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Health Outcomes from Multi-Drug Resistant *Salmonella* Infections in High-Income Countries: A Systematic Review and Meta-Analysis

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Non-typhoidal *Salmonella* (NTS)

- 153 million cases globally[1]
- 56,962 deaths[1]
- WHO Priority Pathogen[2]
- AMR NTS *Salmonella,* USA
  - 36 724 infections[3]
  - 427 hospitalisations[3]
  - 12 deaths in the USA[3], 8 677 LoS[4]

1. Kirk MD, Pires SM, Black RE, et al. World Health Organization Estimates of the Global and Regional Disease Burden of 22 Foodborne Bacterial, Protozoal, and Viral Diseases, 2010: A Data Synthesis. *PLoS medicine* 2015; **12**(12): e1001921.
2. WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. 2017. http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1 (accessed 24 March 2017)
3. Barza M, Travers K. Excess infections due to antimicrobial resistance: the "Attributable Fraction". *Clin Infect Dis* 2002; **34**: S126–30.
4. Travers K, Barza M. Morbidity of infections caused by antimicrobial-resistant bacteria. *Clin Infect Dis* 2002; **34**: S131–S4.

Aims

1) Describe existing studies reporting health outcomes for MDR and susceptible NTS

2) Examine impacts of MDR and susceptible NTS on health in high-income countries

Search Methodology

- According to PRISMA guidelines[1]
  - Scientific databases
  - Grey literature
  - Public request for information (RePORT, http://report.nih.gov/index.aspx)
  - Reference list search

- Key terminology
  - Nontyphoidal *Salmonella*, resistance, bacteraemia, hospitalisation, mortality…

1. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009; **151**(4): 264–9, w64.

Eligibility Criteria & Analyses

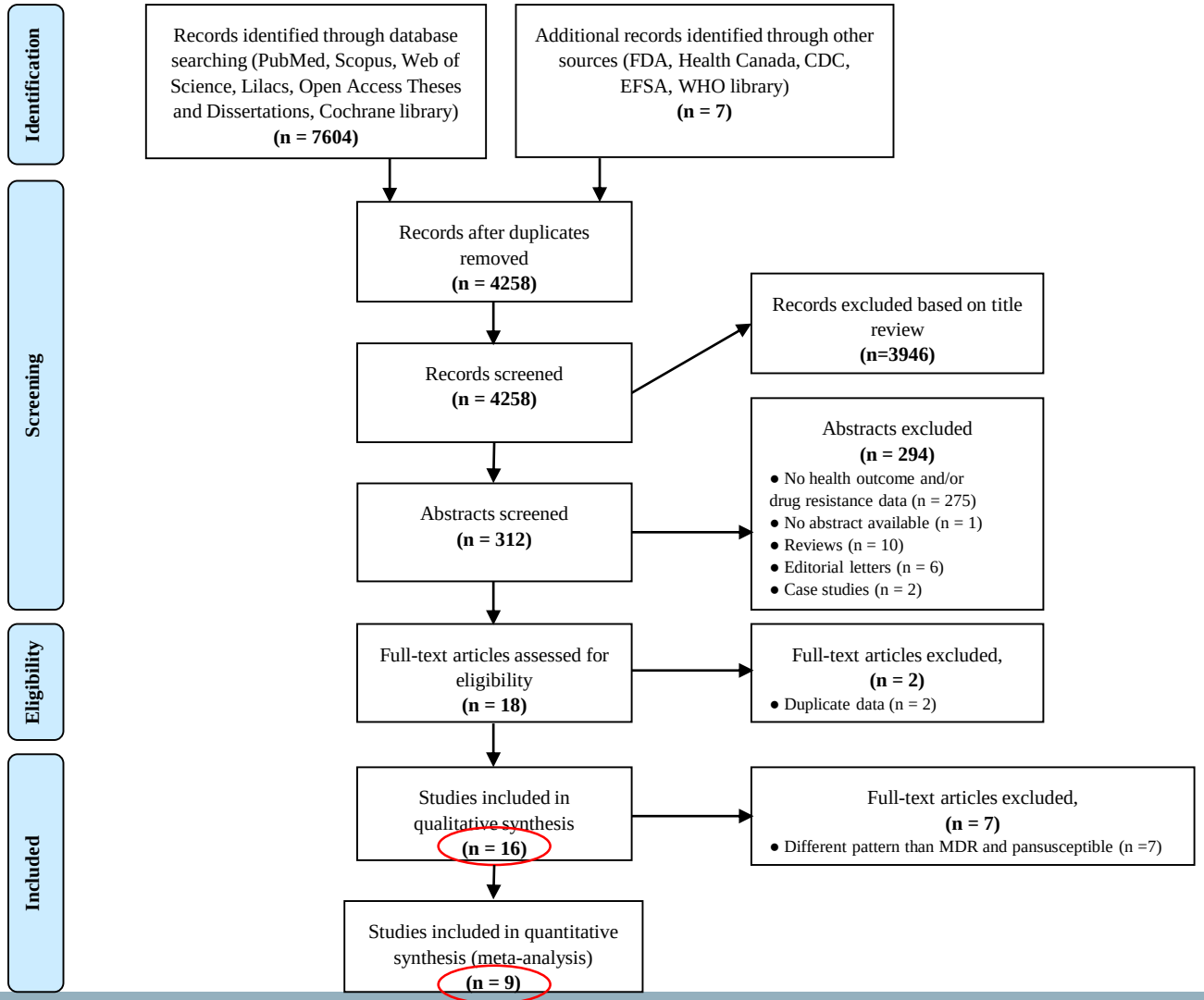
- Studies reporting on health outcomes from Multi-Drug Resistant (MDR) and susceptible NTS isolates
  - MDR = Non-susceptibility to at least 1 agent in ≥3 antimicrobial categories[1]
  - Susceptible to at least ampicillin, chloramphenicol, streptomycin, sulfisoxazole or sulfamethoxazole, tetracycline, ciprofloxacin, and nalidixic acid
- Studies published between 1 January 1990 and 15 September 2016
- Studies from high-income countries as classified by World Bank[2]
- Outcome measure
  - Odds ratio (OR)

1. Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012; **18**(3): 268–81.

2. World Bank. The World Bank country and lending groups. 2016. http://data.worldbank.org/about/country-and-lending-groups#IBRD (accessed 10 September 2016).

Results

Study Selection

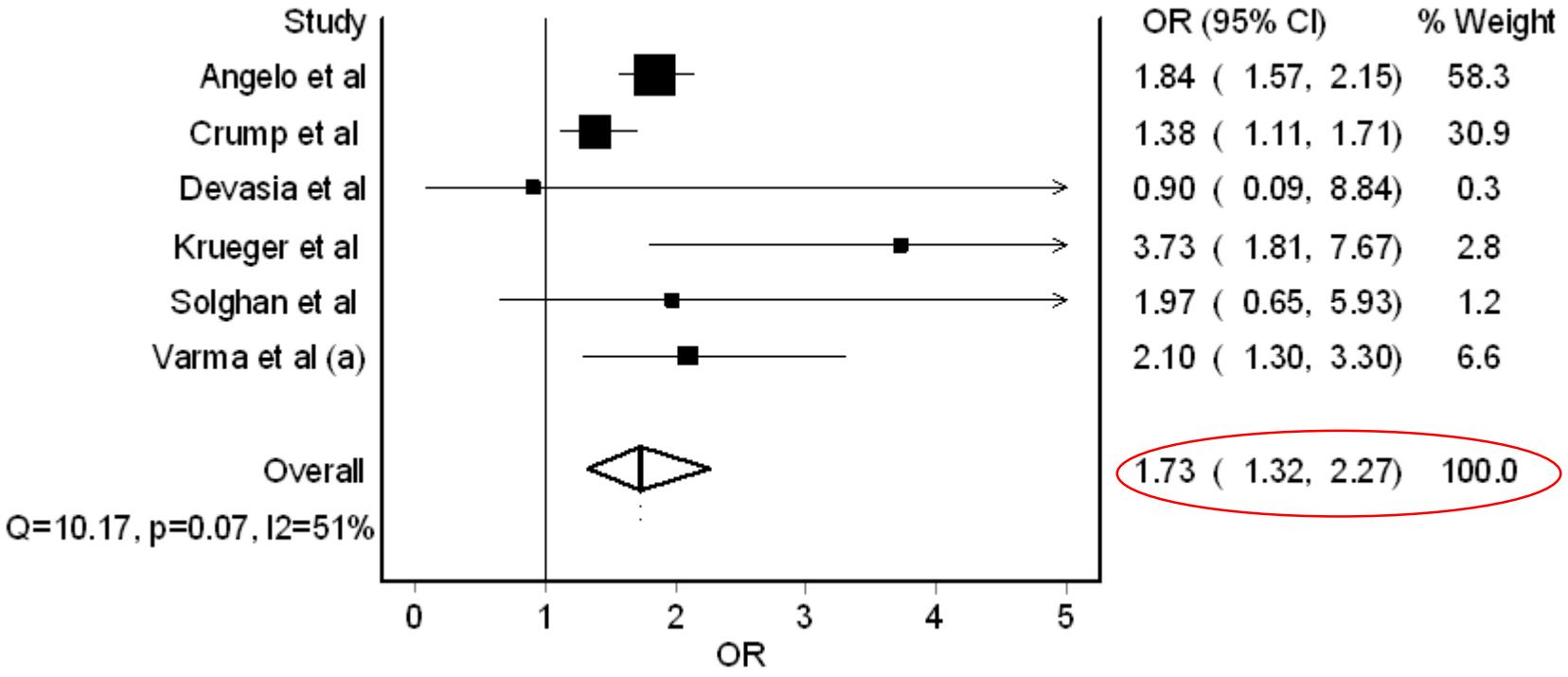


Studies Included in the Meta-analysis

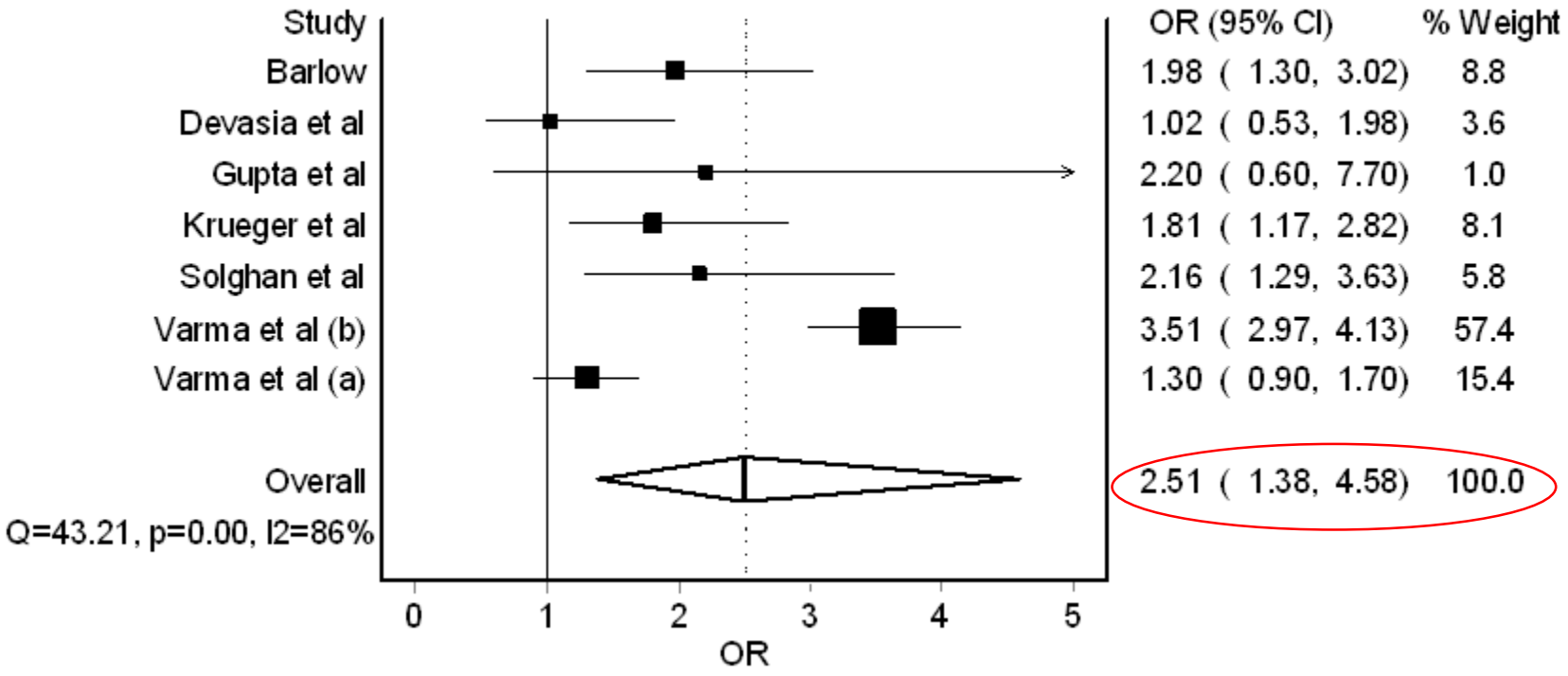
Study and year	Study period	Exposure measured – antimicrobial resistance pattern: cases/controls	Salmonella serotype	Sample size (cases/ controls)
Angelo et al, 2016	2003-2013	Resistant to ≥3 classes/ Susceptible	Typhimurium, Enteritidis, Heidelberg, Newport, other	19 248 (2276/16 972)
Barlow, 2012	2004-2009	R-type ACSSuT*/ Susceptible	Typhimurium, Heidelberg, Typh.van Copenhagen, Newport, other	1371 (158/1213)
Crump et al, 2011	1996-2007	R-type ACSSuT*/ Susceptible	Typhimurium, Enteritidis, Heidelberg, Newport, other	15 001 (1431/13570)
Devasia et al, 2005	04/2002-05/2003	MDR-AmpC†/ Susceptible	Newport	200 (54/146)
Gupta et al, 2003	01/04/ 1999 -31/03/ 2001	MDR-AmpC‡/ Susceptible	Newport	68 (32/36)
Krueger et al, 2014	01/2006-05/2008	Resistant to ≥3 classes/ Susceptible	Typhimurium, Enteritidis, Newport, other	785 (80/705)
Solghan et al, 2010	05/2003- 12/2007	R-type ACCSuT*/ Susceptible	Typhimurium	380 (79/301)
Varma et al, 2005a	1996-2001	R-type ACSSuT*/ Susceptible	Typhimurium, Enteritidis, Newport, Heidelberg, other	5174 (684/4490) 321 (146/175)
Varma et al, 2005b	1984-2002	R-type AC/KSSuT§/ Susceptible	Enteritidis, Typhimurium, other	15 000 (12 806/ 2194) 20 433 (17 150/ 3283)

