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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:** | 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.<br><br>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.<br><br>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 |

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

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

Running title: Meta-analysis of risk factors for CA-CDI

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## ABSTRACT

**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.

**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.

**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 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.

## INTRODUCTION

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

Research, including through meta-analysis, has attempted to describe the risk of CDI specifically in the community setting and found that clindamycin, fluoroquinolones, cephalosporins, macrolides, penicillins and sulphonamides/trimethoprim are associated with an increased CA-CDI risk.[10,11] The evidence however remains uncertain as these meta-analyses used the random-effects (RE) model which has been questioned for its overconfident results.[12] Exposure to gastric-acid suppressive drugs[3-5,13-15] and the presence of comorbidities[6-8] are associated with an increased risk of HA-CDI; but as with antimicrobials, the evidence remains inconclusive in the community setting. Therefore, the current meta-analysis was undertaken to pool the evidence from observational studies so that the magnitude and direction of the association between commonly prescribed medications and comorbidities with CA-CDI can be documented.

## METHODS

### Search methodology

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

### Eligibility criteria

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

### Study selection and data extraction

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

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

**Quality assessment**

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

**Statistical analyses**

The outcome measure was the odds ratio (OR) for the association of CA-CDI with exposure to risk factors such as antimicrobial drugs, gastric acid suppressant drugs (proton-pump inhibitors [PPI] and histamine-2-receptor antagonists [H2RAs]), non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, steroids and the presence of comorbidities. The OR was pooled using three meta-analytic models. This was justified because some have expressed skepticism regarding the appropriateness of the conventional RE model[17] due to its documented underestimation of the statistical error, which leads to overconfident results.[12,18-20] The other two models that were used were the quality-effects (QE) model,[21,22] and a novel

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

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

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

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

## RESULTS

### Yield of search strategy

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

There was overlap in subjects between 2 sets of publications. Two publications (Dial et al., 2005[26] and Delaney et al., 2007[27]) used data from the UK General Practice Research Database (GPRD) between 1994-2004 and a positive toxin test result for CDI as case definition to assess the risk of CA-CDI with antimicrobial exposure. Although, Dial et al., 2006[28] also used data from the UK GPRD, the authors reported that there was no overlap between this and Dial et al., 2005[26] as they used different case definitions for CDI.[28] Additionally, two publications (Soes et al., 2013a[29] and Soes et al., 2013b[30]) reported results from the same Danish cohort. Therefore, Delaney et al., 2007[27] and Soes et al., 2013b[30] were excluded from the analyses.

### Characteristics of the included studies

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

positive *C. difficile* culture in the case definition and another study[32] used a combination of *C. difficile* culture or toxin test results in the case definition. All studies evaluated exposure to medication and presence of comorbidities for at least 6 and 12 weeks prior to the index date, respectively (Table 1). The quality score of the studies ranged from 9 to 13 out of 17 (Table 2).

**Quantitative synthesis**

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

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

**Sensitivity analysis**

A sensitivity analysis was only possible for antimicrobial and PPI exposure because of the small number of studies in the other categories. When stratifying the studies by geographic location, the sensitivity analysis showed that antimicrobial exposure had a greater

association with CA-CDI in the USA (OR:9.16; 95%CI: 5.47-15.34) compared to European countries (OR:4.54; 95%CI: 2.68-7.70; Appendix 4.1). Conversely, exposure to PPIs had a stronger association with CA-CDI in Europe (OR:2.56; 95%CI: 1.40-4.71) compared to the USA (OR:1.12; 95%CI: 0.64-1.95; Appendix 4.2).

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

**Publication bias**

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

## DISCUSSION

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

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

Previous studies found that gastrointestinal comorbidities such as IBD[6] and cirrhosis[8] were associated with a worse prognosis in patients with CDI. Similarly, congestive heart disease, chronic pulmonary disease, renal failure and malignancies were also associated with higher mortality rates among inpatients with CDI.[7] Among the comorbidities examined in this meta-analysis, IBD was the strongest risk factor for CA-CDI followed by renal failure and haematological cancers. In patients with the described comorbidities, early identification and prompt treatment of CA-CDI may reduce mortality rates. The associations found

between CA-CDI and comorbidities may be confounded by medication exposure given that polypharmacy is common among patients with multiple comorbidities. Furthermore, the heterogeneous definition of CA-CDI across the studies (i.e. not hospitalized the year prior to the index date versus not hospitalized 6 weeks prior to the index date) may also be a source of misclassification between CA- and HA-CDI, considering that patients with multiple comorbidities are more likely to be admitted to hospitals.

The sensitivity analyses suggested that risk of CA-CDI with exposure to antimicrobial and PPI differed between Europe and America. The observed difference might be due to the dissimilar prescription of antimicrobials[38] and/or the presence of different strains of *C. difficile* in Europe and America.[39] Similarly, the risk of CA-CDI with exposure to antimicrobials and PPI varied among the life stages. These findings were consistent with Sandora et al.[40] who reported a negative correlation between age and CA-CDI among paediatric populations and with Lessa et al.[41] who reported a higher incidence of CDI among patients at both extremes of life (1-4 years of age and above 65 years of age). In the past two decades, a 12-fold increased incidence of CA-CDI among the paediatric population[42] and numerous outbreaks in long-term-care facilities[43] have been reported, indicating that infants, toddlers and older adults should be considered at high risk of CA-CDI.

Although a comprehensive systematic search for studies was carried out, publication bias could have resulted in more positive associations being published such as those between CA-CDI and exposure to cephalosporins, fluoroquinolones, macrolides, and penicillins and the presence of congestive heart disease and GERD. The actual risks attributable to these risk factors could be less than what we have reported. Nevertheless, heterogeneity across studies could also result in effect size asymmetry and this represents an alternative explanation to selective publication of positive results.

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 1 error. Moreover, the assumption of normally distributed random effects is not easily verified.[44] The use of a moment-based common variance[17] 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

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

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

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## TABLES AND FIGURES

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

| Author, publication year | Data source | Study period | Study design | Study population | Age, years case/control mean (SD) years | Male, % case/control | Community-acquired definition | Case definition | Control definition | Matching | Exposure to medication or presence of comorbidity, days prior index date | N case/control |
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| Dial et al. 2005[26] & Delaney et al. 2007[27] | GPRD, UK | 1 Jan 1994 - 31 Dec 2004 | Case-control | ≥2 years registered in a general practice in the UK and ≥18 years old | 71.0(16) / 70.8(16) | 35 / 42 | Not hospitalized the year prior to the index date | Clinical diagnosis or positive toxin test results for CDI | No clinical diagnosis nor positive toxin test result for CDI | Practice location, age (±2 years) | Gastric acid suppressant, antimicrobials, NSAID, aspirin, 90<br><br>Comorbidity, 720 | 1233 / 12330 |
| Dial et al. 2006[28] | GPRD, UK | 1 Jan 1994 - 31 Dec 2004 | Case-control | Registered in the GPRD without clinical diagnosis or positive toxin | 65.0 (19.6) / 64.9 (19.5) | 36.6 / 41.5 | Not hospitalized the year prior to the index date | Prescription of oral vancomycin therapy | No prescription for oral vancomycin | Practice location, age (±2 years) | Gastric acid suppressant, antimicrobials, 90<br><br>Comorbidity, | 317 / 3167 |

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| | | | | test results for CDI 30 days to 1 year prior the index date | | | | | | | 720 | |
| 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 metronidazole or oral vancomycin 90 days prior 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 with primary diagnosis of CDI (ICD-9 code 008.45) | No primary diagnosis of CDI during the first hospital admission | Unmatched<br>Index date and date of first hospital admission | Antimicrobials, 45<br>Comorbidity, 720 | 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 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 (ICD-9 code 008.45) | No diagnosis of CDI on or before the index date | Unmatched<br>Index date | Gastric acid suppressant, antimicrobials, 180<br>Comorbidity, | 304 / 3040 |

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| | | | | | | | index date | | | | | |
| Kutty et al. 2010[31] † | VA infection control database and Surveillance database of the Duke University Hospital network, USA | Jan 2005 - Dec 2005 | Case-control | ≥18 years old | VA: 62 (38-85) / 64 (38-86) *<br><br>Durham County: 61 (20-101) / 55 (22-87) * | VA: 88 / 96<br><br>Durham County: 42 / 29 | No history of healthcare exposure within 8 weeks of the index date | Nonformed stool specimen with positive toxin test results for CDI | Outpatients with no clinical diagnosis of diarrhea or positive toxin test results for CDI | Unmatched | Gastric acid suppressant, antimicrobials, NSAID, 90<br><br>Comorbidity, NR | VA: 36 / 108<br><br>Durham County: 73 / 48 |
| Lowe et al. 2006[33] | Ontario Drug Benefit Program, Canadian Institute for Health Information Discharge Abstract Database, The Ontario Health Insurance | 1 Apr 2002 - 31 Mar 2005 | Nested case-control | ≥66 years old exposed to antimicrobials | 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 patients from long-term care or nursing homes | Hospitalized with diagnosis of CDI (ICD-10 code A04.7) | Outpatient | Index date, sex, age (±1 years), antimicrobials prescribed | Gastric acid suppressant, 90<br><br>Antimicrobials, 60<br><br>Comorbidity, 180 - 720 | 1389 / 12303 |

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

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|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Durham VA Medical Center, Salisbury VAMC and Asheville VAMC, USA | | | | | | facility. Not hospitalized during the 12-week period prior to the index | | | | 720 | |
| Soes et al. 2013[29,30] ‡ | 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)<br>≥2 years: 50 (2-94) / 50 (2-90) * | <2 years: 53 / 55<br>≥2 years: 25 / 28 | Not hospitalized during the 12-week period prior to the index or onset of symptoms within 48 hours of admission | Positive *C. difficile* culture | Negative *C. difficile* culture | Laboratory location, sex, age (±2 years if ≥5years; ±5 months if ≥6months and <4years; ±6 weeks if <6months) | Antimicrobials, 56<br>Gastric acid suppressant, NSAID, aspirin, 120<br>Comorbidity, 120 | <2 years: 121 / 213<br>≥2 years: 138 / 242 |
| Suissa et al. 2012[49] | 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 date | First positive toxin test results for CDI or first prescription | No clinical diagnosis, positive toxin test result for CDI or | Practice location, age (±2 years) | Gastric acid suppressant, antimicrobials, NSAID, aspirin, 90 | 929 / 10242 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | ≥18 years old | | | | of oral vancomycin | prescription of oral vancomycin | | Comorbidity, 720 | |
| Vesteinsdottir et al. 2012[45] | The National University Hospital of Iceland, Iceland | 1 Jul 2010 - 30 Jun 2011 | Case-control | ≥18 years old | 65 (56-80) / 65 (55-80) * | 42.3 / 42.3 | Not hospitalized during the 6-week period prior to the index or lived in a nursing facility and if hospitalized, diagnosed with CDI within the 72 hours of admission | Positive toxin test results for CDI | Negative toxin test results for CDI | Sex, age (±5 years), | Gastric acid suppressant, antimicrobials, 42<br><br>Comorbidity, 84 | 111 / 222 |
| Wilcox et al. 2008[50] | Cornwall and Leeds, UK | Jan 1999 - Dec 1999 | Case-control | Patients who had fecal sample submitted by their GP for microbiologi | 78 (4-100) / NR * | 44 / NR | Patients that attended the GP | Diarrhea and a positive toxin test results for CDI | Negative toxin test results for CDI | Sex, age categories | Antimicrobials, 180<br><br>Comorbidity, NR | 40 / 112 |

cal testing

*GPRD*: General Practice Research Database, *MED-ECHO:* Provincial hospital discharge summary, *VA:* Veterans Affairs, *ICD*: International Classification of Disease, *GP:* General practitioner, *NR:* Not reported, *Index date:* The date when the cases were identified

* Age, median (range) years

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

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

**Table 2.-** Modified Newcastle-Ottawa quality assessment scale for case-control studies included in the meta-analysis.

| 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) | *Qi* (total 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 |
| Suissa 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 |

(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 (0 points)

(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 a resident of a nursing home (1 point), No description (0 points)

(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), Other or no description (0 points)

(iv) Control selection: Community (2 points), Community and hospital (1 point), No description (0 points)

(v) Analysis adjusted for exposures other than the primary exposure of interest (sex, age, antimicrobial exposure, gastric acid-suppressive medication exposure or presence of comorbidities). Adjusted for: 5 factors (3 points), 3-4 factors (2 points), 1-2 factors (1 point), non adjusted (0 points)

(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 (0 points)

(vii) Method of ascertainment of exposure for cases and controls: Same (1 point), Different (0 points)

**Table 3**.- Pooled effect size using the IVhet model, QE model and the RE model

| Exposure | IVhet model<br>OR (95% CI) | QE model<br>OR (95% CI) | RE model<br>OR (95% CI) | Heterogeneity<br>$I^2$ 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 |

