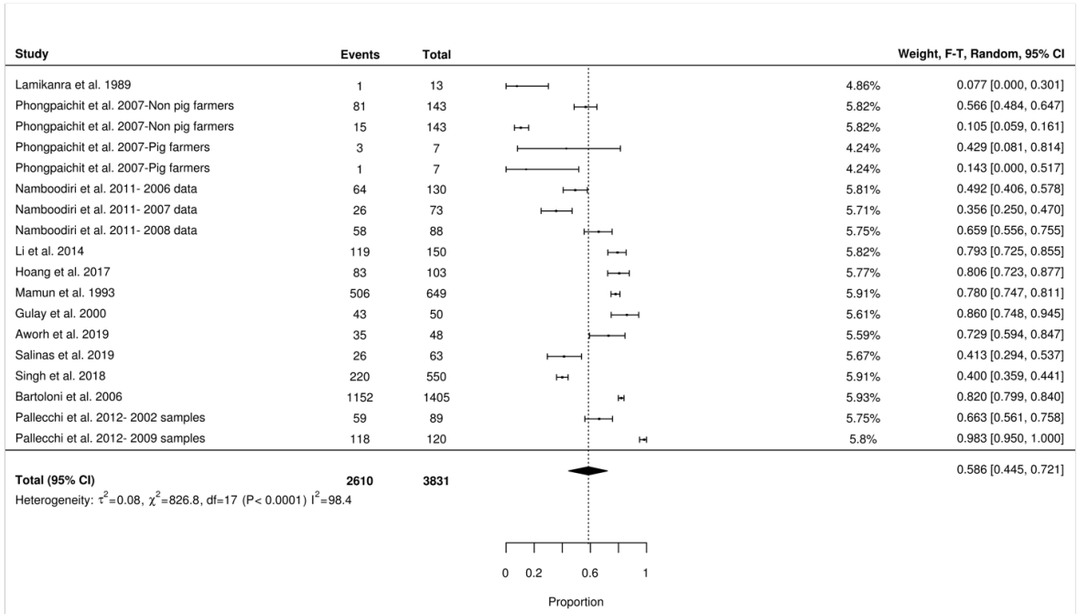
b)



Study	Events	Total	Weight	F-T, Random, 95% CI
van de Mortel et al. 1998 - Grulla	32	84	8.24%	0.381 [0.280, 0.488]
van de Mortel et al. 1998 - Merida	50	77	8.2%	0.649 [0.539, 0.753]
Nys et al. 2004-Venenzuela	120	230	8.51%	0.522 [0.457, 0.586]
Nys et al. 2004-Curac¸ao	83	149	8.42%	0.557 [0.476, 0.636]
Nys et al. 2004-Mexico non urban	96	99	8.3%	0.970 [0.925, 0.996]
Nys et al. 2004-Mexico urban	85	99	8.3%	0.859 [0.782, 0.921]
Nys et al. 2004-Peru	88	95	8.29%	0.926 [0.864, 0.972]
Nys et al. 2004-Zimbabwe	122	207	8.49%	0.589 [0.521, 0.656]
Nys et al. 2004-Ghana	90	100	8.3%	0.900 [0.833, 0.952]
Nys et al. 2004-Kenya	92	100	8.3%	0.920 [0.858, 0.966]
Nys et al. 2004-Philippines urban	99	105	8.32%	0.943 [0.889, 0.981]
Nys et al. 2004-Philippines non urban	90	106	8.32%	0.849 [0.774, 0.912]
Total (95% CI)	**1047**	**1451**		0.781 [0.658, 0.884]