NOTES. OR, Odds ratio; CI, 95% Confidence interval.
*R-type ACSSuT; resistant to at least ampicillin, chloramphenicol, streptomycin, sulphonamide, and tetracycline.
†MDR-AmpC; resistant to amoxicillin/clavulanate, ampicillin, cefoxitin, ceftiofur, cephalothin, chloramphenicol, streptomycin, sulfamethoxazole, tetracycline, and had decreased susceptibility to ceftriaxone.
‡MDR-AmpC: resistant to amoxicillin/clavulanate, ampicillin, cefoxitin, ceftiofur, cephalothin, streptomycin, sulfametoxazole, but not chloramphenicol or tetracycline.
§R-type AC/KSSuT: resistant to at least ampicillin, chloramphenicol, kanamycin, streptomycin, sulfametoxazole, and tetracycline.

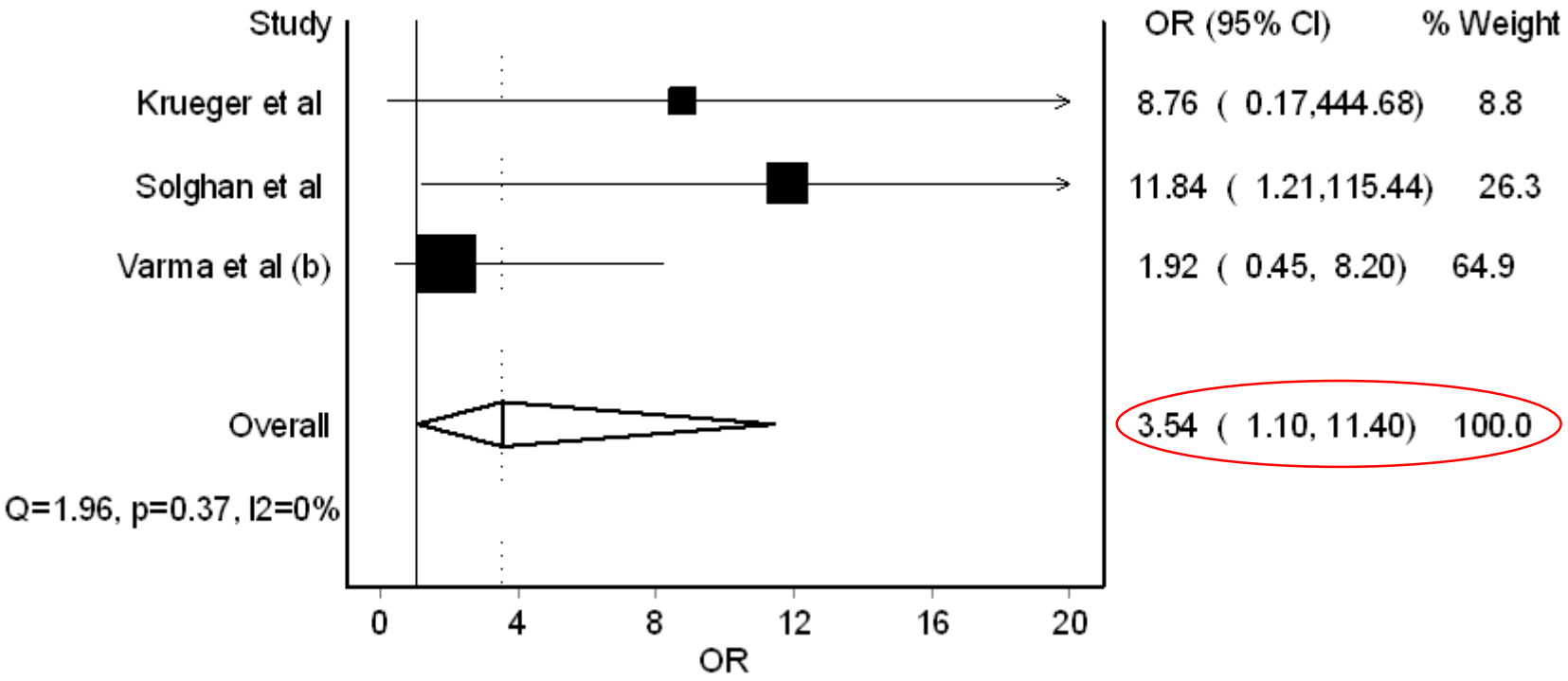
Bloodstream Infection



Hospitalisation



Mortality


Study
OR (95% CI)
% Weight
Krueger et al
8.76 (0.17,444.68) 8.8
Solghan et al
11.84 (1.21,115.44) 26.3
Varma et al (b)
1.92 (0.45, 8.20) 64.9
Overall
3.54 (1.10, 11.40) 100.0
Q=1.96, p=0.37, I2=0%
0
4
8
12
16
20
OR

Discussion

- Why have MDR NTS infections more severe outcomes?
  - The initial therapy might be ineffective
  - Need to choose less desirable drug