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

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

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

**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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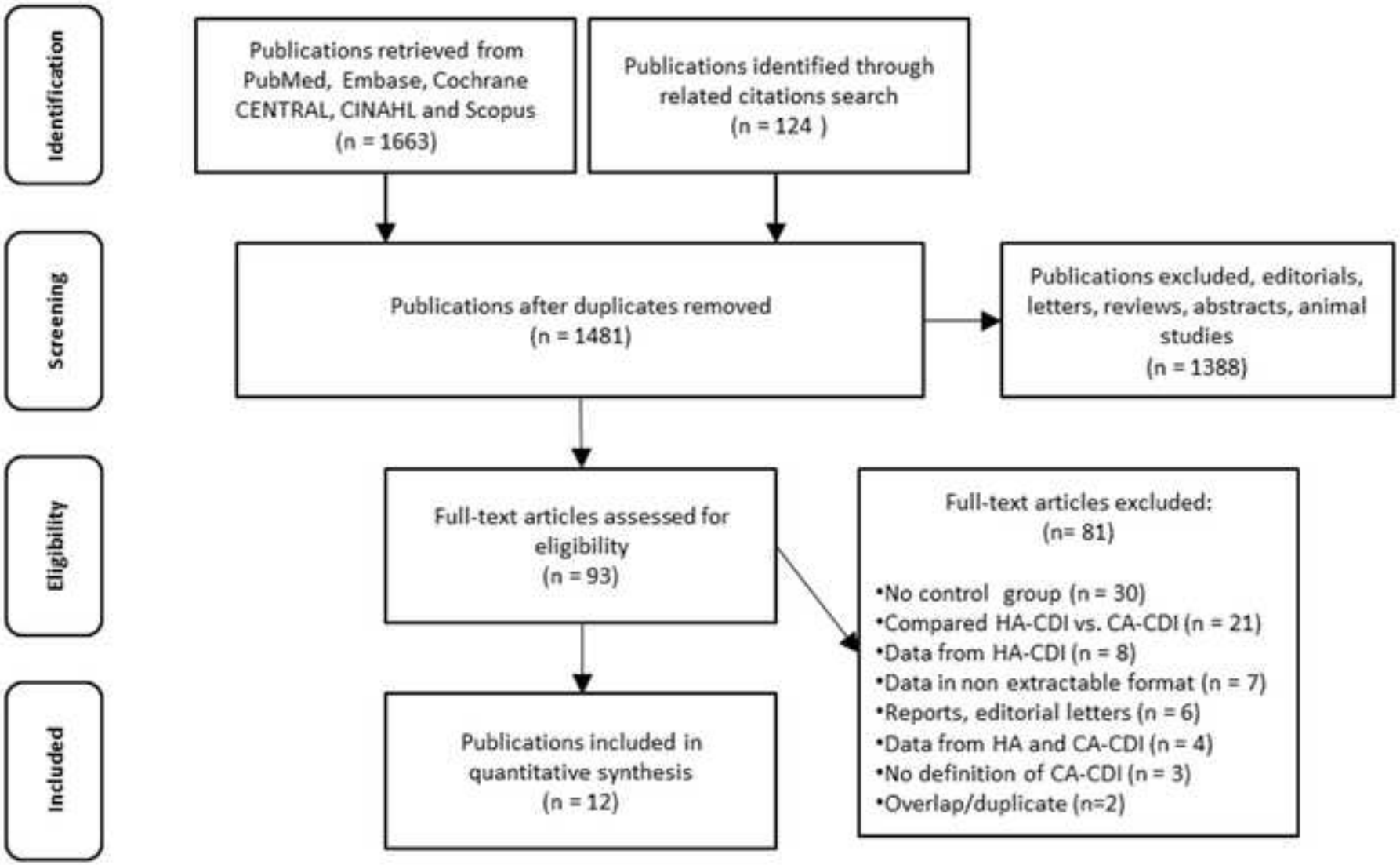
Figure 1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Screening
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Publications after duplicates removed (n = 1481)
Publications excluded, editorials, letters, reviews, abstracts, animal studies (n = 1388)
Full-text articles assessed for eligibility (n = 93)
Full-text articles excluded: (n= 81)
•No control group (n = 30)
•Compared HA-CDI vs. CA-CDI (n = 21)
•Data from HA-CDI (n = 8)
•Data in non extractable format (n = 7)
•Reports, editorial letters (n = 6)
•Data from HA and CA-CDI (n = 4)
•No definition of CA-CDI (n = 3)
•Overlap/duplicate (n=2)
Publications included in quantitative synthesis (n = 12)

**APPENDICES**

**Appendix 1.-** Search strategies

**PubMed**

((((("Community-Acquired Infections"[MeSH Terms]) OR (Community OR Communities OR Residential OR Neighborhood OR Neighborhoods OR Neighbourhood OR Neighbourhoods)))

AND

("Clostridium"[Mesh] OR Clostridium))

AND

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

**CINAHL**

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

AND

(MH "Clostridium+") OR Clostridium

AND

Difficile

**Cochrane CENTRAL**

((((("Community-Acquired Infections"[MeSH Terms]) OR (Community OR Communities OR Residential OR Neighborhood OR Neighborhoods OR Neighbourhood OR Neighbourhoods)))

AND

("Clostridium"[Mesh] OR Clostridium))

AND

Difficile

**Scopus**

(TITLE-ABS-KEY(community OR communities OR residential OR neighborhood OR neighborhoods OR neighbourhood OR neighbourhoods)

AND

TITLE-ABS-KEY(clostridium)

AND

TITLE-ABS-KEY(difficile))

**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 | | Aspiring | | COPD | | IBD | | Solid cancer | |

| Study ID | Study characteristics | | | | | | | | Demographic data | | | | | Exposed group characteristics | | Control group characteristics | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Authors, year | Location / country | Sampling time frame | Follow-up (days) | Data source | Study design | Selection of cases / Inclusion criteria | Selection of controls | Definition of community acquired | Exposure (days) | Sample size | CDI Cases | Non CDI cases | Age (years), mean (SD) | Male, n(%) | Cases | Non-cases | Cases | Non-cases |
| | | | | | | | | | | | | | | | | | | |
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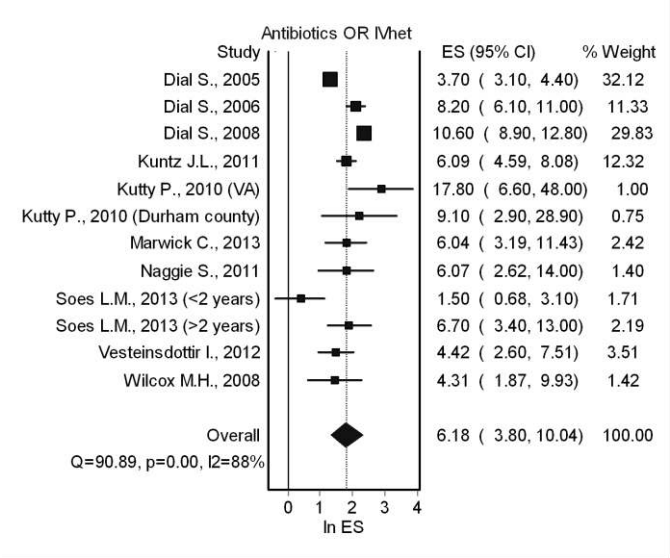
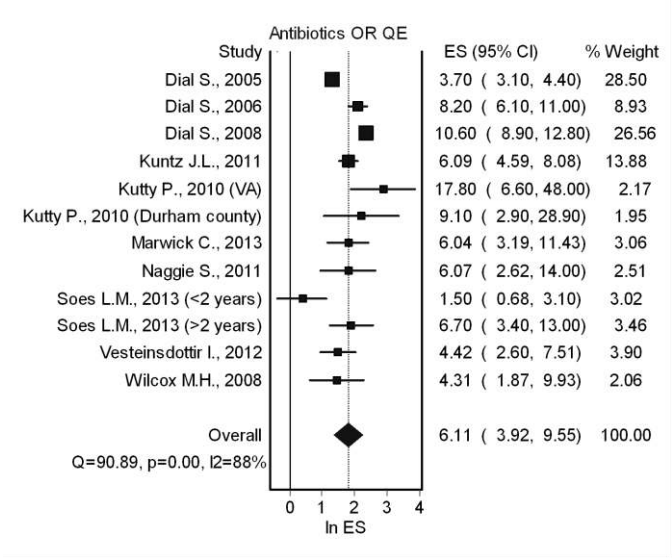
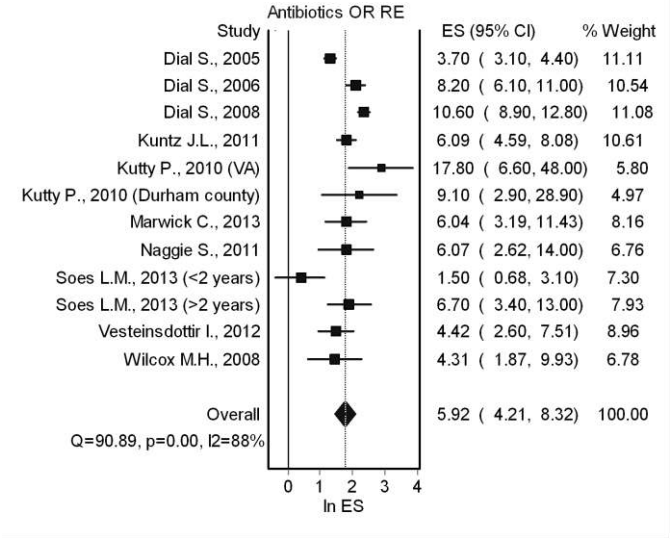
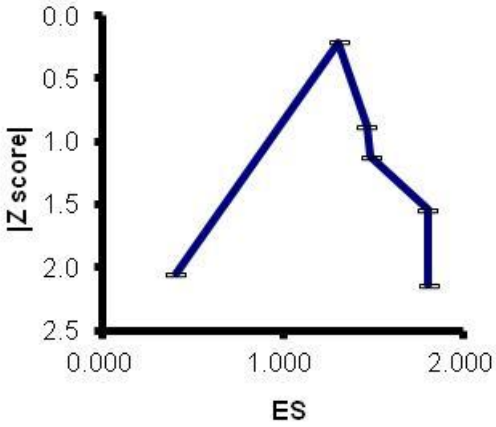
**Appendix 3.-** Forest, Funnel and Doi plots

