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Comorbidities, exposure to medications and the risk of community-acquired Clostridium difficile infection - A systematic review and meta-analysis

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Abstract:	<p>Background: Clostridium difficile infection (CDI) has been extensively described in health-care settings; however, risk factors associated with community-acquired (CA)-CDI remain uncertain. Therefore, this study aimed to synthesise the current evidence for an association between commonly prescribed medications and comorbidities with CA-CDI.</p> <p>Methods: A systematic search was conducted in five electronic databases for epidemiological studies that examined the association between the presence of comorbidities and exposure to medications with the risk of CA-CDI. Pooled odds ratios were estimated using three meta-analytic methods. Subgroup analyses by the location of the studies and by life stages were conducted.</p> <p>Results: Twelve publications ($n=56,776$ patients) met the inclusion criteria. Antimicrobial (OR:6.18; 95%CI:3.80-10.04) and corticosteroid (OR:1.81; 95%CI:1.15-2.84) exposure were associated with an increased risk of CA-CDI. Among the comorbidities, inflammatory bowel disease (OR:3.72; 95%CI:1.52-9.12), renal failure (OR:2.64; 95%CI:1.23-5.68), haematological cancer (OR:1.75; 95%CI: 1.02-5.68) and diabetes mellitus (OR:1.15; 95%CI:1.05-1.27) were associated with CA-CDI. By location, antimicrobial exposure was associated with a higher risk of CA-CDI in the USA, whereas proton pump inhibitor exposure was associated with a higher risk in</p>

Europe. By life stages, the risk of CA-CDI associated with antimicrobial exposure greatly increased in adults aged >65 years.

Conclusions: Antimicrobial exposure was the strongest risk factor associated with CA-CDI. Further studies are required to investigate the risk of CA-CDI associated with medications commonly prescribed in the community and patients with diarrhoea who have inflammatory bowel disease, renal failure, haematological cancer, or diabetes mellitus seem to be the appropriate populations for interventional studies of screening.

1 1 Comorbidities, exposure to medications and the risk of
2 2 community-acquired *Clostridium difficile* infection - A
3 3 systematic review and meta-analysis
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10 5 Running title: Meta-analysis of risk factors for CA-CDI
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1 **ABSTRACT**

2 **Background:** *Clostridium difficile* infection (CDI) has been extensively described in health-
3 care settings; however, risk factors associated with community-acquired (CA)-CDI remain
4 uncertain. Therefore, this study aimed to synthesise the current evidence for an association
5 between commonly prescribed medications and comorbidities with CA-CDI.

6
7 **Methods:** A systematic search was conducted in five electronic databases for
8 epidemiological studies that examined the association between the presence of comorbidities
9 and exposure to medications with the risk of CA-CDI. Pooled odds ratios were estimated
10 using three meta-analytic methods. Subgroup analyses by the location of the studies and by
11 life stages were conducted.

12
13 **Results:** Twelve publications (n=56,776 patients) met the inclusion criteria. Antimicrobial
14 (OR:6.18; 95%CI:3.80-10.04) and corticosteroid (OR:1.81; 95%CI:1.15-2.84) exposure were
15 associated with an increased risk of CA-CDI. Among the comorbidities, inflammatory bowel
16 disease (OR:3.72; 95%CI:1.52-9.12), renal failure (OR:2.64; 95%CI:1.23-5.68),
17 haematological cancer (OR:1.75; 95%CI: 1.02-5.68) and diabetes mellitus (OR:1.15;
18 95%CI:1.05-1.27) were associated with CA-CDI. By location, antimicrobial exposure was
19 associated with a higher risk of CA-CDI in the USA, whereas proton pump inhibitor
20 exposure was associated with a higher risk in Europe. By life stages, the risk of CA-CDI
21 associated with antimicrobial exposure greatly increased in adults aged >65 years.

22
23 **Conclusions:** Antimicrobial exposure was the strongest risk factor associated with CA-CDI.
24 Further studies are required to investigate the risk of CA-CDI associated with medications
25 commonly prescribed in the community and patients with diarrhoea who have inflammatory

1 bowel disease, renal failure, haematological cancer, or diabetes mellitus seem to be the
2 appropriate populations for interventional studies of screening.
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1 **INTRODUCTION**

2 While the previous literature has focused largely on healthcare-associated (HA)
3 *Clostridium difficile* infection (CDI); the incidence, prevalence and severity of community-
4 acquired (CA)-CDI has also increased.² Kuntz et al.⁹ reported similar incidence rates for CA-
5 CDI (11.2 cases/100,000 person-years) and HA-CDI (12.1 cases/100,000 person-years) in the
6 USA. Moreover, the emergence of “hypervirulent” strains of *C. difficile* in the community
7 among patients previously considered to be at low risk of CDI (i.e. young adults without
8 antimicrobial exposure) clearly shows that the epidemiology of CDI is changing and that CDI
9 is no longer exclusively a nosocomial infection as it was previously considered.² It seems that
10 the risk profile of patients from the community points more to increased numbers of younger
11 patients without comorbidities, whereas, in the hospital setting, elderly inpatients with
12 multiple morbidities and exposed to polypharmacy remain most at risk.

13 Research, including through meta-analysis, has attempted to describe the risk of CDI
14 specifically in the community setting and found that clindamycin, fluoroquinolones,
15 cephalosporins, macrolides, penicillins and sulphonamides/trimethoprim are associated with
16 an increased CA-CDI risk.^{10,11} The evidence however remains uncertain as these meta-
17 analyses used the random-effects (RE) model which has been questioned for its overconfident
18 results.¹² Exposure to gastric-acid suppressive drugs^{3-5,13-15} and the presence of
19 comorbidities⁶⁻⁸ are associated with an increased risk of HA-CDI; but as with antimicrobials,
20 the evidence remains inconclusive in the community setting. Therefore, the current meta-
21 analysis was undertaken to pool the evidence from observational studies so that the
22 magnitude and direction of the association between commonly prescribed medications and
23 comorbidities with CA-CDI can be documented.

1 **METHODS**

2 **Search methodology**

3 A systematic search was undertaken in five medical and life sciences databases
4 (PubMed, Embase, Cochrane CENTRAL, CINAHL and Scopus) from their inception to
5 March 1st 2014 (Appendix 1). A related citation search was also performed; by combining the
6 systematic search with the first 20 studies from the related citation search of selected articles
7 in PubMed, a comprehensive evaluation of the published evidence can be achieved.¹⁶

8

9 **Eligibility criteria**

10 The inclusion of studies was restricted to human studies, full-text articles written in
11 English, studies reporting CA-CDI, and data presented in an extractable format. Conference
12 presentations and abstracts, studies that exclusively compared CA-CDI with HA-CDI, and
13 studies that presented data in a non-extractable format (i.e. graphical representations) were
14 excluded. Exclusions were also made for studies that investigated specific groups (i.e.
15 patients with HIV or cirrhosis) as these were not considered representative of the general
16 population.

17

18 **Study selection and data extraction**

19 Two authors (LFK and JCS) independently evaluated all the citations by titles and
20 abstracts for studies that met the eligibility criteria. Full-text version articles of all potentially
21 relevant studies were retrieved and independently assessed for eligibility. Data from the
22 included studies were then independently extracted using a predefined tool (Appendix 2) and
23 summarized in a spreadsheet by the same two authors. Extracted data were cross-checked by
24 the two authors, discrepancies during the selection of studies or data extraction were resolved

1 through discussion and consensus following independent evaluation by another author
2 (SARD).
3

4 **Quality assessment**

5 The quality of each study was assessed using a modified version of the Newcastle-
6 Ottawa quality assessment scale for case-control studies. The modified scale assessed
7 whether seven safe-guards against bias had been undertaken by the authors (i)definition of
8 cases and methods employed for *C. difficile* diagnosis, (ii) selection of CA infection,
9 (iii)control definition and the method used to rule out *C. difficile*, (iv) selection of controls
10 from the community, (v)analysis adjusted for confounders, (vi)method used for ascertainment
11 of exposure, (vii)same method used to ascertain exposure for cases and controls. The quality
12 criteria were combined into a univariate score as outlined in Table 2. The quality score was
13 rescaled between zero and 1 (called *Qi*); this was done by summing the points of each
14 component (maximum sum = 17) and dividing it by the highest sum obtained by a study
15 within the meta-analysis, ensuring that the best quality study always had a *Qi* of 1.

16
17 **Statistical analyses**

18 The outcome measure was the odds ratio (OR) for the association of CA-CDI with
19 exposure to risk factors such as antimicrobial drugs, gastric acid suppressant drugs (proton-
20 pump inhibitors [PPI] and histamine-2-receptor antagonists [H2RAs]), non-steroidal anti-
21 inflammatory drugs (NSAIDs), aspirin, steroids and the presence of comorbidities. The OR
22 was pooled using three meta-analytic models. This was justified because some have
23 expressed skepticism regarding the appropriateness of the conventional RE model¹⁷ due to its
24 documented underestimation of the statistical error, which leads to overconfident results.^{12,18-}
25 ²⁰ The other two models that were used were the quality-effects (QE) model,^{21,22} and a novel

1 method, the inverse variance heterogeneity (IVhet) model.²³ The QE model uses the Qi to
2 redistribute the inverse variance weights in favor of the studies with higher methodological
3 quality and thus studies that provided higher quality of evidence contributed with a higher
4 weighting towards the overall effect size.²² This use of quality information via a univariate
5 score does not imply that quality deficiencies can quantify bias. Rather, the quality score is
6 used to rank studies by methodological rigor and this rank is then linked with a synthetic bias
7 variance that is added to the random error variance.²¹ The other model used was the IVhet
8 model that does not require input of quality information so is less rigorous than the QE
9 model.²³ Both of the latter models use a quasi-likelihood based variance structure without
10 distributional assumptions and thus have coverage probabilities for the confidence interval
11 (CI) well above the nominal level.²³ The reported results are based on the IVhet model;
12 results using the QE and RE models have been presented for comparative purposes.

13 Statistically significant heterogeneity was defined as tau-squared statistic (τ^2) >0,
14 Cochran's Q test p-value <0.1 or I^2 index >0%. A sensitivity analysis was conducted to
15 determine the degree to which the findings vary depending on the geographical location
16 where the studies were conducted (America or Europe) and life stages of the participants
17 (children aged <2 years, children and adults, adults or adults aged >65 years).

18 The *Doi* plots were used to evaluate the presence of publication bias, which plots the
19 lnOR against the absolute value of the z-score for each study.²⁴ Funnel plots were not
20 reported as the graphical assessment of publication bias requires at least 10 studies and even
21 then can be difficult to interpret.²⁵

22 The results of the analyses were considered statistically significant if the 95%CI did
23 not include zero. Analyses were conducted using MetaXL version 2.0 (EpiGear Int Pty Ltd;
24 Brisbane; Australia; www.epigear.com).

1 **RESULTS**

2 **Yield of search strategy**

3 The initial search identified 1,663 publications. An additional 124 publications were
4 retrieved throughout the related citations search. After excluding duplicate citation 1,481
5 publications remained. After screening the publications by title and abstract, 1,388 were
6 excluded. Full-text review of 93 publications was conducted, 12 met the eligibility criteria
7 and were selected for the meta-analysis (Figure 1).

8 There was overlap in subjects between 2 sets of publications. Two publications (Dial
9 et al., 2005²⁶ and Delaney et al., 2007²⁷) used data from the UK General Practice Research
10 Database (GPRD) between 1994-2004 and a positive toxin test result for CDI as case
11 definition to assess the risk of CA-CDI with antimicrobial exposure. Although, Dial et al.,
12 2006²⁸ also used data from the UK GPRD, the authors reported that there was no overlap
13 between this and Dial et al., 2005²⁶ as they used different case definitions for CDI.²⁸
14 Additionally, two publications (Soes et al., 2013a²⁹ and Soes et al., 2013b³⁰) reported results
15 from the same Danish cohort. Therefore, Delaney et al., 2007²⁷ and Soes et al., 2013b³⁰ were
16 excluded from the analyses.

17

18 **Characteristics of the included studies**

19 Twelve publications were included in the meta-analysis. Two publications reported
20 results divided into groups. Kutty et al.³¹ presented the results of two populations (Veterans
21 Affairs and Durham County residents), whereas Soes et al.^{29,30} presented the results divided
22 into two age groups (<2 years and ≥2 years). Among the included studies, seven were case-
23 control studies and five were nested case-control studies. The studies included covered more
24 than 35 years of research and 56,776 patients in 6 different countries. The age of the
25 participants ranged between 3 months and 101 years. Only one study^{29,30} used exclusively

1 positive *C. difficile* culture in the case definition and another study³² used a combination of *C.*
2 *difficile* culture or toxin test results in the case definition. All studies evaluated exposure to
3 medication and presence of comorbidities for at least 6 and 12 weeks prior to the index date,
4 respectively (Table 1). The quality score of the studies ranged from 9 to 13 out of 17 (Table
5 2).

6

14 7 Quantitative synthesis

15 8 When examining the association between drug exposures and CA-CDI using the
16 IVhet model, exposure to antimicrobials (OR:6.18; 95%CI: 3.80-10.04) and corticosteroids
17 (OR:1.81; 95%CI: 1.15-2.84) were significantly associated with CA-CDI. Gastric acid-
18 suppressing drugs (PPIs and H2RAs; OR:1.58; 95%CI: 0.90-2.75), PPIs (OR:1.61; 95%CI:
19 0.90-2.88) and H2RAs (OR:1.24; 95%CI: 0.76-2.01) were not associated with increased odds
20 of CA-CDI. Statistically significant associations were found between CA-CDI and the
21 presence of inflammatory bowel disease (IBD; OR:3.72; 95%CI: 1.52-9.12), renal failure
22 (OR:2.64; 95%CI: 1.23-5.68), leukemia or lymphoma (OR:1.75; 95%CI 1.02-3.03) and
23 diabetes mellitus (OR:1.15; 95%CI: 1.05-1.27; Table 3).

24 17 Visual inspection of the forest plots, Cochran's Q test (Appendix 3), τ^2 (results not
25 shown) and I^2 index (Table 3 and Appendix 3) confirmed heterogeneity across studies,
26 except for exposure to tetracyclines or aspirin and the presence of chronic obstructive
27 pulmonary disease (COPD), diabetes mellitus or diverticular disease.

28 21

29 22 Sensitivity analysis

30 23 A sensitivity analysis was only possible for antimicrobial and PPI exposure because
31 of the small number of studies in the other categories. When stratifying the studies by
32 geographic location, the sensitivity analysis showed that antimicrobial exposure had a greater
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1 association with CA-CDI in the USA (OR:9.16; 95%CI: 5.47-15.34) compared to European
2 countries (OR:4.54; 95%CI: 2.68-7.70; Appendix 4.1). Conversely, exposure to PPIs had a
3 stronger association with CA-CDI in Europe (OR:2.56; 95%CI: 1.40-4.71) compared to the
4 USA (OR:1.12; 95%CI: 0.64-1.95; Appendix 4.2).

5 The subgroup analysis by life stages showed that older adults (>65 years) had the
6 highest risk (OR:10.16; 95%CI: 5.56-18.58) of CA-CDI when exposed to antimicrobials
7 followed by children and adults (OR:5.98; 95%CI: 4.67-7.67; Appendix 4.3). When exposed
8 to PPIs, adults had the highest risk of CA-CDI (OR:2.78; 95%CI: 2.02-3.81; Appendix 4.4).

10 **Publication bias**

11 On visual inspection of the *Doi* plots, there was gross asymmetry for some exposures
12 suggesting publications bias in relation to cephalosporins, fluoroquinolones, macrolides,
13 penicillin, presence of congestive heart failure and gastro-esophageal reflux disease. The bias
14 was towards selective publication that reported medication exposure and presence of
15 comorbidities as risk factors for CA-CDI (Appendix 3).

1 **DISCUSSION**

2 Exposure to antimicrobials remained the strongest risk factor associated with CA-
3 CDI. No statistical significance was observed in the majority of the analyses by antimicrobial
4 class, likely due to the largest study (Lowe et al.³³) reporting ORs close to the null value.
5 However, point estimates confirmed a trend towards an association with CA-CDI regardless
6 of antimicrobial class exposure. These observations corroborated previous findings published
7 by Deshpande et al.¹⁰ and Brown et al.¹¹ which suggested an increased risk of CA-CDI as a
8 result of antimicrobial exposure.