Heterogeneity: τ^2=0.06, χ^2=303.86, df=11 (P< 0.0001) I^2=96.4

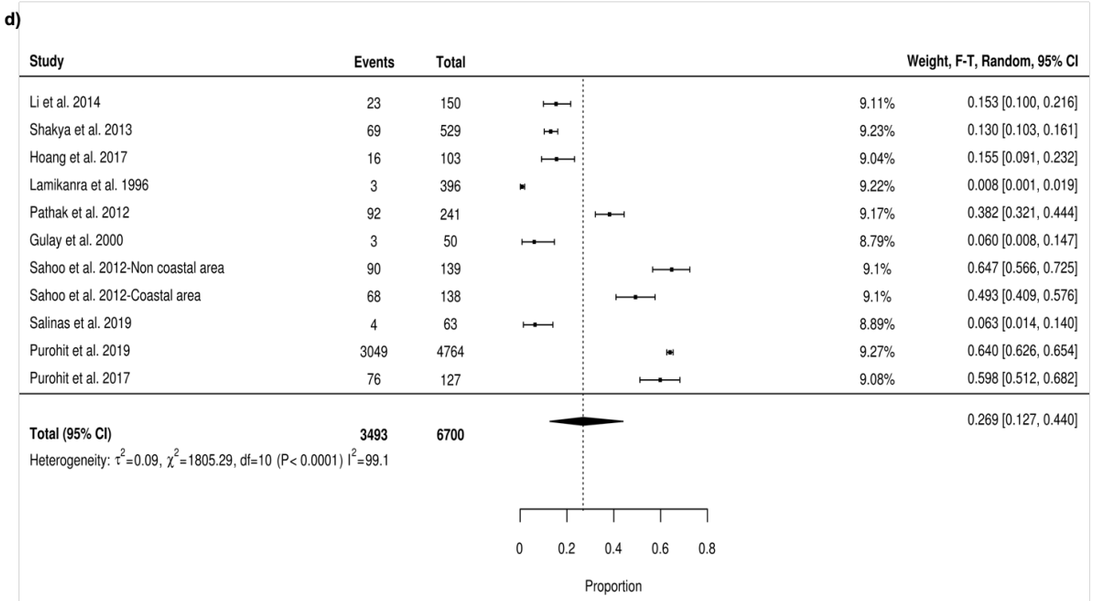
c)



Study	Events	Total	Weight, F-T, Random, 95% CI
Lamikanra et al. 1989	1	13	4.86% 0.077 [0.000, 0.301]
Phongpaichit et al. 2007-Non pig farmers	81	143	5.82% 0.566 [0.484, 0.647]
Phongpaichit et al. 2007-Non pig farmers	15	143	5.82% 0.105 [0.059, 0.161]
Phongpaichit et al. 2007-Pig farmers	3	7	4.24% 0.429 [0.081, 0.814]
Phongpaichit et al. 2007-Pig farmers	1	7	4.24% 0.143 [0.000, 0.517]
Namboodiri et al. 2011- 2006 data	64	130	5.81% 0.492 [0.406, 0.578]
Namboodiri et al. 2011- 2007 data	26	73	5.71% 0.356 [0.250, 0.470]
Namboodiri et al. 2011- 2008 data	58	88	5.75% 0.659 [0.556, 0.755]
Li et al. 2014	119	150	5.82% 0.793 [0.725, 0.855]
Hoang et al. 2017	83	103	5.77% 0.806 [0.723, 0.877]
Mamun et al. 1993	506	649	5.91% 0.780 [0.747, 0.811]
Gulay et al. 2000	43	50	5.61% 0.860 [0.748, 0.945]
Aworh et al. 2019	35	48	5.59% 0.729 [0.594, 0.847]
Salinas et al. 2019	26	63	5.67% 0.413 [0.294, 0.537]
Singh et al. 2018	220	550	5.91% 0.400 [0.359, 0.441]
Bartoloni et al. 2006	1152	1405	5.93% 0.820 [0.799, 0.840]
Pallecchi et al. 2012- 2002 samples	59	89	5.75% 0.663 [0.561, 0.758]
Pallecchi et al. 2012- 2009 samples	118	120	5.8% 0.983 [0.950, 1.000]
Total (95% CI)	**2610**	**3831**	0.586 [0.445, 0.721]

