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Adverse events of fluoroquinolones vs. other antimicrobials prescribed in primary care: A systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background

Fluoroquinolones (FQs) are second line antimicrobial agents. Once the decision to prescribe an antimicrobial is made, its choice should be based on both the benefits and harms. This systematic review quantifies the occurrence of common adverse events (AEs) related to FQs in relation to any other antimicrobial for any indication in primary care.

Methods

We searched randomized controlled trials from Embase, PubMed, Cochrane Central Register of Controlled Trials and CINHAL. FQs had to be administered orally, for any indication, to adults and in primary care. Data were extracted independently in standard forms in "Covidence". Pooled estimates of the intervention effects for AEs were determined by the Peto odds ratios (ORs) and 95% confidence intervals in Revman.

Results

Of the 39 studies selected, the most commonly reported AEs were nausea, vomiting, diarrhoea, headache, dizziness, and rash. A meta-analysis of 28 studies reporting AEs showed central nervous system (CNS) (OR 1.40 (1.12-1.75) p=0.003, heterogeneity (I^2) = 0%) and gastrointestinal (GI) related AEs (OR 1.20 (1.06-1.36) p=0.005, I^2=80%) were significantly associated with FQs use compared to other antimicrobials. Compared to FQs, co-amoxiclav

showed significantly more total AEs (OR 0.70 (0.54-0.90) p=0.006, I^2=78%) and GI-related AEs (OR 0.69(0.52-0.91) p=0.008, I^2=94%). Withdrawal and/or discontinuation due to drug-related AEs were higher for FQs (OR 1.19 (1.00-1.42) p=0.05, I^2=5%). Sensitivity analyses did not change these results.

Conclusion

FQs are associated with more CNS and GI-related AEs compared to other types of antimicrobial. This information is relevant to support decision making in relation to antimicrobial prescribing.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO registration number CRD42016035358

Introduction

Fluoroquinolones (FQs) are broad-spectrum antimicrobial agents that are highly effective for the treatment of a variety of infections however, their use as a first-line treatment is limited at least in part due to antimicrobial resistance (1). FQs are recommended as second-line treatment for urinary tract infections (UTIs) or respiratory tract infections (RTIs) in general practice (2-5). FQ are associated with common AEs impacting the gastrointestinal ((GI), such as nausea, vomiting, diarrhoea and abdominal pain and central nervous system (CNS) (headache, dizziness) (6-8).

Both prescriber and patient have to balance the expected benefits with the potential harms when choosing appropriate antimicrobials. However, the risk of AEs from antimicrobials are often ill-defined and reported (9, 10). In clinical practice the decision to prescribe an antimicrobial agent usually precedes the choice of a specific antimicrobial (11). The choice of the antimicrobial is therefore made relative to other antimicrobials, not against 'no antimicrobial', i.e. placebo.

This systematic review and meta-analysis assesses the risk of common AEs related to FQs used in primary care and compares their occurrence to other antimicrobials drug classes.

Methods

Design and registration

This systematic review with meta-analysis was registered with the international prospective register for systematic reviews (PROSPERO), the registration number is CRD42016035358 (12).

Data sources and search strategy

A systematic search of the literature was performed adopting Cochrane handbook methodology (13). We limited our search to PubMed, EMBASE Cochrane Central Register of Controlled trials (CENTRAL), and CINAHL from February 15th to March 5th, 2016. The search terms included were fluoroquinolones, quinolone, ciprofloxacin, cipro, norfloxacin, lexinor, noroxin, quinabic, janacin, ofloxacin, floxin, oxaldin, tarivid, levofloxacin, leflox, cravait, Levaquin, tavaric, gemifloxacin, moxifloxacin, acflox woodward, avelox, vigamox, randomized trial, randomized controlled trial, RCT, primary health care, primary care, general practice, general practitioners. Controlled vocabulary terms (MeSH term and Emtree entries) along with appropriate Boolean Operators (OR, AND, NOT) were combined to make a search strategy. A citation search was performed to identify additional relevant literature.

Study selection

This review followed the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) guidelines (14). Two authors (MT and AV) independently searched relevant literature (studies) using the above-mentioned search terms, exported to EndNoteX7 and assessed title and abstract for eligibility. The selected studies were transferred and assessed in Covidence for full-texts eligibility for final inclusion (15).

Inclusion criteria

A study was considered eligible if it was a randomised controlled trial (RCT) conducted in primary care or general practice and administered any FQ orally to adults. Any AEs, GI, CNS

or skin related (see section: outcome analysed) were included. No restrictions by publication date of the literature were applied.

Exclusion criteria

Studies excluded were: non-randomised studies, post-marketing surveillance studies, experimental trials and trials focusing on pharmacokinetics or pharmacodynamics, studies with experimental groups using antimicrobials other than FQs, FQs used for the treatment of tuberculosis, HIV, liver transplant and cystic fibrosis patients, FQs administered parenterally, studies conducted in hospitals, tertiary care, and nursing homes, in animals and studies published in languages other than English.

Assessment of risk of bias

Risk of bias was assessed independently by two authors. The risk of bias assessment includes: sequence generation, allocation concealment, blinding of the participants, incomplete outcome data and selective outcome reporting. Bias judgment (high risk, low risk, unclear risk) was done according to Cochrane collaboration's tools for assessing the risk of bias (16).

Outcomes analysed

The main outcome analysed was total AEs, GI-related, CNS-related and skin-related AEs related to FQ use compared AEs observed with other classes of antimicrobials. Included in GI were diarrhoea, nausea, vomiting, dyspepsia, abdominal pain, gastritis, loss of appetite, loose stools, heavy stomach and flatulence. CNS related AEs included dizziness, insomnia, headache, drowsiness, influence on sleep, tremor, shaking/trembling, muzzy head and asthenia. Skin-related AEs included rashes, blisters, pruritus, vaginal/vulval itching, allergy and photosensitivity. Withdrawal or discontinuation due to drug-related AEs was recorded as secondary outcome.

Data Extraction

Data was extracted independently in Covidence by MT and AV. A slight modification in the two standard forms (data extraction and quality assessment) available in Covidence was made after the first 10 papers to accommodate improved reporting of the outcome of interests. The following data was extracted from each study: detailed information about the study (settings, country, authors' details); methods (study design, groups); characteristics of the study population (sample, indication, duration of the study, age, sex); characteristics of the intervention and comparison groups (sample, dose, duration); outcomes (common AEs); and risk of bias.

Data analysis and statistical methods

Pooled estimates of the intervention effects for AEs were determined by Peto odds ratios (ORs) and 95% confidence intervals (CIs). For binary outcomes of rare events, the Peto odds ratio is the relative effect estimators of choice as it does not encounter computational problems due to zero counts in one or more cells (17, 18). Statistical heterogeneity was assessed using the Chi-square test for heterogeneity and the I^2 statistic for measuring inconsistency (larger value of I^2 indicating increasing heterogeneity). When the heterogeneity was above 25% for the primary outcome, subgroup analyses were performed by FQ agent (ciprofloxacin, moxifloxacin) including sensitivity analyses. Publication bias was assessed by examining the funnel plots. All the meta-analyses and risk of bias analyses were performed using Review Manager (Revman) V5.3 (Cochrane Collaboration, Oxford, United Kingdom). The descriptive statistics were calculated in Microsoft Excel 2010 (Microsoft Corporation, Redmond, WA, USA).

Results

Randomized controlled trial selection

A total of 233 studies were selected out of 342 extracted studies (after removal of 109 duplicates) from five databases. Of the 223 selected studies, 165 were classified as ineligible

during title and abstract screening resulting in 68 studies. A further 29 studies were identified through citation searches yielding 97 studies for full-text review. Of these, 59 were excluded because they were not a RCT (29), not performed in primary care (18), not in English (3), the administration of FQ was not oral (5) or it was combined with another treatment (1) or the intervention was behavioural (1) or prophylactic (1), comparison group was usual care (1) (Figure 1-PRISMA). Therefore, 38 studies (19-56) were included for qualitative synthesis and 30 studies (19-21, 23-30, 33-35, 37-44, 46-48, 50-52, 55, 56) for meta-analysis. In the meta-analysis specific to AEs, 28 of the 30 studies were included (19-21, 23-29, 33-35, 37-42, 44, 46, 48, 50-52, 55, 56). Nine studies (22, 30-32, 36, 45, 49, 53, 54) were excluded from this AEs meta-analysis because the study compared types of FQs (5) or dose/duration (4) and 2 studies (43, 47) did not report specific AEs in quantifiable form even though the occurrence of AEs was recorded.

Characteristics of included studies

A total of 17,735 patients participated in 38 trials published from 1974 to 2010. The duration of the study periods ranged from 4 to 25 months (not shown in table). All trials selected for meta-analysis reported AEs, but 2 studies (43, 47) didn't report number of AEs (Table 1).