9 Despite the increasing evidence in the past decade with respect to increased risk of
10 HA-CDI after exposure to PPIs^{3,4,13-15} or H2RAs,^{5,26} no significant association was observed
11 in the community setting. The observed difference between the risk of CA-CDI and HA-CDI
12 with gastric-acid suppressive medication can be explained by the overutilization of these
13 medications in healthcare facilities.³⁴ Exposure to corticosteroids was associated with CA-
14 CDI. In contrast to antimicrobials which disrupt the normal gut microbiome facilitating the
15 proliferation of *C. difficile*,³⁵ and gastric-acid suppressive medication that may allow survival
16 of vegetative forms of *C. difficile*,³⁶ a plausible biological mechanism for the observed
17 association could be the negative impact of corticosteroids on the gastrointestinal mucosal
18 integrity.³⁷

19 Previous studies found that gastrointestinal comorbidities such as IBD⁶ and cirrhosis⁸
20 were associated with a worse prognosis in patients with CDI. Similarly, congestive heart
21 disease, chronic pulmonary disease, renal failure and malignancies were also associated with
22 higher mortality rates among inpatients with CDI.⁷ Among the comorbidities examined in
23 this meta-analysis, IBD was the strongest risk factor for CA-CDI followed by renal failure
24 and haematological cancers. In patients with the described comorbidities, early identification
25 and prompt treatment of CA-CDI may reduce mortality rates. The associations found

1 between CA-CDI and comorbidities may be confounded by medication exposure given that
2 polypharmacy is common among patients with multiple comorbidities. Furthermore, the
3 heterogeneous definition of CA-CDI across the studies (i.e. not hospitalized the year prior to
4 the index date versus not hospitalized 6 weeks prior to the index date) may also be a source of
5 misclassification between CA- and HA-CDI, considering that patients with multiple
6 comorbidities are more likely to be admitted to hospitals.
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9 The sensitivity analyses suggested that risk of CA-CDI with exposure to antimicrobial
10 and PPI differed between Europe and America. The observed difference might be due to the
11 dissimilar prescription of antimicrobials³⁸ and/or the presence of different strains of *C.*
12 *difficile* in Europe and America.³⁹ Similarly, the risk of CA-CDI with exposure to
13 antimicrobials and PPI varied among the life stages. These findings were consistent with
14 Sandora et al.⁴⁰ who reported a negative correlation between age and CA-CDI among
15 paediatric populations and with Lessa et al.⁴¹ who reported a higher incidence of CDI among
16 patients at both extremes of life (1-4 years of age and above 65 years of age). In the past two
17 decades, a 12-fold increased incidence of CA-CDI among the paediatric population⁴² and
18 numerous outbreaks in long-term-care facilities⁴³ have been reported, indicating that infants,
19 toddlers and older adults should be considered at high risk of CA-CDI.
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22 Although a comprehensive systematic search for studies was carried out, publication
23 bias could have resulted in more positive associations being published such as those between
24 CA-CDI and exposure to cephalosporins, fluoroquinolones, macrolides, and penicillins and
25 the presence of congestive heart disease and GERD. The actual risks attributable to these risk
26 factors could be less than what we have reported. Nevertheless, heterogeneity across studies
27 could also result in effect size asymmetry and this represents an alternative explanation to
28 selective publication of positive results.
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Recent meta-analyses have investigated the risk of CDI associated with exposure to antimicrobials^{3,10,11} and gastric acid suppressant drugs^{3-5,13} using the widely adopted RE model.¹⁷ However, it is known that the coverage probability of the RE CI can be substantially below the nominal level of 95 percent and thus does not adequately reflect the statistical error especially when there are few included studies.^{12,23,44} By underestimating the statistical error, the RE model produces tight CIs which potentially causes overconfident results prone to type I error. Moreover, the assumption of normally distributed random effects is not easily verified.⁴⁴ The use of a moment-based common variance¹⁷ within this model is in the redistribution of the weights from larger to smaller studies.¹⁹ The QE and IVhet models have both been created to do away with the problems that affect the RE model and both have coverage of the CI at or above the nominal level.²³ As an example, with the clindamycin pooled estimates, the IVhet model distributed the weight (83.5%) toward the biggest study (Lowe et al.³³; n=13,692). The QE model took into account the extra information regarding the quality of the studies and penalized the biggest study by reducing the assigned weight (from 83.5% to 69.0%) because it had the lowest quality score; whereas the RE model redistributed the weights by equalizing weights (by transferring from big to small studies) and thus, it gave a similar weight percentage to the biggest study (Lowe et al.³³; n=13,692; weight 25.85%) and the smallest study (Vesteinsdottir et al.⁴⁵; n=333; weight 23.98%). Moreover, the RE model produced a tighter CI (with a statistically significant result) but its coverage may have been under the nominal level and thus may not capture the true value of the effect (Appendix 3.3).

Several limitations of the present meta-analysis were noted. Kuntz et al.⁹ and Marwick et al.³² reported a positive relationship between time exposed to antimicrobials and CA-CDI. However, the small number of studies precluded a subgroup analysis by time of exposure to antimicrobials. All studies included in this meta-analysis were conducted in

1 Northern Hemisphere countries. A recent study has described a different seasonal pattern of
2 CDI in Australia which remains largely unexplained.⁴⁶ The epidemiological patterns of *C.*
3 *difficile* transmission and infection may differ between hemispheres and thus generalizability
4 of the findings to southern hemisphere countries is limited.

5 In conclusion, while antimicrobial use remains the dominant risk factor for CA-CDI,
6 corticosteroid use should also be considered as an important risk factor. Given these are
7 commonly prescribed medications in the community, the attributable risk of CDI due to
8 exposure may be high and thus further research is warranted. In addition, patients with IBD,
9 renal failure and haematological cancer are at higher risk of CA-CDI, making them
10 appropriate populations for interventional studies of screening for *C. difficile*.

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6 **TABLES AND FIGURES**
7

8 **Table 1.-** Characteristics of the studies included in the meta-analysis.
9

10 Author,	11 Data source	12 Study period	13 Study design	14 Study	15 Age, years	16 Male, %	17 Community-	18 Case	19 Control	20 Matching	21 Exposure to	22 N
12 publication				population	case/control	case/control	acquired	definition	definition		medication	case/control
13 year					mean (SD)			definition			or presence	
14					years						of	
15											comorbidity,	
16											days prior	
17											index date	
18 Dial et al.	GPRD, UK	1 Jan 1994 -	Case-control	≥2 years	71.0(16) /	35 / 42	Not	Clinical	No clinical	Practice	Gastric acid	1233 / 12330
19 2005 ²⁶		31 Dec 2004		registered in	70.8(16)		hospitalized	diagnosis or	diagnosis nor	location, age	suppressant,	
20 &				a general			the year prior	positive toxin	positive toxin	(±2 years)	antimicrobial	
21 Delaney et al.				practice in			to the index	test results	test result for		s, NSAID,	
22 2007 ²⁷				the UK and			date	for CDI	CDI		aspirin, 90	
23				≥18 years old							Comorbidity,	
24											720	
25 Dial et al.	GPRD, UK	1 Jan 1994 -	Case-control	Registered in	65.0 (19.6) /	36.6 / 41.5	Not	Prescription	No	Practice	Gastric acid	317 / 3167
26 2006 ²⁸		31 Dec 2004		the GPRD	64.9 (19.5)		hospitalized	of oral	prescription	location, age	suppressant,	
27				without			the year prior	vancomycin	for oral	(±2 years)	antimicrobial	
28				clinical			to the index	therapy	vancomycin		s, 90	
29				diagnosis or			date				Comorbidity,	
30				positive toxin								
31												
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Dial et al. 2008 ⁴⁷	Régie de l'assurance maladie du Québec and the MED-ECHO, Canada	1996 - 2004	Nested case-control	Hospitalized during the study period, ≥65 years old and have not received metronidazol e or oral vancomycin 90 days prior to the index date	79.8 (6.8) / 77.5 (6.3)	33.7 / 40.9	Not admitted to any type of institution in the 90-day period before the index date	First hospital admission diagnosis of CDI during the first hospital admission	No primary diagnosis of CDI during the first hospital admission	Unmatched Index date	Antimicrobia ls, 45	836 / 8360
Kuntz et al. 2011 ⁹	The University of Iowa Wellmark Data Repository, USA	1 Jan 2004 - 31 Dec 2007	Nested case-control	Patients with at least 1 year of health care facility and pharmacy insurance	NR / NR	39.47 / 48.36	No history of long-term care facility 6 months or hospitalized 12 weeks before the	Primary or secondary diagnosis of CDI before the index date	No diagnosis of CDI on or before the index date	Unmatched Index date	Gastric acid suppressant, antimicrobial s, 180	304 / 3040

index date													
1	Kutty et al.	VA infection	Jan 2005 -	Case-control	≥18 years old	VA: 62 (38- 85) / 64 (38- 86) *	VA: 88 / 96	No history of healthcare	Nonformed stool	Outpatients	Unmatched	Gastric acid	VA: 36 / 108
2	2010 ³¹ †	control	Dec 2005					Durham	exposure	specimen	clinical	suppressant,	
3		database and						County: 42 /	within 8	with positive	diagnosis of	antimicrobial	Durham
4		Surveillance						Durham	29	weeks of the	toxin test	diarrhea or	
5		database of						County: 61		index date	results for	positive toxin	Comorbidity,
6		the Duke						(20-101) / 55			CDI	test results	NR
7		University						(22-87) *				for CDI	
8		Hospital											
9		network,											
10		USA											
11	Lowe et al.	Ontario Drug Benefit	1 Apr 2002 - 31 Mar 2005	Nested case-control	≥66 years old exposed to antimicrobial	78.7 (7.2) / 78.0 (6.8)	59.8 / 60.5	Not hospitalized during the 90-day period prior to the index date nor Discharge	Hospitalized with diagnosis of CDI (ICD-10 code A04.7)	Outpatient	Index date, sex, age (± 1 year), s prescribed	Gastric acid suppressant, antimicrobial	1389 / 12303
12		Program, Canadian Institute for Health Information Discharge Abstract Database, The Ontario Health Insurance			s								
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Plan Database and The Ontario Registered Persons Database, Canada

Marwick et al.	The Health	1 Nov 2008 -	Nested case-	≥ 65 year old	81 (8.9) / 81	27.4 / 27.4	Not	Diarrhea and	NR	Sex, age (± 1)	Gastric acid	62 / 620
2013 ³²	Information	31 Oct 2009	control		(8.9)		hospitalized	a positive		years),	suppressant,	
	Center at the						during the	toxin test			antimicrobial	
	University of						120-day	results for			s, 180	
	Dundee,						period prior	CDI or				
	Scotland						to the index	positive <i>C.</i>			Comorbidity,	
								<i>difficile</i>			360	
								culture and				
								pseudomemb				
								ranous colitis				
Naggie et al.	Duke	1 Oct 2006 -	Case-control	≥ 18 years old	64 (50-73) /	44 / 45	Symptom	Diarrhea and	Outpatient	Unmatched	Gastric acid	66 / 114
2011 ⁴⁸	University	31 Nov 2007			63 (52-74) *		onset in the	a positive	with no		suppressant,	
	Medical						community	toxin test	diagnosis of	Geographic	antimicrobial	
	Center,						or within 72	results for	CDI	location	s, NSAID,	
	Durham						hours of	CDI			aspirin, 90	
	Regional						admission to					
	Hospital,						a healthcare				Comorbidity,	

		Durham VA					facility.				720		
		Medical					Not						
		Center,					hospitalized						
		Salisbury					during the						
		VAMC and					12-week						
		Asheville					period prior						
		VAMC, USA					to the index						
17	Soes et al.	NR, Denmark	24 Aug 2009 - 28 Feb 2011	Nested case-control	Patients who had fecal sample submitted by their GP for microbiological testing due to diarrhea or other gastrointestinal symptoms	<2 years: 0.95 (0.30-1.98) / 1.06 (0.25-1.98)	<2 years: 53 / 55 ≥2 years: 25 / 28 ≥2 years: 50 (2-94) / 50 (2-90)*	Not hospitalized during the 12-week period prior to the index	Positive <i>C. difficile</i> culture	Negative <i>C. difficile</i> culture	Laboratory location, sex, age (± 2 years) if ≥ 5 years; ± 5 months if ≥ 6 months	Antimicrobials, Gastric acid, NSAID, aspirin, 120 weeks if ≤ 6 months) Comorbidity, 120	<2 years: 121 / 213 ≥2 years: 138 / 242
18	2013 ^{29,30} ‡												
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36	Suissa et al.	GPRD, UK	1 Jan 1994 - 31 Dec 2005	Case-control	≥2 years registered in a general practice in the UK and	NR / NR	NR / NR	Not hospitalized the year prior to the index	First positive toxin test results for CDI or first date	No clinical diagnosis, positive toxin test result for CDI or prescription	Practice location, age (± 2 years) (± 2 years) s, NSAID, aspirin, 90	Gastric acid, antimicrobial, 929 / 10242	
37	2012 ⁴⁹												
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					≥ 18 years old			of oral	prescription		
								vancomycin	of oral		Comorbidity,
								vancomycin		720	
10	Vesteinsdottir	The National	1 Jul 2010 -	Case-control	≥ 18 years old	65 (56-80) /	42.3 / 42.3	Not	Positive	Sex, age (± 5)	Gastric acid
11	et al. 2012 ⁴⁵	University	30 Jun 2011			65 (55-80) *		hospitalized	toxin test	years),	suppressant,
12		Hospital of						during the 6-	results for		antimicrobial
13		Iceland,						week period	CDI	CDI	
14		Iceland						prior to the			s, 42
15								index or			Comorbidity,
16								lived in a			84
17								nursing			
18								facility and if			
19								hospitalized,			
20								diagnosed			
21								with CDI			
22								within the 72			
23								hours of			
24								admission			
25											
26	Wilcox et al.	Cornwall and	Jan 1999 -	Case-control	Patients who	78 (4-100) /	44 / NR	Patients that	Diarrhea and	Negative	Sex, age
27	2008 ⁵⁰	Leeds, UK	Dec 1999		had fecal	NR *		attended the	a positive	toxin test	categories
28					sample			GP	toxin test	results for	
29					submitted by				results for	CDI	Comorbidity,
30					their GP for						NR
31					microbiologi						

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8 GPRD: General Practice Research Database, MED-ECHO: Provincial hospital discharge summary, VA: Veterans Affairs, ICD: International Classification of Disease, GP: General practitioner,

9 NR: Not reported, *Index date*: The date when the cases were identified

10 * Age, median (range) years

11 † Presented in 2 groups: Patients from the VA and Durham County

12 ‡ Presented in 2 groups: Patients aged <2 years and ≥2 years

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6 **Table 2.- Modified Newcastle-Ottawa quality assessment scale for case-control studies included in the meta-analysis.**
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Author, publication year	Definition of cases	Case selection for community-acquired infection	Definition of controls	Control selection	Analysis adjusted for confounders	Ascertainment of exposure	Method of ascertainment of exposure for cases and controls	Total score (points)	<i>Qi</i> score/13)
Dial et al. 2005 ²⁶	1	1	1	2	2	3	1	11	0.85
Dial et al. 2006 ²⁸	0	1	0	2	2	3	1	9	0.69
Dial et al. 2008 ⁴⁷	1	1	1	1	3	3	1	11	0.85
Kuntz et al. 2011 ⁹	1	2	1	2	3	3	1	13	1.00
Kutty et al. 2010 ³¹	2	2	2	1	1	3	0	11	0.85
Lowe et al. 2006 ³³	1	2	0	1	2	3	1	10	0.77
Marwick et al. 2013 ³²	2	1	0	2	1	3	1	10	0.77
Naggie et al. 2011 ⁴⁸	2	2	2	1	2	1	1	11	0.85
Soes et al. 2013 ²⁹	3	2	3	2	0	1	1	12	0.92
Suisse et al. 2012 ⁴⁹	0	1	0	2	2	3	1	9	0.69
Vesteinsdottir et al. 2012 ⁴⁵	2	2	2	2	0	1	1	10	0.77
Wilcox et al. 2008 ⁵⁰	2	0	2	2	0	2	1	9	0.69

40 (i) Definition of cases. Method used for *C. difficile* diagnosis: Stool culture (3 points), Toxin detection (2 points), Clinical diagnosis or ICD code (1 point), Other or no description
41 (0 points)
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6 (ii) Case selection for community-acquired infection: Patient not previously hospitalized and not a resident of a nursing home (2 points), Patient not previously hospitalized or not
7 a resident of a nursing home (1 point), No description (0 points)
8
9 (iii) Definition of controls. Method used for exclusion (non infection) of *C. difficile*: Stool culture (3 points), Toxin detection (2 points), Clinical diagnosis or ICD code (1 point),
10 Other or no description (0 points)
11
12 (iv) Control selection: Community (2 points), Community and hospital (1 point), No description (0 points)
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14 (v) Analysis adjusted for exposures other than the primary exposure of interest (sex, age, antimicrobial exposure, gastric acid-suppressive medication exposure or presence of
15 comorbidities). Adjusted for: 5 factors (3 points), 3-4 factors (2 points), 1-2 factors (1 point), non adjusted (0 points)
16
17 (vi) Ascertainment of exposure: Objective methods i.e. charts or medical records (3 points), Reported by the general practitioner (2 points), Self-reported (1 point), No description
18 (0 points)
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20 (vii) Method of ascertainment of exposure for cases and controls: Same (1 point), Different (0 points)
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Table 3.- Pooled effect size using the IVhet model, QE model and the RE model