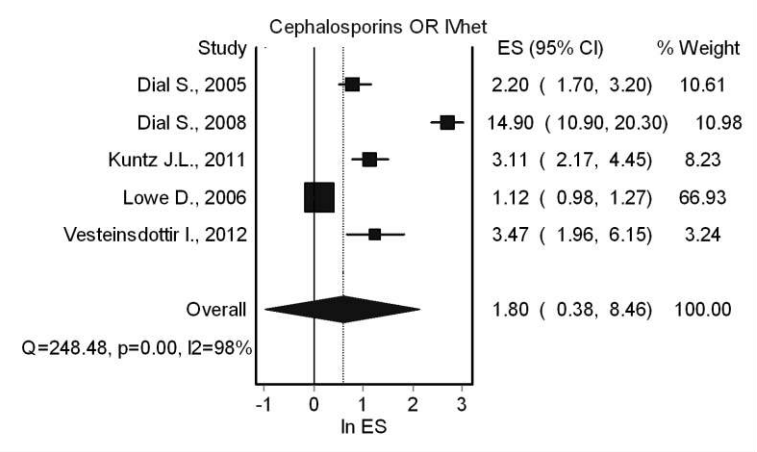


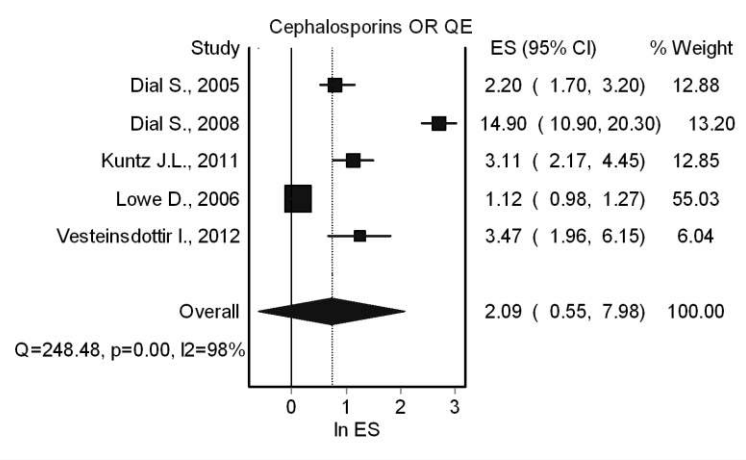



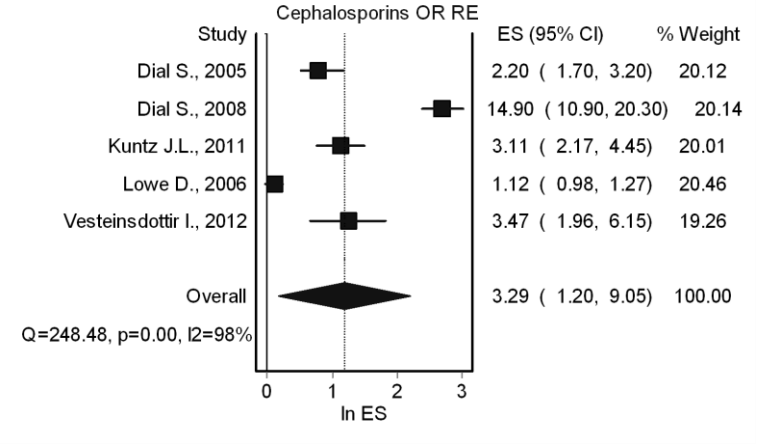



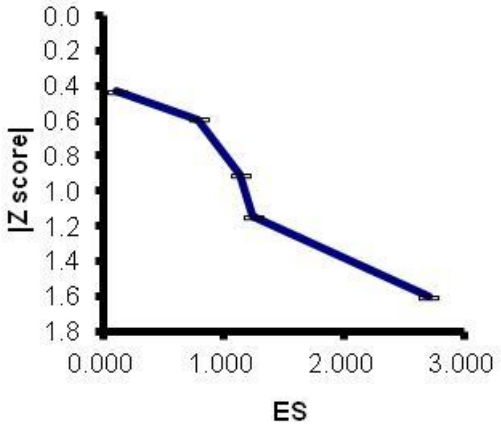




3.1.- Antimicrobials

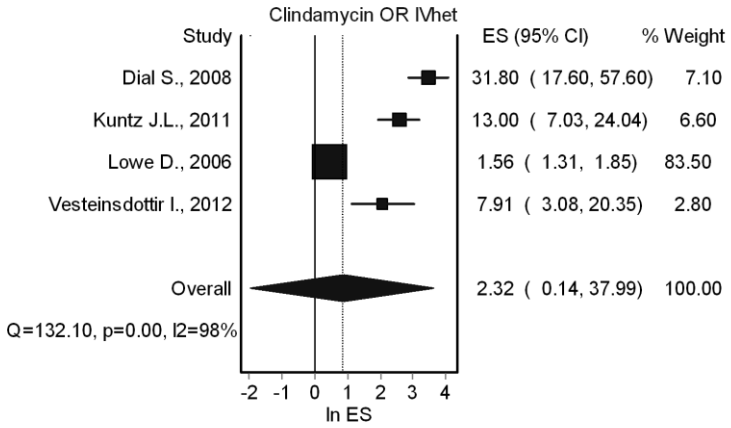


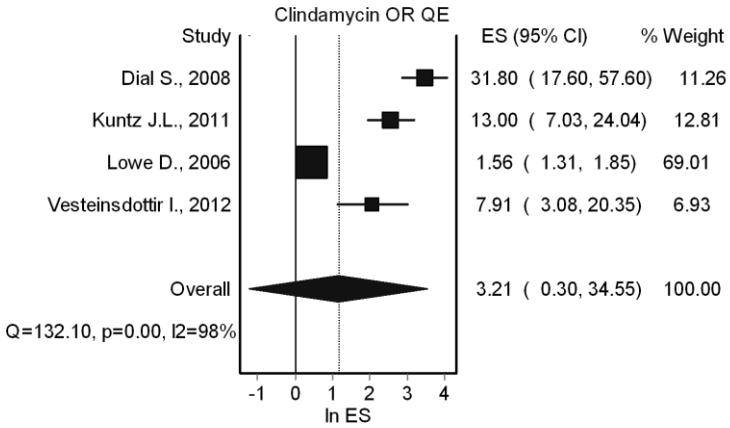



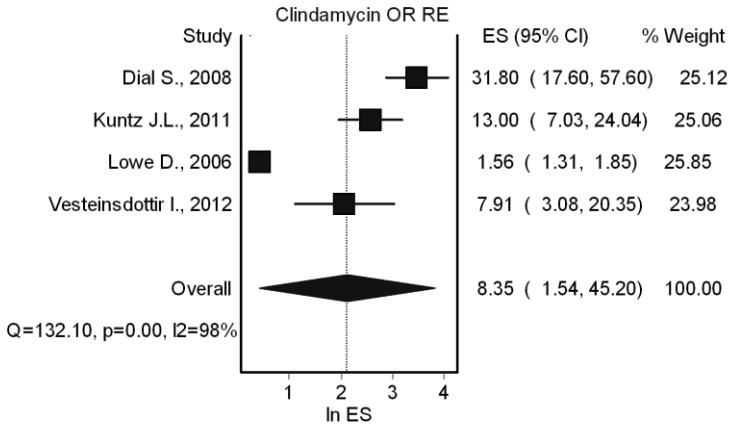




3.2.- Cephalosporins

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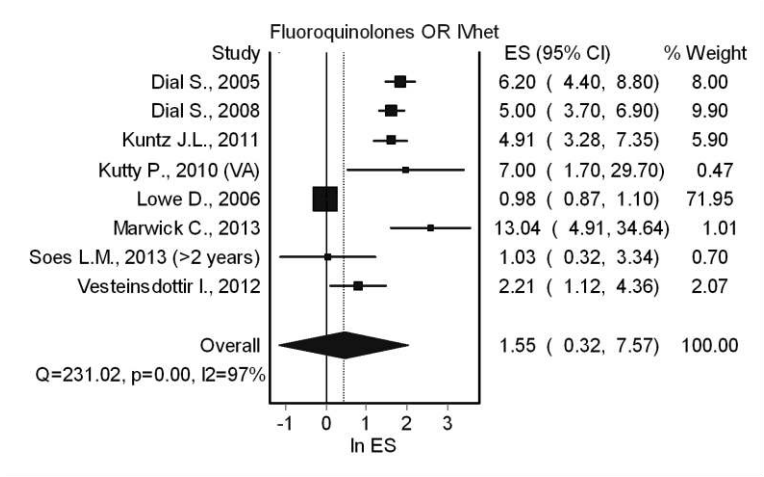


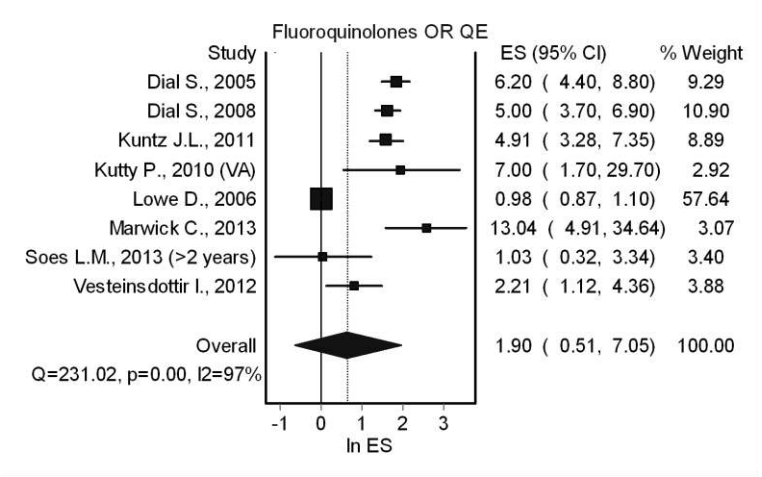


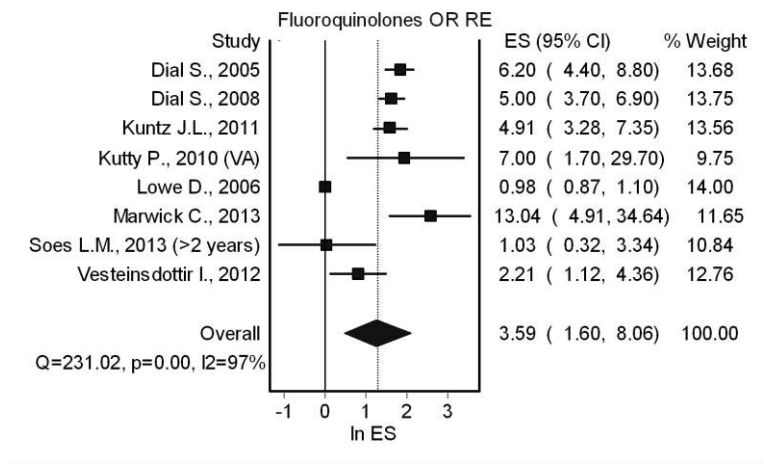


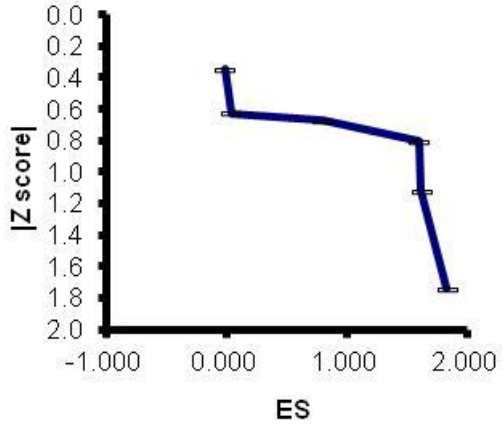


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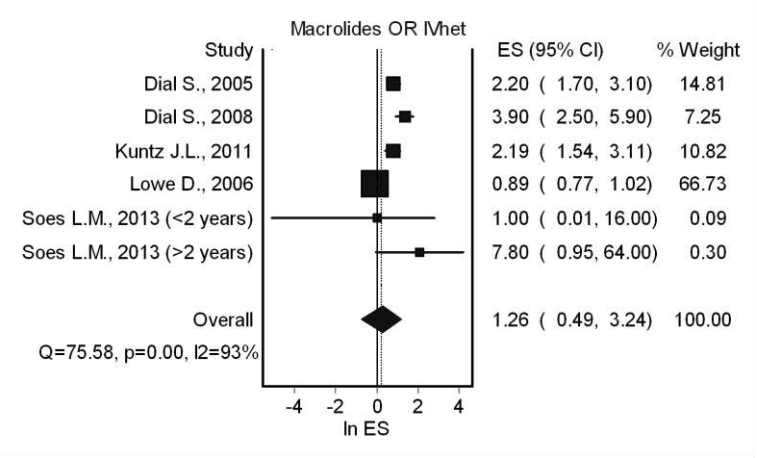
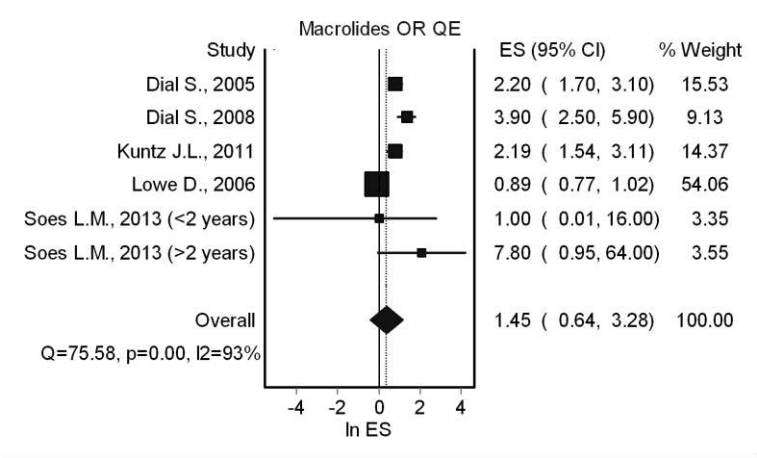
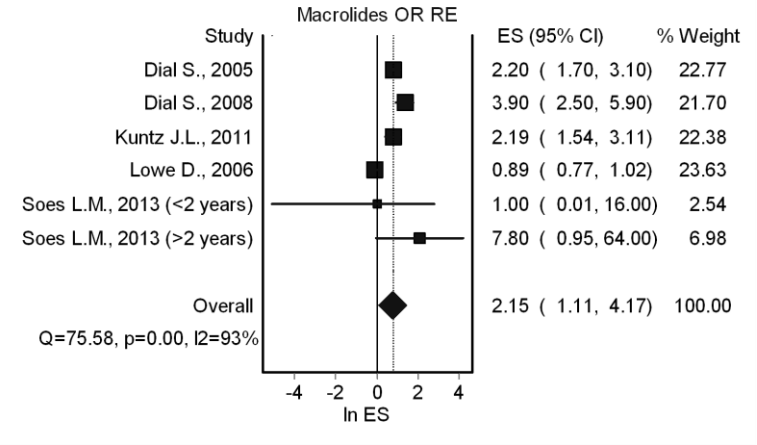
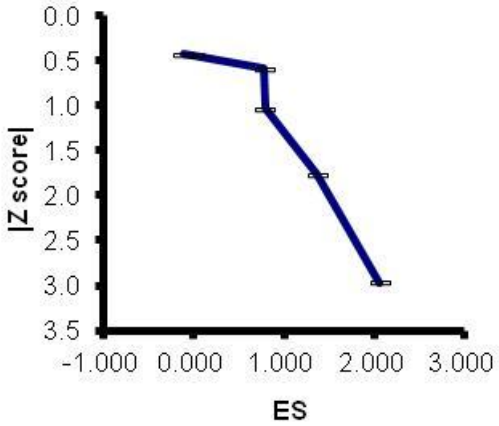
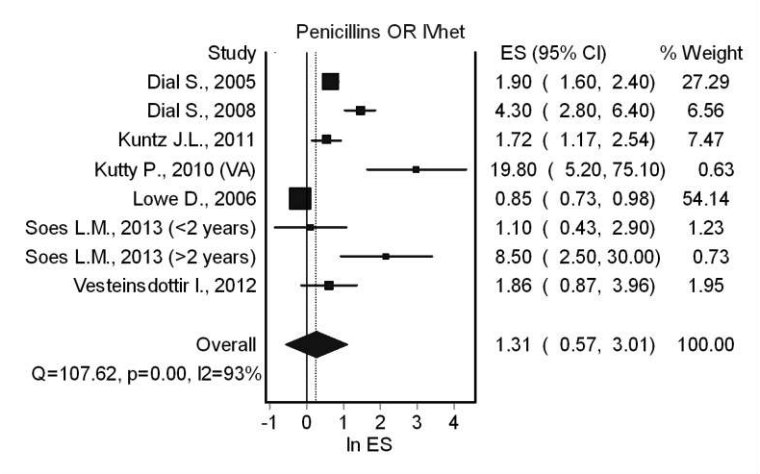