The FQs assessed as treatment were: ciprofloxacin (9 studies), moxifloxacin (8 studies), norfloxacin (5 studies), ofloxacin (3 studies), levofloxacin (2 studies), enoxacin (1 study), Oxolinic acid (1 study) and Nalidixic acid (mictral) (1 study). The comparison groups were: co-amoxiclav (6 studies), trimethoprim/sulfamethoxazole (6 studies), clarithromycin (4 studies), cefuroxime axetil (3 studies), fosfomycin (3 studies), placebo (2 studies), azithromycin (2 studies) and one study each for, ampicillin, erythromycin, and doxycycline (Table 1). For the purpose of the analysis, trimethoprim was included in the subgroup trimethoprim/sulfamethoxazole (25) and the two comparisons (Ofloxacin with Cotrimoxazole and with Trimethoprim) were included separately (51).

1. Table 1: Characteristics of studies included for meta-analysis (treatment vs comparison groups)

Study ID	*Total Sample (N)*	Mean age (yrs)	Indication	Study duration	Quinolones (treatment groups)				Others (comparison groups)			
					Drugs	Daily Dose	Duration of Rx	# AEs	Drugs	Dose	Duration of Rx	# AEs
Abbas 1989	189	42	UTI	NR	Cipro	250 mg every 12 hours	5 days	2	Amoxi/Clav	250/150 mg every 8 hours	5 days	4
Adelglass 1998	216	NR	Sinusitis	NR	Levo	500 mg o.d	14 days	13	Clarithro	500 mg b.d	14 days	13
Adelglass 1999	615	39	Sinusitis	NR	Levo	Normal- 500 mg o.d creatinine clearance 50ml/min - 500 mg every 48 hrs	10 to 14 days	6	Amoxi/Clav	500/125 mg every 8 hours	10-14 days	7
Anzueto 1997	743	62	AECB	NR	Cipro	750 mg b.d	10 days	8	Clarithro	500 mg b.d	10 days	9
Anzueto 1998	2180	62	Severe AECB	12 months	Cipro	750 mg b.d	10 days	11	Clarithro	500 mg b.d	10 days	11
Bailey 1987	55	NR	Cystitis	NR	Enox	400 mg single dose	1 day	5	Trim	600 mg single dose	1 day	4
Bantz 1987	108	NR	LRTI	4 months	Cipro	250 mg every 12 hrs & o.d subsequently	4 to 12 days	2	Doxycycline	100 mg every 12 hrs & o.d subsequently	5 -12 days	2
Bleidorn 2010	80	NR	UTI	10 months	Cipro + P	250 mg b.d	3 days	26	Ibuprofen + P	400 mg three times a day	3 days	32
Boerema 1990	158	30	UTI	NR	Nor+ P	400 mg b.d	7 days	2	Fosfo+ P	3 g single dose	1 day	7
Burke 1999	457	40	Maxillary sinusitis	NR	Moxi + P	400 mg b.d	10 days	11	Cefuro Axetil	250 mg b.d	10 days	11
Chodosh 2000	926	55	ABECB	18 months	Moxi + P	400 mg o.d	10 days	11	Clarithro	500 mg b.d	10 days	11
Deabate 2000	464	NR	AECB	7 months	Moxi + P	400mg o.d	5 days	11	Azithro + P 1day	500 mg loading dose and 250 mg o.d	5 days	7
Goldstein 1985	45	48	UTI	NR	Nor	400 mg b.d.	7 to 10 days	4	TMP/SMX	160/800 mg b.d	7 - 10 days	3
Guyer 1974	60	NR	UTI	NR	Oxolin	750 mg b.d.	14 days	2	AMP	500 mg 3 times a day	14 days	0
Hoeffken 2001	675	NR	CAP	NR	Moxi	400 mg o.d	10 days	12	Clarithro	500 mg o.d	10 days	10
Hooton 1991	150	NR	UTI	NR	Oflo	200 mg o.d	3 days	3	TMP/SMX	160/800 mg b.d	7 days	4
Hooton 2005	370	NR	UTI	NR	Cipro	250 mg b.d.	3 days	6	Amoxi/Clav	500/125 mg b.d	3 days	6
Kreis 2000	401	NR	AECB	9 months	Moxi	400 mg o.d	5days	5	Azithro	500 mg loading & 250 mg o.d	5 days	5

Study ID	*Total Sample (N)*	Mean age (yrs)	Indication	Study duration	Quinolones (treatment groups)				Others (comparison groups)			
					Drugs	**Daily Dose**	**Duration of Rx**	**# AEs**	**Drugs**	**Dose**	**Duration of Rx**	**# AEs**
McCarty 1999	688	NR	UTI	NR	Cipro	100 mg b.d.	3 days	11	TMP/SMX	160/800 mg b.d	3 days	9
Nielsen 1993	119	NR	CAP	NR	Oflo	400 mg o.d	*NR*	5	Erythro	500 mg b.d	NR	5
Paparo 1994[@]	100	30	UTI	NR	Cipro	250 mg every 12 hours	5 days	*NR*	Amoxi/Clav	500 mg every 8 hours	7 days	*NR*
Rakkar 2001	471	NR	Maxillary Sinusitis	NR	Moxi	400 mg o.d	10 days	15	Amoxi/Clav	875 mg b.d	10 days	15
Reynaert 1990	32	46	UTI	NR	Nor	400 mg b.d.	3days	1	Fosfo trometamol	3g single dose	1 day	1
Sethi 2010	1404	NR	COPD	NR	Moxi	400 mg o.d, Repeat every 8 weeks for 6 course	5 days X 6 course	7	P	N/A	N/A	8
Siegert 2000	493	NR	Bacterial Sinusitis	NR	Moxi + P	400 mg o.d	7 days	5	Cefuro Axetil	250 mg b.d	10 days	5
Selvaggi 1990[@]	83	NR	UTI	NR	Nor	800 mg single dose	1 day	*NR*	Fosfo trometamol	3g single dose	1 day	*NR*
Spencer 1992	1069	48	UTI	NR	Oflo	200 mg o.d	5 days	13	TMP/SMX	160/800 mg b.d	5 days	13
Stein 1987	209	NR	UTI	NR	Nor	400 mg b.d.	3 days	13	TMP/SMX	160/800 mg b.d	10 days	13
Weis 1998	1414	44	Rhinosinusitis	4 months	Cipro	500 mg b.d.	10 days	8	Cefuro Axetil	250 mg b.d	10 days	8
Winwick 1981	58	42	UTI	NR	Mictral/Nalidixic acid	One sachet	3 days	2	AMP	500 mg three times a day	7 days	2

Note : @ No of AE not reported, o.d = Once Daily, b.d. = Twice Daily, NR = Not Reported, P= Placebo, Levo= Levofloxacin, Cipro= Ciprofloxacin, Moxi= Moxifloxacin, Enox= Enoxacin, Nor = Norfloxacin, OXolin = Oxolinic Acid, Oflo = Ofloxacin, Clarithro= Clarithromycin, Amoxi/Clav = Amoxxicilin Clavunic Acid, Azithro= Azithromycin, Doxy= Doxycycline, Cefuro Axetil = Cefuroxime Axetil, TMP/SMX = Trimethoprim/sulfamethoxazole, Trim= Trimethoprim, Fosfo= Fosfomycin, AMP= Ampicillin, Erythro= Erythromycin, UTI= Urinary Tract Infection, CAP= Community Acquired Pneumonia, LRTI= Lower Respiratory Tract Infection, COPD = Chronic Obstructive Pulmonary Disease, AECB= Acute Exacerbations of Chronic Bronchitis, ABECB = Acute Bacterial Exacerbations of Complicated Chronic Bronchitis

Reported common AEs

Nausea (25 studies), diarrhoea (22 studies), headache (17 studies), vomiting (13) and dizziness (13 studies) were the most commonly reported AEs (Figure 2). *C.difficile* associated diarrhoea was only reported in one study (48). Tendon rupture was not reported in any of the included studies.

Meta-analysis of AEs

All but two (43, 47) studies reported the total number of AEs. Comparison of FQs with other antimicrobials showed no significant difference in the total number of AEs (Figure 3). A separate meta-analysis was performed to compare effect estimates of the GI-related, CNS-related and skin-related AEs. The analysis included 20 studies for GI-related AEs (out of 28 studies reporting at least one GI-related AE), 14 studies for CNS-related AEs (out of 22 studies reporting at least one CNS-related AE) and 9 studies skin-related AEs (out of the 14 studies reporting at least one skin-related AE). The remaining studies (8 each, reporting GI and CNS-related and 5 skin-related) were removed from the meta-analysis because the FQ comparison was against another FQ. Subgroup analysis showed a higher occurrence of total AEs for FQs compared to cefuroxime axetil (OR 1.31 (1.06-1.61) p= 0.01, I^2=61%) and placebo (OR 1.85 (1.21-2.83) p=0.004, I^2=87%) but significantly lower for co-amoxiclav (OR 0.70 (0.54-0.90) p=0.006, I^2=78%) (Figure 3).

The risk of GI-related AEs (OR 1.20 (1.06-1.36) p=0.005, I^2=80%) was significantly higher among FQs users compared to other antimicrobials and specifically when compared to macrolides (OR 1.39 (1.14 -1.70) p= 0.001, I^2=71%) and cefuroxime axetil (OR 1.45 (1.14-1.85), p= 0.003, I^2=72%) (Figure 4). GI-related AEs were significantly lower for FQ when compared to co-amoxiclav (OR 0.69(0.52-0.91) p=0.008, I^2=94%).