  - Linkage of virulence and resistance genes[1]
  - Role of host factors
    - Children and older adults in higher risk of invasive disease[2]
    - Underlying immunosuppressing condition associated with worse outcomes[3]
  - Role of serotype
    - *Salmonella* serotypes Heidelberg, Dublin, and Choleraesuis are more invasive than serotype Typhimurium[4]
    - *Salmonella* serotype Newport is less fatal when compared to serotype Typhimurium[4]

1. Barza M. Potential mechanisms of increased disease in humans from antimicrobial resistance in food animals. *Clin Infect Dis* 2002; **34**: S123–5.

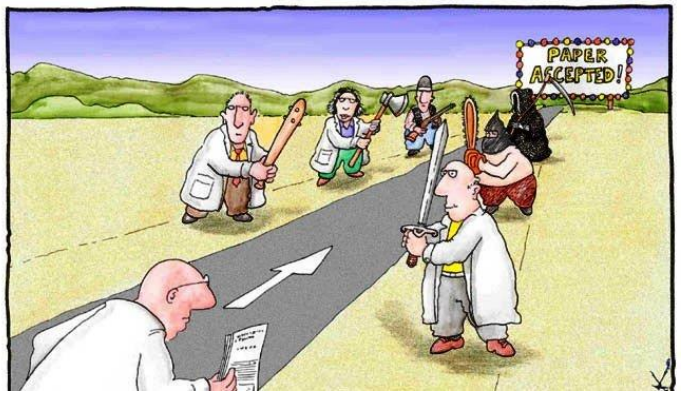
2. Parry CM, Thomas S, Aspinall EJ, et al. A retrospective study of secondary bacteraemia in hospitalised adults with community acquired non-typhoidal *Salmonella* gastroenteritis. *BMC Infect Dis* 2013; **13**: 107.

3. Gordon MA. *Salmonella* infections in immunocompromised adults. *J Infect* 2008; **56**(6): 413–22.

4. Jones TF, Ingram LA, Cieslak PR, et al. Salmonellosis outcomes differ substantially by serotype. *J Infect Dis* 2008; **198**(1): 109–14.

