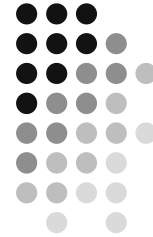


Prophylaxis of Travellers' Diarrhoea

-an examination of existing evidence

Dennis Ip



Outline:

- Travellers' diarrhoea (TD) – some basic facts
- Treatment vs prevention – the dilemma in managing TD
- Current evidence regarding chemoprophylaxis of TD





Travellers' diarrhoea (TD) – some basic facts



What is travellers' diarrhoea

- Travelers' diarrhoea (TD) is the most common illness affecting travelers
- 20%-50% of international travelers
- >10 million episodes/ year

What is travellers' diarrhoea



- The development of diarrhoea in persons travelling outside of their country
- Three or more unformed stool in 24 hours occurring during or shortly after travel

Risk of travellers' diarrhoea



Low-risk	<8%	<ul style="list-style-type: none">• North America• Northern and Central Europe• Australia & New Zealand
Intermediate-risk	8-20%	<ul style="list-style-type: none">• Caribbean• Northern Mediterranean• Israel• South Africa
High-risk	30-50%	<ul style="list-style-type: none">• Latin America• Africa• the Middle East• Asia

Environmental & Host factors



Environmental factors	<ul style="list-style-type: none"> • Prevalence of microbial pathogens • Local water quality • Sewage disposal
Individual host factors	<ul style="list-style-type: none"> • Mode of travel • Food practice • Model of residence • Extremes of age • Impaired gastric acid barrier • Immune deficiency

Etiological agents



Enteropathogen	%	Acute watery diarrhoea	Dysentery	Persistent diarrhoea
Viruses	10	+	-	-
Bacteria	80	+	+	-
Enterotoxigenic <i>E.coli</i> (ETEC)	50			
Enteroinvasive <i>E. coli</i> (EIEC)	25			
Protozoa	15	+	-	+
Helminths		-	-	+
Miscellaneous		-	-	+

Clinical features:

- usually a self-limiting disease
- lasting for an mean duration of 4 days
- 5-10% ill for more than 7 days
- 15-40% disruption of travel plans
- 10-30% causing confinement to bed
- Up to 1% need to be hospitalized



Treatment vs prevention
– the dilemma in managing TD



Management of TD



Treatment

- Oral fluids
- Antimicrobial chemotherapy
- Other non-antibiotic agent
- Antidiarrhoeal agents

vs

Prevention

- Dietary restriction
- Chemoprophylaxis

CDC recommendation for treatment of established TD



- ciprofloxacin 500 mg BD for 3-5 days
- norfloxacin 400 mg BD for 3-5 days

- Bismuth subsalicylate

- Trimethoprim-sulfamethoxazole and doxycycline are no longer recommended because of the high level of resistance to these agents

Systematic review on antibiotic treatment



deBruyn 2002:

- demonstrated a significant beneficial effect of antibiotic treatment
- in terms of the proportion of persons cured of diarrhoea by 72 hours of treatment
- and in reducing the severity of illness

Prevention



- behavioural restriction
- “boil it, cook it, peel it or forget it”

High risk items:	Safer items:
<ul style="list-style-type: none">•Foods from street vendors•Raw or undercooked meat and seafood•Raw fruits and vegetables•Tap water & ice•Unpasteurized milk/ dairy products	<ul style="list-style-type: none">•Food served steaming hot•Dry items such as bread•Bottled carbonated beverages•Hot coffee or tea•Boiled water•Iodine-treated water

Effect of pretravel health advice on the incidence of TD



- Swiss travellers to Africa and Asia
- only 2% were able to adhere consistently to all recommendations
- In the first 3 days, 71% consumed salads or uncooked vegetables, and 53% used ice cubes in drinks
- incidence of TD significantly associated with the number of mistakes made

'Boil it, cook it, peel it or forget it': does this rule prevent travellers' diarrhoea? *Int J Epidemiol* 1985; 14: 169–72.

Chemoprophylaxis of TD



- Antibiotics
 - doxycycline
 - trimethoprim-sulfamethoxazole (TMP/SMX)
 - trimethoprim alone
 - fluoroquinolone agents ciprofloxacin and norfloxacin
- Bismuth subsalicylate
- Probiotics
 - Lactobacilli
- Vaccine
 - ETEC
 - Cholera

Cost-effectiveness analyses



- daily antibiotic prophylaxis vs three day treatment regimen
- the cost-effectiveness of prophylaxis was found to be greater than that of treatment
- short-term travellers (ie, 3–5 days)
- recommended for travellers going to high-risk areas

A cost-effectiveness comparison of the use of antimicrobial agents for treatment or prophylaxis of travelers' diarrhea. *Arch Intern Med* 1988; **148**: 2421–27.

Prophylaxis – current recommendations



- NIH consensus conference (1985):
 - effectiveness of chemoprophylaxis acknowledged
 - but did not recommend
- potential side effects
- unable to identify any particular group of travellers for whom prophylaxis would be especially important

Current CDC recommendation



- prophylactic antibiotics should not be recommended for most travelers

Arguments against Prophylaxis



- Usually self-limiting
- Short duration
- Easily treated once diagnosed
- False sense of security
- Potentially fatal allergic or adverse reactions
- Other minor but common side effects
- Antimicrobial resistance

Arguments for Prophylaxis



- Very common problem
- Disruption to important trips
- 20 % bed confinement
- Adherence to food practice usually difficult and poor
- Effective prophylactic agents available
- Serious side effects rare

Discrepancy between recommendation & practice



- only 2% of clinical microbiologists normally prescribe prophylactic antibiotics for travellers' diarrhoea
- 28% took daily ciprofloxacin prophylaxis themselves during a visit to India
(and luckily, none of them developed diarrhoea!)