The risk of CNS-related AEs was significantly higher among FQs users compared to other comparator antimicrobial (OR 1.40 (1.12-1.75) p= 0.003, I^2= 0%) and specifically when compared to macrolides (OR 1.49 (1.02-2.17) p=0.04, I^2=0%), cefuroxime axetil (OR 1.77(1.01-3.12) p=0.05, I^2=0%) and co-amoxiclav (OR 1.90(1.03-3.51) p= 0.04, I^2=0%) (Figure 5).

Skin-related AEs did not differ between FQs and comparator antimicrobials but the odds of FQ related AEs was significantly lower when compared to TMP/SMX (OR 0.25 (0.10-0.63) p=0.003, I^2 =0%) (Figure 6).

Meta-analysis of withdrawal/discontinuity due to AEs

The meta-analysis included 17 of the 24 studies that reported on withdrawal or discontinuation due to study drugs and 7 were excluded as these compared FQs with FQs. Overall, there was a higher risk of withdrawing/discontinuation related to FQs compared to other antimicrobials (OR 1.19 (1.00-1.42), p=0.05, I^2=5%) (Figure 7). Subgroup analysis did not indicate significant results.

Risk of bias

Nearly 40% of the studies had a higher risk of bias in blinding of outcome assessment and random sequence generation (Supplementary Figure 1). Nearly 80% of the studies had low attrition and reporting bias. Two of the studies (34, 46) were very poorly reported in all of the six domains evaluated. Symmetric funnel plots showed a very small number of studies suffered from publication bias except for those studies included in the meta-analysis of skin-related AEs (Supplementary Figure 2: funnel plot).

Heterogeneity

A high level of heterogeneity was observed in total AEs, GI-related and skin-related AEs among the included studies. For total AEs, a slight increase in heterogeneity (67% to 72%) and effect estimate (1.07 to 1.14) was observed when studies with a higher risk of bias (20,

34, 35, 39, 40, 44, 46, 51, 52, 56) were excluded. Subgroup analysis by FQ agents did not change heterogeneity. Sensitivity analysis excluding high bias studies (20, 38, 42, 55) and placebo controlled trials (27, 48) reduced the heterogeneity score (I^2) from 69% to 21% and increased the probability of total AEs from 1.07 to 1.12. For GI-related AEs, the sensitivity analysis decreased heterogeneity slightly and increased the estimated probability from 1.20 to 1.33. Heterogeneity in the included studies was not observed for CNS-related studies. For skin-related AEs, removing highly biased studies (39, 44, 52) decreased heterogeneity from 54% to 38% without a change in the estimated probability.

Discussion

Summary

In general, the total number of AEs was not significantly different for FQs compared to all other antimicrobial agents however, the occurrence of GI-related and CNS-related AEs were significantly higher with FQs compared to any other antimicrobial. Both GI- and CNS-related AEs were significantly more often observed with FQs compared to macrolides or cefuroxime axetil. AEs are generally less often observed with the use of FQs compared to TMP/SMX and fosfomycin.

Skin-related AEs were not associated with FQs use in particular but this may be due to higher publication bias observed in these studies or due to relatively less skin related AEs reported with FQs use than other groups of antimicrobials (6).

In consultations, when considering a FQ, consideration should be given to the increased risk of AEs compared to cefuroxime axetil and the lower risk compared to co-amoxiclav. If there is particular concern regarding GI-related AEs, prescribers may prefer the use of macrolides and cefuroxime axetil over FQ but prefer FQs over co-amoxiclav. Similarly, when there is a particular concern about any of the CNS-related AEs, cefuroxime axetil, macrolides and co-

amoxiclav may be favoured over FQs. Trimethoprim/sulfamethoxazole did not show any advantage or disadvantage over FQs in relation to AEs.

Comparison with existing literature

Although benefits of antimicrobials are well documented by RCTs, to our knowledge, there have been no meta-analyses to compare harms associated with different antimicrobial treatments. A previous review conducted to understand the common harms of amoxicillin only included RCTs of amoxicillin vs placebo which may not reflect routine practice (57). This systematic review and meta-analysis is the first review that compares FQ-related AEs from RCTs in primary care with other antimicrobials, which can inform the choice of antimicrobial once the decision to prescribe an antimicrobial is made.

Limitations

The primary outcome of every trial is clinical efficacy of the drugs rather than reporting of AEs, which is the foremost limitation of this review. The reported AEs in every study depended on the definition used and how information was obtained (58). Recording of AEs was not consistent. Some of the studies recorded AEs based on patient reported symptoms or patient diaries while others only report AEs after clinical or laboratory examinations. Few studies reported AEs in qualitative terms (like mild, moderate and severe) or in other subjective formats, which excluded these studies from analysis. Some of the studies were not explicit about the name and types of AEs. If explicit, only drug-related AEs that account for more than 1% of the total events were reported. This implies that less common AEs (below 1%) were missing from the analysis. Tendon rupture, a severe adverse event reported in association with fluoroquinolone use (59), may have fallen in this category. Exclusion of few studies (3) reported in language other than English is unlikely to have affected the outcome of the study.

Significant heterogeneity was observed among the included studies and subgroup analysis by FQ agent failed to provide an explanation for this heterogeneity. Subgroup analyses are observational in nature and might be confounded by other study level characteristics (60). The

presence of heterogeneity as well as some high biased trials and few studies in comparison groups affects the quality and strength of the evidence.

The AEs reported may not be fully representative of patients above 65 years of age because the median age of patients is below 65 years except in the studies reporting on COPD. Therefore, comparative analysis of AEs in relation to different doses and durations with specific reference to older patients who are often on multiple medications and comorbid conditions as well as pregnant women who are typically excluded from trials is an area for explorations in the future.

Conclusions

Despite the underreporting and selective reporting of the AEs in many trials this review provides evidence that FQs are associated with a higher occurrence of GI and CNS-related AEs compared to comparator antimicrobials. The presented results can provide useful information on the common harms of FQs during a consultation when considering the prescription of antimicrobials and support the choice of appropriate antimicrobial.

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Conflict of interest

None to declare

Author's contributions

MT and AV conceived the study, conducted the systematic literature search, study inclusion, data extraction, quality assessment, and evidence synthesis. MT performed the meta-analysis

and drafted the article. AV supported writing and analysis extensively and shaped the discussion. MC contributed in discussing, writing and finalising the manuscript.

Disclaimer

The views expressed in this article are those of the authors and not necessarily of NUIG or any other organisation.

References

1. Hammerum AM, Heuer OE. Human Health Hazards from Antimicrobial-Resistant Escherichia coli of Animal Origin. Clin Infect Dis. 2009;48(7):916-21.
2. HSE. Guidelines for Antimicrobial Prescribing in Primary Care in Ireland: Health Service Executive; 2012 [Available from: http://www.antibioticprescribing.ie/.
3. Altiner A, Wilm S, Wegscheider K, Sielk M, Brockmann S, Fuchs A, et al. Fluoroquinolones to treat uncomplicated acute cough in primary care: predictors for unjustified prescribing of antibiotics. J Antimicrob Chemother. 2010;65(7):1521-5.
4. Heidelbaugh JJ, Holmstrom H. The perils of prescribing fluoroquinolones. J Fam Pract. 2013;62(4):191-7.
5. Tandan M, Duane S, Vellinga A. Do general practitioners prescribe more antimicrobials when the weekend comes? Springerplus. 2015;4:725.
6. Stahlmann R, Lode HM. Risks associated with the therapeutic use of fluoroquinolones. Expert Opinion on Drug Safety. 2013;12(4):497-505.
7. Imhof A, Laffer R. 26 Miscellaneous antibacterial drugs. In: Jeffrey KA, editor. Side Effects of Drugs Annual. Volume 29: Elsevier; 2007. p. 253-79.
8. Owens RC, Jr., Ambrose PG. Antimicrobial safety: focus on fluoroquinolones. Clin Infect Dis. 2005; 41 Suppl 2: S144-57
9. Mandell L, Tillotson G. Safety of fluoroquinolones: An update. Can J Infect Dis. 2002;13(1):54-61.
10. CIOMS. Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals. 1998.
11. Tonkin-Crine SY, Lucy Little, Paul. Antibiotic prescribing for acute respiratory tract infections in primary care: a systematic review and meta-ethnography. J Antimicrob Chemother. 2011; 66(10):2215-23.
12. PROSPERO. International prospective register of systematic reviews. 2016 [Available from: https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42016035358.
13. Higgins JPT GS. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration; March 2011.
14. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339.
15. Covidence systematic review software. Veritas Health Innovation, Melbourne, Australia [Available from: www.covidence.org.
16. Higgins JPT AD, Sterne, JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors) Cochrane Handbook for Systematic Reviews of Interventions Version 510 [updated March 2011]. The Cochrane CollaborationMarch 2011.
17. Brockhaus AC, Bender R, Skipka G. The Peto odds ratio viewed as a new effect measure. Statistics in medicine. 2014;33(28):4861-74.