Exposure	IVhet model	QE model	RE model	Heterogeneity
	OR (95% CI)	OR (95% CI)	OR (95% CI)	I^2 index %
Antimicrobials	6.18 (3.80 - 10.04)	6.11 (3.92 - 9.55)	5.92 (4.21 - 8.32)	87.90
Cephalosporins	1.80 (0.38 - 8.46)	2.09 (0.55 - 7.98)	3.29 (1.20 - 9.05)	98.39
Clindamycin	2.32 (0.14 - 37.99)	3.21 (0.30 - 34.55)	8.35 (1.54 - 45.20)	97.73
Fluoroquinolones	1.55 (0.32 - 7.57)	1.90 (0.51 - 7.05)	3.59 (1.60 - 8.06)	96.97
Macrolides	1.26 (0.49 - 3.24)	1.45 (0.64 - 3.28)	2.15 (1.11 - 4.17)	93.38
Penicillins	1.31 (0.57 - 3.01)	1.54 (0.75 - 3.16)	2.40 (1.40 - 4.11)	93.50
Tetracyclines	0.98 (0.68 - 1.41)	0.98 (0.67 - 1.41)	0.98 (0.68 - 1.41) *	0
TMP-SMX	1.26 (0.75 - 2.12)	1.30 (0.80 - 2.10)	1.37 (0.87 - 2.15)	77.37
Gastric acid suppressant	1.58 (0.90 - 2.75)	1.58 (0.95 - 2.63)	1.58 (1.06 - 2.34)	68.89
H2RA	1.24 (0.76 - 2.01)	1.24 (0.78 - 1.96)	1.37 (0.96 - 1.96)	73.95
PPI	1.61 (0.90 - 2.88)	1.63 (0.95 - 2.80)	1.68 (1.11 - 2.55)	92.23
Other medication				
Aspirin	0.97 (0.87 - 1.08)	0.96 (0.85 - 1.08)	0.97 (0.87 - 1.08) *	0
NSAIDs	1.14 (0.67 - 1.93)	1.04 (0.63 - 1.71)	0.83 (0.56 - 1.23)	90.42
Corticosteroids	1.81 (1.15 - 2.84)	1.84 (1.22 - 2.77)	1.65 (1.14 - 2.38)	34.79
Comorbidities				
Congestive heart disease	0.95 (0.45 - 2.01)	0.98 (0.46 - 2.06)	1.40 (0.77 - 2.54)	68.70

1	COPD	1.04 (0.93 - 1.16)	1.04 (0.93 - 1.16)	1.04 (0.93 - 1.16) *	0
2	Diabetes mellitus	1.15 (1.05 - 1.27)	1.14 (1.04 - 1.26)	1.15 (1.05 - 1.27) *	0
3	Diverticular disease	1.15 (0.98 - 1.36)	1.15 (0.98 - 1.35)	1.15 (0.98 - 1.36) *	0
4	GERD	1.02 (0.74 - 1.43)	1.03 (0.74 - 1.43)	1.07 (0.80 - 1.44)	45.53
5	IBD	3.72 (1.52 - 9.12)	4.11 (1.78 - 9.49)	5.19 (2.49 - 10.83)	89.39
6	Leukemia or Lymphoma	1.75 (1.02 - 3.03)	1.74 (1.01 - 3.01)	1.88 (1.09 - 3.21)	38.95
7	Peptic ulcer	0.97 (0.60 - 1.57)	0.96 (0.59 - 1.56)	0.94 (0.58 - 1.51)	14.72
8	Renal failure	2.64 (1.23 - 5.68)	2.59 (1.20 - 5.59)	3.02 (1.66 - 5.48)	85.96
9	Solid cancer	1.34 (0.83 - 2.17)	1.35 (0.84 - 2.17)	1.51 (1.01 - 2.27)	81.64

22 * No heterogeneity, pooled estimated report using the inverse variance model.

23
24 *IVhet*: Inverse variance heterogeneity, *QE*: Quality effects, *RE*: Random effects, *OR*: odds ratio, *TMP-SMX*: Trimethoprim/sulfamethoxazole, *H2RA*: histamine-2-
25 receptor antagonists, *PPI*: Proton pump inhibitors, *NSAIDs*: Non-steroidal anti-inflammatory drugs, *COPD*: Chronic obstructive pulmonary disease, *GERD*: Gastro-
26 esophageal reflux disease, *IBD*: Inflammatory bowel disease

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Figure 1.- PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis)

flowchart of the literature search conducted on the 1st March 2014 for the meta-analysis

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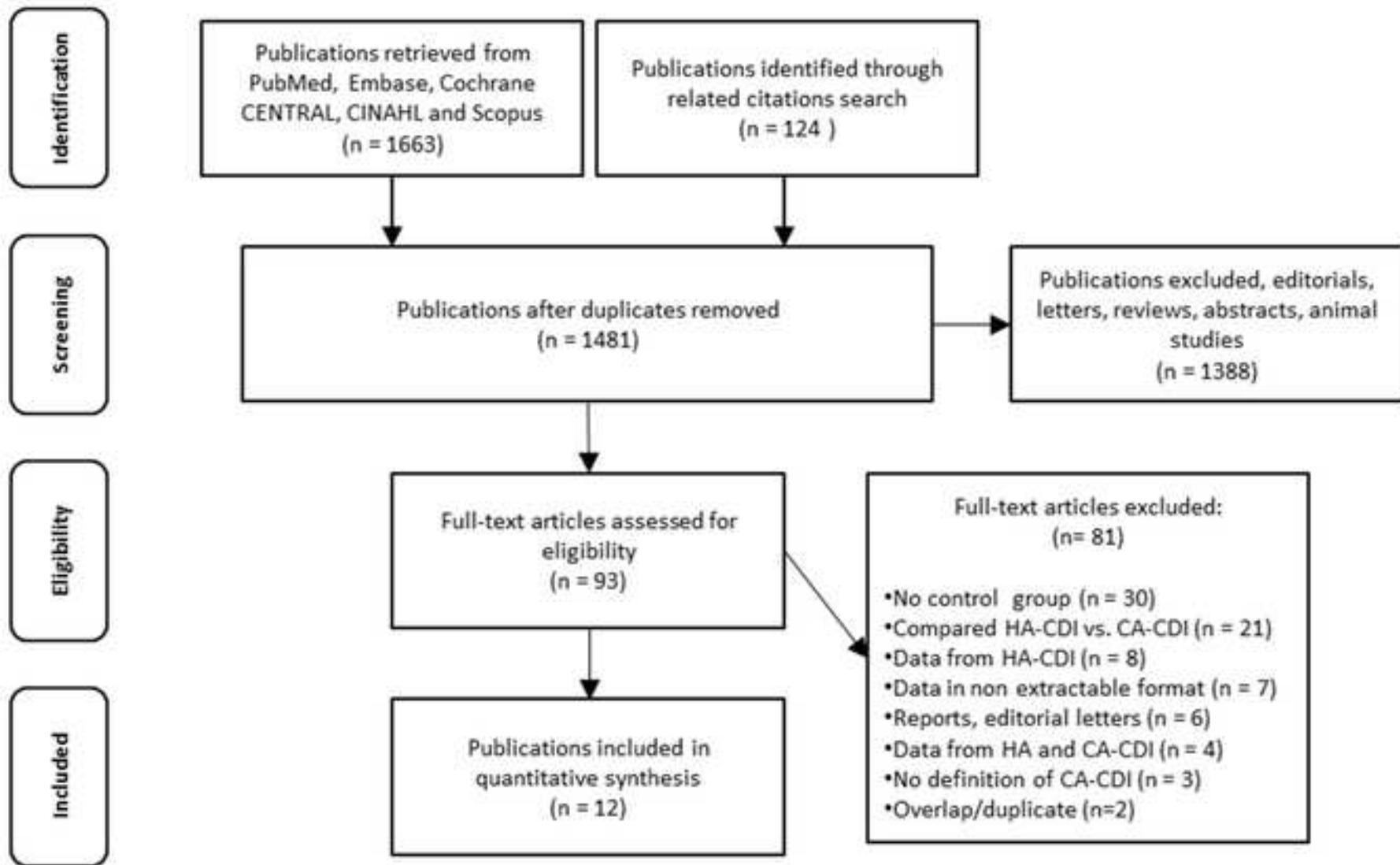
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Figure 1



APPENDICES

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2 **Appendix 1.- Search strategies**
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(((("Community-Acquired Infections"[MeSH Terms]) OR (Community OR Communities OR Residential OR Neighborhood OR Neighborhoods OR Neighbourhood OR Neighbourhoods)))
AND

("Clostridium"[Mesh] OR Clostridium))
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Difficile

Embase

('communicable disease'/exp OR community OR communities OR residential OR neighborhood OR neighborhoods OR neighbourhood OR neighbourhoods)

AND
'clostridium'/exp OR clostridium

AND

Difficile

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(MH "Community-Acquired Infections+") OR Community OR Communities OR Residential OR Neighborhood OR Neighborhoods OR Neighbourhood OR Neighbourhoods

AND
(MH "Clostridium+") OR Clostridium

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Difficile

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9 Residential OR Neighborhood OR Neighborhoods OR Neighbourhood OR
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27 **Scopus**
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29 (TITLE-ABS-KEY(community OR communities OR residential OR neighborhood OR
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31 neighborhoods OR neighbourhood OR neighbourhoods)
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Appendix 2.- Data extraction tool

Select one medication exposure / comorbidity	Overall antimicrobials	Macrolides	Overall gastric supres.	NSAIDs	DM	Leukemia/lymphoma
	Cephalosporins	Penicillins	H2RA	Corticosteroids	Diverticular disease	Peptic ulcer
	Clindamycin	Tetracyclines	PPI	CHD	GERD	Renal failure
	Fluoroquinolones	TMP-SMX	Aspirin	COPD	IBD	Solid cancer

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2 Appendix 3.- Forest, Funnel and Doi plots