A microbiologist's guide to travellers abroad: do as I say not as I do.
J Hosp Infect. 1997 Apr;35(4):255-7

Discrepancy between recommendation & practice



- 22.8% of clinical pharmacists took antibiotics prophylactically when travelling to high risk countries

Pharmacists' self-medication for the travelers' diarrhea.
DICP 1989;23:800-5.

Current evidence regarding
chemoprophylaxis of TD



Need for a systemic review



- No consensus for recommendation
- Discrepancy in practice
- No systemic review available

Current review - Objectives



- to give a more precise estimation of the effect size in altering incidence and clinical course of travellers' diarrhoea by different prophylactic agents
- to have a systematic examination of the scale of problems regarding adverse events reported for their use
- to formulate a better evidence-based recommendation for their use in different travellers

Selection criteria

- randomized trials
- in any language
- people travelling from one country to another for any length of time
- chemoprophylaxis aimed at preventing diarrhoea during or shortly after travelling
- compared with placebo/no treatment/other chemoprophylactic



Outcome measures

Primary:

- Incidence of diarrhoea

Secondary:

- Duration of illness
- Severity of illness
- Tolerability



Methods



- Cochrane Library +Medline + Embase
- 32 RCTs finally included
- data extraction for outcome of concern
- trial quality assessed with regard to
 - Allocation concealment
 - Blinding
 - Generation of allocation sequence
 - Inclusion of all randomised participants
- Meta-analysis

Studies included in the review



Antibiotics	Doxycycline	6
	Trimethoprim	2
	Norfloxacin	3
	Ciprofloxacin	3
	Others	6
Bismuth subsalicylate		3
Probiotics & Prebiotics		5
Vaccines		3
Others		1



- 27 - 1383 participants
- Age ranged from 17 to 86 years
- All trials compared a chemoprophylactic agent with a placebo as the control
- All studies involved travellers departing from a low risk country and going to a high/ intermediate risk destination
- All trials were double-blinded and placebo-controlled in design



Types of participants

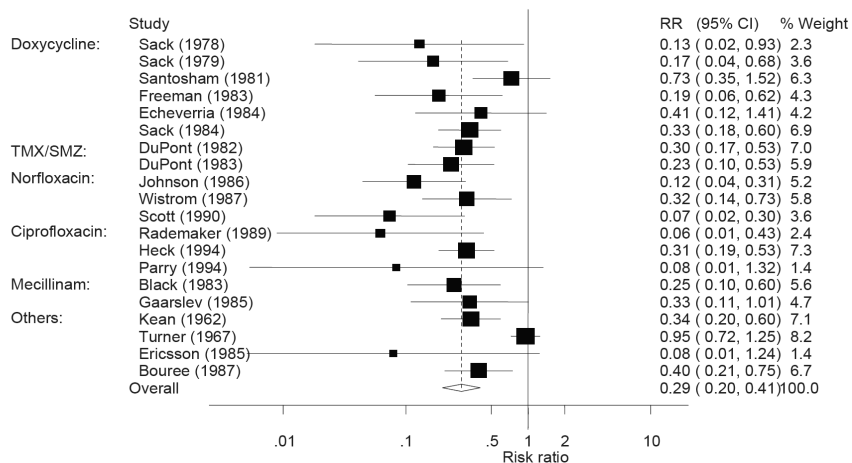
students	10 studies
military personnel	3 studies
Peace Corps volunteers	5 studies
"package" tourists	6 studies
independent travellers	4 studies
health professionals in a medical mission	1 study
mountaineers	1 study
car rally participants	1 study
airline personnel	1 study

Case definitions of TD



a minimum of three loose stools per 24 hours or a smaller number of stools + symptoms of enteric infection	27/32
three or more loose stools in an eight hour period + symptoms of enteric infection	1/32
case definition not explicitly reported	4/32

Figure 2: Meta-analysis of the prophylactic effect of antibiotics on the incidence of travellers' diarrhoea

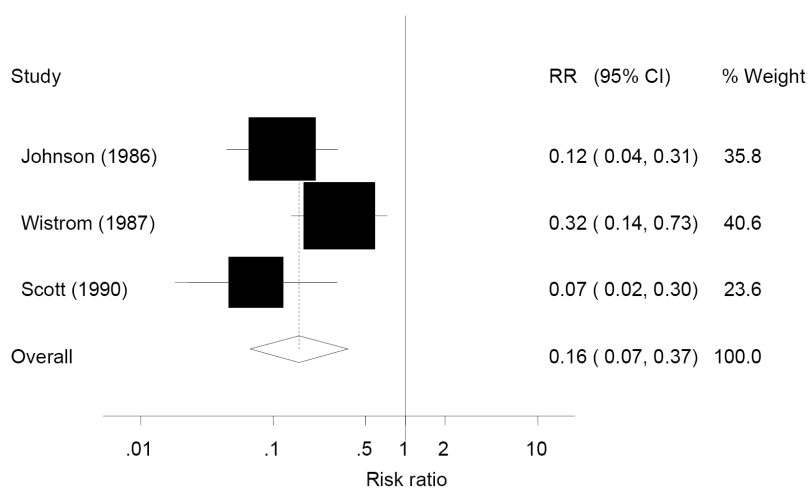


Norfloxacin: Primary Outcome



- 3 RCTs
- 509 travellers randomised & 452 finally analysed
- norfloxacin 400mg daily vs placebo
- Incidence rate of diarrhoea
 - from 25.6% to 61% among placebo groups
 - from 1.9% to 10.7% among intervention groups
- meta-analysis of the incidence of diarrhoea showed an overall significant risk reduction of 84% (pooled RR 0.16, 95%CI 0.07-0.37) by norfloxacin