18. Deeks JJ HJ, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analysis. In: In:Higgins JPT GSe, editor. Cochrane Handbook for Systematic Reviews of Interventions. Chichester (UK): John Wiley & Sons; 2008.
19. Abbas AM, Chandra V, Dongaonkar PP, Goel PK, Kacker P, Patel NA, et al. Ciprofloxacin versus amoxycillin/clavulanic acid in the treatment of urinary tract infections in general practice. J Antimicrob Chemother. 1989; 24(2):235-9.
20. Adelglass J DeAbate CA MP, Fowler CL, LoCocco J, Campbell T. Comparison of the effectiveness of levofloxacin and amoxicillin-clavulanate for the treatment of acute sinusitis in adults. Otolaryngol Head and Neck Surg. 1999;120(3):320-7.
21. Adelglass J, Jones TM, Ruoff G, Kahn JB, Wiesinger BA, Rielly-Gauvin K, et al. A Multicenter, Investigator-Blinded, Randomized Comparison of Oral Levofloxacin and Oral Clarithromycin in the Treatment of Acute Bacterial Sinusitis. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 1998;18(6):1255-63.
22. Anonymous. Double-blind comparison of 3-day versus 7-day treatment with norfloxacin in symptomatic urinary tract infections. The Inter-Nordic Urinary Tract Infection Study Group. Scand J Infect Dis. 1988;20(6):619-24.
23. Anzueto A, Niederman MS, Haverstock DC, Tillotson GS. Efficacy of ciprofloxacin and clarithromycin in acute bacterial exacerbations of complicated chronic bronchitis: interim analysis. Bronchitis Study Group. Clin Ther. 1997;19(5):989-1001.
24. Anzueto A, Niederman MS, Tillotson GS. Etiology, susceptibility, and treatment of acute bacterial exacerbations of complicated chronic bronchitis in the primary care setting: ciprofloxacin 750 mg b.i.d. versus clarithromycin 500 mg b.i.d. Bronchitis Study Group. Clin Ther. 1998;20(5):885-900.
25. Bailey RR, Gorrie SI, Peddie BA, Davies PR. Double blind, randomised trial comparing single dose enoxacin and trimethoprim for treatment of bacterial cystitis. N Z Med J. 1987;100(833):618-9.
26. Bantz PM, Grote J, Peters HW, Stahmann J, Timm J, Kasten R, et al. Low-dose ciprofloxacin in respiratory tract infections. A randomized comparison with doxycycline in general practice. Am J Med 1987; 82 (suppl 4A):208-10
27. Bleidorn J, Gágyor I, Kochen MM, Wegscheider K, Hummers-Pradier E. Symptomatic treatment (ibuprofen) or antibiotics (ciprofloxacin) for uncomplicated urinary tract infection? - Results of a randomized controlled pilot trial. BMC medicine. 2010;8.
28. Boerema JB, Willems FT. Fosfomycin trometamol in a single dose versus norfloxacin for seven days in the treatment of uncomplicated urinary infections in general practice. Infection. 1990;18 Suppl 2:S80-8.
29. Burke T, Villanueva C, Mariano H, Huck W, Orchard D, Haverstock D, et al. Comparison of moxifloxacin and cefuroxime axetil in the treatment of acute maxillary sinusitis. Clin Ther. 1999;21(10):1664-77.
30. Chodosh S, Deabate CA, Haverstock D, Aneiro L, Church D. Short-course moxifloxacin therapy for treatment of acute bacterial exacerbations of chronic bronchitis. Respir Med. 2000;94(1):18-27.
31. DeAbate CA, Henry D, Bensch G, Jubran A, Chodosh S, Harper L, et al. Sparfloxacin vs ofloxacin in the treatment of acute bacterial exacerbations of chronic bronchitis: a multicenter, double-blind, randomized, comparative study. Chest. 1998;114(1):120-30.
32. Cox CE, Marbury TC, Pittman WG, Brown GL, Auerbach SM, Fox BC, et al. A randomized, double-blind, multicenter comparison of gatifloxacin versus ciprofloxacin in the treatment of complicated urinary tract infection and pyelonephritis. Clin Ther. 2002;24(2):223-36.
33. Deabate CA, Mathew CP, Warner JH, Heyd A, Church D. The safety and efficacy of short course (5-day) moxifloxacin vs. azithromycin in the treatment of patients with acute exacerbation of chronic bronchitis. Respir Med. 2000;94(11):1029-37.
34. Goldstein EA, ML Ginsberg,BP. Norfloxacin versus trimethoprim-sulfamethoxazole in the therapy of uncomplicated, community-acquired urinary tract infections. Antimicrob Agents Chemother. 1985;27(3):422-3.

35. Guyer BM, Whitford GM. Oxolinic acid in urinary tract infection: a multi-centre trial. Curr Med Res Opin. 1974;2(10):636-40.
36. Henry DC, Bettis RB, Riffer E, Haverstock DC, Kowalsky SF, Manning K, et al. Comparison of once-daily extended-release ciprofloxacin and conventional twice-daily ciprofloxacin for the treatment of uncomplicated urinary tract infection in women. Clin Ther. 2002;24(12):2088-104.
37. Hoeffken G, Meyer HP, Winter J, Verhoef L. The efficacy and safety of two oral moxifloxacin regimens compared to oral clarithromycin in the treatment of community-acquired pneumonia. Respir Med. 2001;95(7):553-64.
38. Hooton TM, Scholes D, Gupta K, Stapleton AE, Roberts PL, Stamm WE. Amoxicillin-clavulanate vs ciprofloxacin for the treatment of uncomplicated cystitis in women: A randomized trial. JAMA. 2005;293(8):949-55.
39. Hooton TM, Johnson C, Winter C, Kuwamura L, Rogers ME, Roberts PL, et al. Single-dose and three-day regimens of ofloxacin versus trimethoprim-sulfamethoxazole for acute cystitis in women. Antimicrob Agents Chemother. 1991;35(7):1479-83.
40. Kreis SR, Herrera N, Golzar N, Fuller H, Heyd A. A comparison of moxifloxacin and azithromycin in the treatment of acute exacerbations of chronic bronchitis. J Clin Outcomes Manage. 2000;7(12):33-7.
41. McCarty JM, Richard G, Huck W, Tucker RM, Tosiello RL, Shan M, et al. A randomized trial of short-course ciprofloxacin, ofloxacin, or trimethoprim/sulfamethoxazole for the treatment of acute urinary tract infection in women. Am J Med. 1999;106(3):292-9.
42. Nielsen PB, Husfeldt P, Egede F. Ofloxacin vs erythromycin in community-acquired pneumonia in general practice. Drugs [Internet]. 1993; 46(Suppl. 3):[421-2 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/379/CN-00250379/frame.html.
43. Paparo SB, De Rosa FG, Marangi M, Polimeni A, Bertucci P, Terzaroli P, et al. Ciprofloxacin versus amoxicillin/clavulanic acid in the treatment of urinary tract infection. Mediterranean Journal of Infectious and Parasitic Diseases. 1994;9(2):111-3.
44. Rakkar S, Roberts K, Towe BF, Flores SM, Warner J. Moxifloxacin versus amoxycillin clavulanate in the treatment of acute maxillary sinusitis: A primary care experience. Int J Clin Pract. 2001;55(5):309-15.
45. Reeves DS, Lacey RW, Mummery RV, Mahendra M, Bint AJ, Newsom SW. Treatment of acute urinary infection by norfloxacin or nalidixic acid/citrate: a multi-centre comparative study. J Antimicrob Chemother. 1984; 13 Suppl B:99-105.
46. Reynaert J, Van Eyck D, Vandepitte J. Single dose fosfomycin trometamol versus multiple dose norfloxacin over three days for uncomplicated UTI in general practice. Infection. 1990;18 Suppl 2:S77-9.
47. Selvaggi FP, Ditonno P, Traficante A, Battaglia M, Di Lorenzo V. Fosfomycin trometamol (Monuril) versus norfloxacin in single dose for adult female uncomplicated UTIs. Multicenter randomized, double-blind study. Chemotherapy. 1990;36 Suppl 1:31-3.
48. Sethi S, Jones PW, Theron MS, Miravitlles M, Rubinstein E, Wedzicha JA, et al. Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Respiratory Research. 2010;11(1):1-13.
49. Sethi S, Fogarty C, Fulambarker A. A randomized, double-blind study comparing 5 days oral gemifloxacin with 7 days oral levofloxacin in patients with acute exacerbation of chronic bronchitis Respir Med. 2004;98(8):697-707.
50. Siegert R, Gehanno P, Nikolaidis P, Bagger-SjÖBÄCk D, Ibanez JM, Hampel B, et al. A comparison of the safety and efficacy of moxifloxacin (BAY 12-8039) and cefuroxime axetil in the treatment of acute bacterial sinusitis in adults. Respir Med. 2000;94(4):337-44.
51. Spencer RC, Cole TP. Ofloxacin versus trimethoprim and co-trimoxazole in the treatment of uncomplicated urinary tract infection in general practice. Br J Clin Pract. 1992;46(1):30-3.