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44 3.1.- Antimicrobials

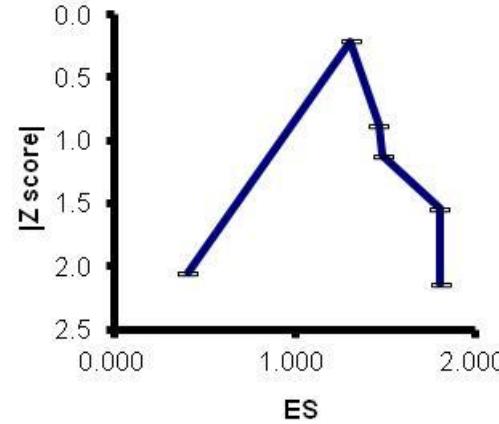
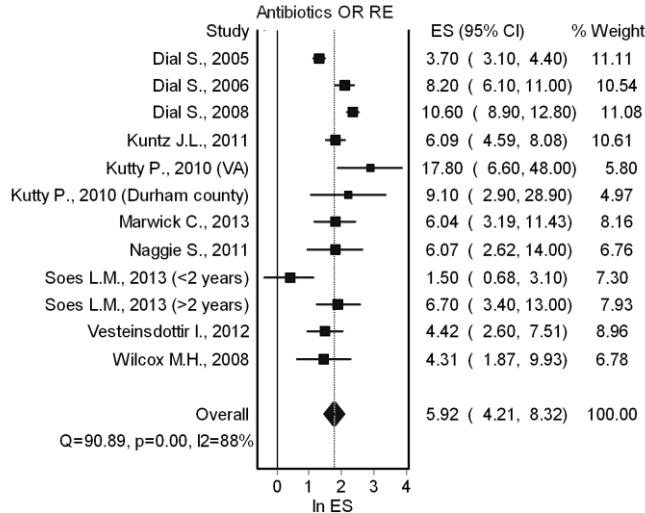
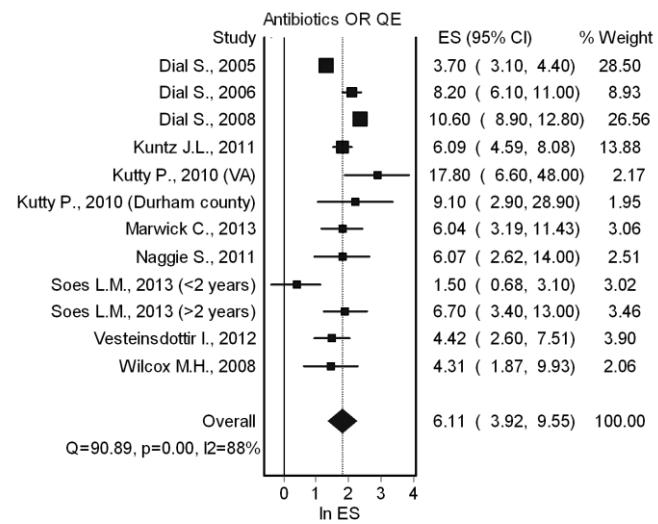
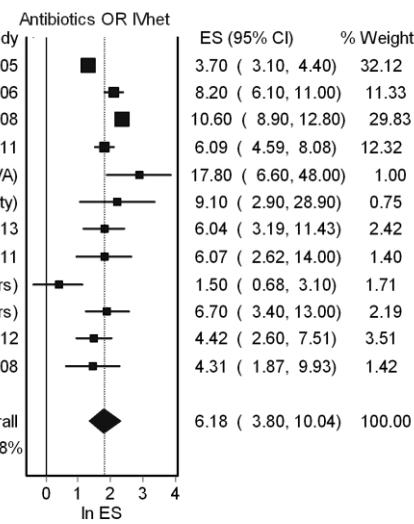
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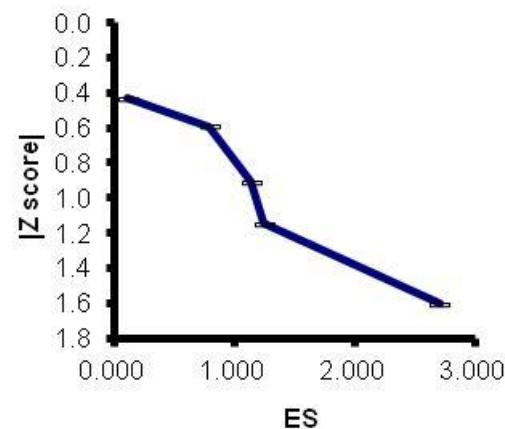
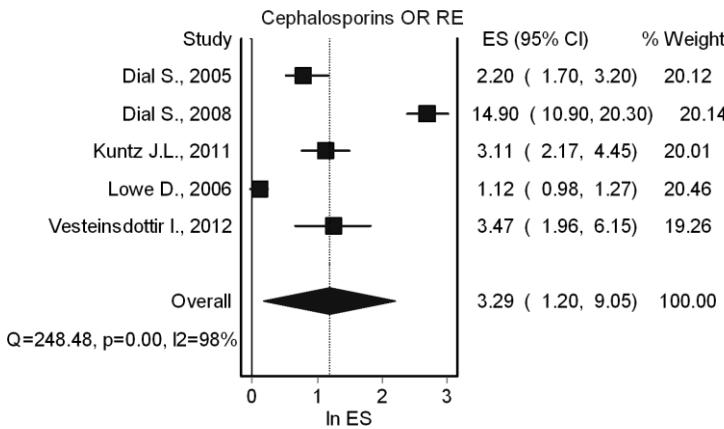
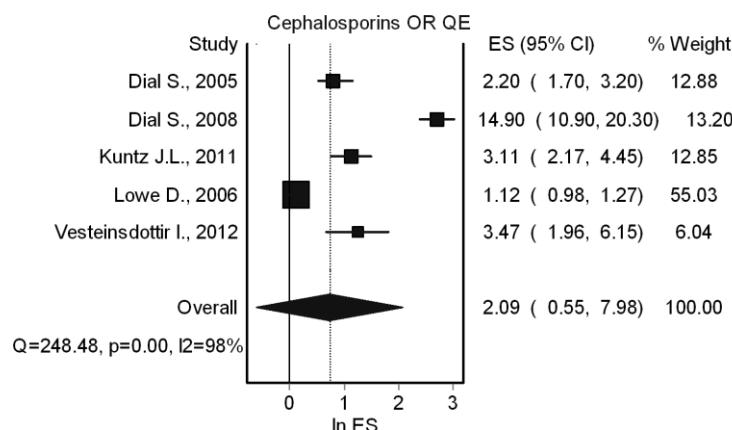
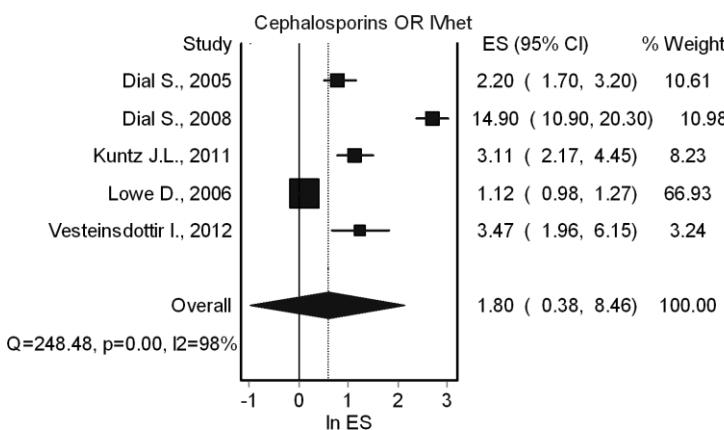
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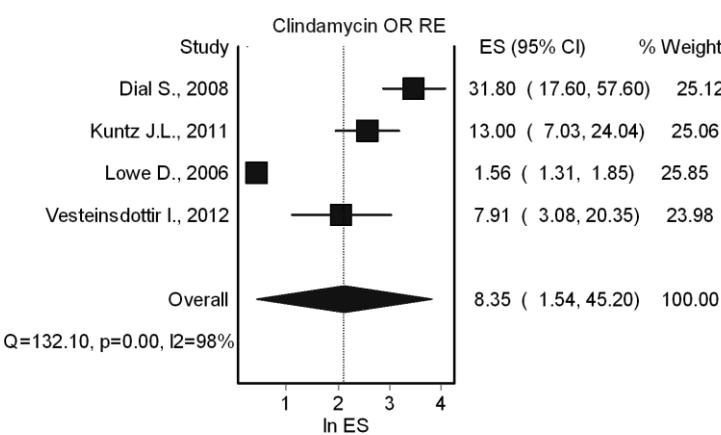
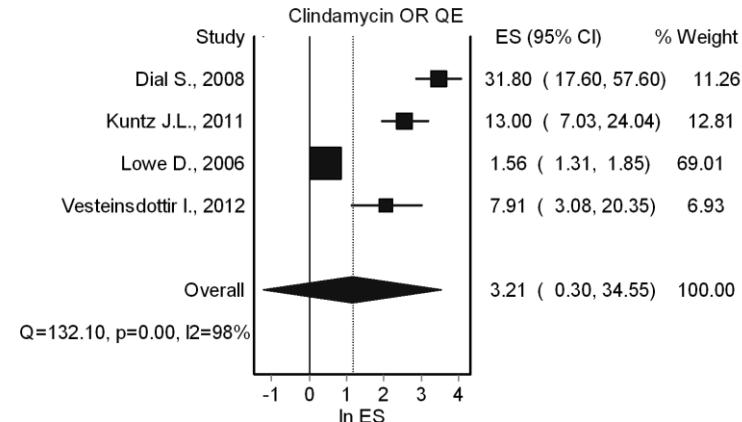
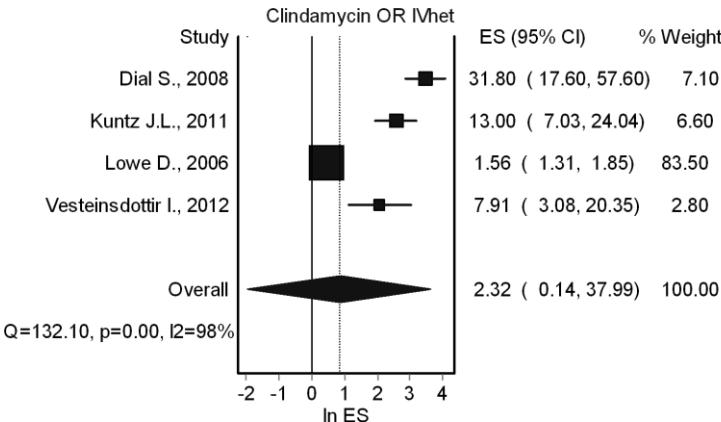
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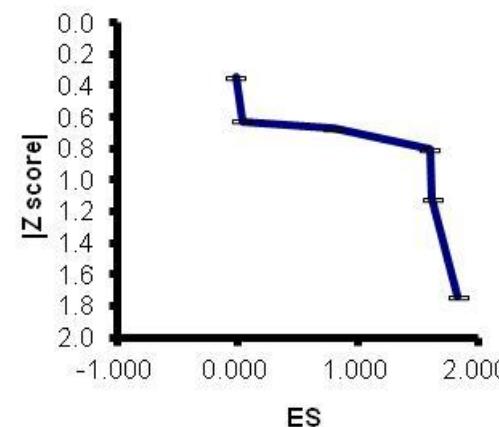
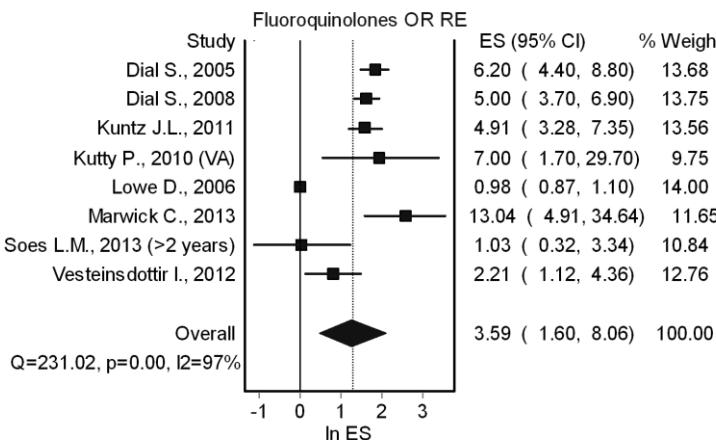
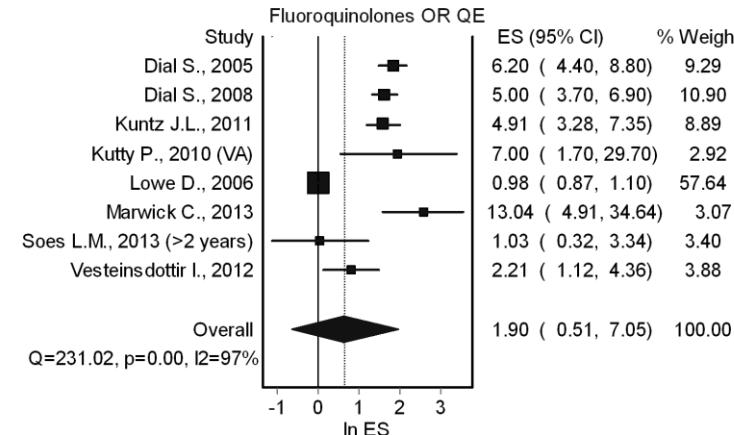
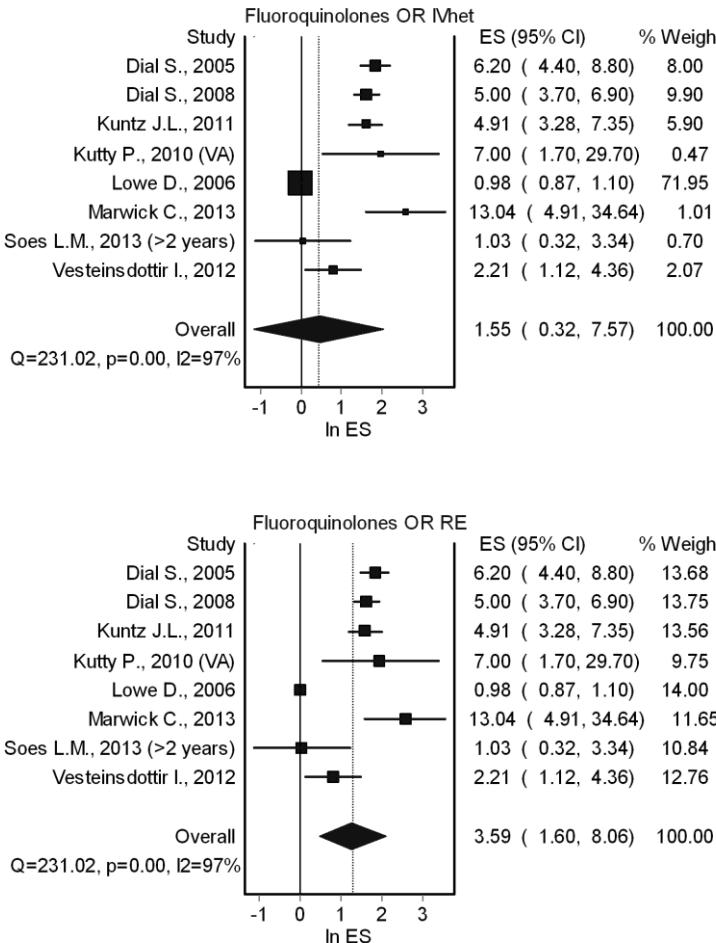




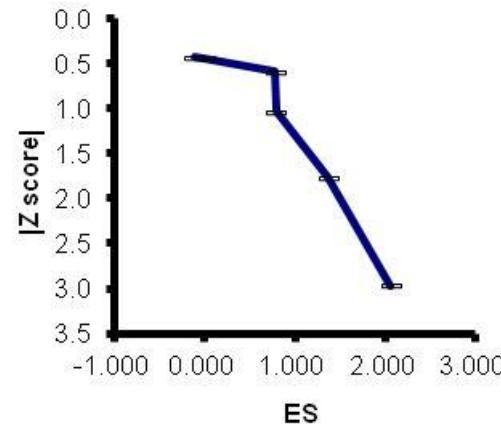
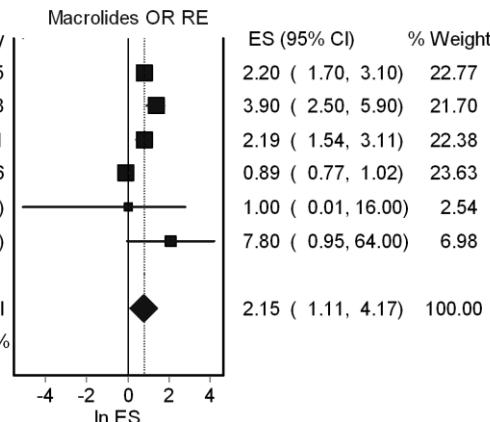
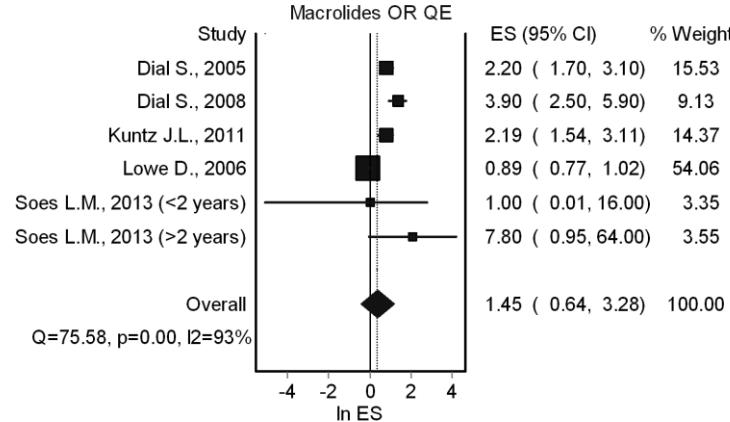
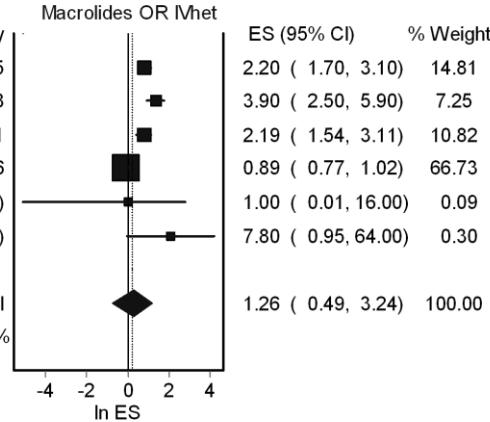
3.2.- Cephalosporins



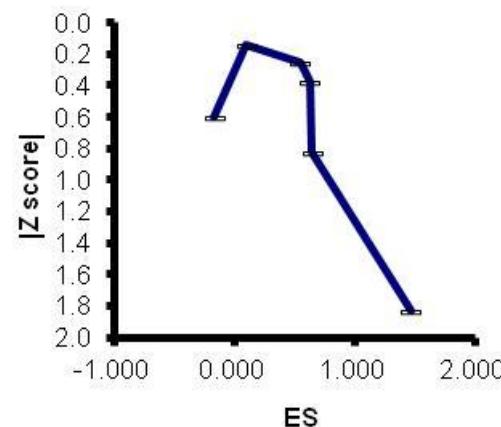
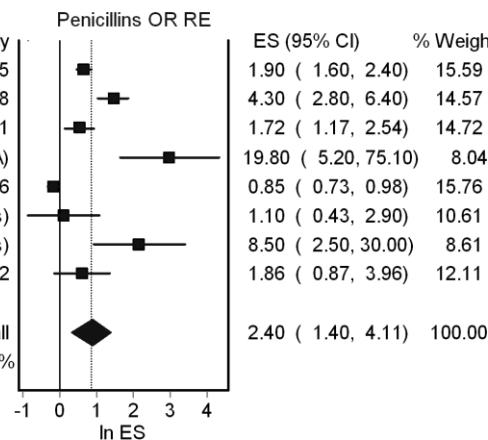
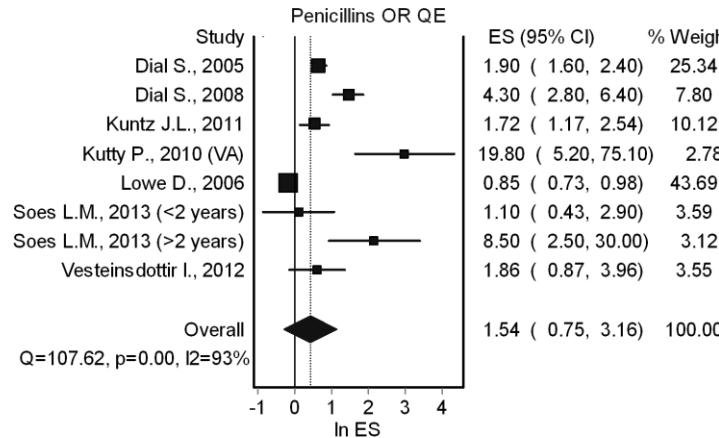
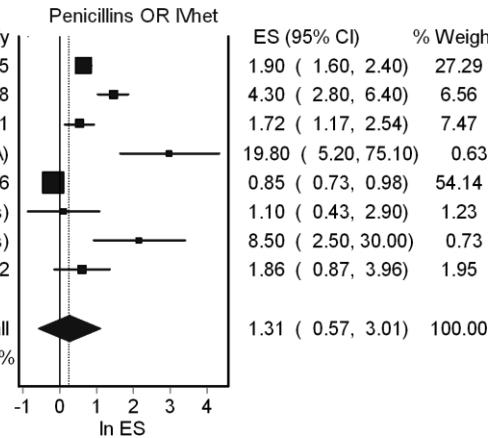
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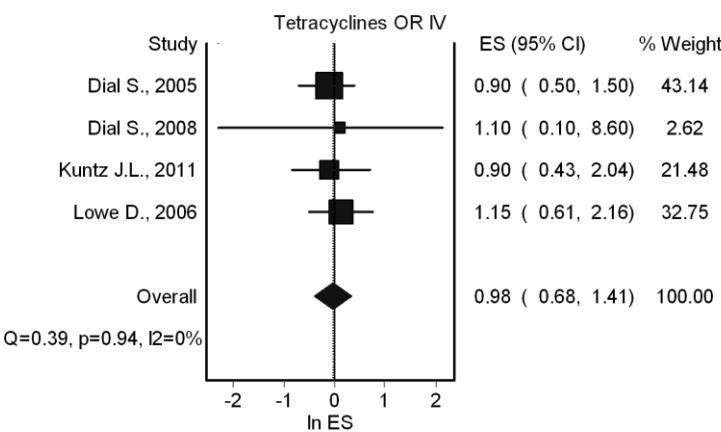
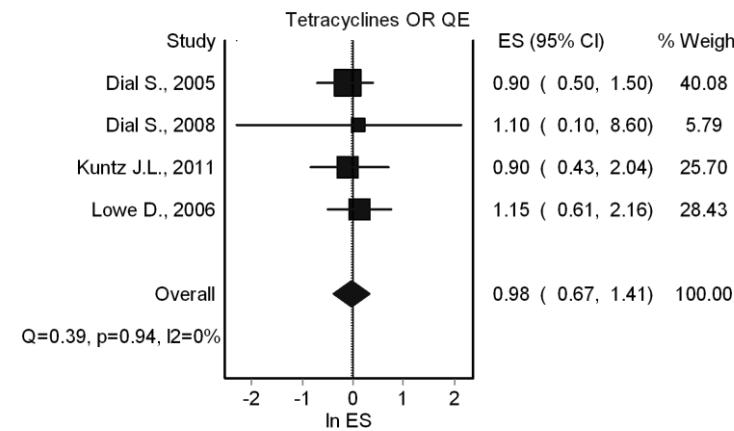
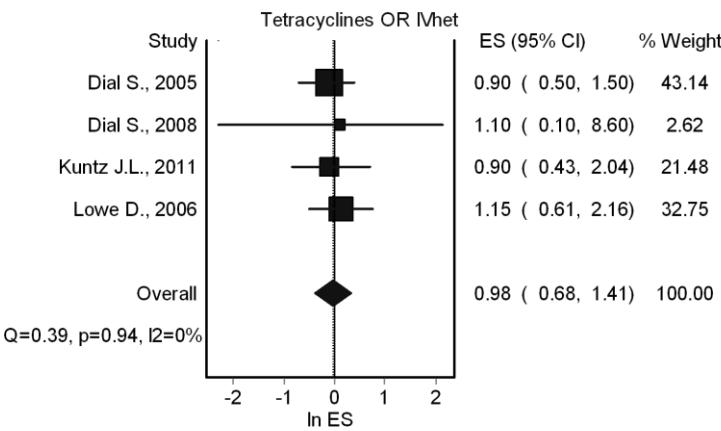
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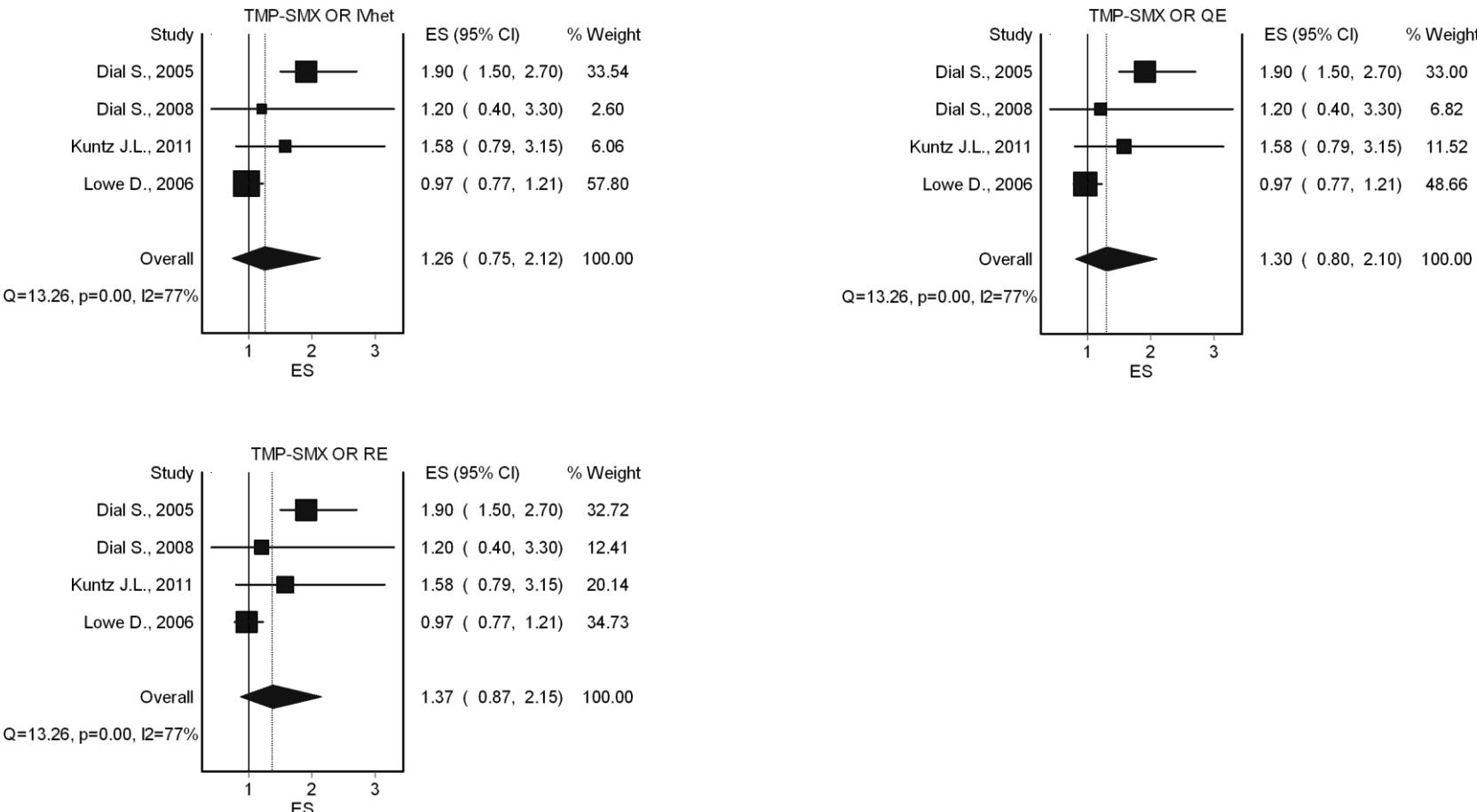
3.5.- Macrolides