Figure 7: Meta-analysis of the prophylactic effect of norfloxacin on the incidence of travellers' diarrhoea



Norfloxacin: Secondary Outcome



- None of the three studies addressed the duration or severity of diarrhoea in participants

Adverse events:

- “no significant side effects in either group”
- 1/217 (0.5%) travellers taking norfloxacin in the 3 studies developed generalised rash that necessitated termination of the medication
- Other adverse events were rare

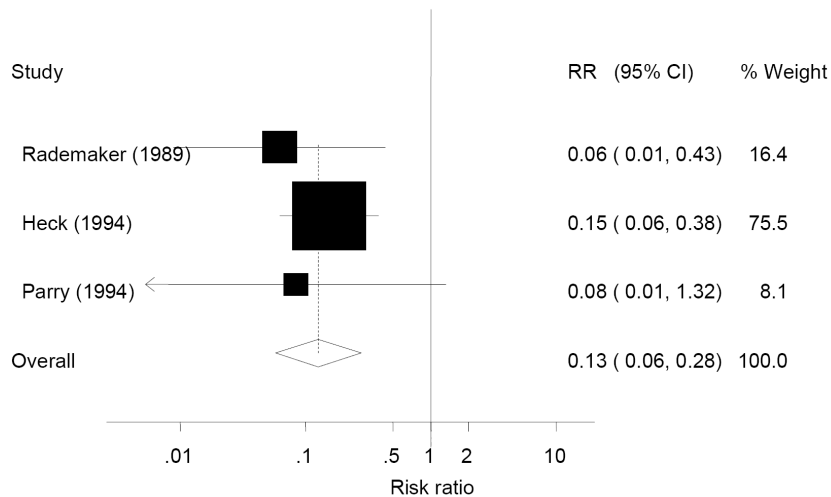
Ciprofloxacin: Primary Outcome



- 3 RCTs
- 425 travellers randomised & 352 finally analysed
- ciprofloxacin 250-500mg daily vs placebo
- Incidence rate of diarrhoea
 - from 32.6% to 64% among placebo groups
 - from 0% to 5.1% among intervention groups
- meta-analysis of the incidence of diarrhoea showed an overall significant risk reduction of 87% (pooled RR 0.13, 95%CI 0.06-0.28) by ciprofloxacin



Figure 8: Meta-analysis of the prophylactic effect of ciprofloxacin on the incidence of travellers' diarrhoea



Ciprofloxacin: Secondary Outcomes

- None of the three studies addressed the duration or severity of diarrhoea in participants

Adverse events:

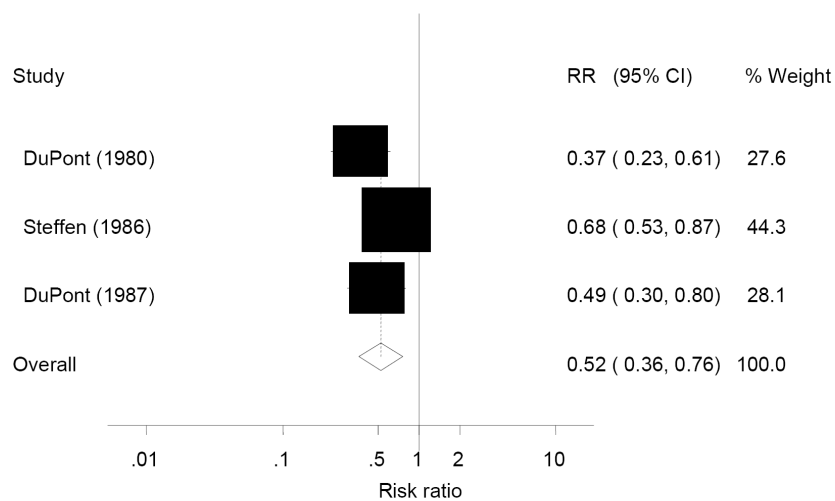
- 3/134 (2.2%) travellers taking ciprofloxacin in the 3 studies reported an adverse event that required termination of the medication
- The frequency of any events combined, all events needing discontinuation, and photosensitivity were similar among the intervention and placebo groups.