Heterogeneity: τ^2=0.08, χ^2=826.8, df=17 (P< 0.0001) I^2=98.4

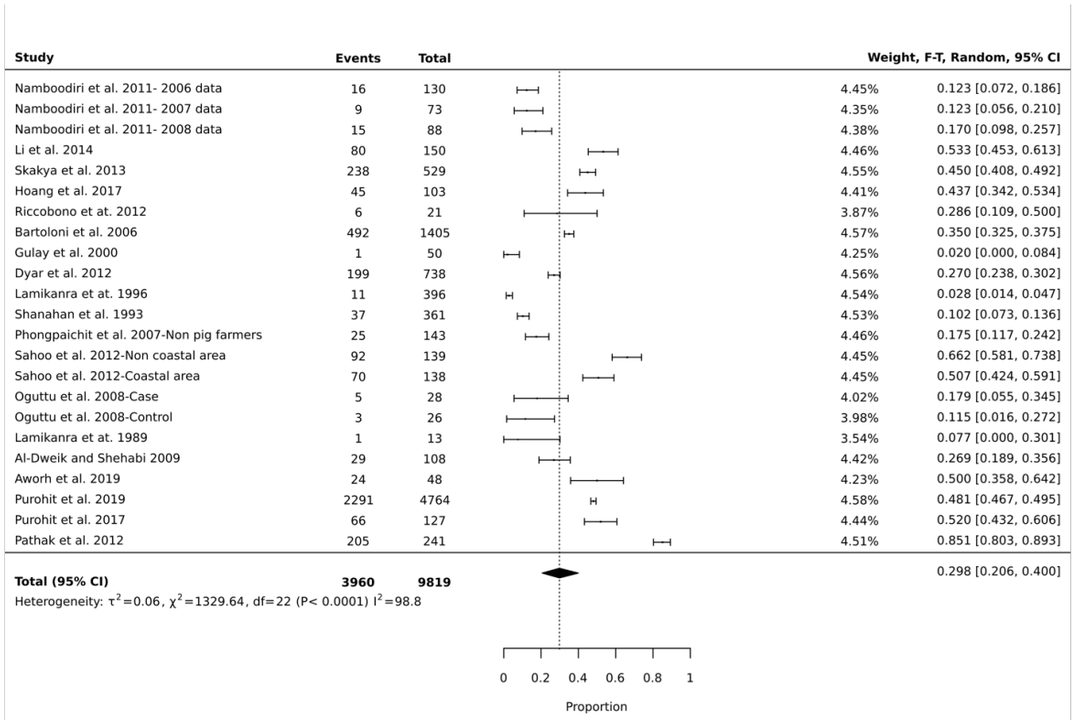
d)