52. Stein GE, Mummaw N, Goldstein EJ, Boyko EJ, Reller LB, Kurtz TO, et al. A multicenter comparative trial of three-day norfloxacin vs ten-day sulfamethoxazole and trimethoprim for the treatment of uncomplicated urinary tract infections. Arch Intern Med. 1987;147(10):1760-2.
53. Trienekens TA, London NH, Houben AW, De Jong RA, Stobberingh EE. Treating acute urinary tract infections. An RCT of 3-day versus 7-day norfloxacin. Can Fam Physician. 1993;39:514-8.
54. Van Balen FA, Touw-Otten FW, de Melker RA. Single-dose pefloxacin versus five-days treatment with norfloxacin in uncomplicated cystitis in women. J Antimicrob Chemother. 1990; 26 Suppl B:153-60.
55. Weis M, Hendrick K, Tillotson G, Gravelle K. Multicenter comparative trial of ciprofloxacin versus cefuroxime axetil in the treatment of acute rhinosinusitis in a primary care setting. Rhinosinusitis Investigation Group. Clin Ther. 1998;20(5):921-32.
56. Winwick JG, Savage SJ. A comparison of a 3-day course of Mictral with a 7-day course of ampicillin in the treatment of urinary tract infection. J Int Med Res. 1981;9(1):58-61.
57. Gillies M, Ranakusuma A, Hoffmann T, Thorning S, McGuire T, Glasziou P, et al. Common harms from amoxicillin: a systematic review and meta-analysis of randomized placebo-controlled trials for any indication. CMAJ. 2015;187(1):E21-E31.
58. Lipsky BA, Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. Clin Infect Dis. 1999;28(2):352-64
59. Arabyat RM, Raisch DW, McKoy JM, Bennett CL. Fluoroquinolone-associated tendon-rupture: a summary of reports in the Food and Drug Administration's adverse event reporting system. Expert Opinion on Drug Safety. 2015;14(11):1653-60.
60. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924-6.