Bismuth subsalicylate : Primary Outcome



- 3 RCTs
- 744 travellers randomised & 541 finally analysed
- BSS dosage ranged from 0.5 gm to 4.2 gm/ day
- A meta-analysis of the incidence of diarrhoea showed an overall significant risk reduction of 48% (pooled RR 0.52, 95%CI 0.36-0.76) by BSS

Figure 11: Meta-analysis of the prophylactic effect of bismuth subsalicylate on the incidence of travellers' diarrhoea



Bismuth subsalicylate

: Secondary Outcomes

- both the duration and severity were similar among the intervention and placebo groups (DuPont1987)
- tongue darkening and stool darkening (> 80% Vs ~10% in placebo group)
- tinnitus (13% Vs 5% in placebo group)
- Constipation reported to be higher
- 1 grand mal seizures + 1 pancreatitis on taking BSS
? medication related



Figure 12: Meta-analysis of the prophylactic effect of probiotics on the incidence of travellers' diarrhoea

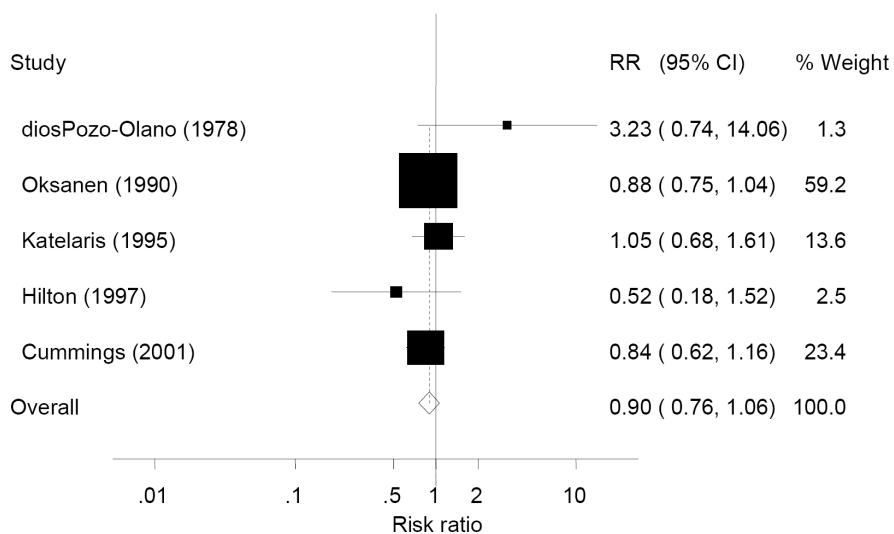




Figure 14: Meta-analysis of the prophylactic effect of vaccines on the incidence of travellers' diarrhoea

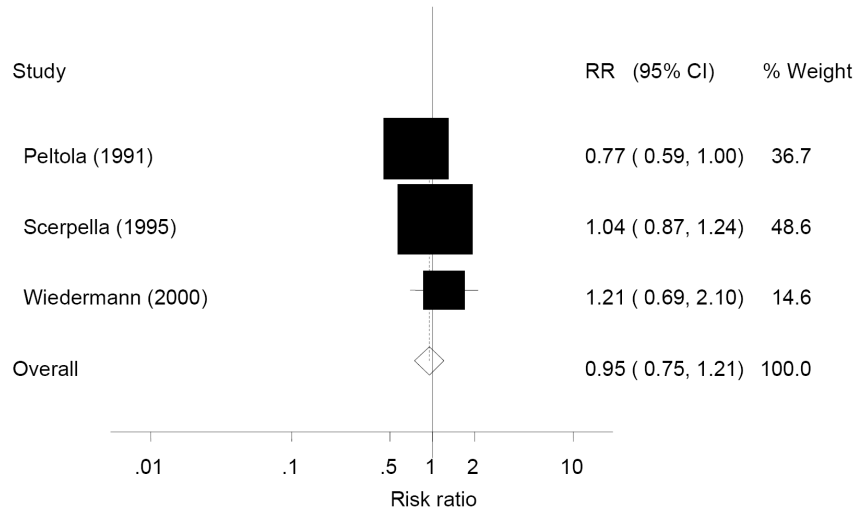
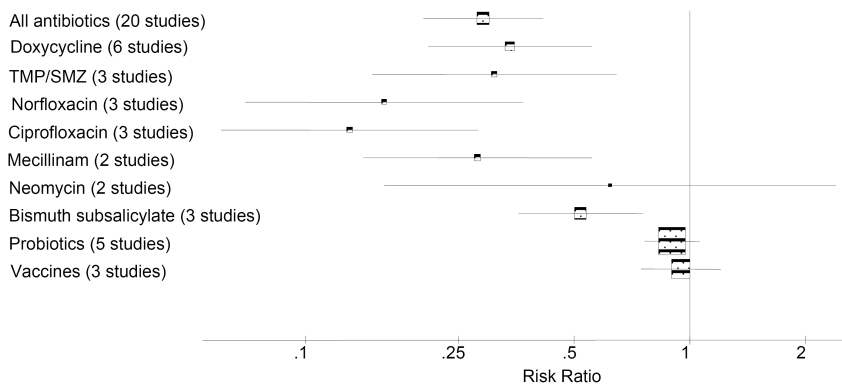


Figure 14: Summary of main meta-analysis findings





Antibiotics & BSS

- both effective in preventing the TD
- previous concerns over their side effects may not be entirely justified
- should always be considered for high risk travellers



Ciprofloxacin & norfloxacin

- wide antimicrobial spectrum
 - high effectiveness in risk reduction
 - rare occurrence of serious adverse reaction
-
- prescription be individualised
 - susceptibility pattern of enteropathogens
 - pooled estimate of the overall effect size

A Randomized, Double-Blind, Placebo-Controlled Trial of Rifaximin To Prevent Travelers' Diarrhea

Herbert L. DuPont, MD; Zhi-Dong Jiang, PhD; Pablo C. Okhuysen, MD; Charles D. Ericsson, MD; Francisco Javier de la Cabada, MD; Shi Ke, MD; Margaret W. DuPont, MA; and Francisco Martinez-Sandoval, MD, PhD

Background: Travelers' diarrhea causes substantial morbidity and postinfectious irritable bowel syndrome.