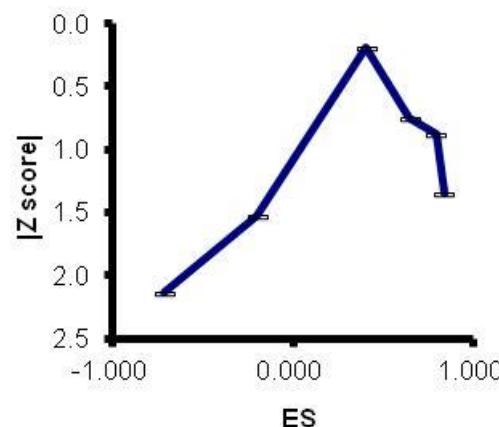
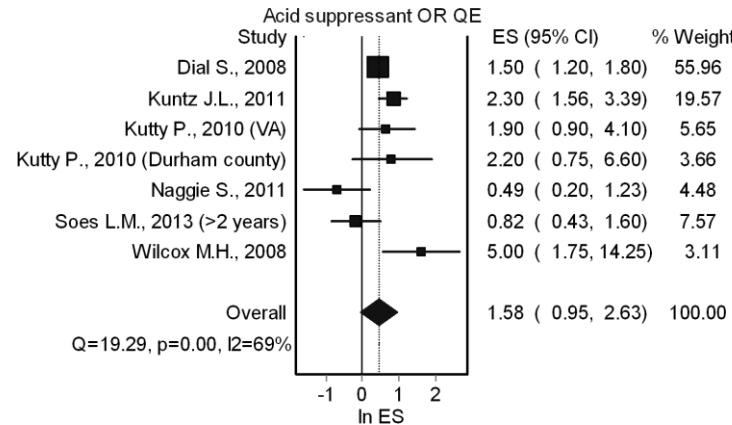
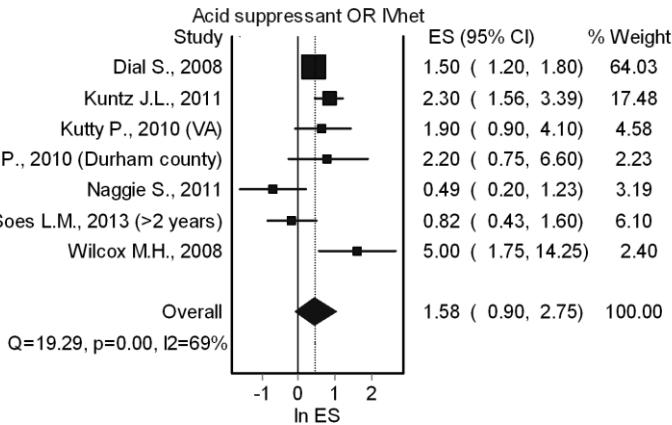
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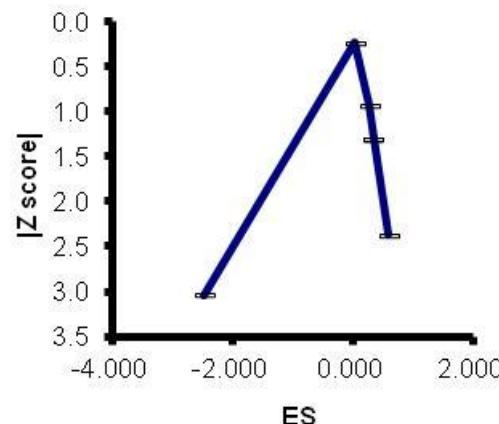
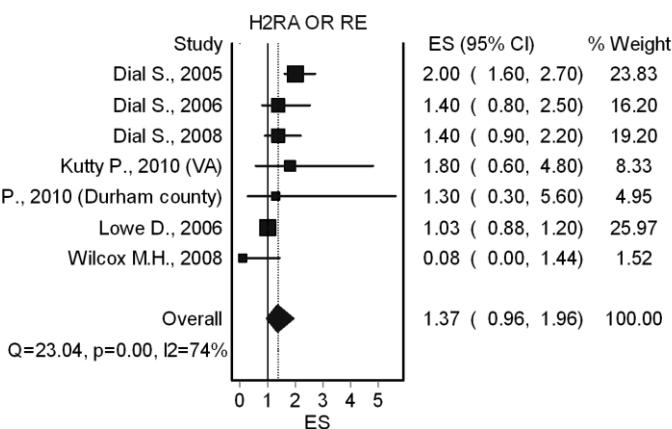
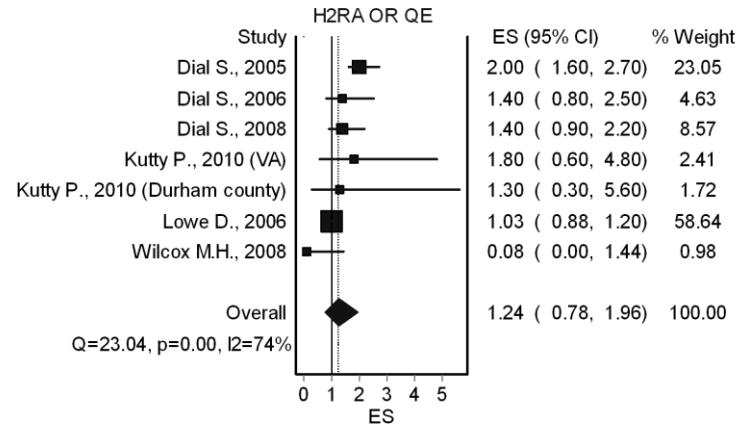
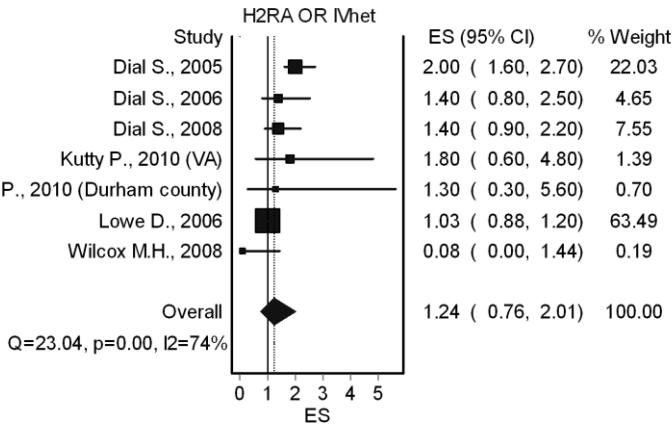


3.7.- Tetracyclines

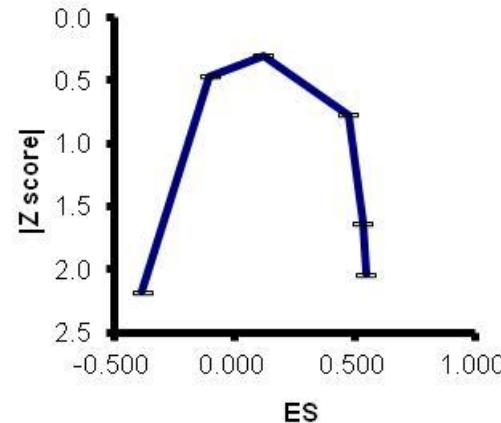
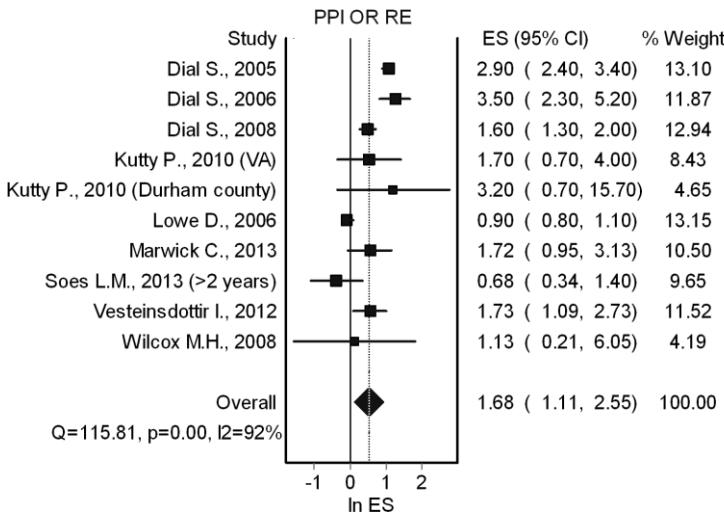
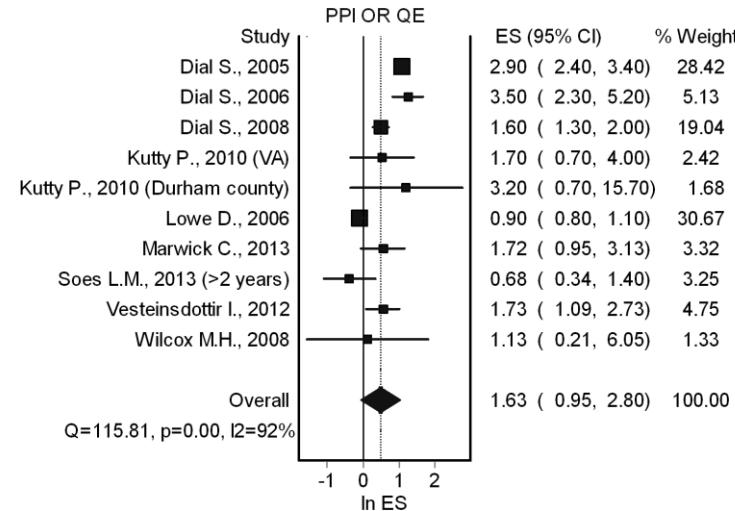
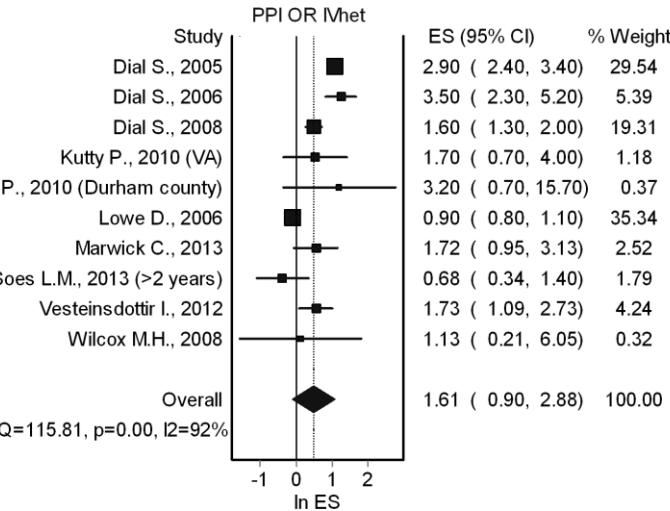


35 3.8.- Trimethoprim/sulfamethoxazole
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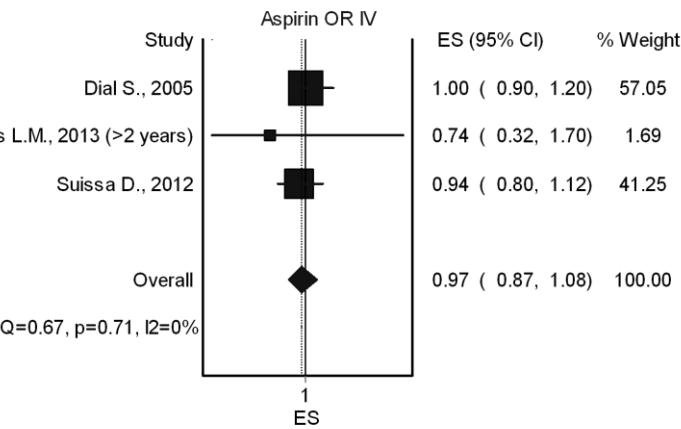
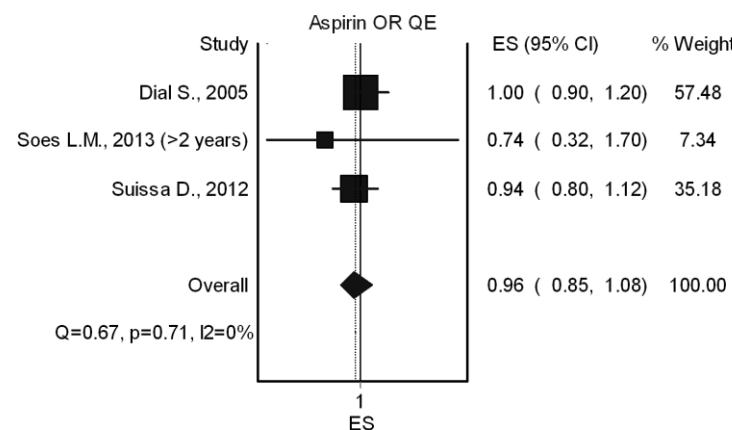
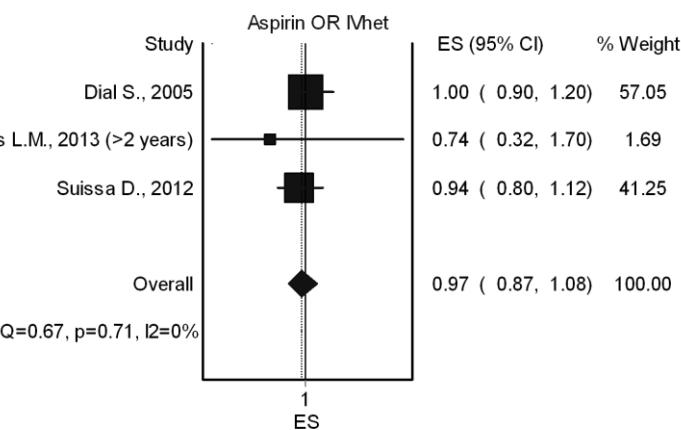