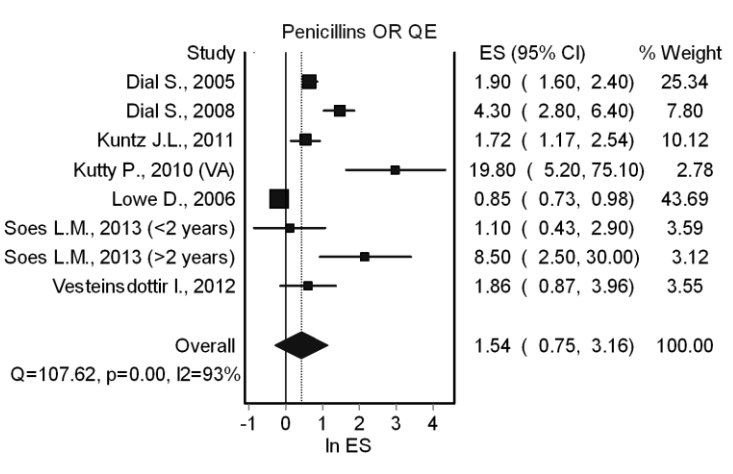



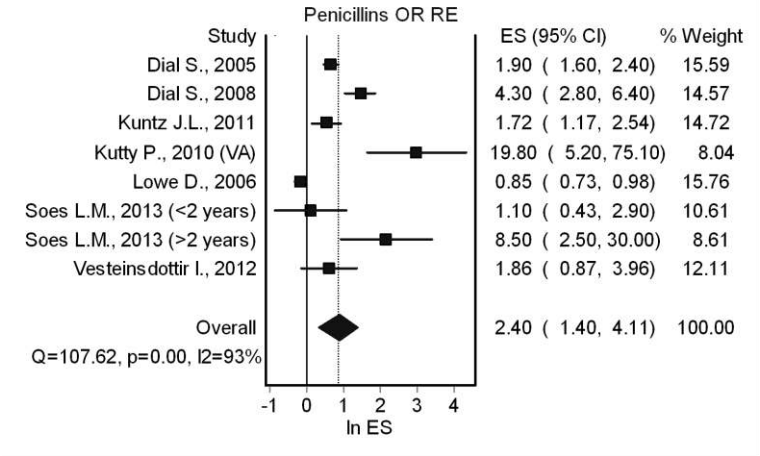



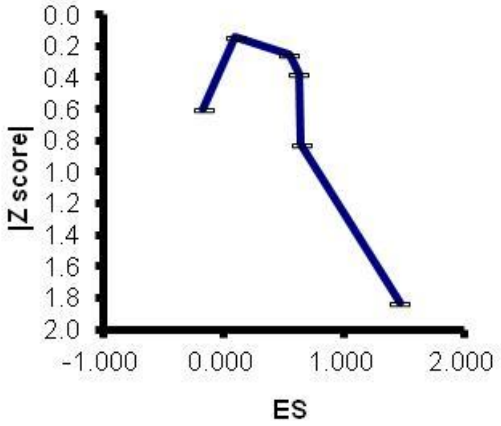




3.5.- Macrolides

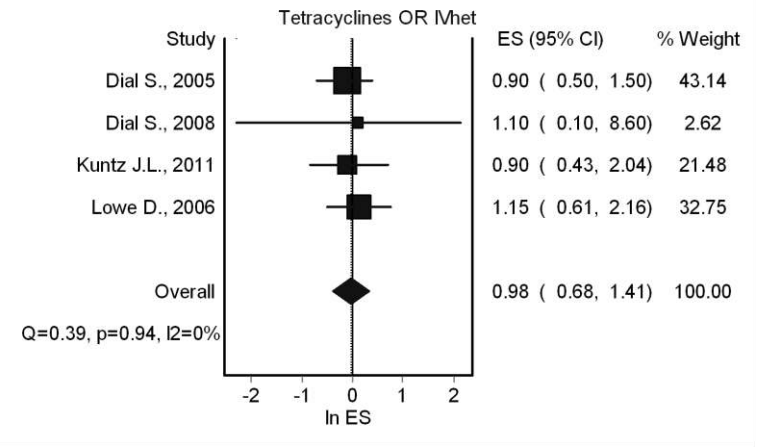


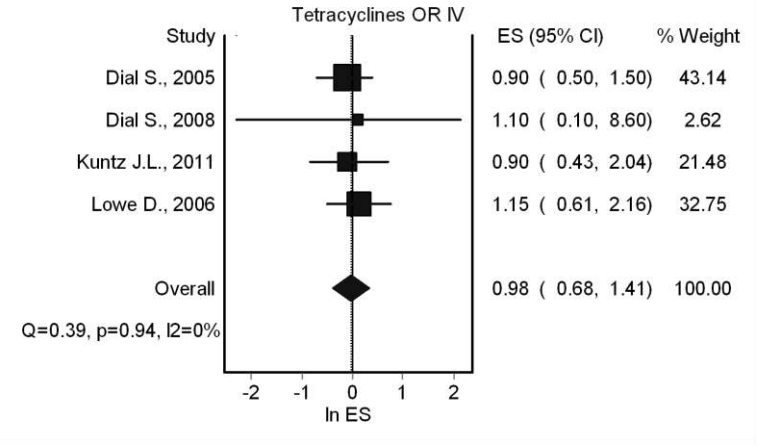



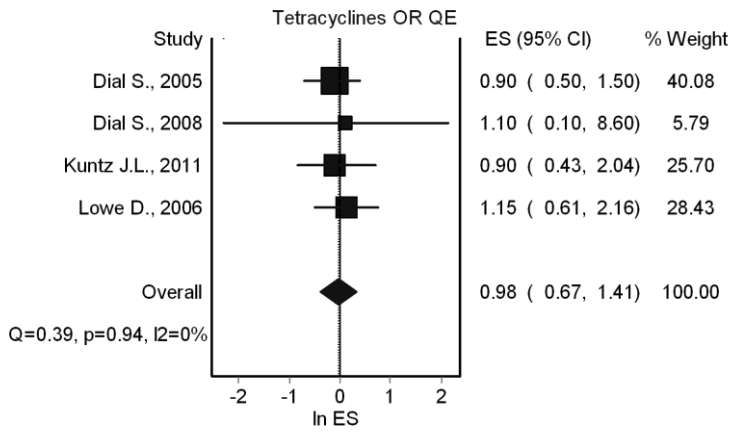



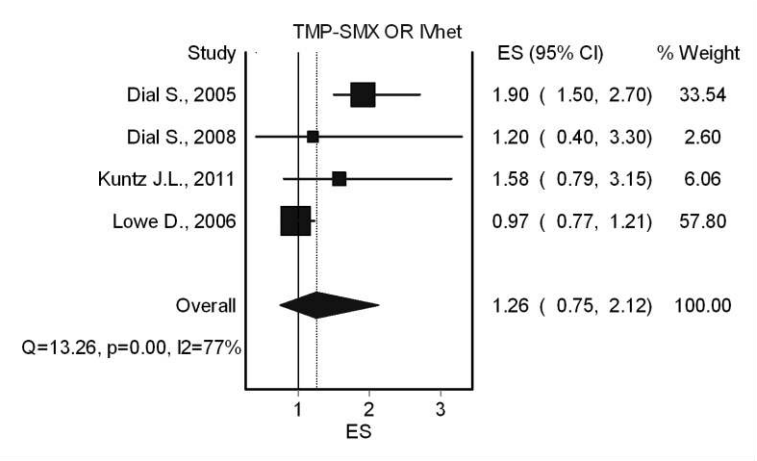

3.6.- Penicillins

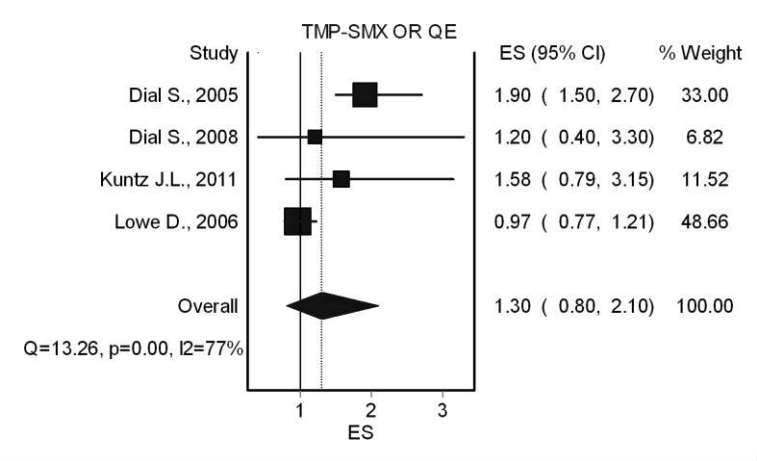


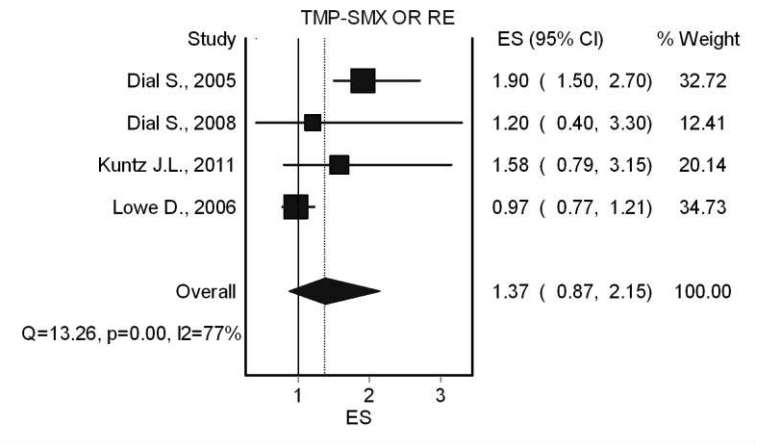



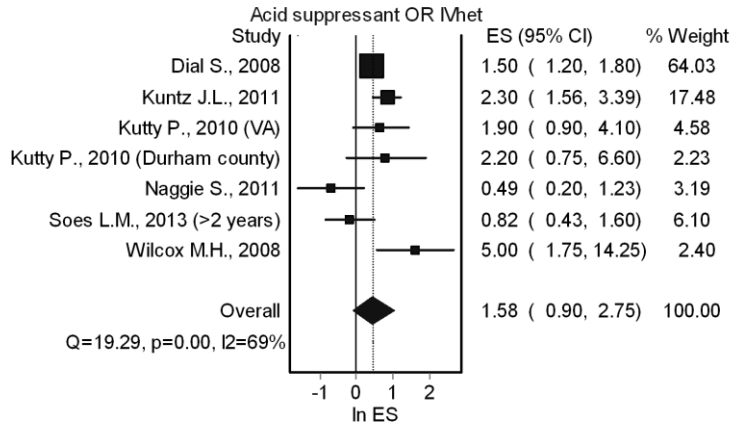

3.7.- Tetracyclines

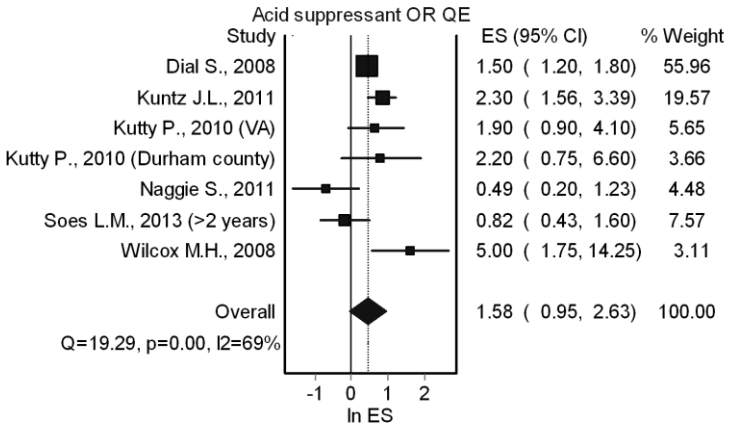


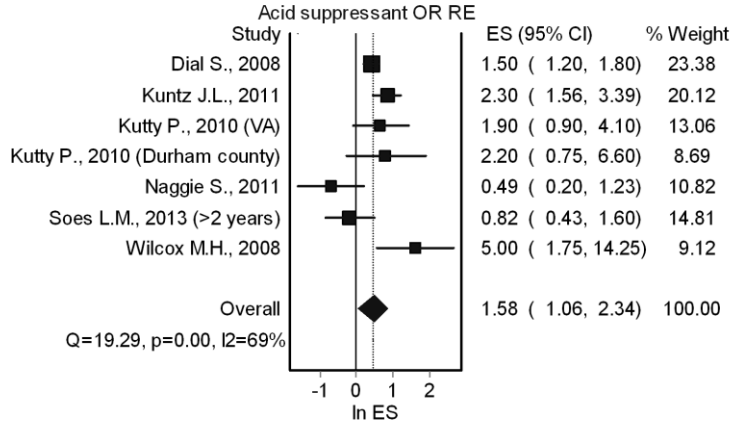



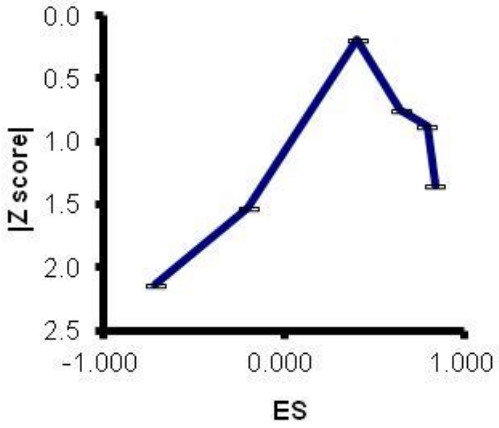




3.8.- Trimethoprim/sulfamethoxazole

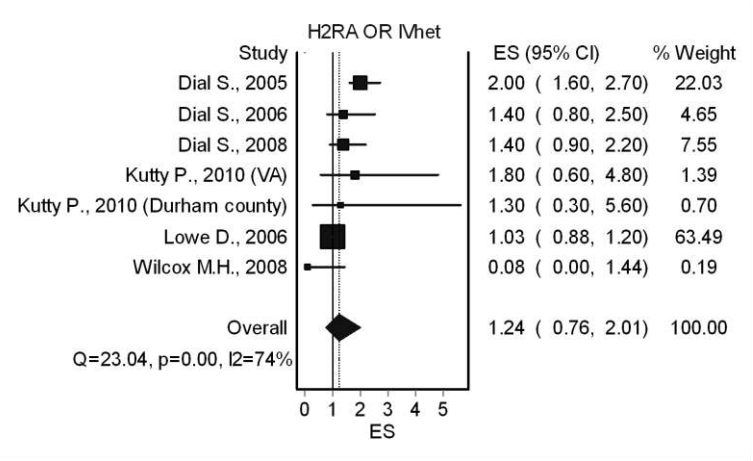


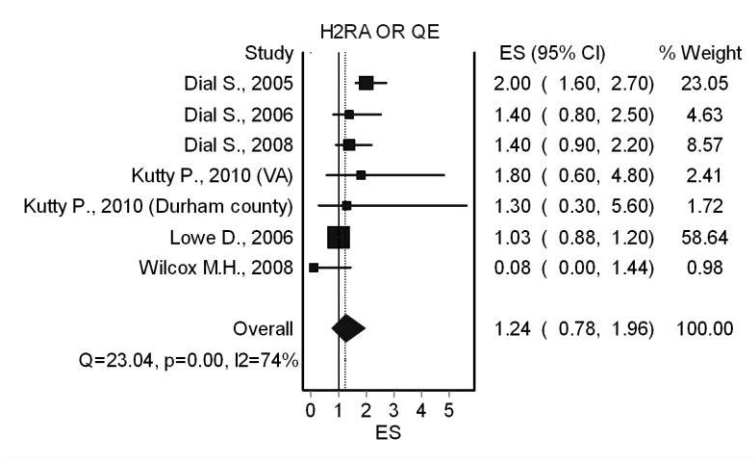



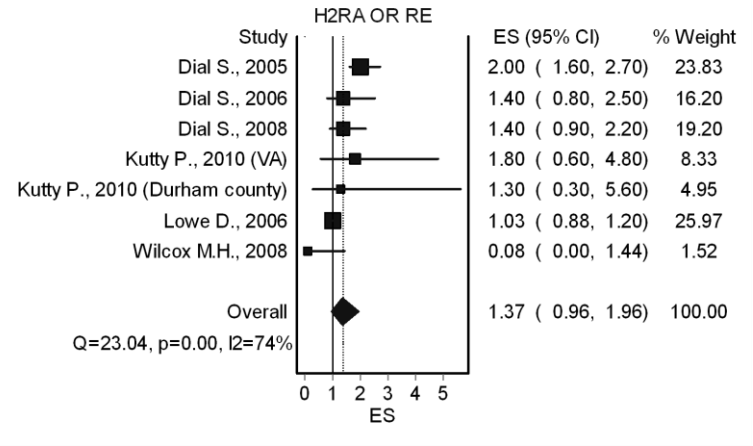



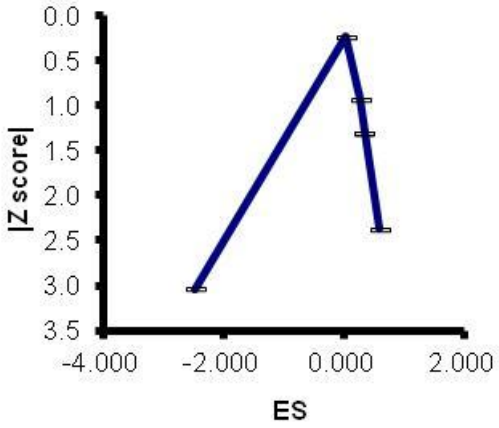




3.9.- Gastric acid suppressant

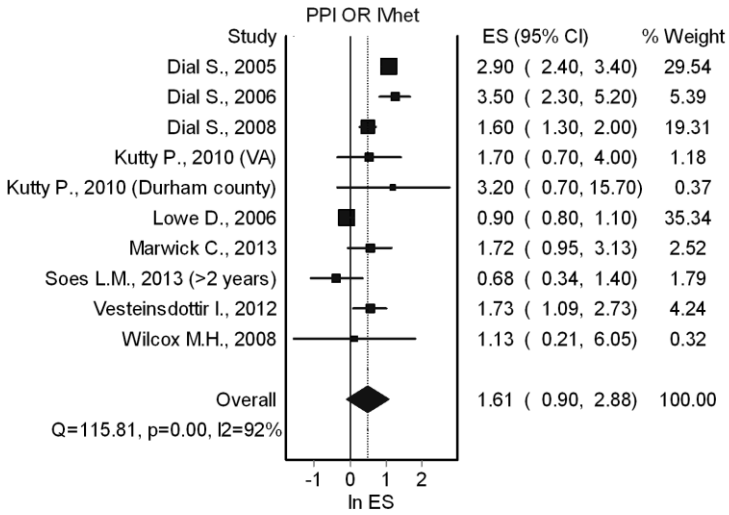


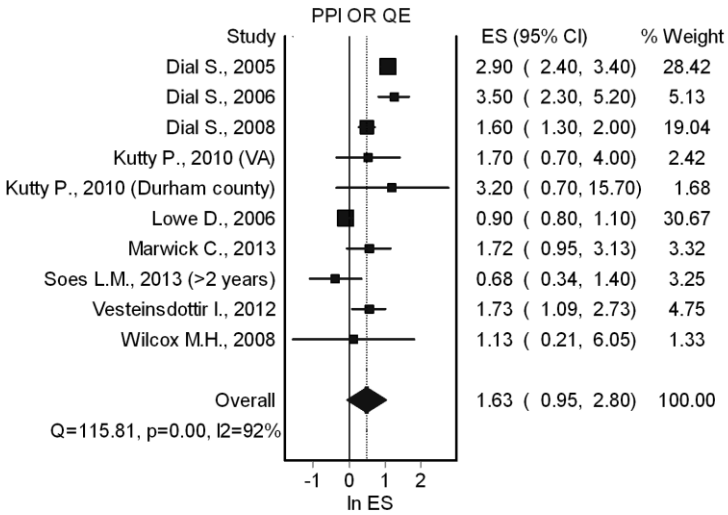



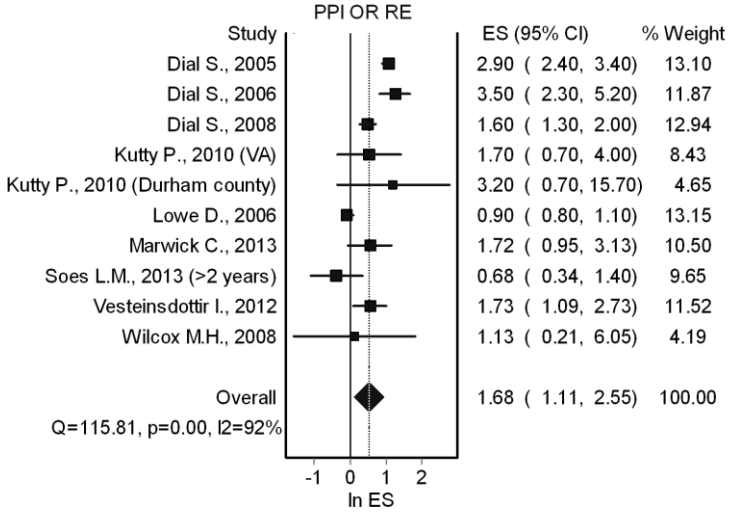



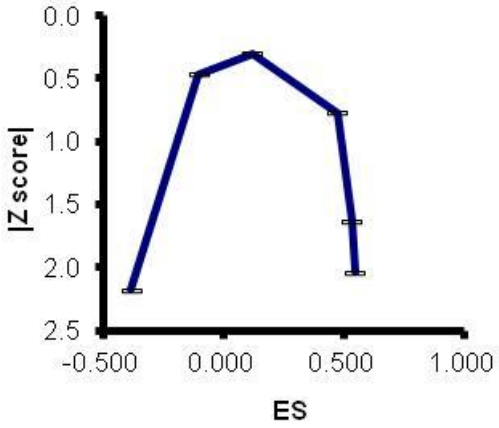




3.10.- Histamine-2 receptor antagonists