Objective: To evaluate nonabsorbable rifaximin for prevention of travelers' diarrhea.

Design: Randomized, double-blind, placebo-controlled clinical trial.

Setting: Guadalajara, Mexico.

Participants: U.S. students.

Intervention: On arrival in Guadalajara, Mexico, 210 U.S. adults received rifaximin (200 mg/d, 200 mg twice daily, or 200 mg 3 times daily) or placebo for 2 weeks.

Measurements: Participants were followed daily for 3 weeks for enteric disease and symptoms and daily for 5 weeks for drug side effects. Changes in intestinal coliform flora were studied.

Results: Travelers' diarrhea developed in 14.74% of participants taking rifaximin and 53.70% of those taking placebo (rate ratio, 0.27 [95% CI, 0.17 to 0.43]). Rifaximin provided 72% and 77% protection against travelers' diarrhea and antibiotic-treated travel-

ers' diarrhea, respectively ($P < 0.001$ for both), and all rifaximin doses were superior to placebo. In the groups that did not report travelers' diarrhea, rifaximin significantly reduced the occurrence of mild diarrhea ($P = 0.02$) and moderate and severe intestinal problems ($P = 0.009$ for pain or cramps; $P = 0.02$ for excessive gas). Rates of adverse events were comparable in the rifaximin and placebo groups. Minimal changes in coliform flora were found during rifaximin therapy.

Limitations: Rifaximin safely prevented travelers' diarrhea in Mexico, where most cases are caused by diarrhea-producing *Escherichia coli*. A study is needed in Asia to determine whether rifaximin can prevent diarrhea caused by invasive bacterial pathogens.

Conclusions: Rifaximin prevents travelers' diarrhea with minimal changes in fecal flora, and more liberal chemoprophylaxis against this disease should be considered. Future studies should evaluate whether rifaximin is effective in preventing postinfectious irritable bowel syndrome.

Ann Intern Med. 2005;142:805-812.
For author affiliations, see end of text.
Trial NCT00098384.

www.annals.org

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Behind the headlines What is RSS?

Patch prevents travellers' diarrhoea

Thursday June 12 2008

"Traveller's tummy" may be cured by E. Coli patch" is the headline in *The Independent* today. The newspaper goes on to say that for people who get "holiday tummy, a vaccine patch can cut the incidence of traveller's diarrhoea by 75%."

The patch is worn on the upper arm and delivers a tiny dose of toxin produced by an enterotoxigenic *E. coli* (ETEC) bacteria, a major cause of diarrhoea in people travelling overseas. Travellers' diarrhoea lasts on average between four and five days, involves many trips to the toilet and can leave sufferers dehydrated. The patch is applied for a six-hour period three weeks before travel and works by stimulating the body's immune response, which then protects the traveller. A second booster patch is applied one week before travel.



Travellers' diarrhoea involves many toilet visits

Previous articles

- Prostate cancer and lifestyle
- Looking scared could be protective
- Health risks of piercings
- Fungal exposure and gardening
- Brittle bones drug and breast cancer

Useful links

- NHS Choices - Travel health
- NHS Choices - Travellers' diarrhoea
- National Travel Health Network and Centre
- Travax
- MASTA



Infectious disease

Travelling overseas expose you to diseases and health problems. How to reduce your risk.



How to beat jet lag

Find out how to beat jet lag and enjoy your holiday from the moment you leave.



- Dr. Julian Higgins (IPH, Cambridge)
- Dr. Eric Walker (FTM, RCPSGlasg)



Current review - Objectives



- Primary
 - To evaluate the extent to which chemoprophylactic measures can reduce the incidence of travellers' diarrhoea.
- Secondary
 - To evaluate the differential effects of prevention with regard to:
 - different interventions
 - different destinations
 - different personal characteristics

Table 5: Assessment of allocation concealment

A	Procedure for concealment of randomization sequence adequate and clearly described
B	Attempt for concealment of randomization sequence unclear/ not described
C	Allocation sequence open to the person(s) allocating participants to intervention groups





Table 6: Assessment of blinding of outcome assessment

A	Assessors blinded to the randomization
B	Blinding of outcome assessment unclear/ not described
C	Assessors unblinded to the randomization



Table 7: Assessment of withdrawal/ dropouts

A	Possible intention-to-treat analysis
B	Drop out rate < 20% and intention-to-treat analysis not possible
C	Drop out rate > 20%, or Wide differential dropout rate between the two groups, or Drop out rate unclear/ not described

Assessing the presence of significant heterogeneity among studies included



Cochran's heterogeneity statistics Q

- computation of the sum of squared deviations of each study's estimate from the overall meta-analysis estimate
- each study's contribution weighted in the same manner as in a fixed effect meta-analysis
- P values obtained by comparing this statistics with a χ^2 distribution with $k-1$ degree of freedom, where k equals the number of studies

Measuring the extent of inconsistency across studies



- The I^2 statistic
- $I^2 = 100\% \times (Q - df) / Q$
- where Q is the Cochran's heterogeneity statistic
- df is the degrees of freedom
- describes the percentage of total variation across studies that is due to heterogeneity rather than chance
- With negative values of I^2 put equal to zero, the value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity.