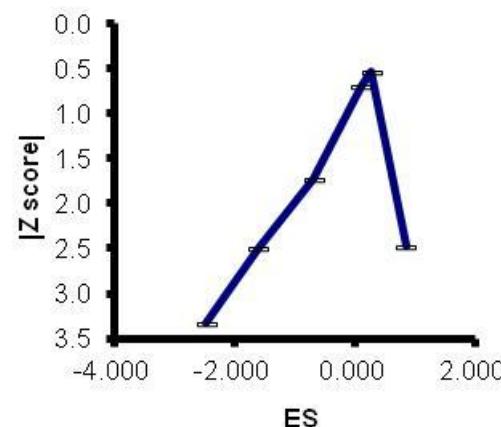
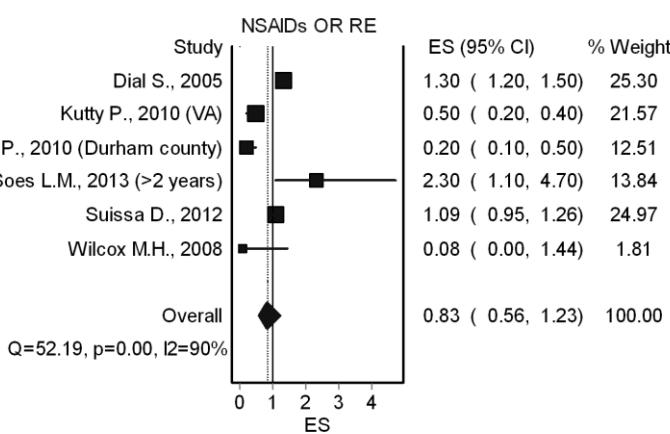
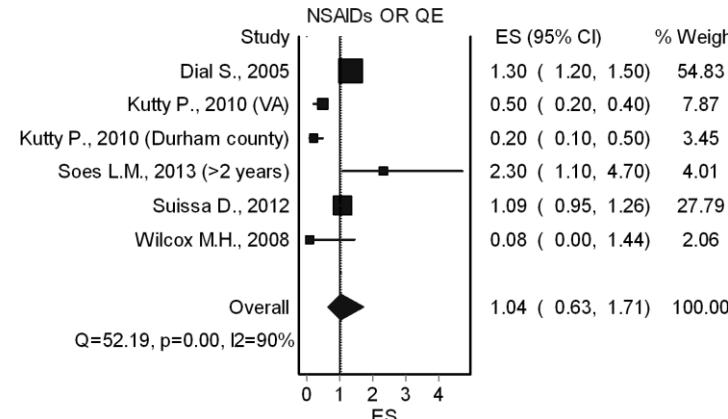
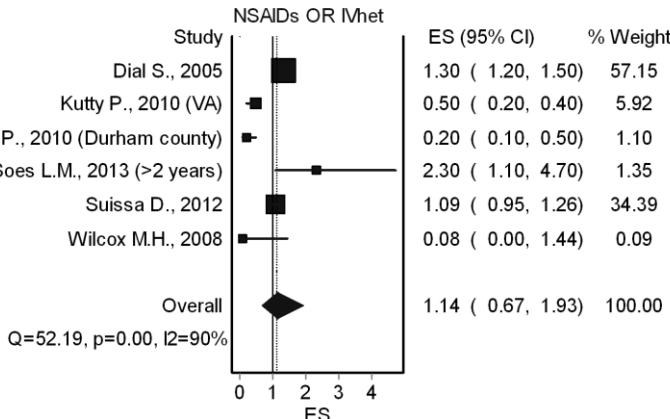
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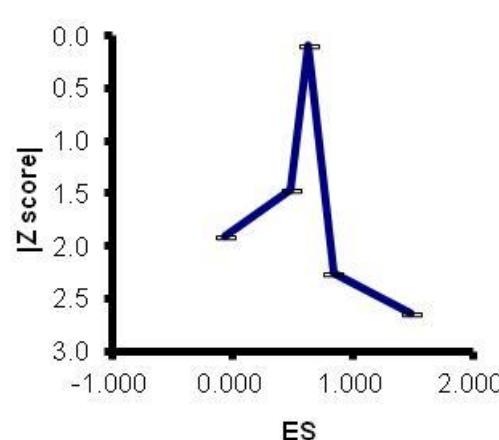
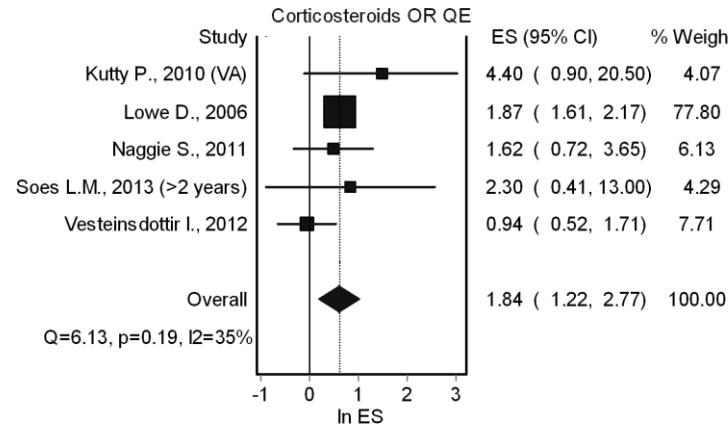
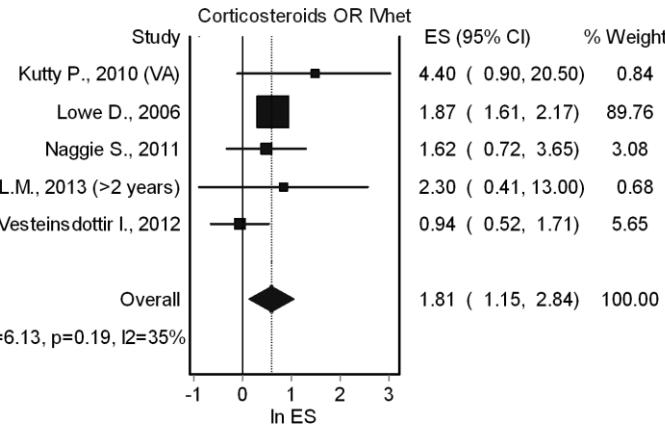
3.11.- Proton pump inhibitor



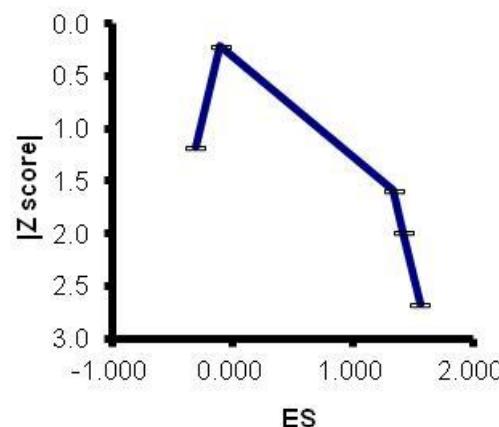
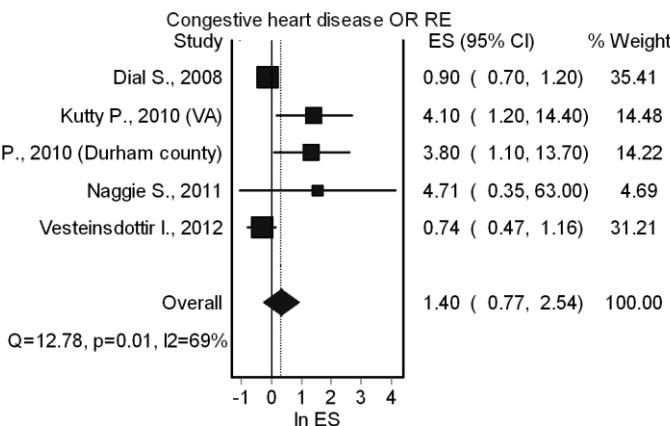
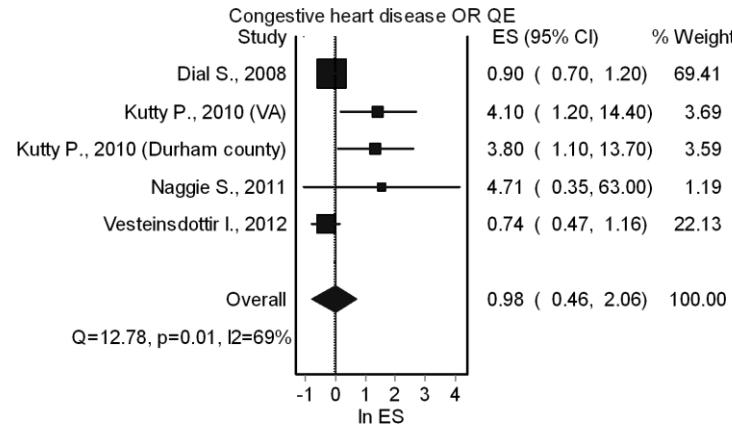
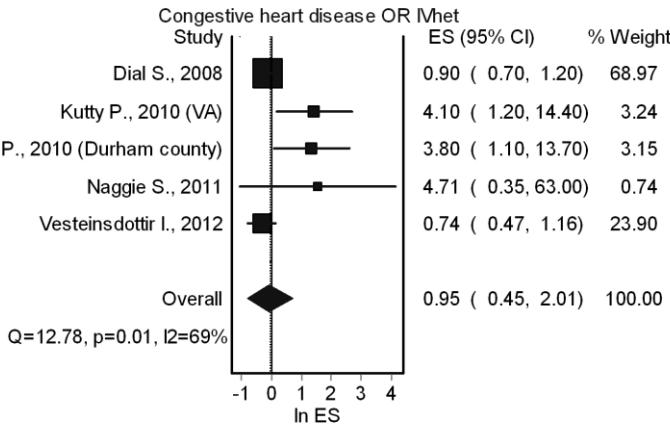
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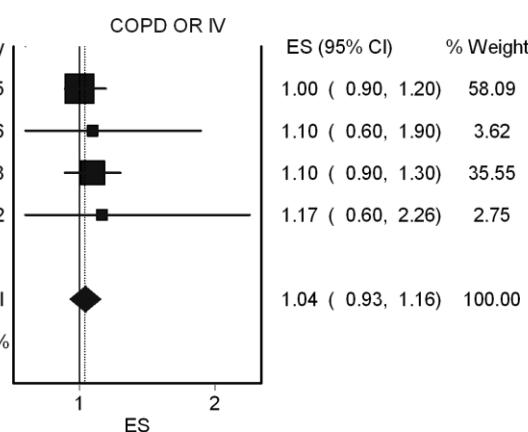
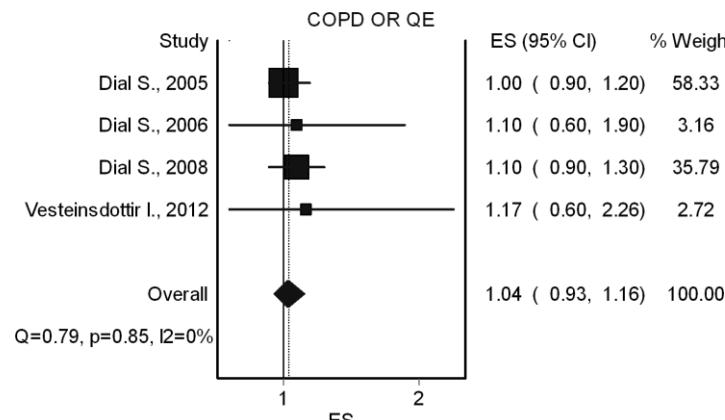
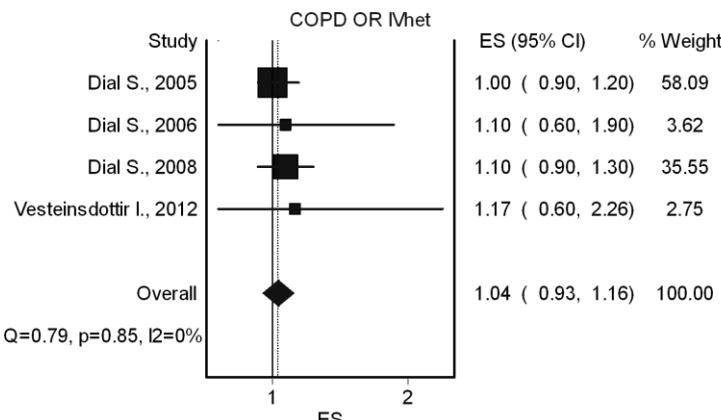
3.13.- Non-steroidal anti-inflammatory drugs



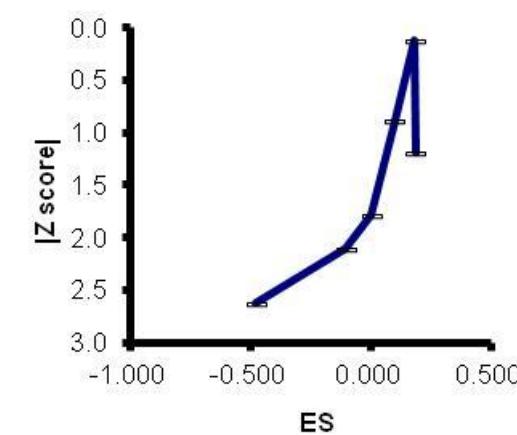
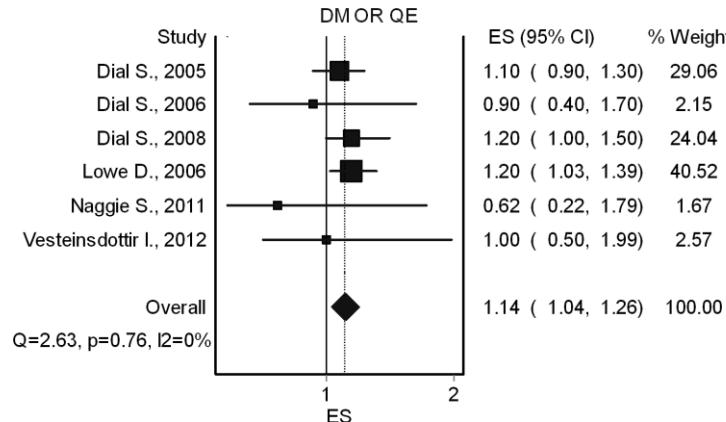
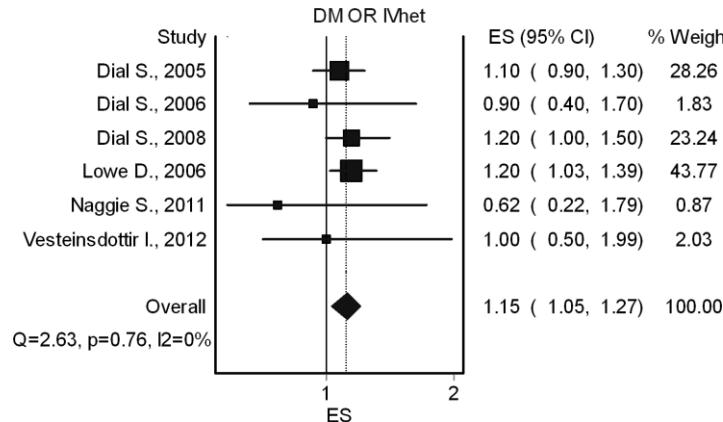
3.14.- Corticosteroids