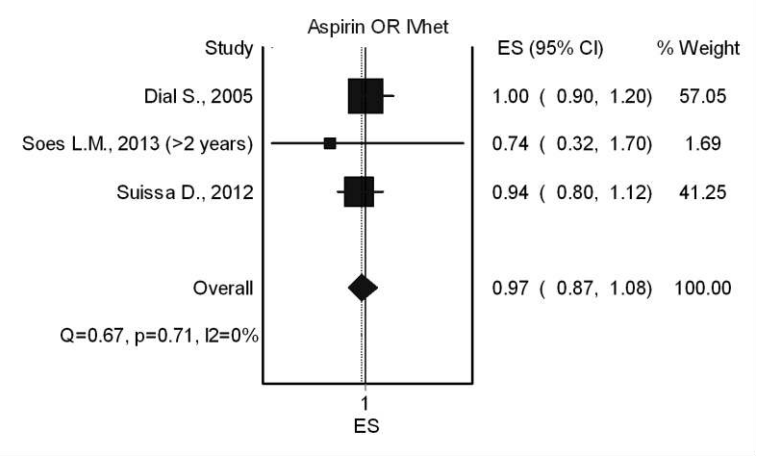


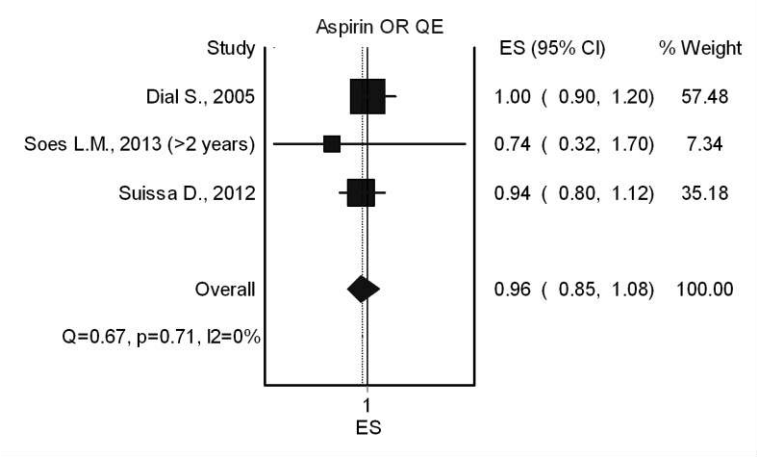




3.11.- Proton pump inhibitor


Aspirin OR IVhet
Study
ES (95% CI)
% Weight
Dial S., 2005
1.00 ( 0.90, 1.20) 57.05
Soes L.M., 2013 (>2 years)
0.74 ( 0.32, 1.70) 1.69
Suissa D., 2012
0.94 ( 0.80, 1.12) 41.25
Overall
0.97 ( 0.87, 1.08) 100.00
Q=0.67, p=0.71, I2=0%
1
ES


Aspirin OR QE
Study
ES (95% CI)
% Weight
Dial S., 2005
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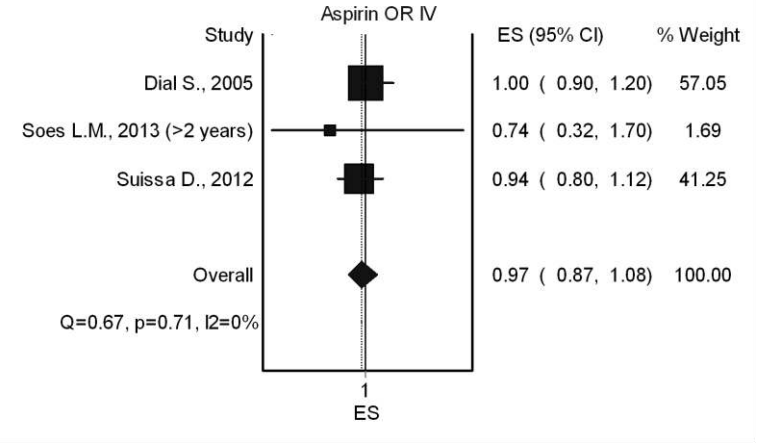
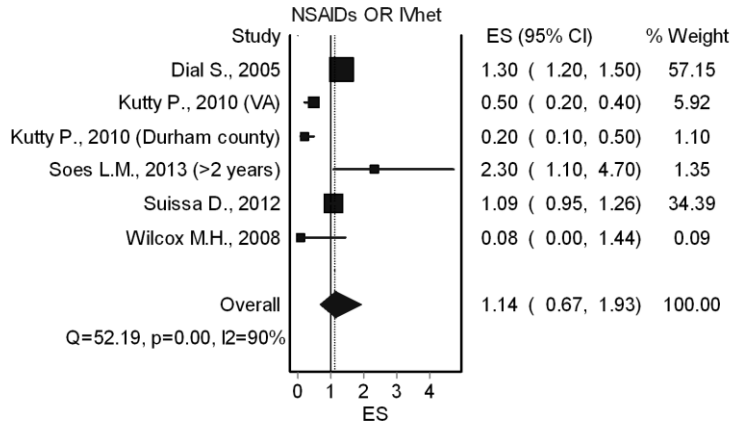
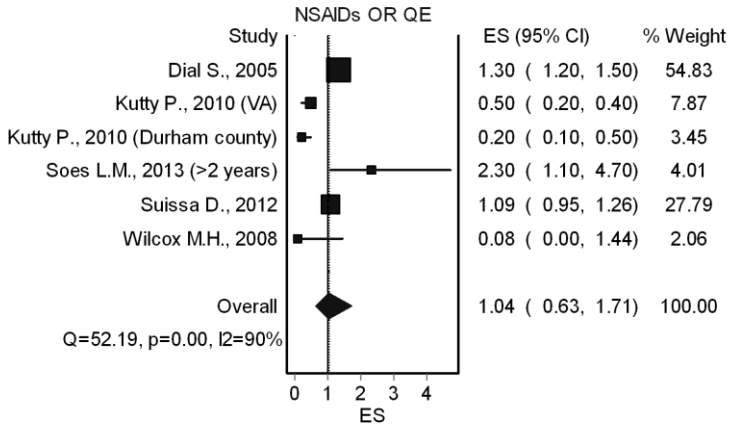
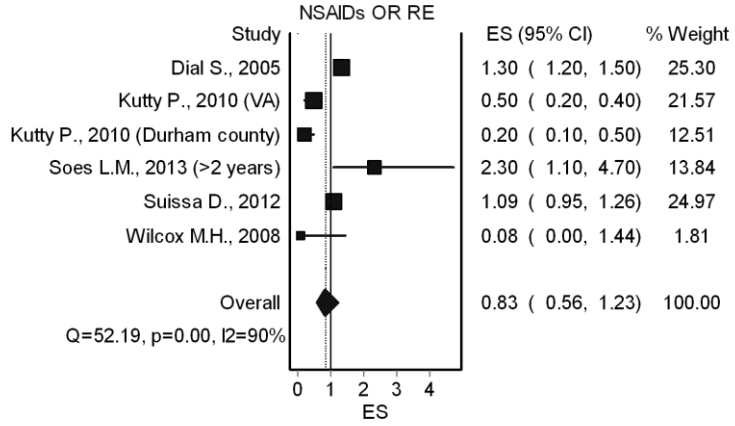
Soes L.M., 2013 (>2 years)
0.74 ( 0.32, 1.70) 7.34
Suissa D., 2012
0.94 ( 0.80, 1.12) 35.18
Overall
0.96 ( 0.85, 1.08) 100.00
Q=0.67, p=0.71, I2=0%
1
ES

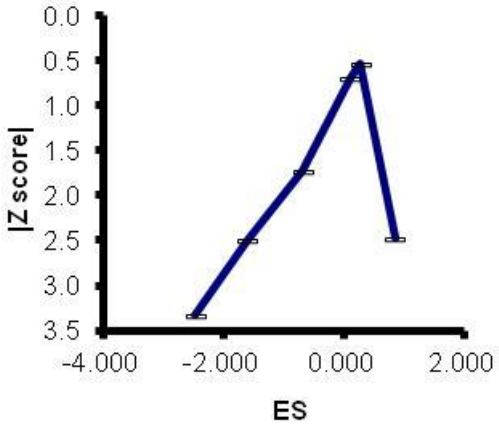

Aspirin OR IV
Study
ES (95% CI)
% Weight
Dial S., 2005
1.00 ( 0.90, 1.20) 57.05
Soes L.M., 2013 (>2 years)
0.74 ( 0.32, 1.70) 1.69
Suissa D., 2012
0.94 ( 0.80, 1.12) 41.25
Overall
0.97 ( 0.87, 1.08) 100.00
Q=0.67, p=0.71, I2=0%
1
ES