Limitations

- Limited number of studies
  - All from the USA
- Potential unmeasured confounders
  - Host factors, serotype
- Assessment of bacteraemia
- Possible publication bias



Conclusions and Future Directions

- MDR NTS infections linked with worse health outcomes
- Need for more adequately designed studies
  - Address potential confounders
  - Broader description of health outcomes
  - Address specific antimicrobial patterns
- Restrict the use of antimicrobials

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- **Funding:** Endeavour Postgraduate Scholarship, Department of Agriculture and Water Resources, Canberra

- Authors of included studies who provided additional information

References

Angelo KM, Reynolds J, Karp BE, Hoekstra RM, Scheel CM, Friedman C. Antimicrobial resistance among nontyphoidal *Salmonella* isolated from blood in the United States, 2003–2013. *J Infect Dis* 2016. **214**(10): 1565-70.

Barlow RS. Emerging nontyphoidal *Salmonella* antibiotic resistance in Oregon 2004–2009 : risk factors and trends. OHSU Digital Commons 2012.

Crump JA, Medalla FM, Joyce KW, et al. Antimicrobial resistance among invasive nontyphoidal *Salmonella enterica* isolates in the United States: National Antimicrobial Resistance Monitoring System, 1996 to 2007. *Antimicrob Agents Chemother* 2011; **55**(3): 1148–54.

Devasia RA, Varma JK, Whichard J, et al. Antimicrobial use and outcomes in patients with multidrug-resistant and pansusceptible *Salmonella* Newport infections, 2002–2003. *Microb Drug Resist* 2005; **11**(4): 371–7.

Gupta A, Fontana J, Crowe C, et al. Emergence of multidrug-resistant *Salmonella* enterica serotype Newport infections resistant to expanded-spectrum cephalosporins in the United States. *J Infect Dis* 2003; **188**(11): 1707–16.

Krueger AL, Greene SA, Barzilay EJ, et al. Clinical outcomes of nalidixic acid, ceftriaxone, and multidrug-resistant nontyphoidal *Salmonella* infections compared with pansusceptible infections in FoodNet sites, 2006–2008. *Foodborne Pathog Dis* 2014; **11**(5): 335–41.

Solghan SM, Dumas NB, Root TP, et al. Multidrug-resistant nontyphoidal *Salmonella* in New York state's foodborne diseases active surveillance network counties. *Foodborne Pathog Dis* 2010; **7**(2): 167–73.

Varma JK, Mølbak K, Barrett TJ, et al. Antimicrobial-resistant nontyphoidal Salmonella is associated with excess bloodstream infections and hospitalizations. *J Infect Dis* 2005a; **191**(4): 554–61.

Varma JK, Greene KD, Ovitt J, Barrett TJ, Medalla F, Angulo FJ. Hospitalization and antimicrobial resistance in *Salmonella* outbreaks, 1984–2002. *Emerg Infect Dis* 2005b; **11**(6): 943–6.

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Quality Assessment of studies

Bloodstream infection								
Study	Representativeness of study population*	Representativeness of isolates†	Selection of cases and controls‡	Assessment of cases and controls§	Assessment of exposure¶	Assessment of outcome‖	Analysis adjusted for confounders**	Qi (max 9)
Angelo et al, 2016	1	2	1	1	1	0	0	6
Crump et al, 2011	1	2	1	1	1	0	0	6
Devasia et al, 2005	1	1	1	1	1	0	0	5
Krueger et al, 2014	1	2	1	1	1	1	0	7
Solghan et al, 2009	1	1	1	1	1	0	0	5
Varma et al, 2005b	1	2	1	1	1	1	2	9
Hospitalisation								
Study	Representativeness of study population*	Representativeness of isolates†	Selection of cases and controls‡	Assessment of cases and controls§	Assessment of exposure¶	Assessment of outcome††	Analysis adjusted for confounders**	Qi (max 8)
Barlow et al, 2012	1	2	1	1	1	1	1	8
Devasia et al, 2005	1	1	1	1	1	1	0	6
Gupta et al, 2003	1	1	1	1	1	1	0	6
Krueger et al, 2014	1	2	1	1	1	1	0	7
Solghan et al, 2009	1	1	1	1	1	1	0	6
Varma et al, 2005a	1	1	1	1	0	1	0	5
Varma et al· 2005b	1	2	1	1	1	1	0	7
Mortality								
Study	Representativeness of study population*	Representativeness of isolates†	Selection of cases and controls‡	Assessment of cases and controls§	Assessment of exposure¶	Assessment of outcome‡‡	Analysis adjusted for confounders**	Qi (max 7)
Krueger et al, 2014	1	2	1	1	1	1	0	7
Solghan et al, 2009	1	1	1	1	1	1	0	6
Varma et al, 2005a	1	1	1	1	0	1	0	5