funnel plot

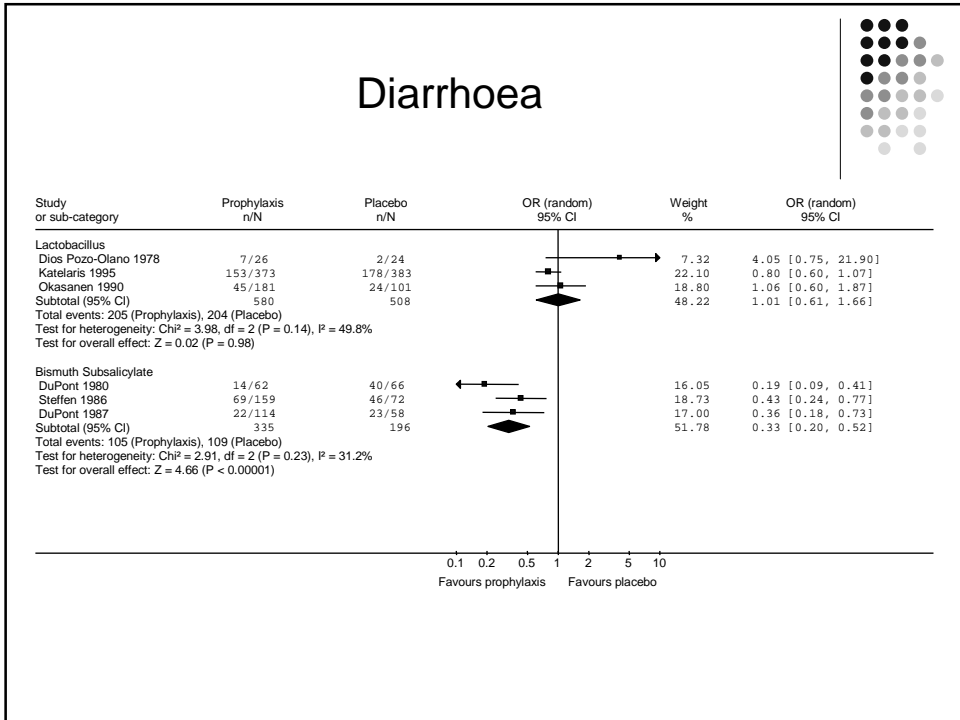
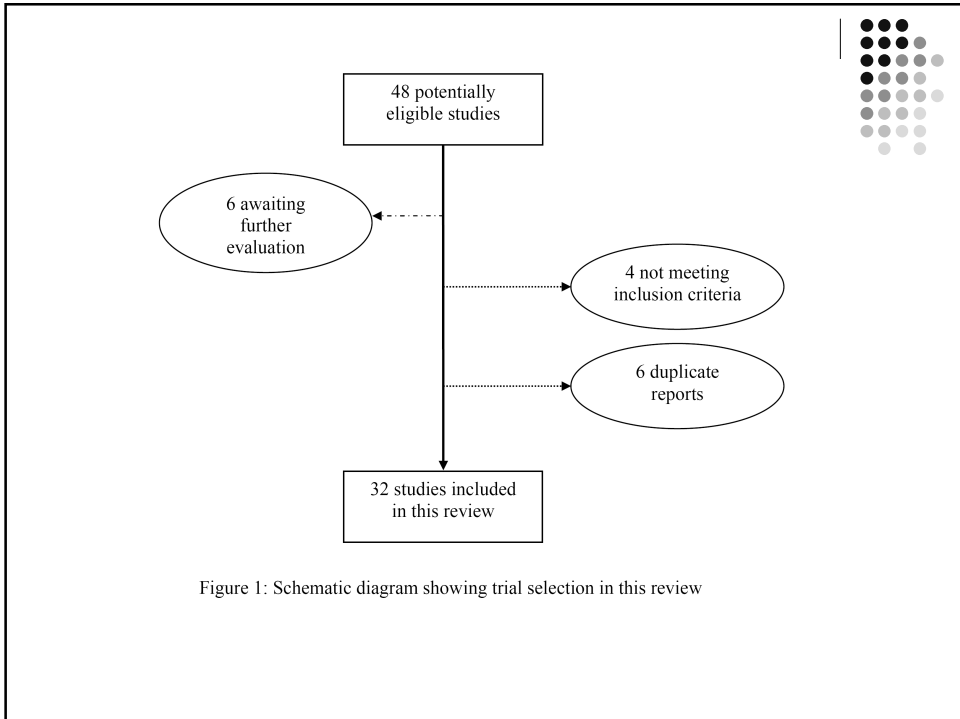


- a scatter plot of treatment effect against a measure of study size
- a scatter plot of $1/se[\log RR]$ Vs $[\log RR]$
- degree of asymmetry reflects the appropriateness of the underlying normality assumption in the random effect model in the meta-analysis
- identify potential selection biases such as publication bias or genuine relationships between treatment effects and study size
- In an ideal world, the funnel plot has a symmetric inverted funnel shape, since large studies (with small standard errors) would lie near to the truth and smaller studies (with larger standard errors) would be evenly and more widely scattered around the truth.

Quality assessment



- Method of randomisation was described in 13 out of the 32 studies.
- Method of allocation concealment was judged to be adequate (A) in 10 studies, unclear (B) in 21 studies and open (C) in one study.
- Blinding of outcome assessment was judged to be adequate in all 32 studies.
- None of the studies analysed using an intention-to-treat approach.
- Dropout rate varied from 0% to 40.8% and was greater than 20% in seven studies.