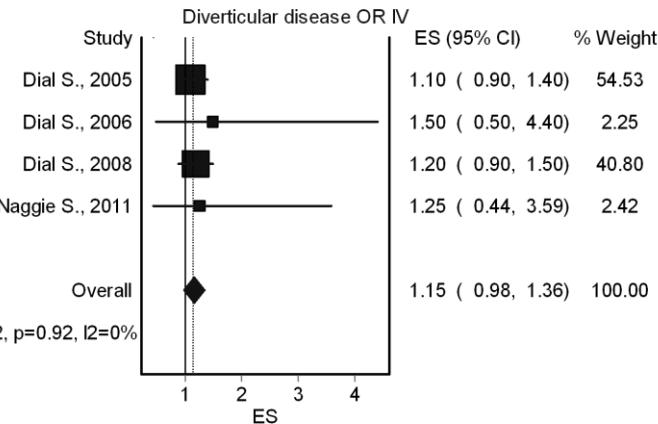
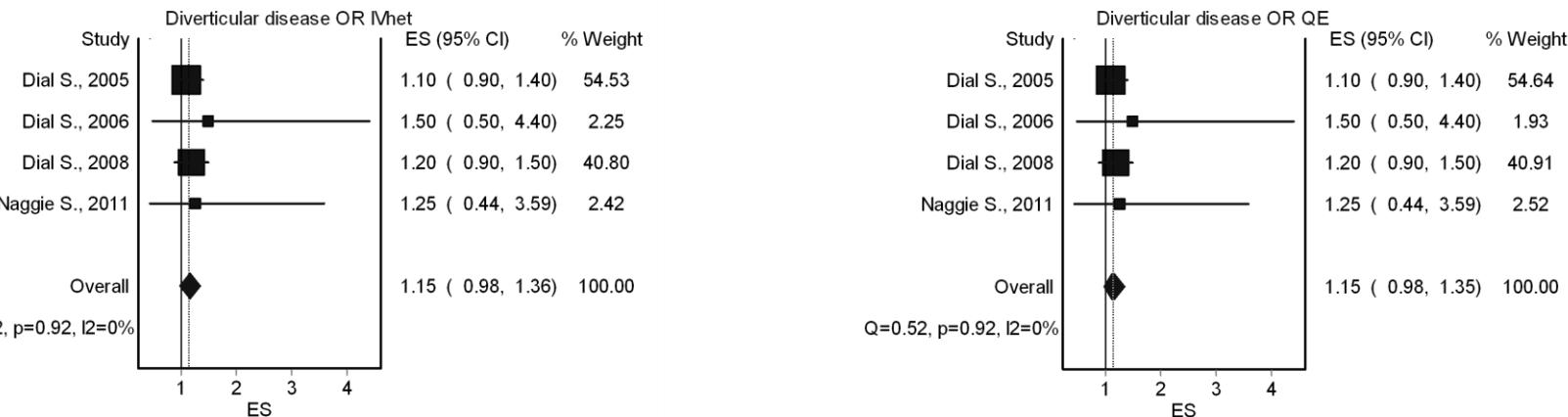
3.15.- Congestive heart disease



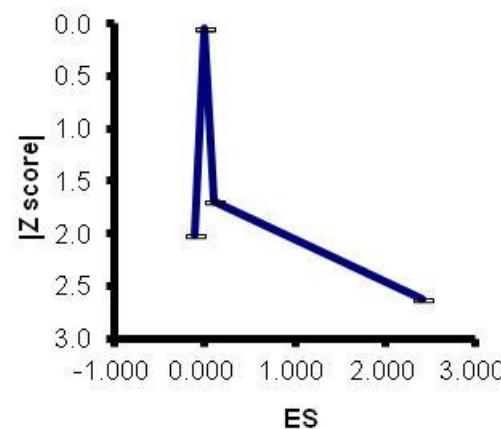
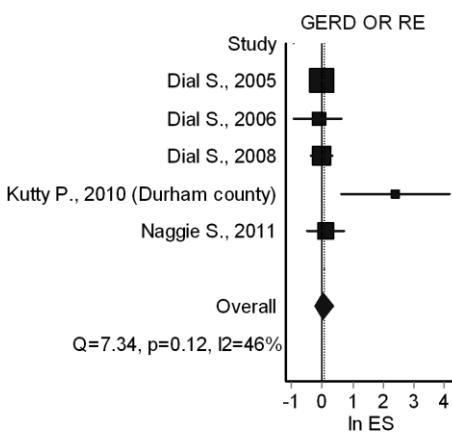
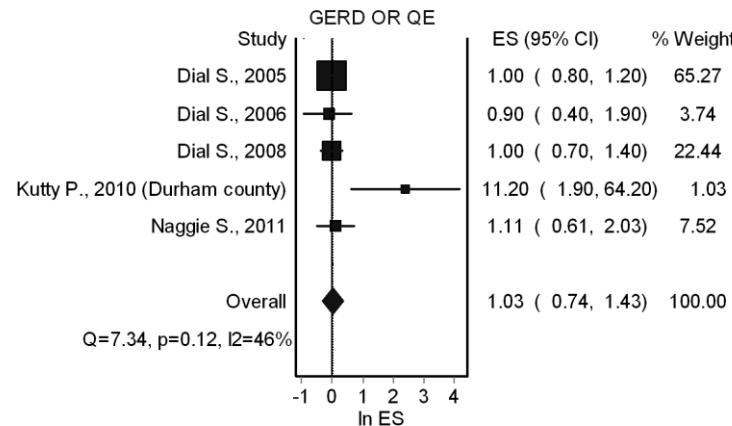
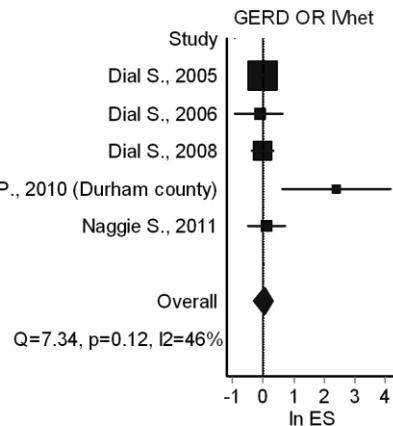
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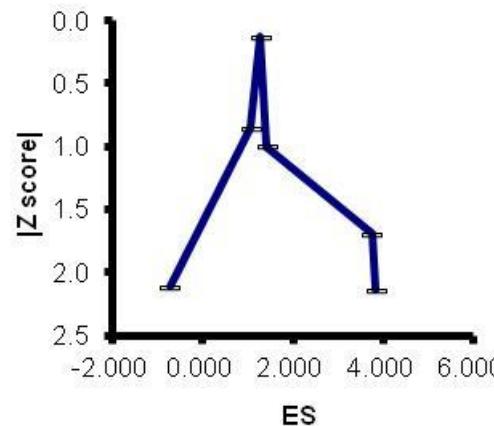
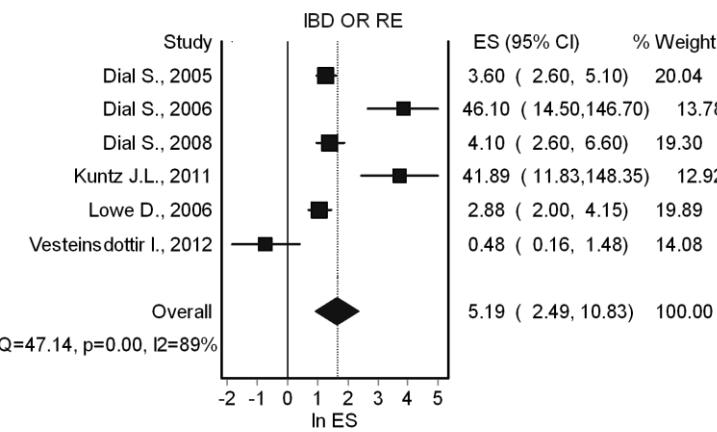
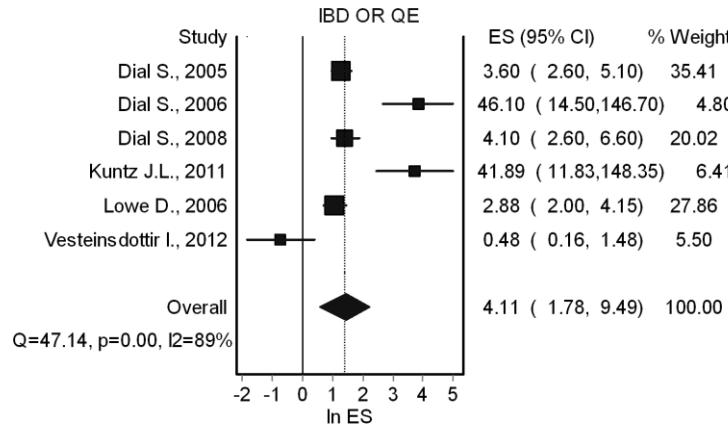
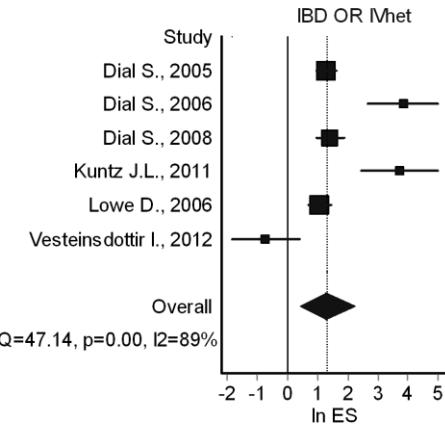
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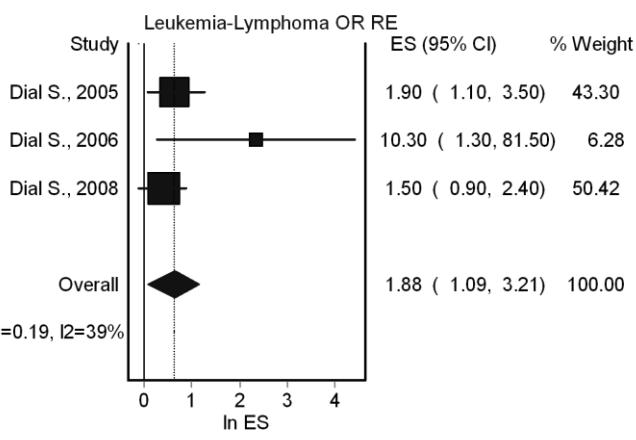
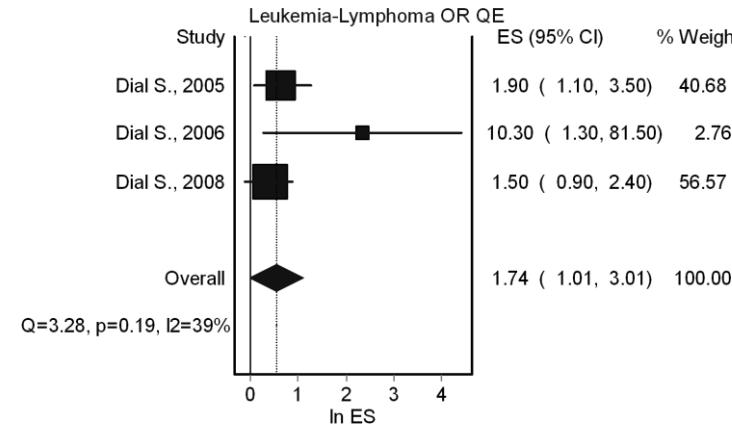
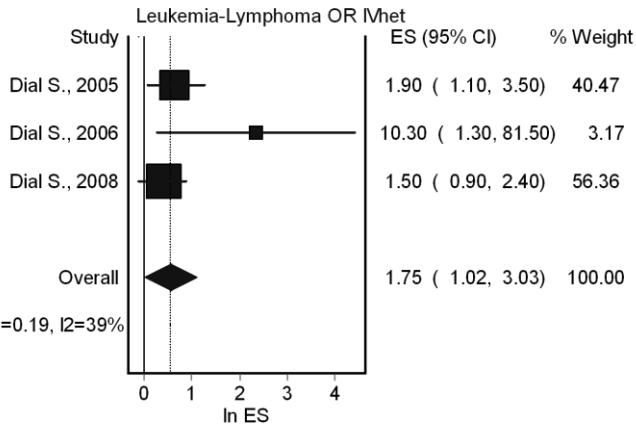
3.18.- Diverticular disease



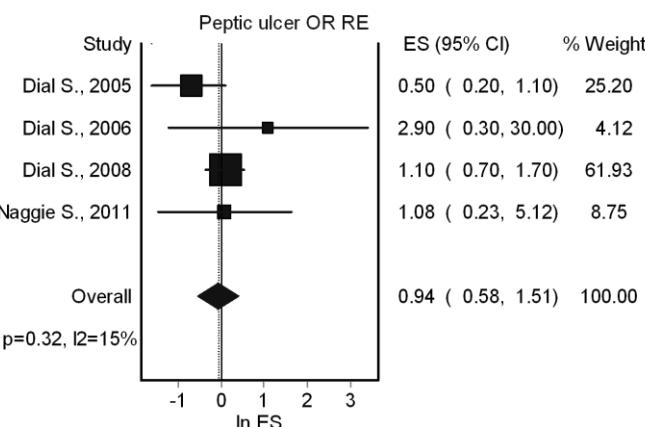
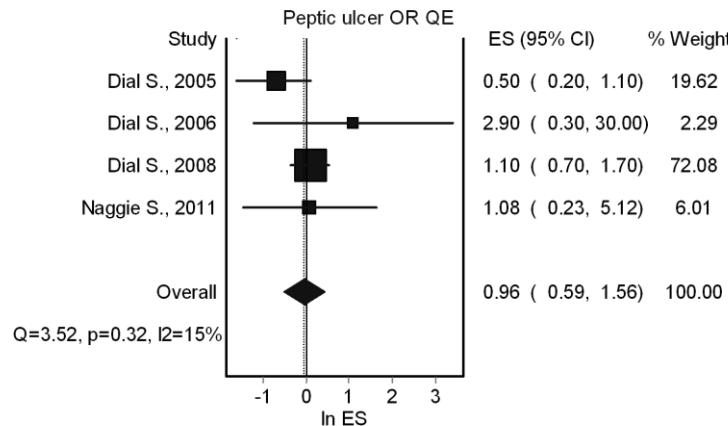
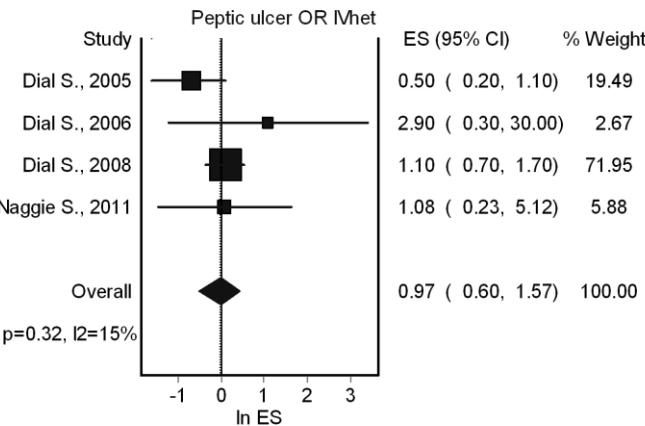
3.19.- Gastroesophageal reflux disease