NOTES

* Representativeness of study population: study population was clearly defined (1 point), unclear or not defined (0 points)
† Representativeness of isolates: truly representative of the community (2 points), somewhat representative (1 serotype only) (1 point), not representative or not stated (0 points)
‡ Selection of cases and controls: from the same community with no significant differences (1 point), significant differences (0 points)
§ Assessment of cases and controls: same (1 point), other or not defined (0 point)
¶ Assessment of exposure: clear information on antimicrobial testing, same methods used for all isolates (1 point), unclear or no definition (0 points)
||Assessment of outcome: clear information on bloodstream infection in both cases and controls (1 point), other or not defined (0 points)
** Analysis adjusted for confounders (age, comorbidities, sex, serotype): adjusted for at least 2 factors (2 points), adjusted for 1 factor (1 point), not adjusted or not stated (0 points)
††Assessment of outcome: patients with Salmonella infection (both bloodstream and gastroenteritis) who were hospitalised (1 point), other or not defined (0 points)
‡‡Assessment of outcome: patients with Salmonella infection (both bloodstream and gastroenteritis) who died during the hospitalisation or Salmonella outbreak (1 point), other or not defined (0 points)

1. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (accessed 10 November 2016).

Statistical Analyses

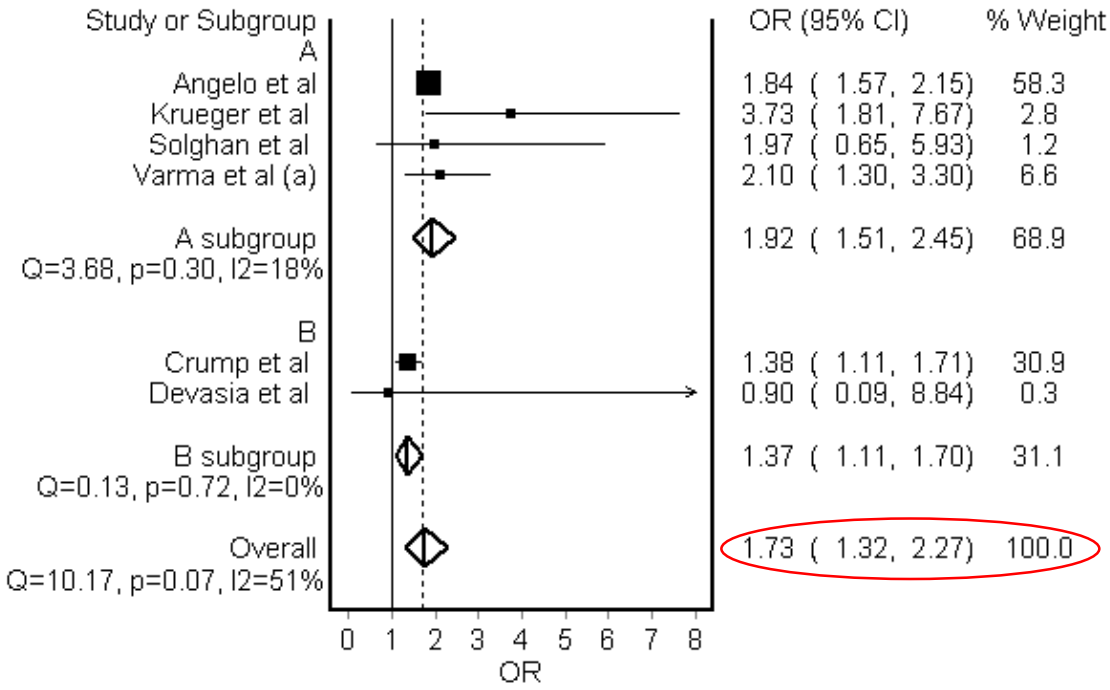
- Outcome measure
  - Odds ratio (OR)
- Statistical models
  - Inverse variance heterogeneity (IVHet)
  - Random effect model (RE)
  - Quality effect model (QE)
- Subgroup analysis
  - Bloodstream infection
- Sensitivity analyses
- Statistical heterogeneity
  - Higgins's I^2
- Publication bias
  - Doi plots and LFK index

All analyses were performed using MetaXL, version 5.3 (http://www.epigear.com)

Pooled Effect Sizes Using All Three Models

Health Outcome	IVHet model OR (95% CI)	RE model OR (95% CI)	QE model OR (95% CI)	Heterogeneity I^2 index %
Bloodstream infection	**1.73** (1.32-2.27)	**1.82** (1.43-2.31)	**1.79** (1.39 - 2.31)	50.86
Hospitalisation	**2.51** (1.38-4.58)	**1.82** (1.19-2.79)	**2.21** (1.37-3.55)	87.38
Mortality	**3.54** (1.10-11.40)	**3.54** (1.10-11.40)	**4.32** (1.26-14.83)	0