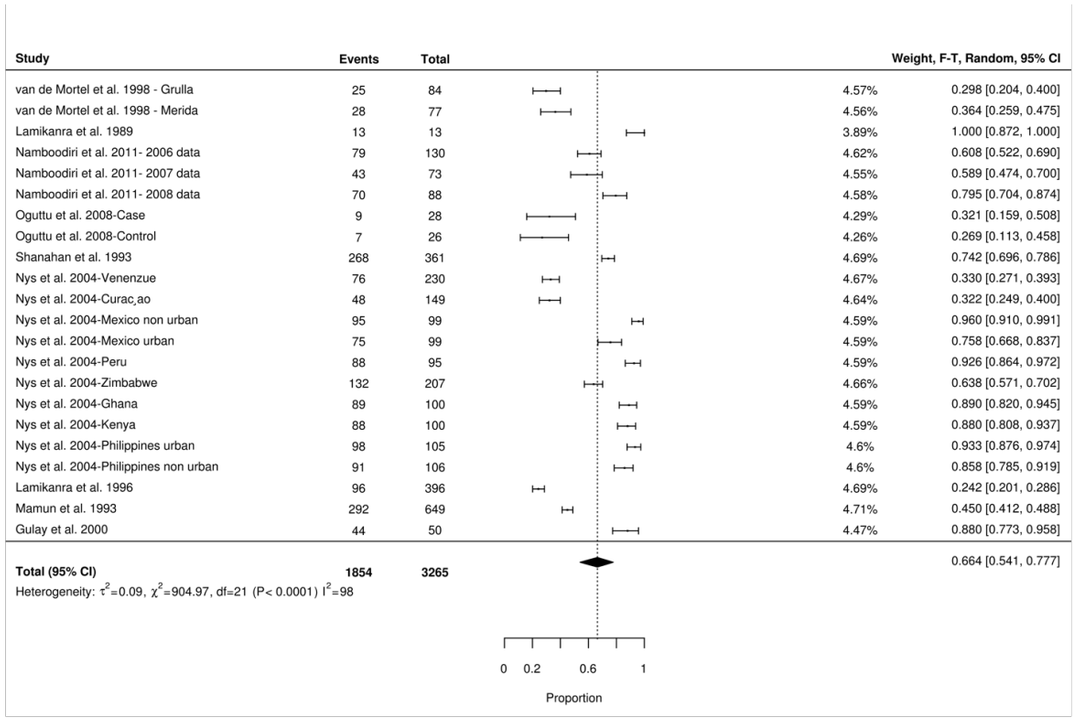
Study	Events	Total	Weight, F-T, Random, 95% CI
Li et al. 2014	23	150	9.11% 0.153 [0.100, 0.216]
Shakya et al. 2013	69	529	9.23% 0.130 [0.103, 0.161]
Hoang et al. 2017	16	103	9.04% 0.155 [0.091, 0.232]
Lamikanra et al. 1996	3	396	9.22% 0.008 [0.001, 0.019]
Pathak et al. 2012	92	241	9.17% 0.382 [0.321, 0.444]
Gulay et al. 2000	3	50	8.79% 0.060 [0.008, 0.147]
Sahoo et al. 2012-Non coastal area	90	139	9.1% 0.647 [0.566, 0.725]
Sahoo et al. 2012-Coastal area	68	138	9.1% 0.493 [0.409, 0.576]
Salinas et al. 2019	4	63	8.89% 0.063 [0.014, 0.140]
Purohit et al. 2019	3049	4764	9.27% 0.640 [0.626, 0.654]
Purohit et al. 2017	76	127	9.08% 0.598 [0.512, 0.682]
Total (95% CI)	**3493**	**6700**	0.269 [0.127, 0.440]