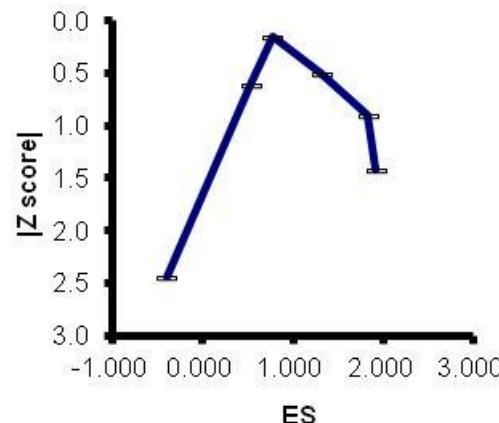
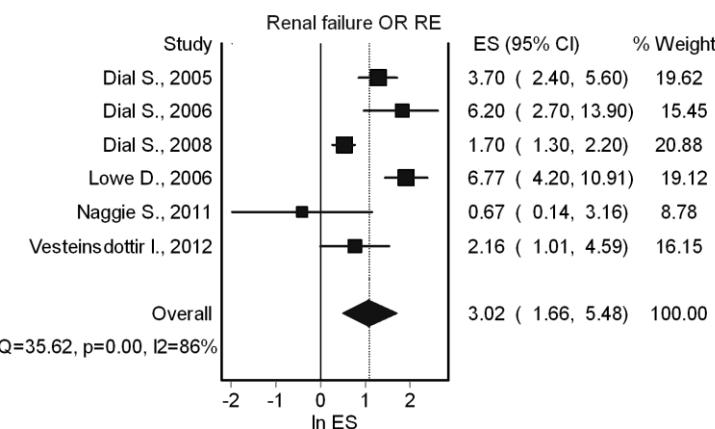
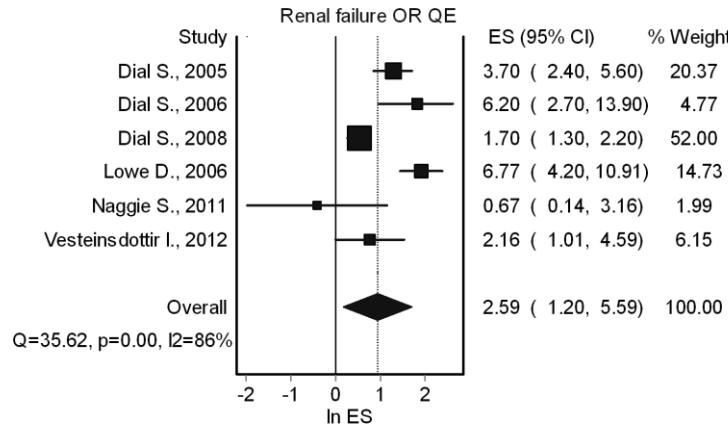
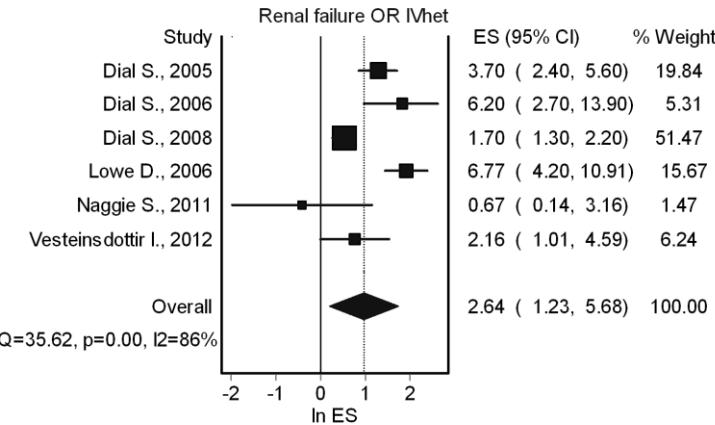
3.20.- Inflammatory bowel disease



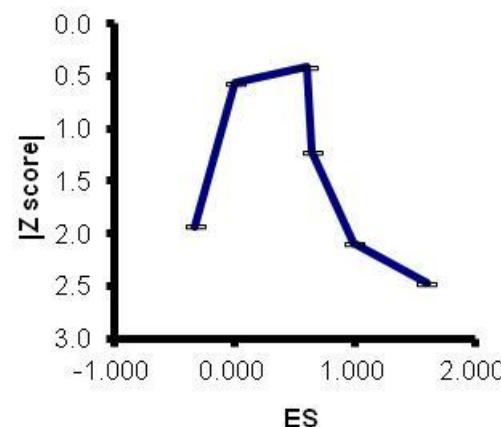
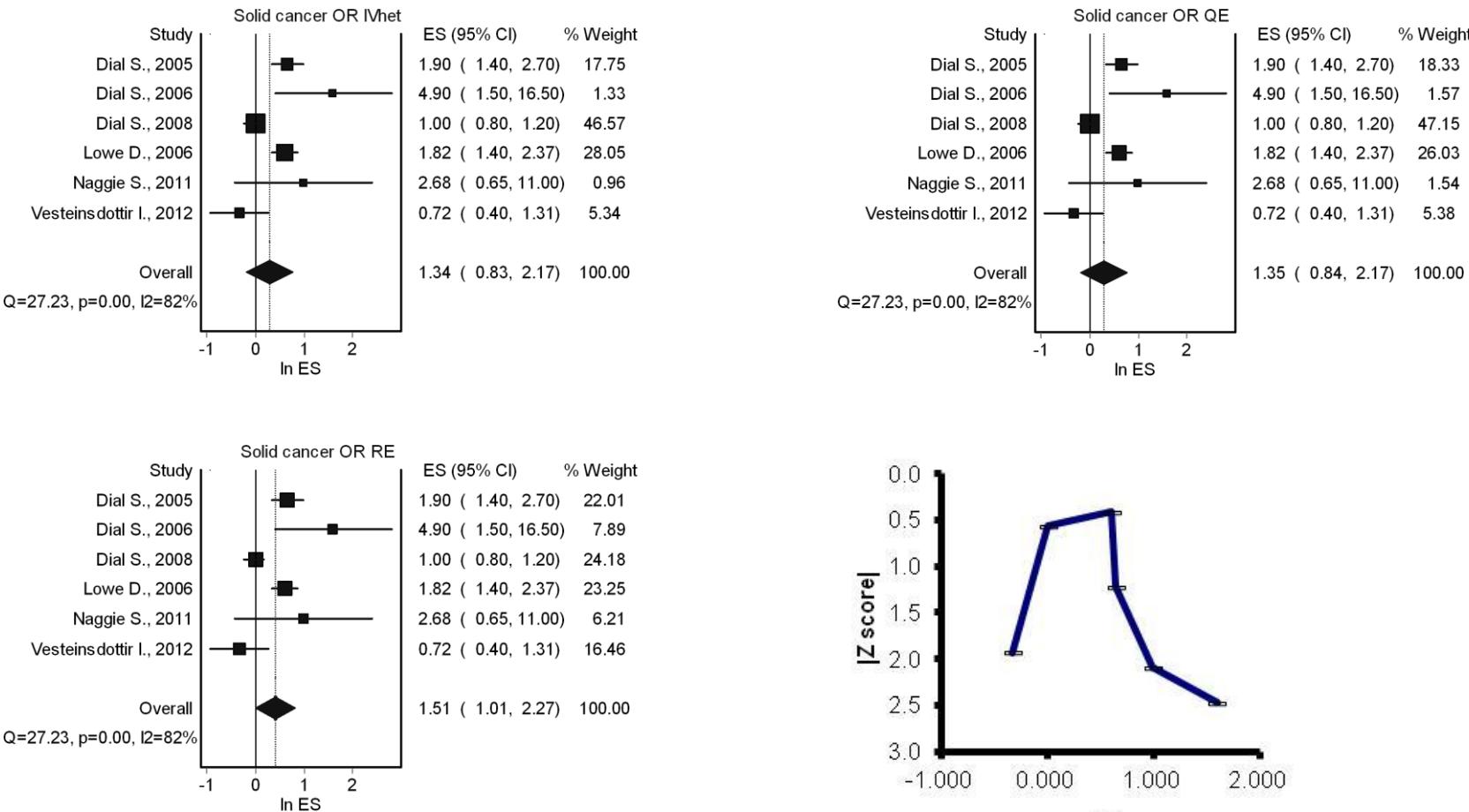
3.21.- Leukemia or Lymphoma



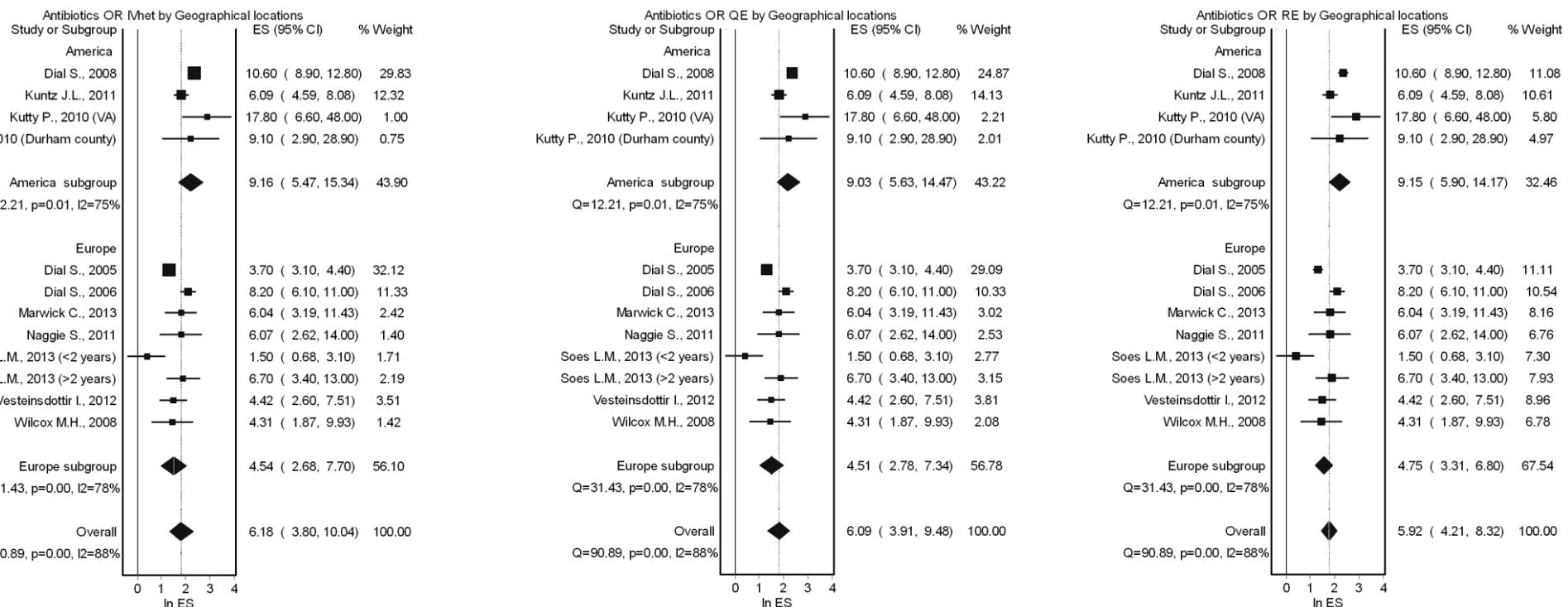
3.22.- Peptic ulcer



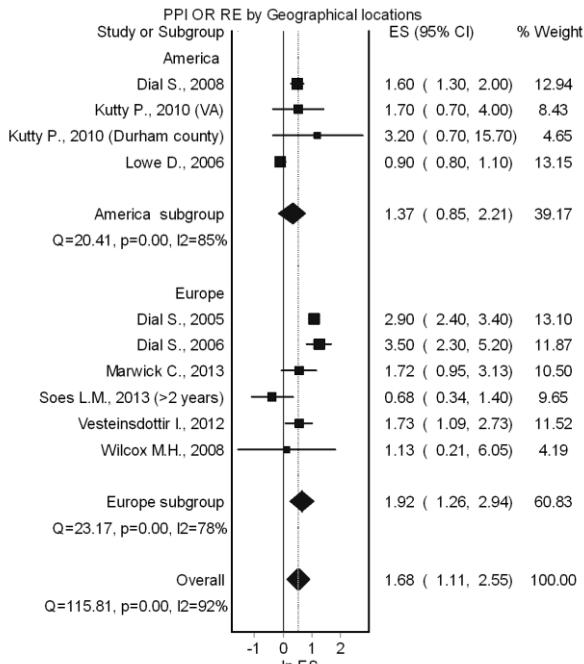
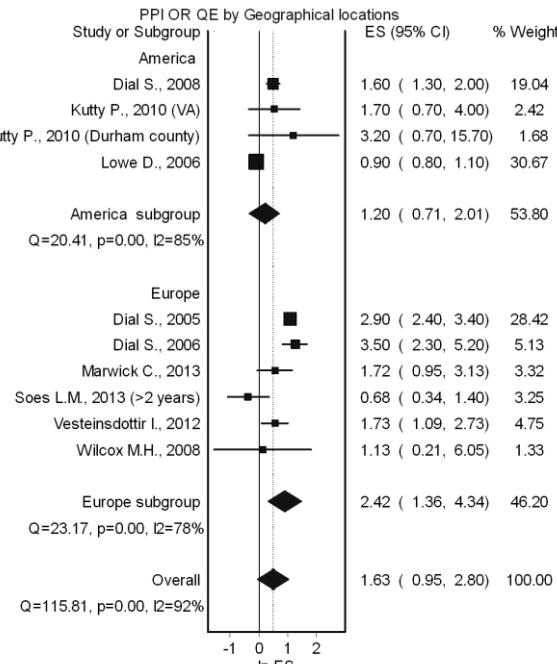
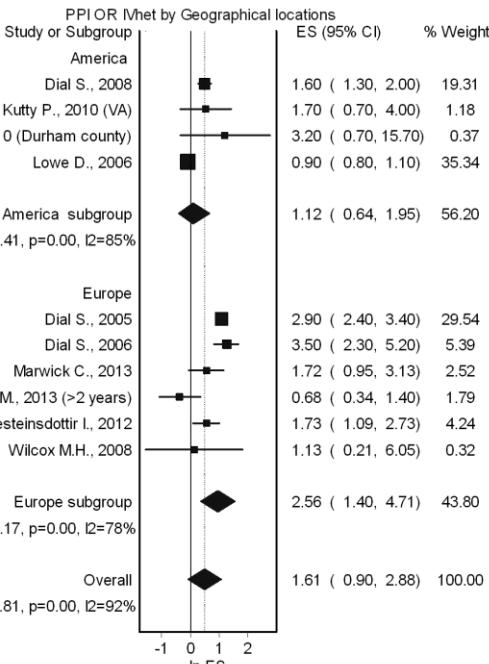
3.23.- Renal failure

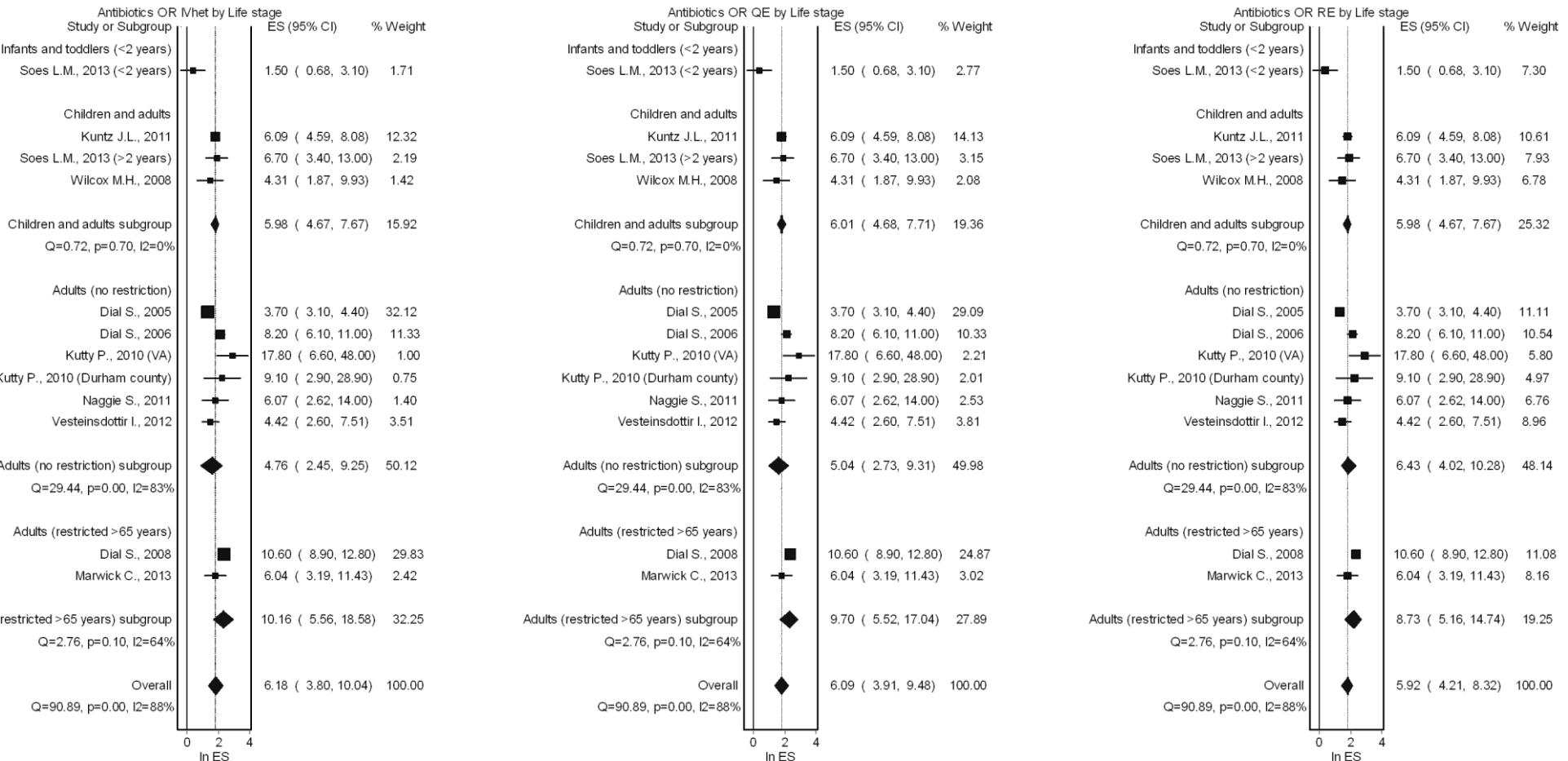


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2 Appendix 4.- Sensitivity analysis
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33 4.1.- Antimicrobials by location
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4.3.- Antimicrobials by life stage