Subgroup Analysis



Subgroup A: studies reporting "bloodstream infection"
Subgroup B: studies reporting "blood isolate"

Sensitivity Analyses

Bloodstream Infection

Excluded study	IVhet Pooled OR	LCI 95%	HCI 95%	I^2
Angelo et al, 2016	1.59	0.95	2.64	54.34
Crump et al, 2011	1.91	1.63	2.25	2.27
Devasia et al, 2005	1.73	1.30	2.31	59.44
Krueger et al, 2014	1.69	1.40	2.05	29.85
Solghan et al, 2009	1.73	1.28	2.32	60.48
Varma et al, 2005b	1.71	1.24	2.34	57.73

Excluded study	RE Pooled OR	LCI 95%	HCI 95%	I^2
Angelo et al, 2016	1.92	1.27	2.91	54.34
Crump et al, 2011	1.93	1.64	2.26	2.27
Devasia et al, 2005	1.84	1.43	2.37	59.44
Krueger et al, 2014	1.68	1.40	2.02	29.85
Solghan et al, 2009	1.82	1.40	2.37	60.48
Varma et al, 2005b	1.78	1.34	2.37	57.73

Excluded study	QE Pooled OR	LCI 95%	HCI 95%	I^2
Angelo et al, 2016	1.71	1.10	2.65	54.34
Crump et al, 2011	1.96	1.60	2.39	2.27
Devasia et al, 2005	1.86	1.44	2.40	59.44
Krueger et al, 2014	1.68	1.35	2.09	29.85
Solghan et al, 2009	1.79	1.35	2.37	60.48
Varma et al, 2005b	1.73	1.28	2.34	57.73

Hospitalisation

Excluded study	IVhet Pooled OR	LCI 95%	HCI 95%	I 2
Barlow, 2012	2.57	1.26	5.24	88.06
Devasia et al, 2005	2.60	1.44	4.68	86.01
Gupta et al, 2003	2.52	1.36	4.67	88.42
Krueger et al, 2014	2.59	1.29	5.17	87.77
Solghan et al, 2009	2.54	1.29	5.01	88.34
Varma et al, 2005a	1.60	1.28	2.01	19.95
Varma et al, 2005b	2.83	1.58	5.10	78.89

Excluded study	RE Pooled OR	LCI 95%	HCI 95%	I 2
Barlow, 2012	1.87	1.15	3.05	88.06
Devasia et al, 2005	2.07	1.35	3.17	86.01
Gupta et al, 2003	1.87	1.21	2.90	88.42
Krueger et al, 2014	1.90	1.18	3.07	87.77
Solghan et al, 2009	1.84	1.14	2.97	88.34
Varma et al, 2005a	1.62	1.30	2.03	19.95
Varma et al, 2005b	2.06	1.38	3.09	78.89

Excluded study	QE Pooled OR	LCI 95%	HCI 95%	I 2
Barlow, 2012	2.29	1.26	4.14	88.06
Devasia et al, 2005	2.31	1.44	3.72	86.01
Gupta et al, 2003	2.19	1.33	3.61	88.42
Krueger et al, 2014	2.25	1.29	3.90	87.77
Solghan et al, 2009	2.20	1.28	3.78	88.34
Varma et al, 2005a	1.62	1.29	2.03	19.95
Varma et al, 2005b	2.46	1.55	3.90	78.89

Mortality

Excluded study	IVHet Pooled OR	LCI 95%	HCI 95%	I^2
Krueger et al, 2014	3.25	0.56	18.84	42.57
Solghan et al, 2009	2.30	0.59	8.99	0.00
Varma et al, 2005a	10.98	1.53	78.88	0.00

Excluded study	RE Pooled OR	LCI 95%	HCI 95%	I^2
Krueger et al, 2014	3.82	0.68	21.55	42.57
Solghan et al, 2009	2.30	0.59	8.99	0.00
Varma et al, 2005a	10.98	1.53	78.88	0.00

Excluded study	QE Pooled OR	LCI 95%	HCI 95%	I2
Krueger et al, 2014	3.66	0.65	20.63	42.57
Solghan et al, 2009	2.88	0.65	12.82	0.00
Varma et al, 2005a	10.79	1.48	78.88	0.00