3.12.- Aspirin

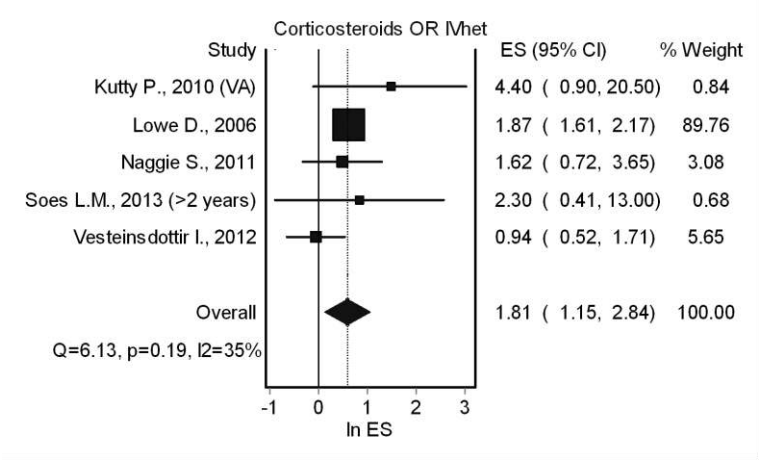


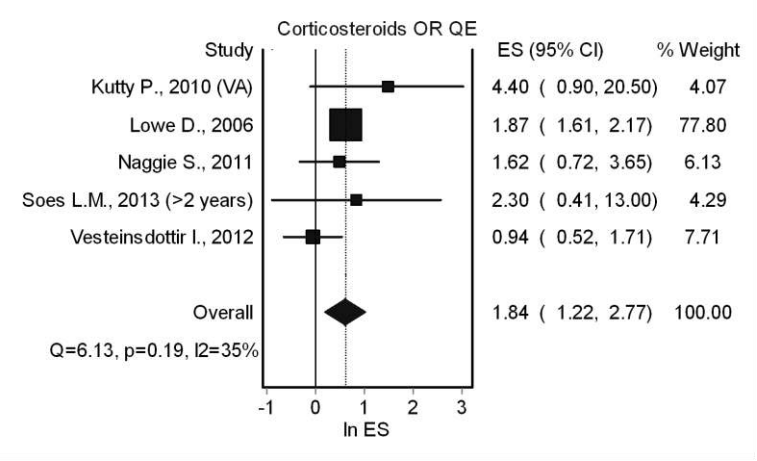



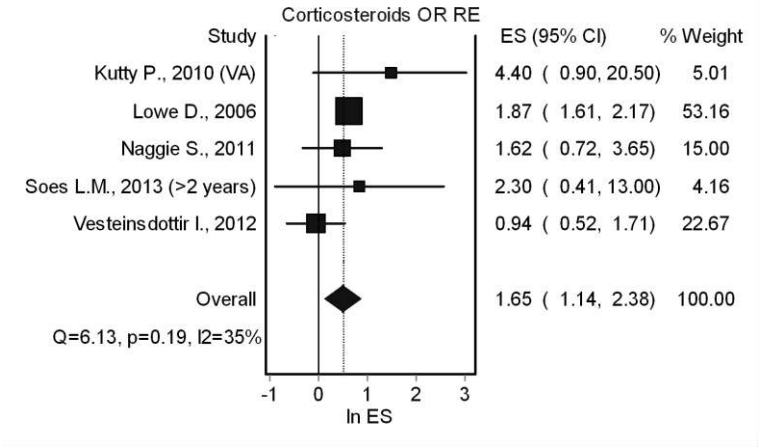



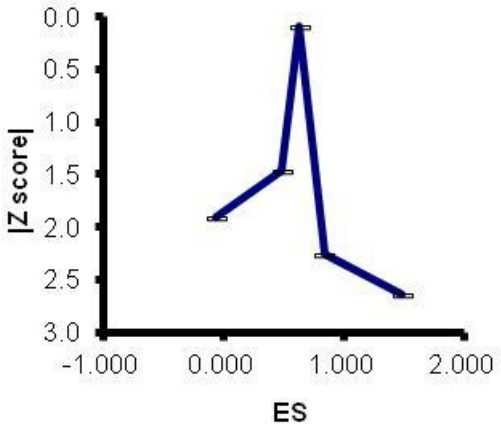




3.13.- Non-steroidal anti-inflammatory drugs

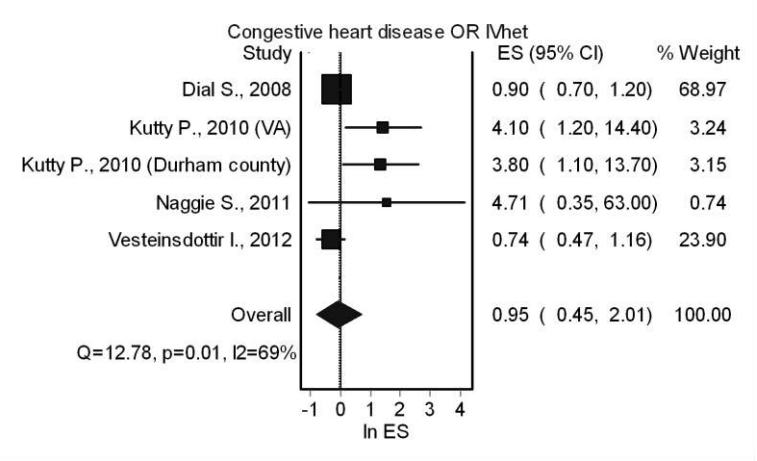


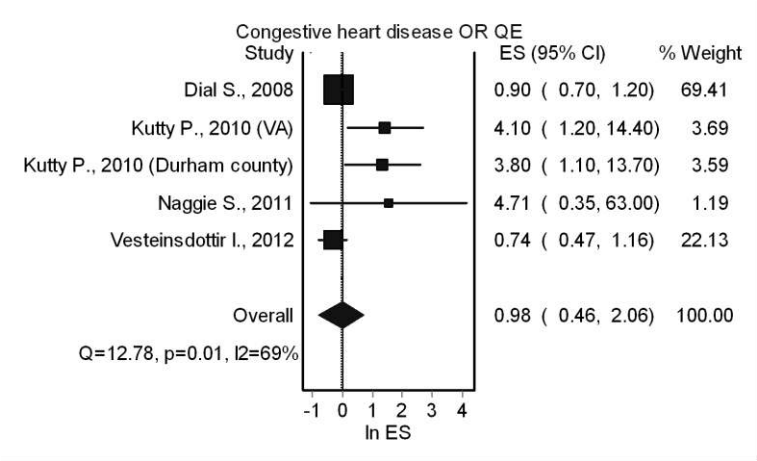



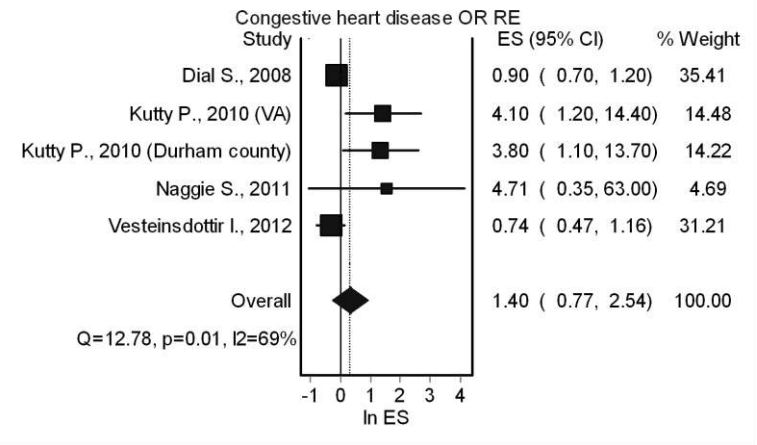



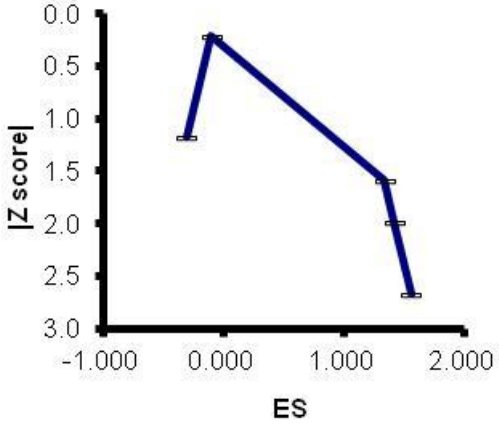




3.14.- Corticosteroids

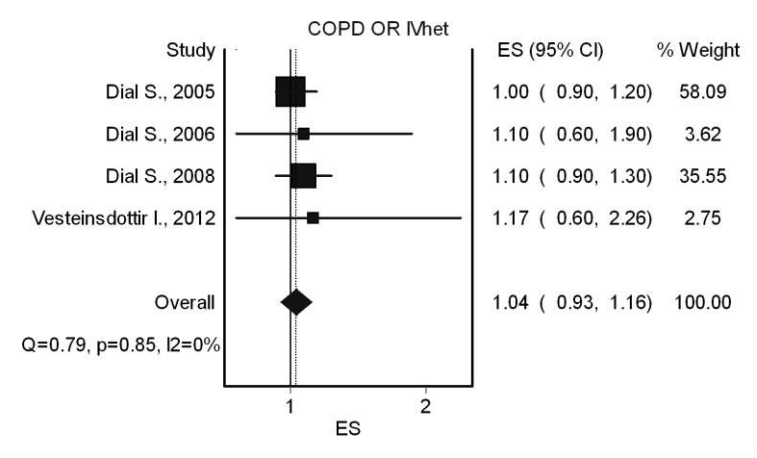


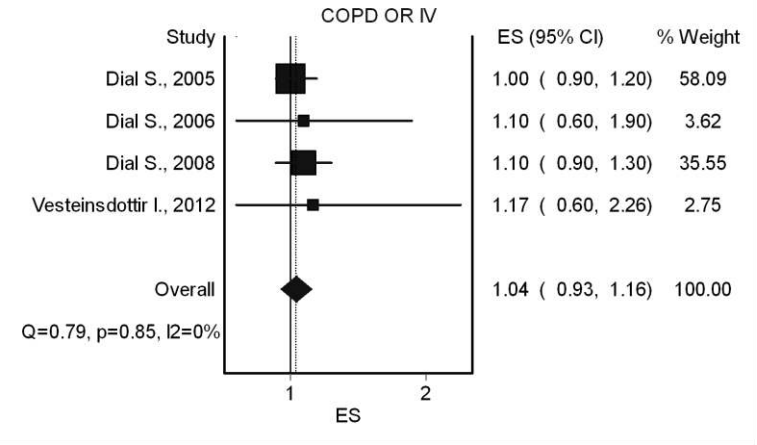



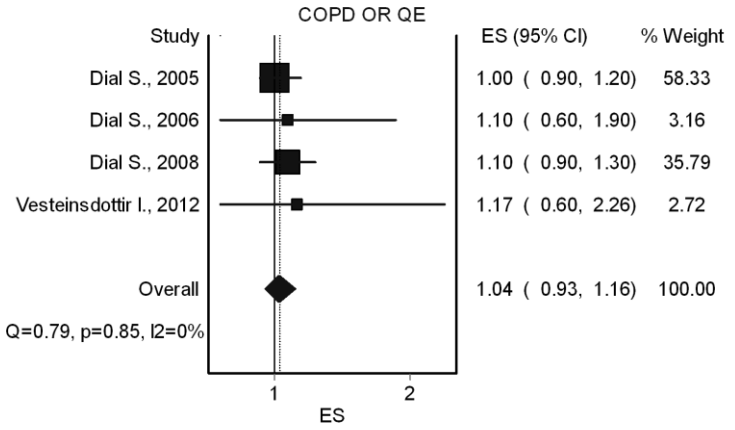



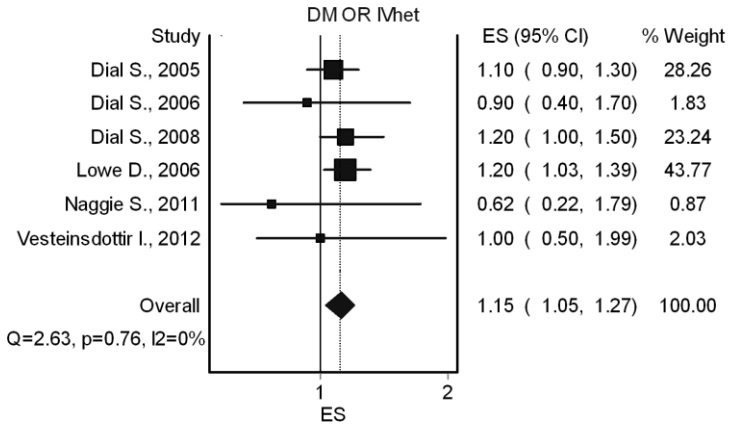

3.15.- Congestive heart disease

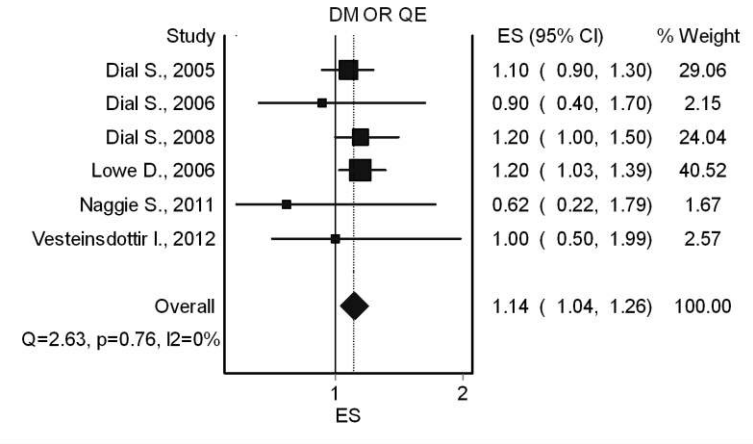