Heterogeneity: τ^2=0.09, χ^2=1805.29, df=10 (P< 0.0001) I^2=99.1

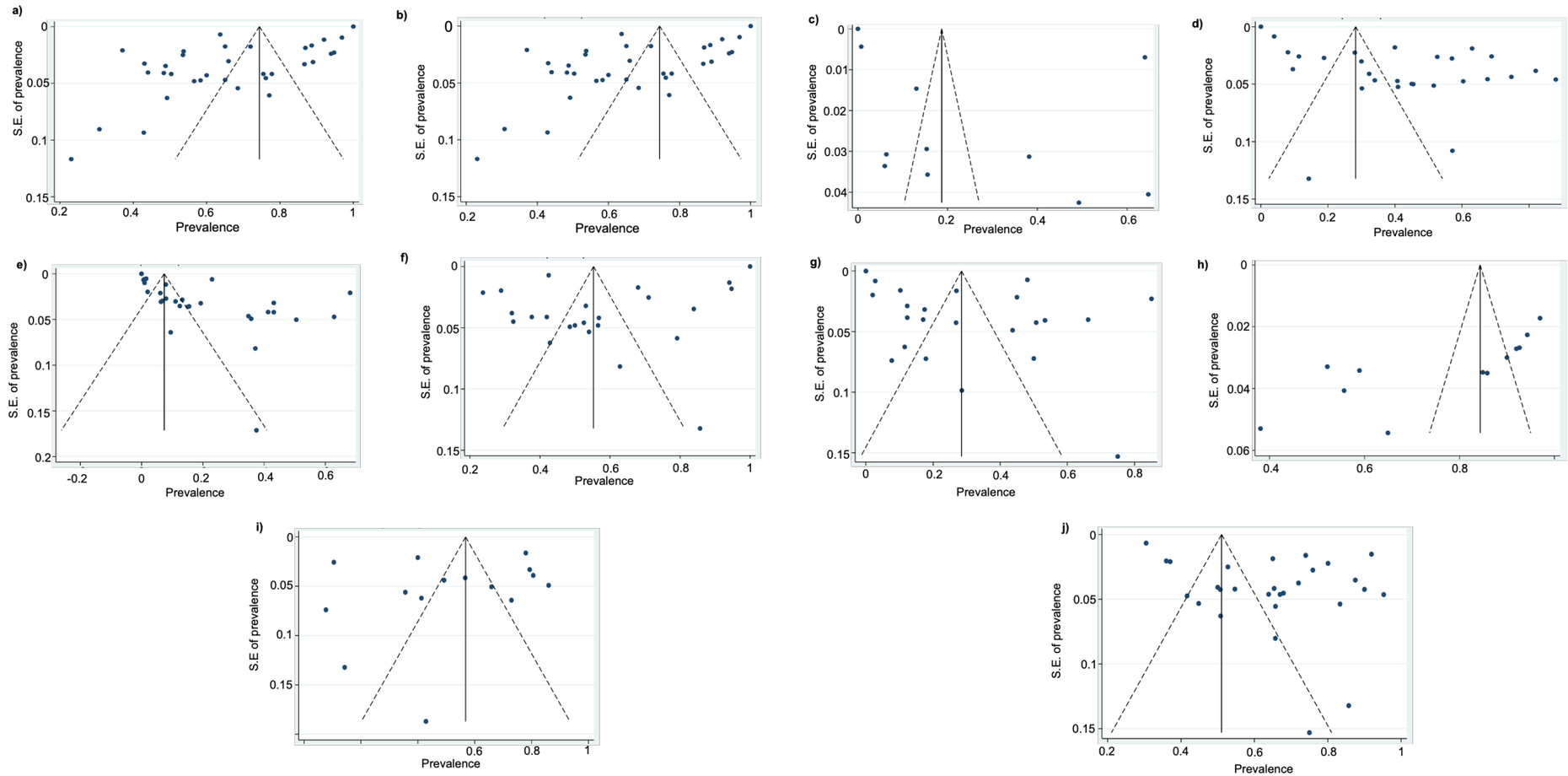
e)



f)



Supplementary Figure 1. Forest plots showing the prevalence of antibiotic resistance in commensal *E. coli* isolated from human sources in community settings in low- and middle-income countries. Protein synthesis inhibitor a) chloramphenicol, b) oxytetracycline, and c) streptomycin. d) Cell wall synthesis inhibitor (cefotaxime), e) Nucleic acid synthesis inhibitor (nalidixic acid), and f) Folate synthesis inhibitor (trimethoprim).



Supplementary Figure 2. Funnel plots for antibiotic resistance in commensal *E. coli* isolated from human sources in community settings in low- and middle-income countries, a) ampicillin, b) cefotaxime, c) chloramphenicol, d) ciprofloxacin, e) co-trimoxazole, f) nalidixic acid, g) oxytetracycline, h) streptomycin, and i) tetracycline.

Supplementary Table 5. Table showing the Egger's regression test results of the top ten antibiotics commonly prescribed in low- and middle-income countries.

Antibiotic	Number of studies	Egger bias	P value
All the ten antibiotics	221	9.28	**0.00**
Ampicillin	34	3.50	0.145
Cefotaxime	10	6.97	0.583
Chloramphenicol	27	10.17	**0.002**
Ciprofloxacin	29	6.10	**0.016**
Co-trimoxazole	23	1.13	0.753
Nalidixic acid	22	0.955	0.811
Oxytetracycline	12	14.40	**0.002**
Streptomycin	15	-2.20	0.575
Tetracycline	28	7.71	**0.007**
Trimethoprim	21	-3.06	0.562

Note: Confidence interval - 95%

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