Figure 1: PRISMA- Selection of studies for inclusion in meta-analysis

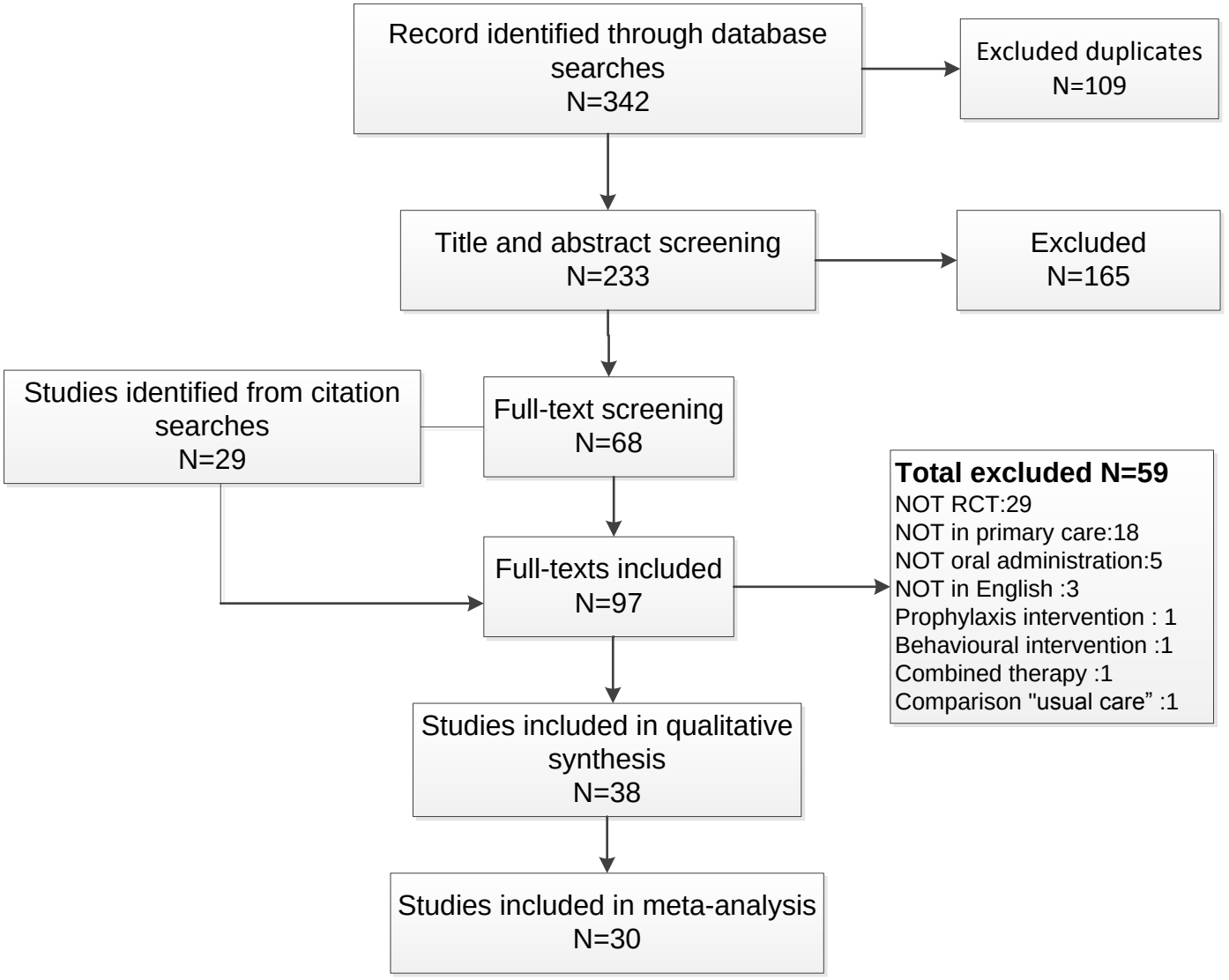


Figure 2: Reporting status of common adverse events in the included studies

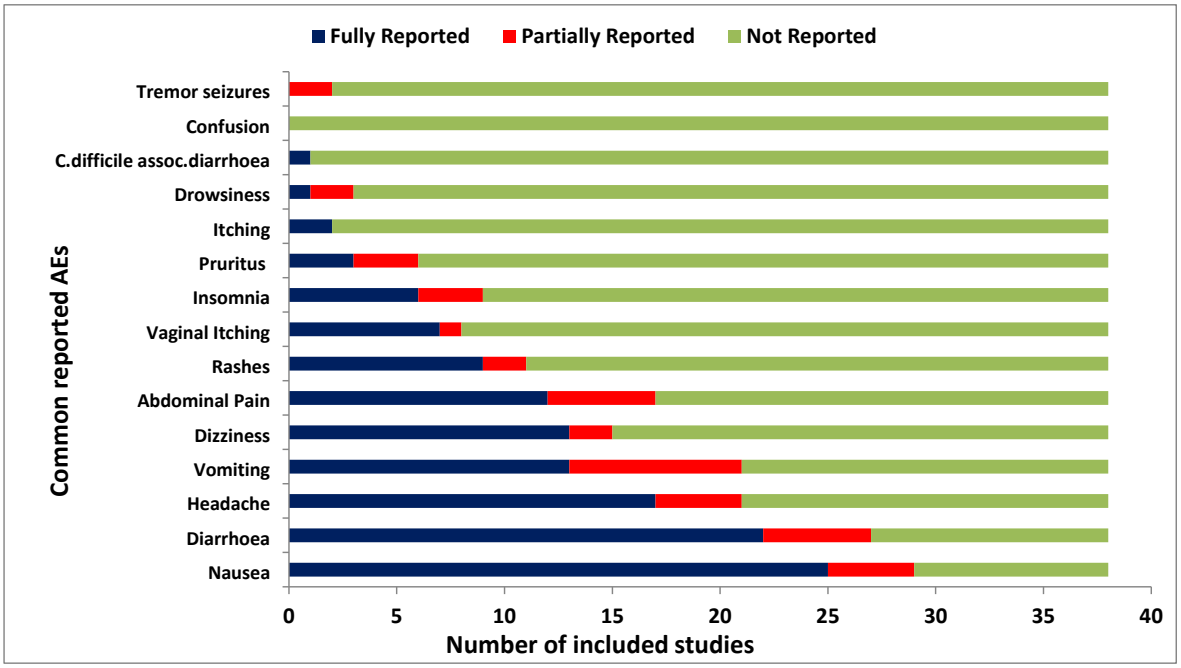


Figure 3: Meta-analysis of total AEs

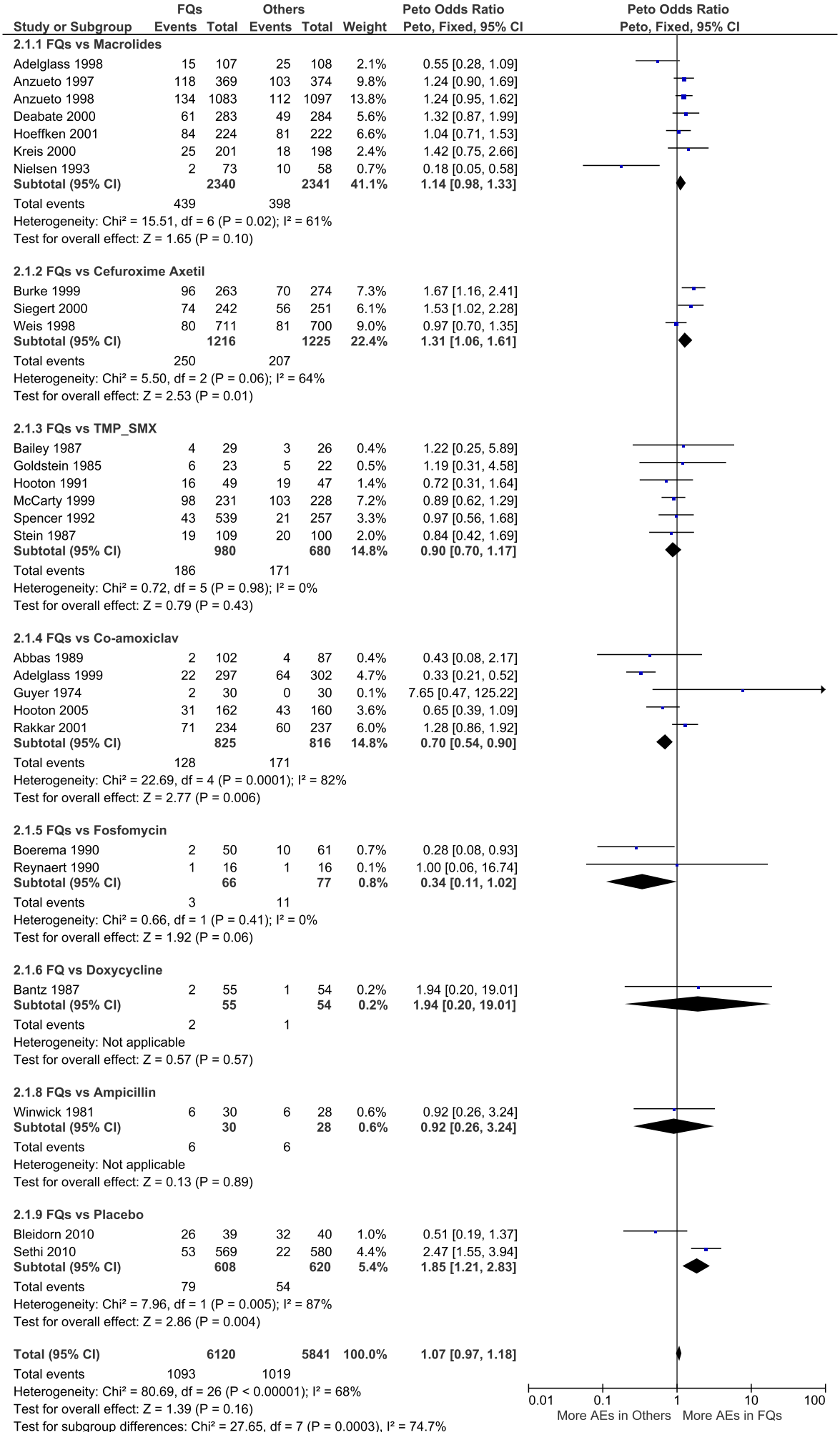


Figure 4: Meta-analysis of gastrointestinal (GI) related AEs