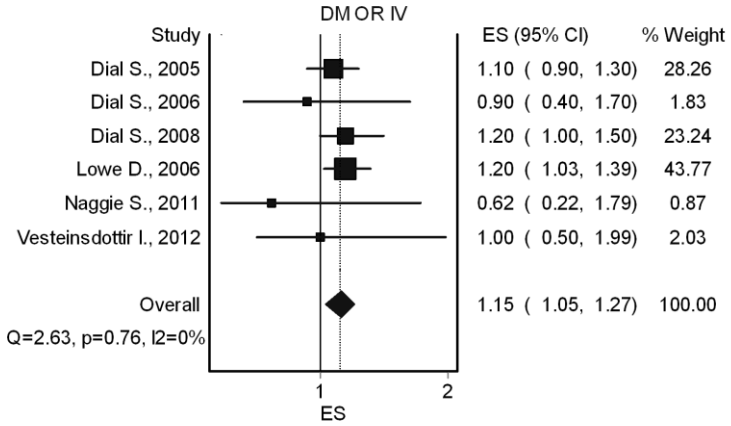



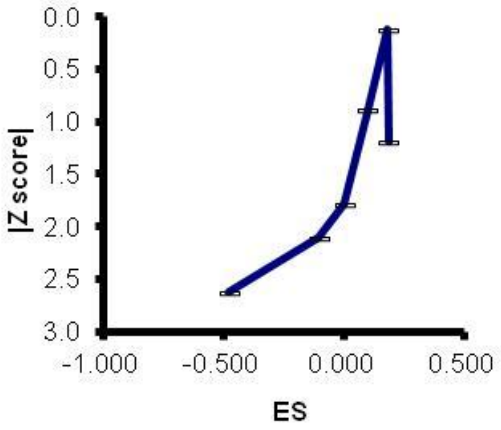




3.16.- Chronic obstructive pulmonary disease

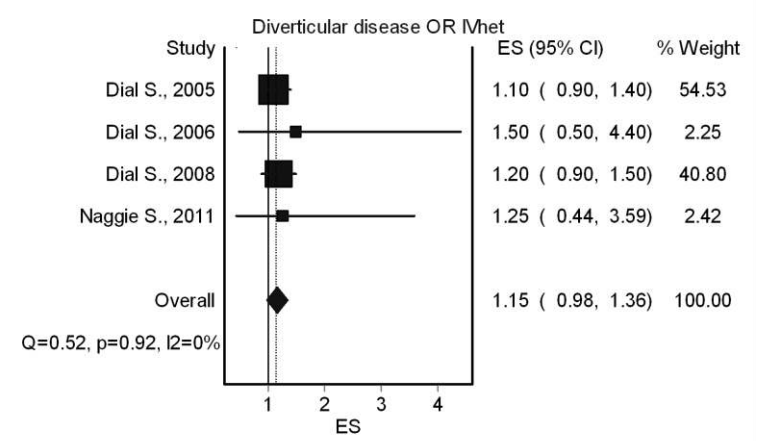


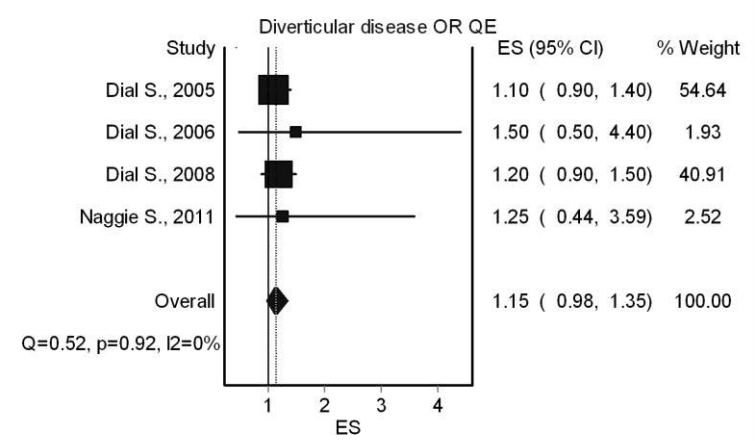



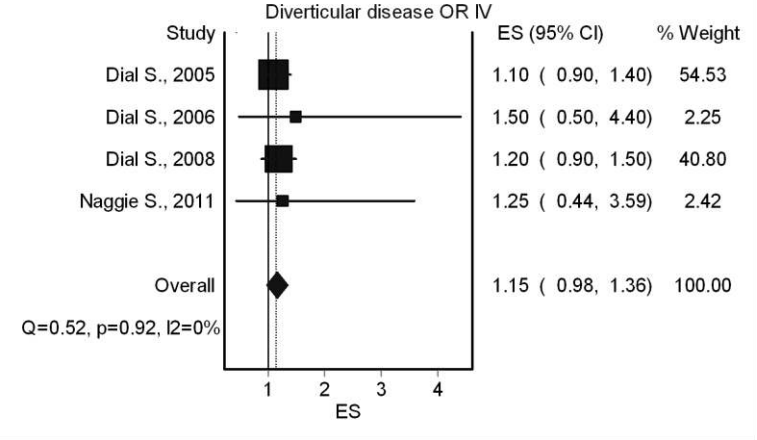



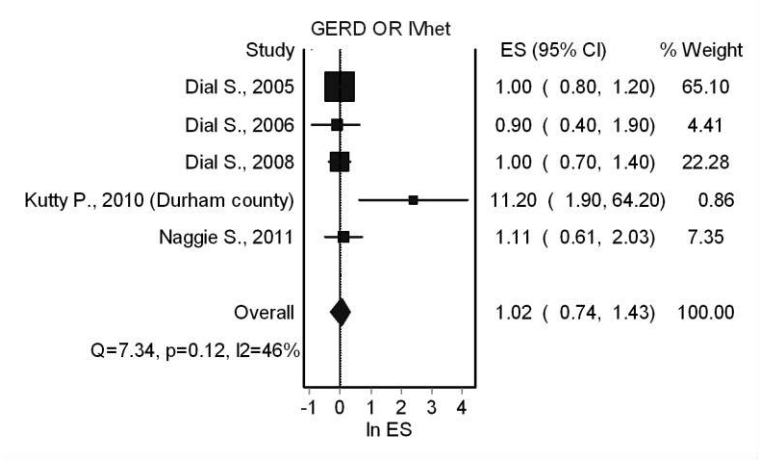

3.17.- Diabetes mellitus

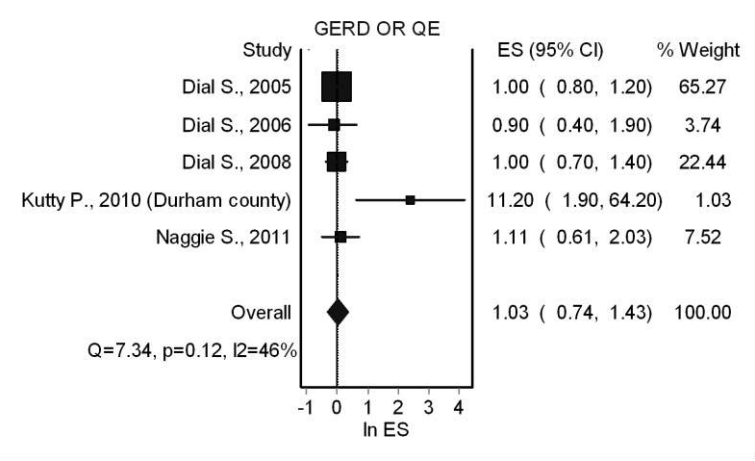


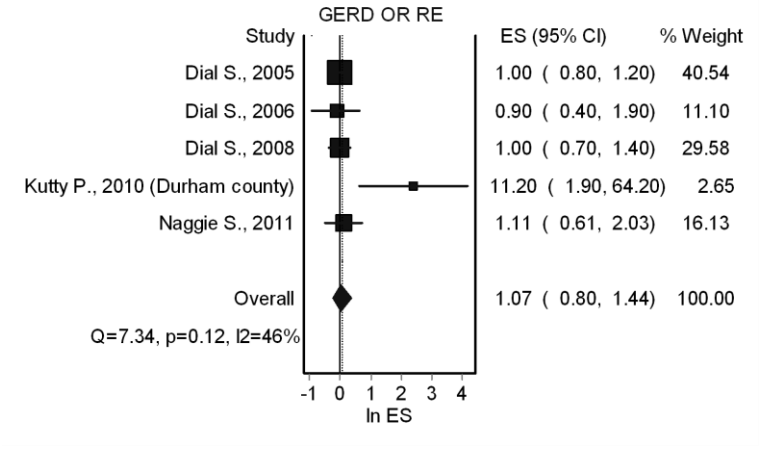



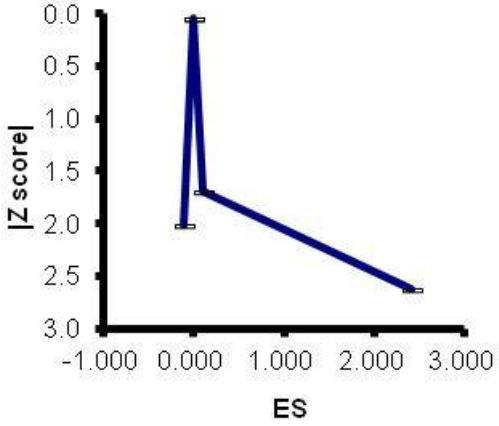




3.18.- Diverticular disease

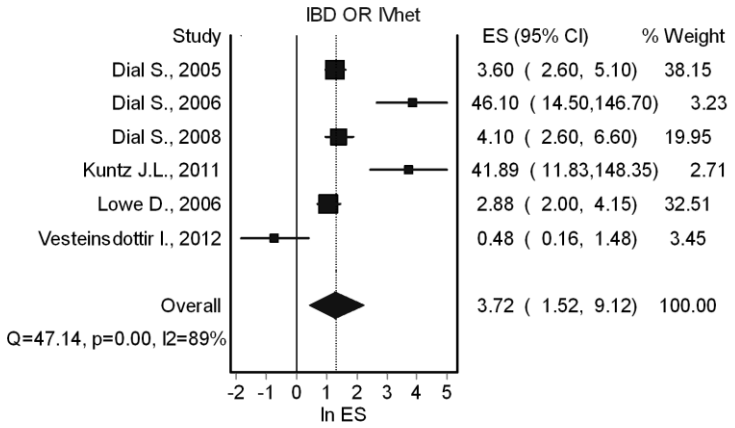


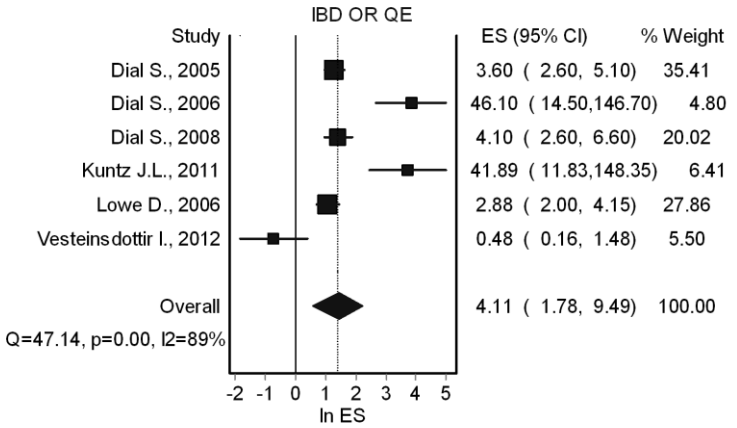



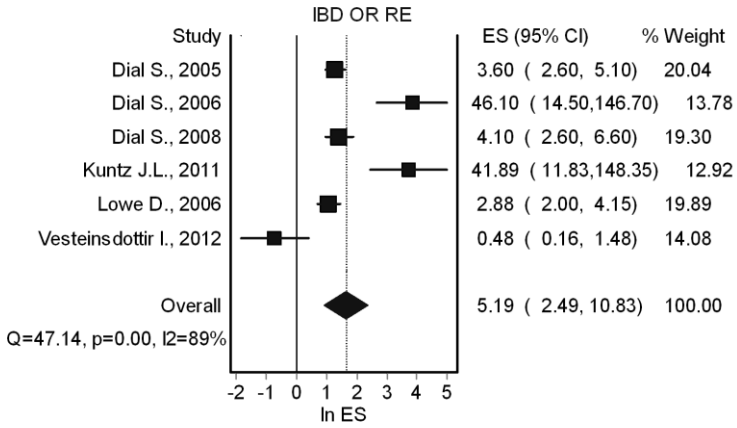



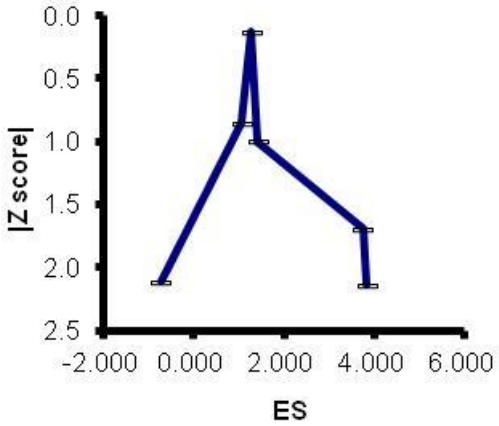




3.19.- Gastroesophageal reflux disease