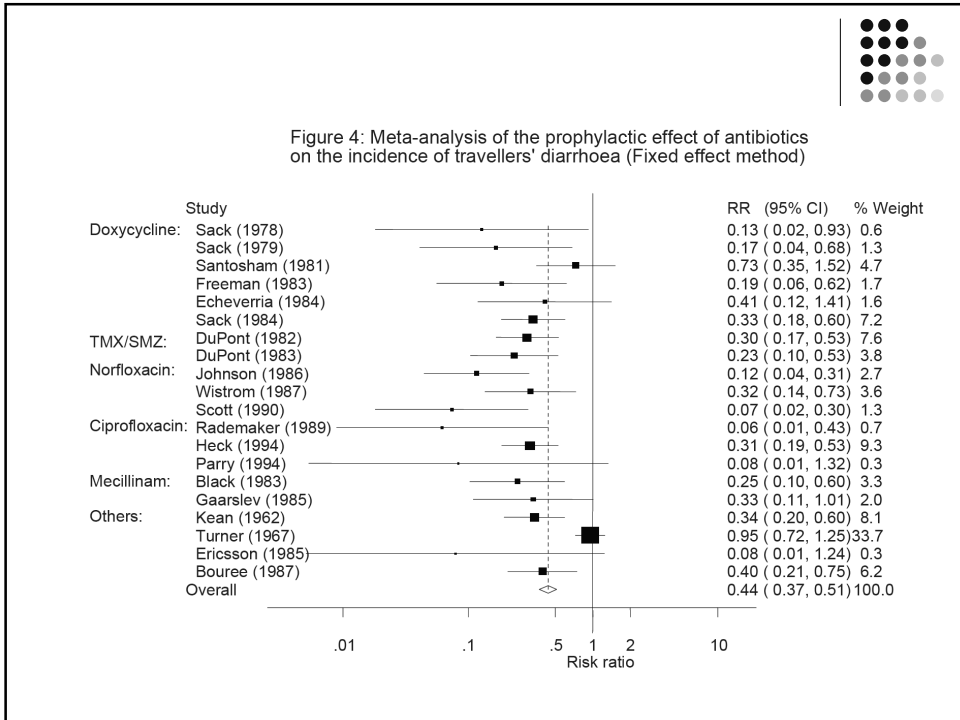
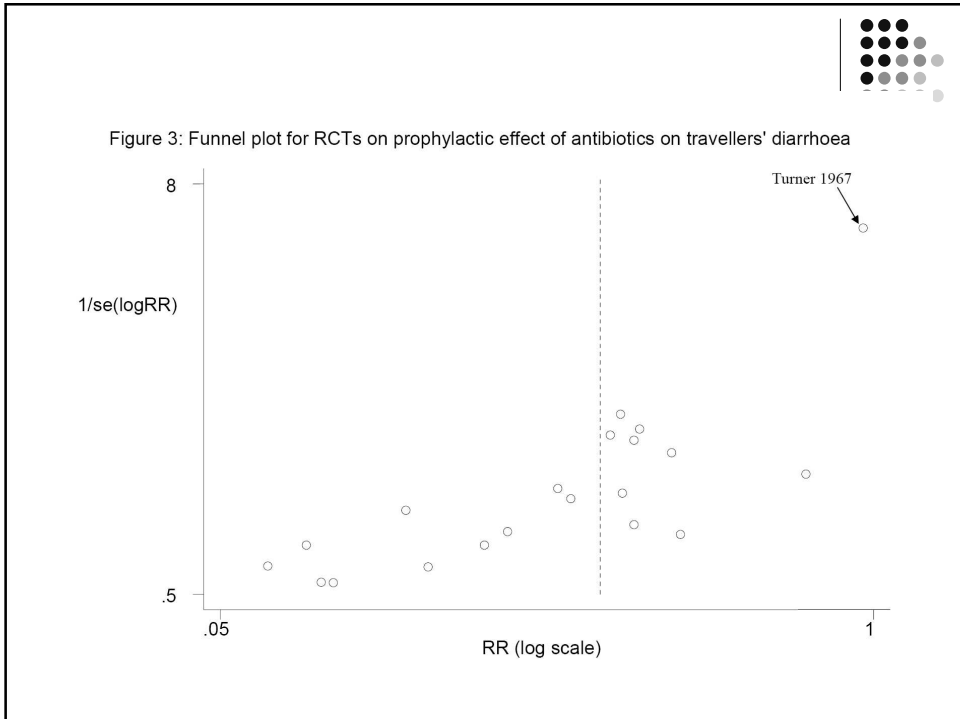




Figure 5: Meta-analysis of the prophylactic effect of doxycycline on the incidence of travellers' diarrhoea

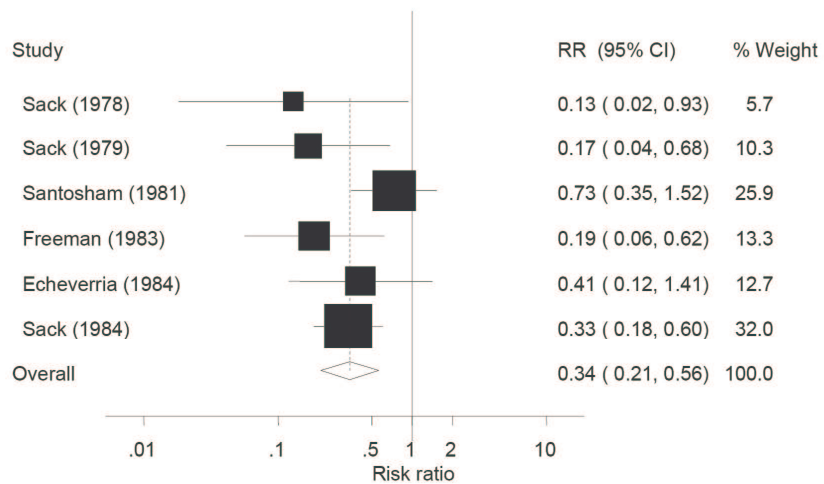


Figure 6: Meta-analysis of the prophylactic effect of TMP/SMZ on the incidence of travellers' diarrhoea