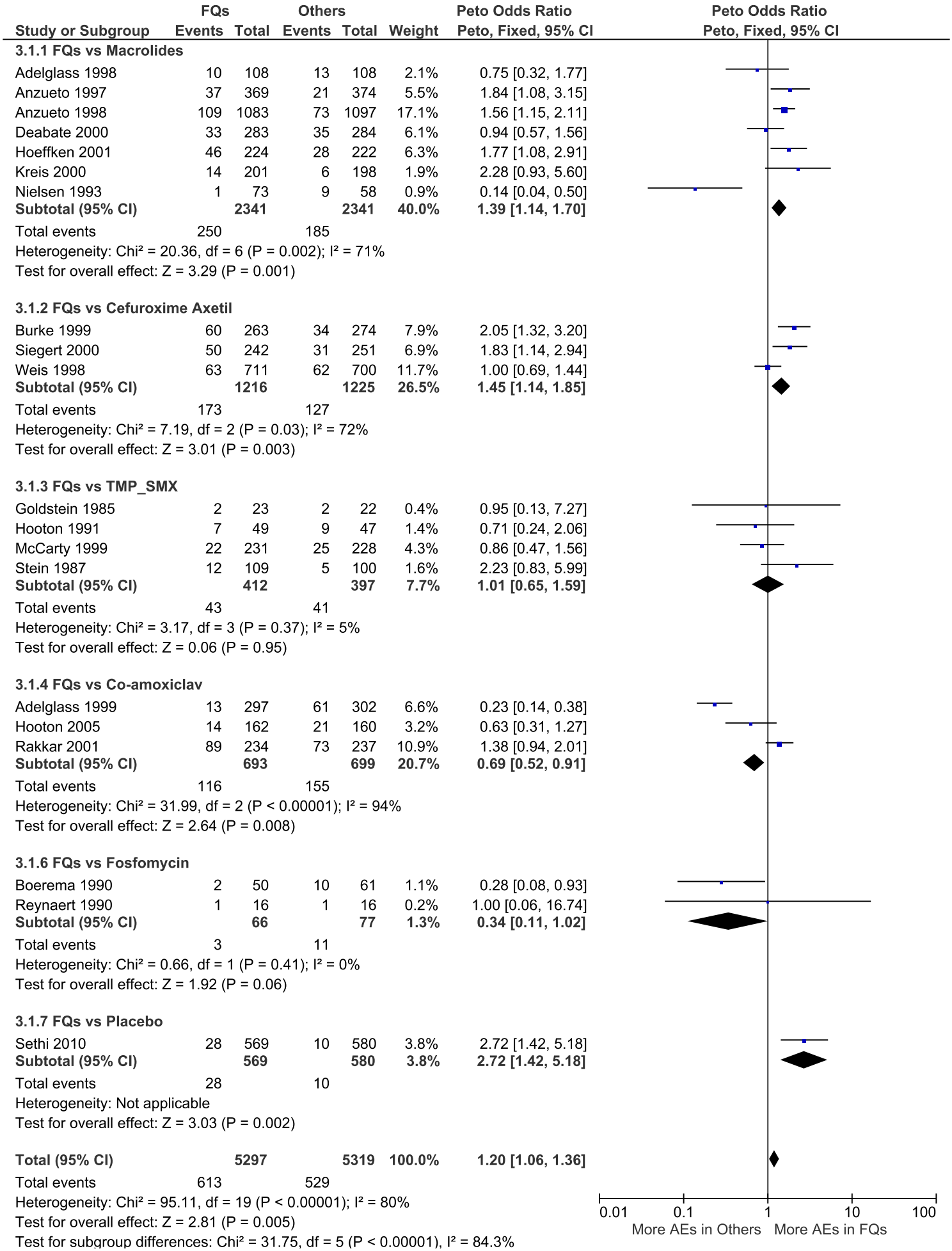


Figure 5: Meta-analysis of central nervous system (CNS) related AEs

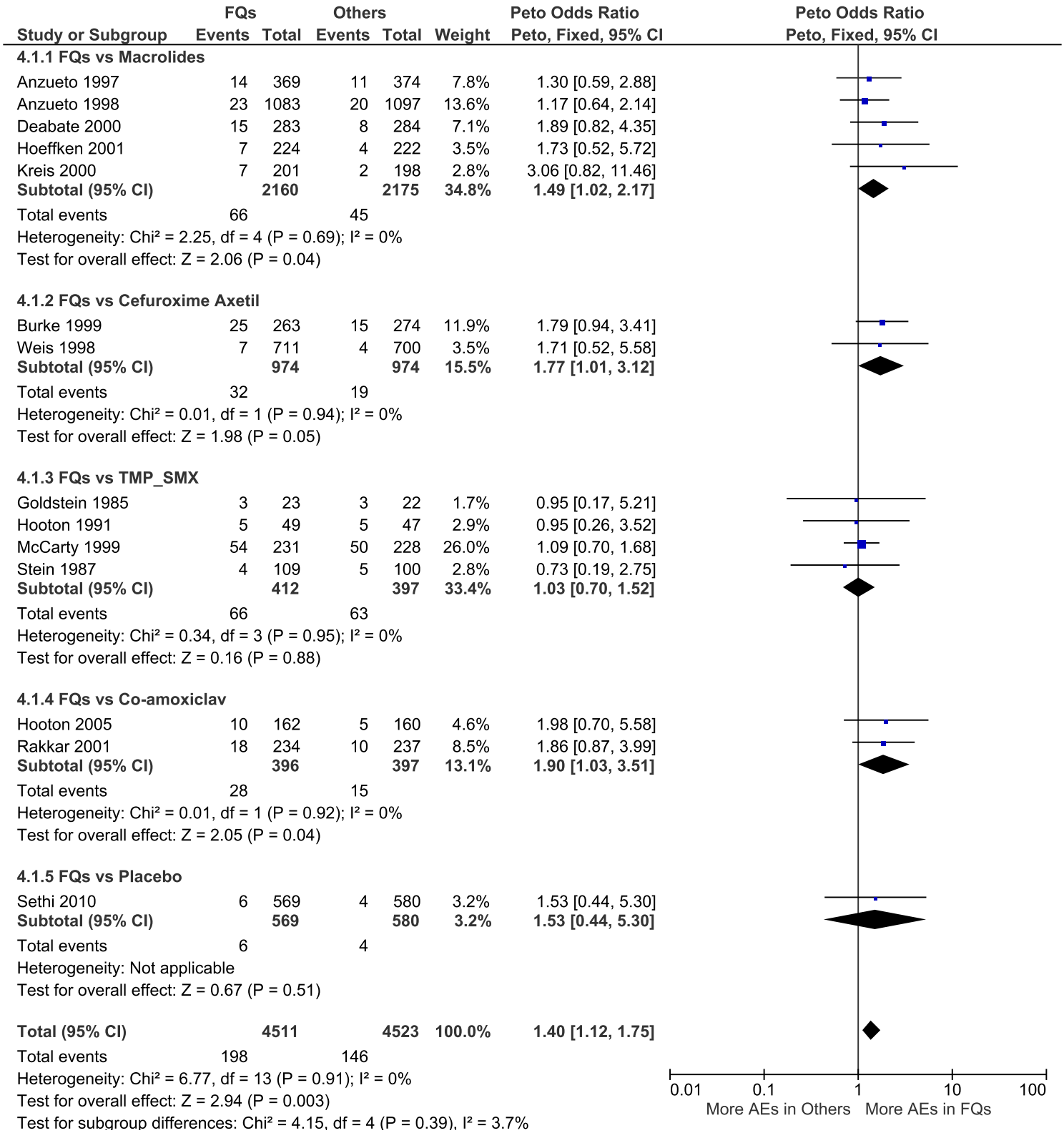


Figure 6: Meta-analysis of skin-related AEs

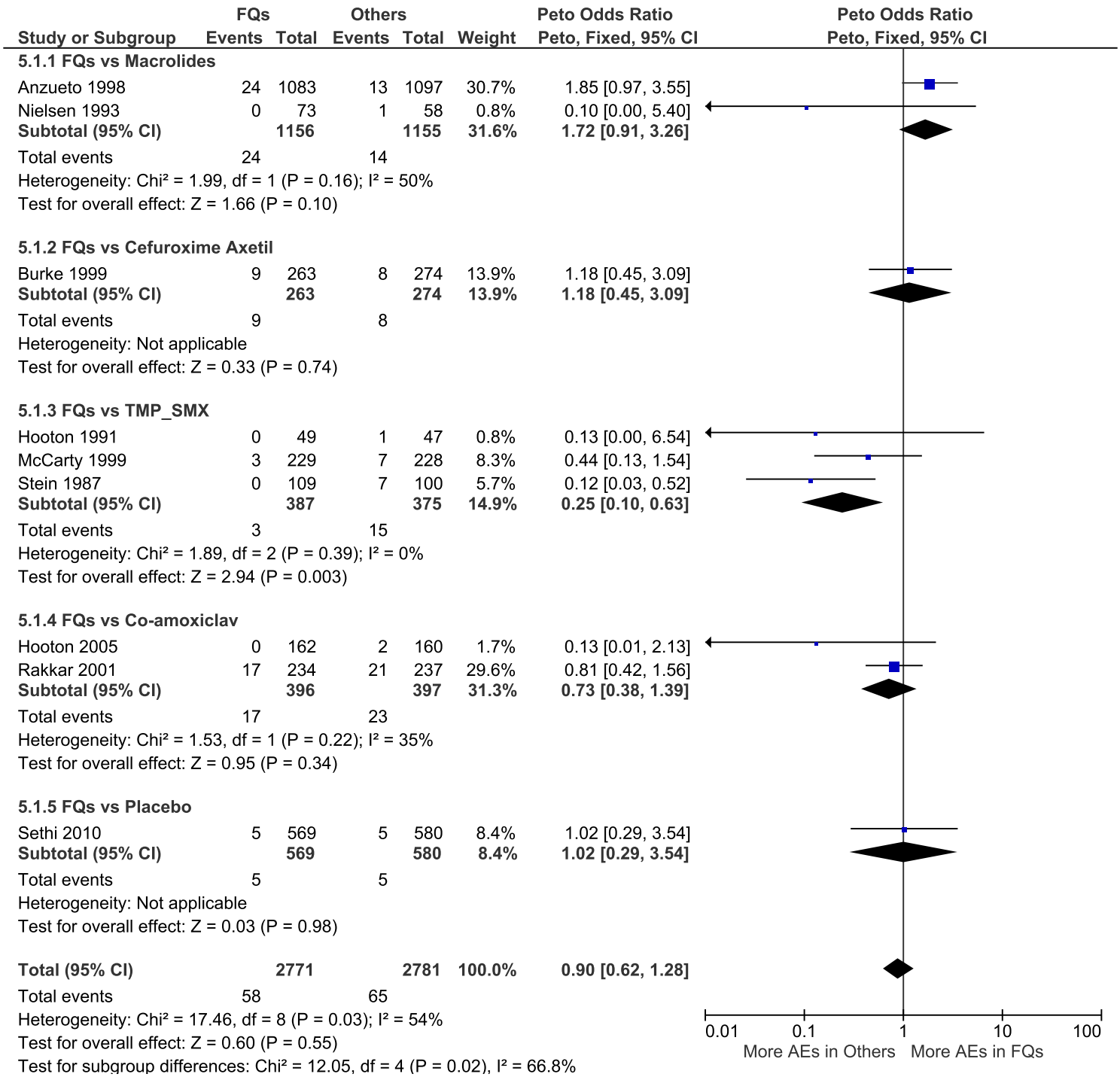
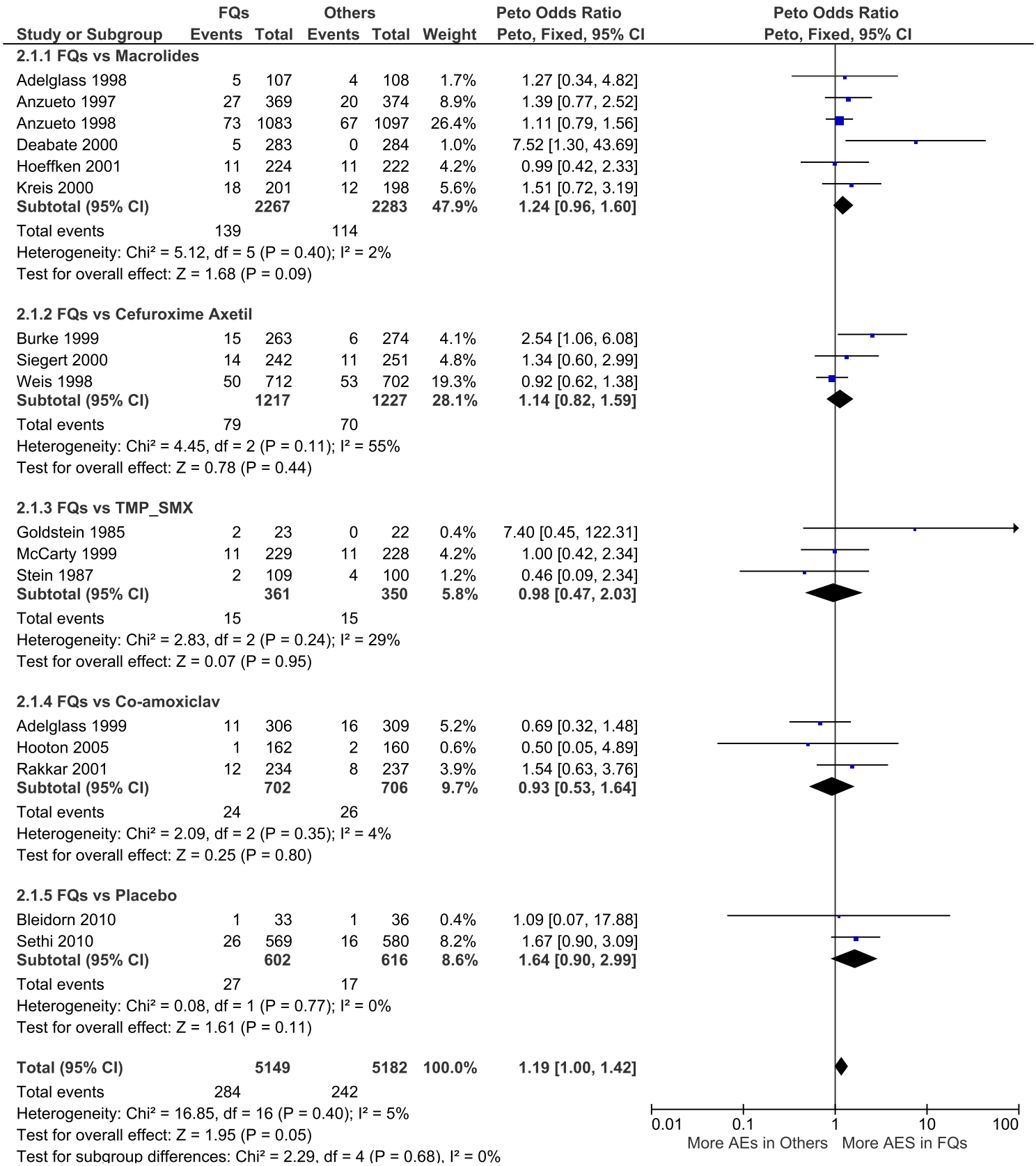
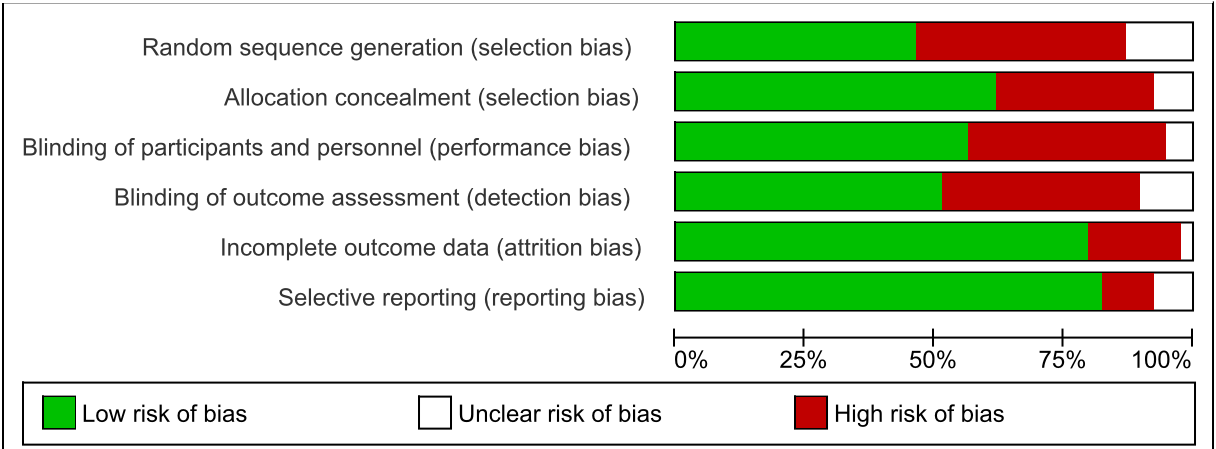


Figure 7: Meta-analysis of withdraw/discontinuity due to drug related AEs

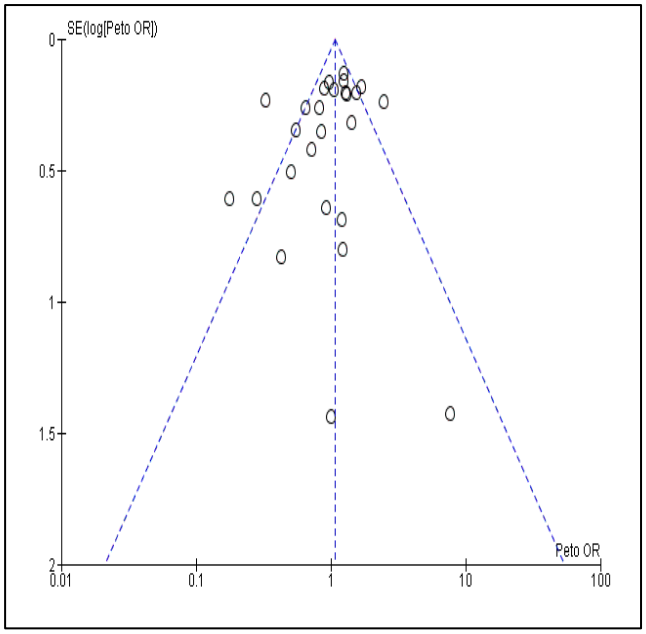


Supplementary figure 1: Risk of bias summary: review author's judgement about each methodological quality item for each included study

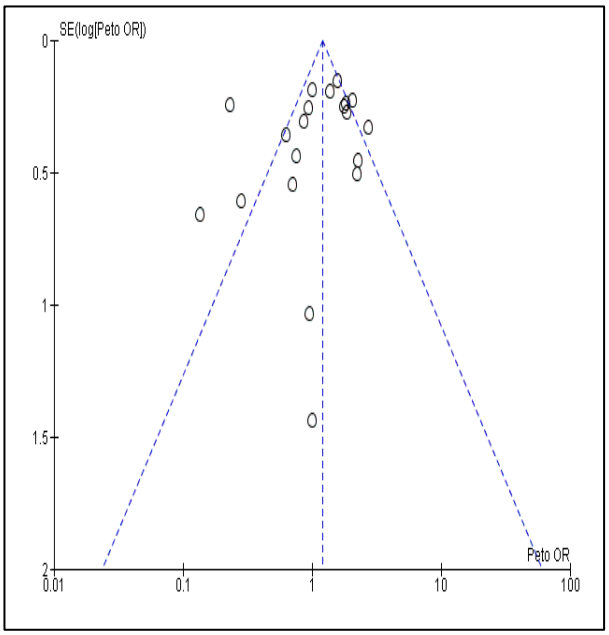


Supplementary figure 2: Funnel plot of publication bias for AEs

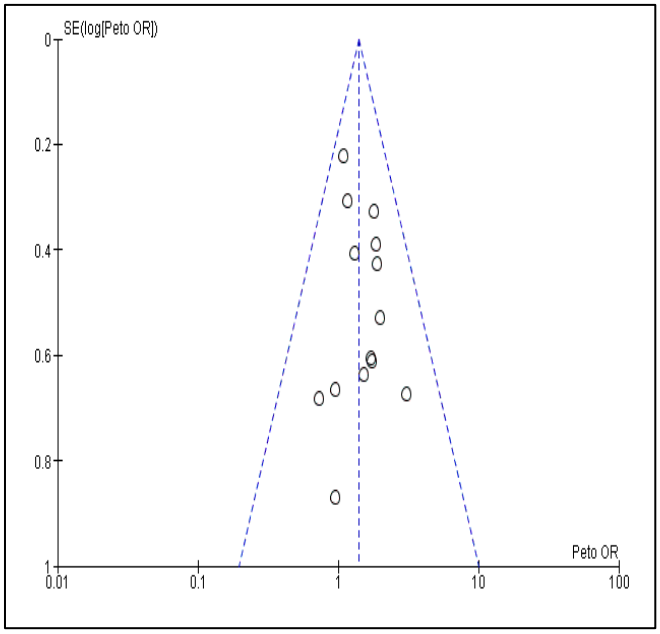
a. Total adverse events



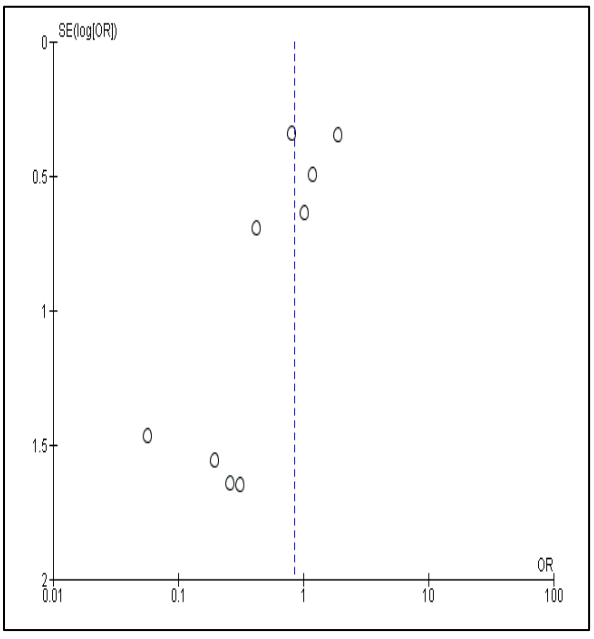
b. GI related adverse events



c. CNS related adverse events



d. Skin related adverse events



Example of searches strategy used in Pubmed

# ▲	Searches	Results
Search	((((((((((((((Gemifloxacin) OR "Factive")) OR (((((Levofloxacin) OR "leflox") OR "Cravit") OR "Levaquin") OR "Tavanic")) OR ((((((norfloxacin) OR "lexinor"[MeSH Terms]) OR "Noroxin"[MeSH Terms]) OR "Quinabic"[MeSH Terms]) OR "Janacin"[MeSH Terms]))) OR ((Ciprofloxacin) OR "Cipro"[MeSH Terms])) OR (((((Moxifloxacin) OR "Acflox"[MeSH Terms]) OR "Woodward"[MeSH Terms]) OR "Avelox"[MeSH Terms]) OR "Vigamox"[MeSH Terms])) OR ((((Ofloxacin) OR "floxin") OR "oxaldin") OR "tarivid")) OR ((fluoroquinolone) OR quinolone))) AND ((((("Primary care") OR "Primary health care") OR "general practice") OR "GPs")) AND ((((("randomized control trial") OR "randomised control trial") OR Trial) OR "controlled clinical trial")) AND Adult) NOT children) AND human) NOT animal	