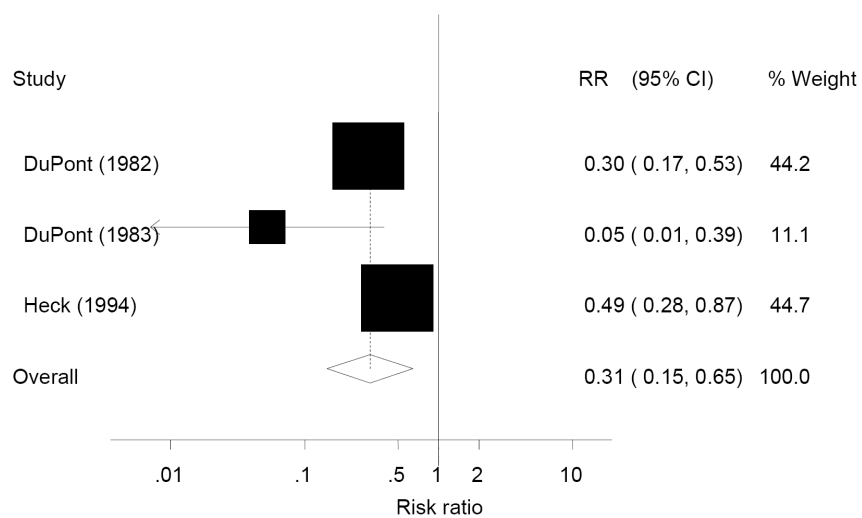


Figure 9: Meta-analysis of the prophylactic effect of mecillinam on the incidence of travellers' diarrhoea

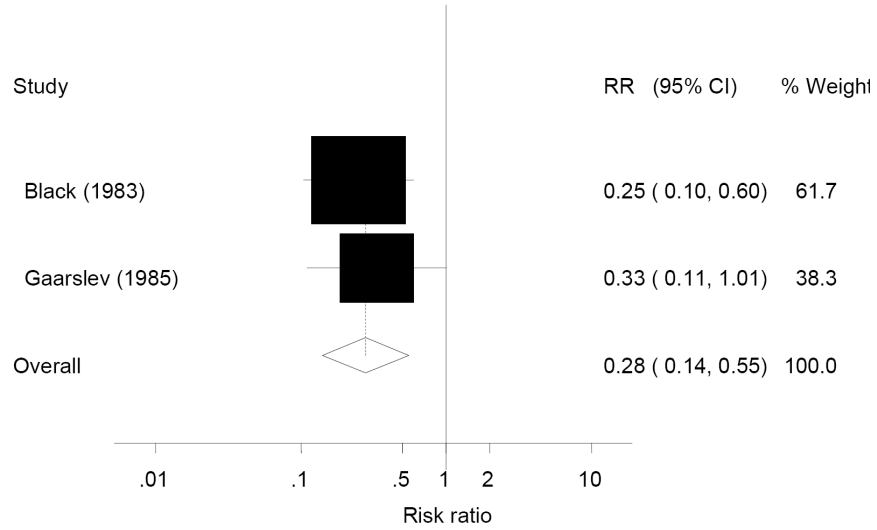


Table 4: RCTs on norfloxacin: secondary outcomes

		Johnson 1986		Wistrom 1987		Scott 1990	
		NF	PB	NF	PB		
Duration (in days) Mean (range)							
Severity (no. of stools/ day) Mean (range)							
Adverse events	Overall					4%	2.7%
Rash	Total			0/56	2/59	No significant side effects in either group	
Rash	Generalised [#]	1/56 (1.8%)	0/59 (0%)				
	Dizziness			0/56	1/59		
	Tendonitis			0/56	1/59		
	Common cold			1/56	1/59		
	Parotid enlargement			1/56	0/59		
	Constipation			1/56	1/59		
Poor/ non-compliance				1/63	0/64		

NF: norfloxacin PB: placebo

Blank entry: no relevant information reported

Requiring termination of medication



Table 15: RCTs on ciprofloxacin: secondary outcomes

		Rademaker 1989		Heck 1994			Parry 1994	
		CF	PB	CF	TMP/SMZ	PB	CF	PB
Duration (in days)								
Mean (range)								
Severity (no. of stools/ day)								
Mean (range)								
Adverse events	Serious sunburn	1/26	0/28					
	Event needing discontinuation			2 (1.8%)	8 (7%)	2 (1.7%)		
	Any events			10 (9%)	16 (14.8%)	8 (7.5%)		
	Nausea/Dizziness	4/26	1/28					
	Generalised rash [#]						1/10	0/11
	Vaginitis	2/26	0/28					
	Photosensitivity	1/26	5/26	2 (1.8%)	3 (2.8%)	2 (1.9%)		
	Acid stomach						1/10	0/11
	Constipation							
	Poor/ non-compliance						1/10	0/11

CF: ciprofloxacin TMP/SMZ: trimethoprim/sulfamethoxazole PB: placebo

Blank entry: no relevant information reported

Requiring termination of medication