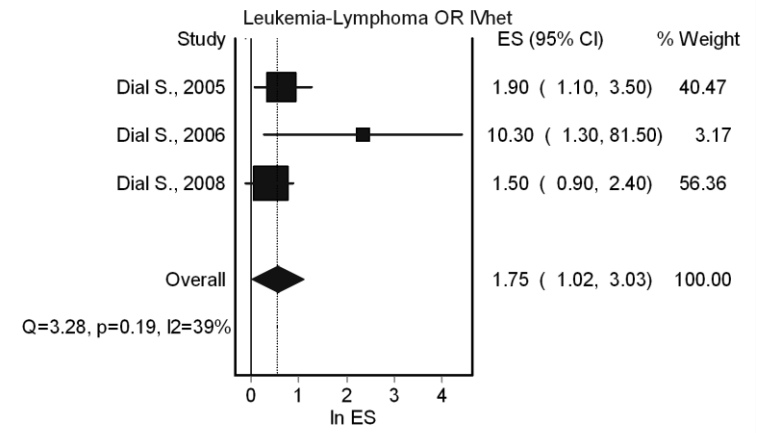


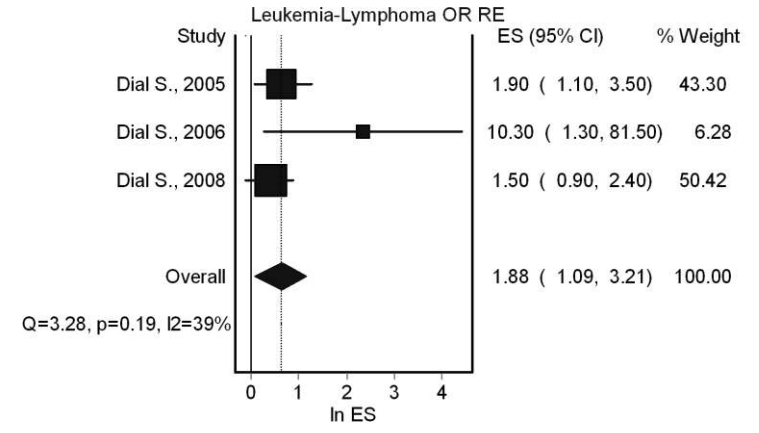



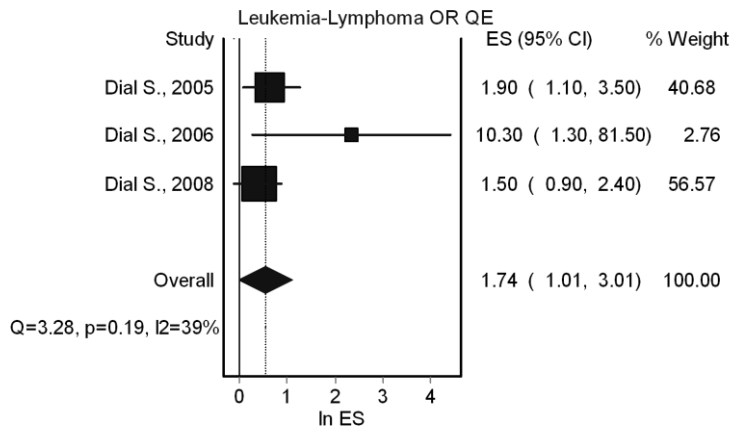



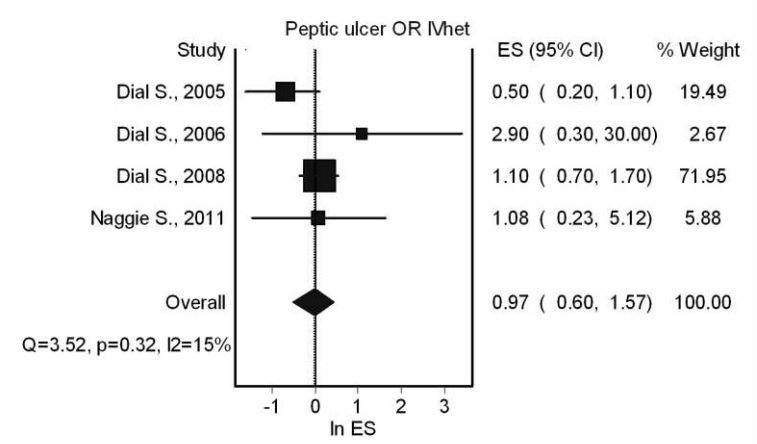

3.20.- Inflammatory bowel disease

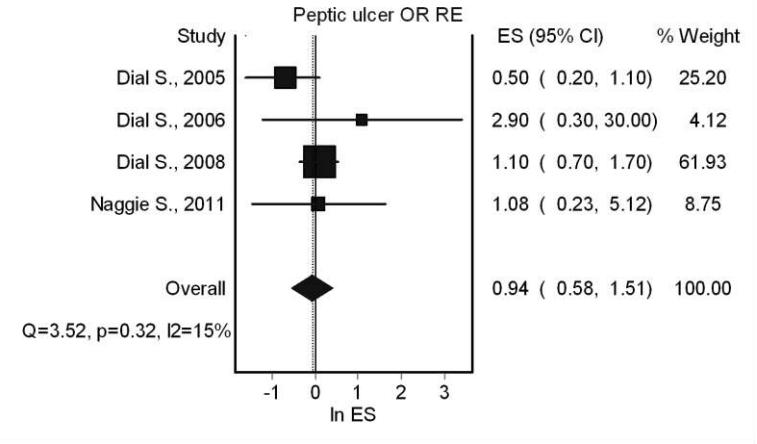


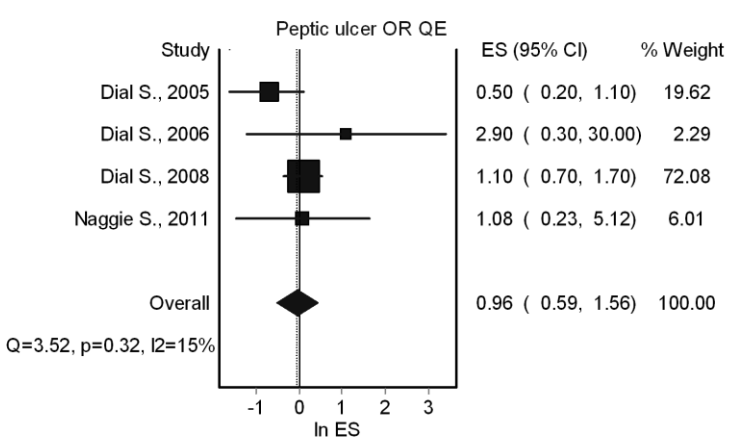



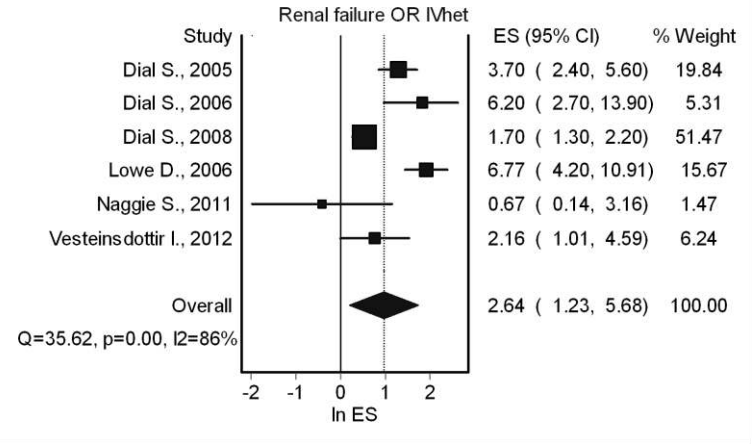

3.21.- Leukemia or Lymphoma

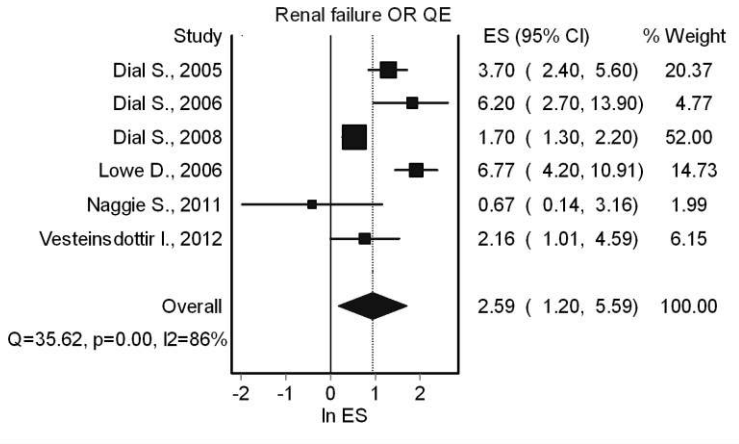


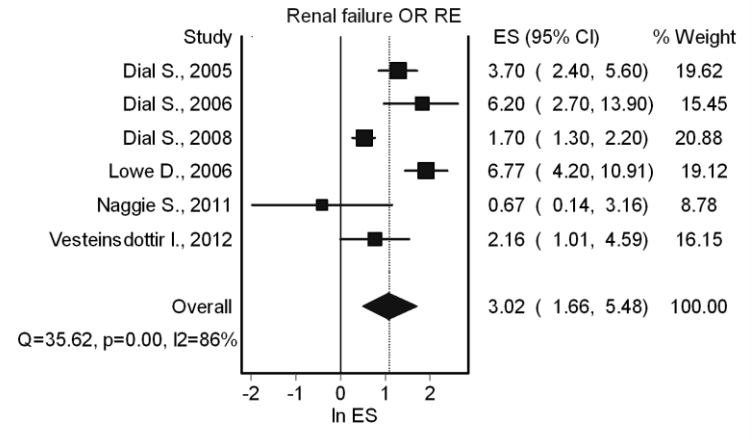



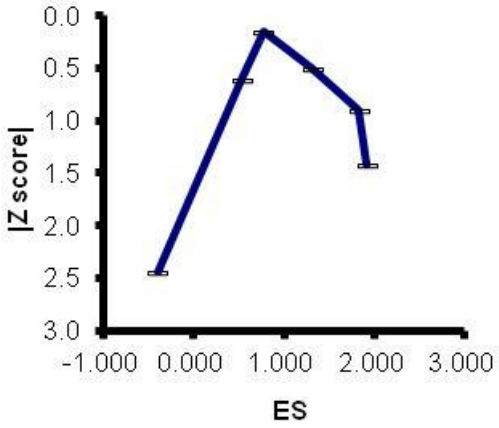




3.22.- Peptic ulcer

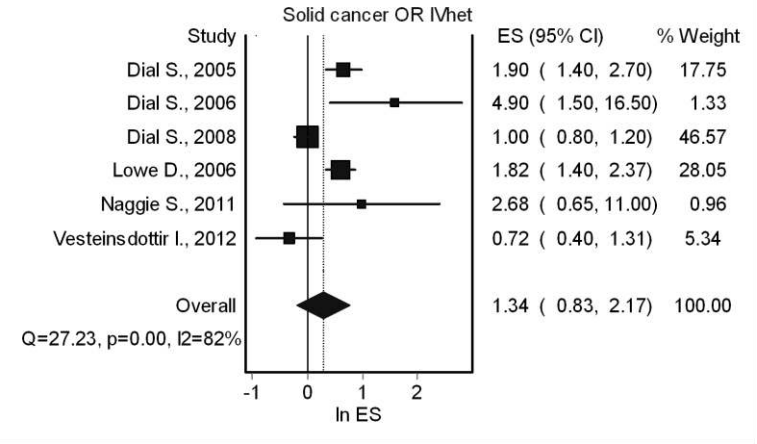


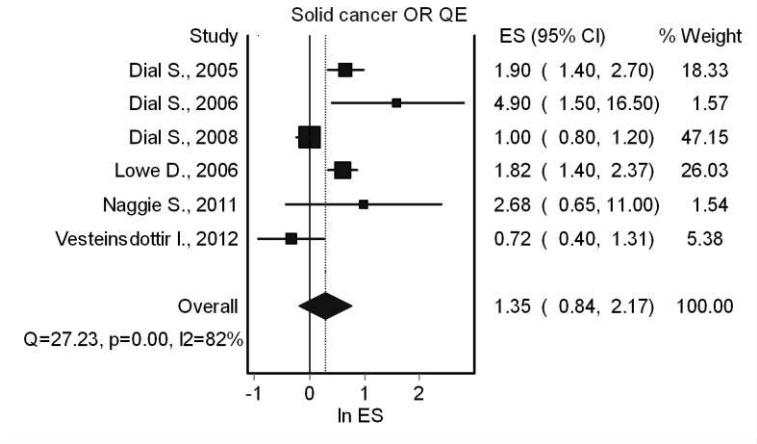



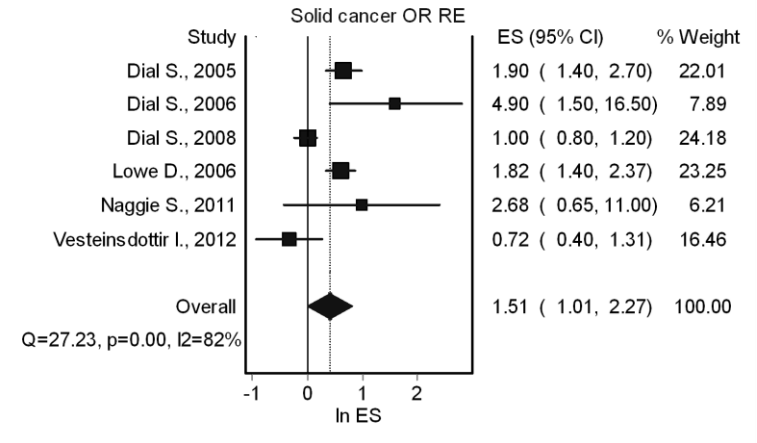



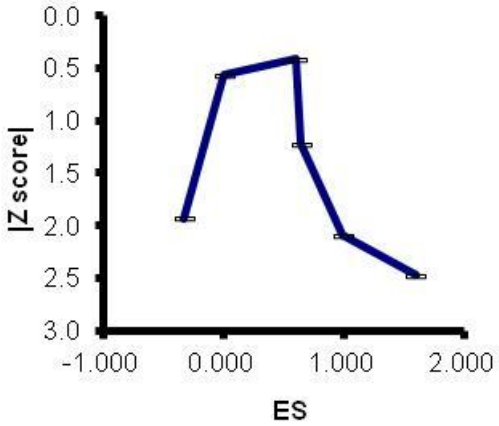




3.23.- Renal failure



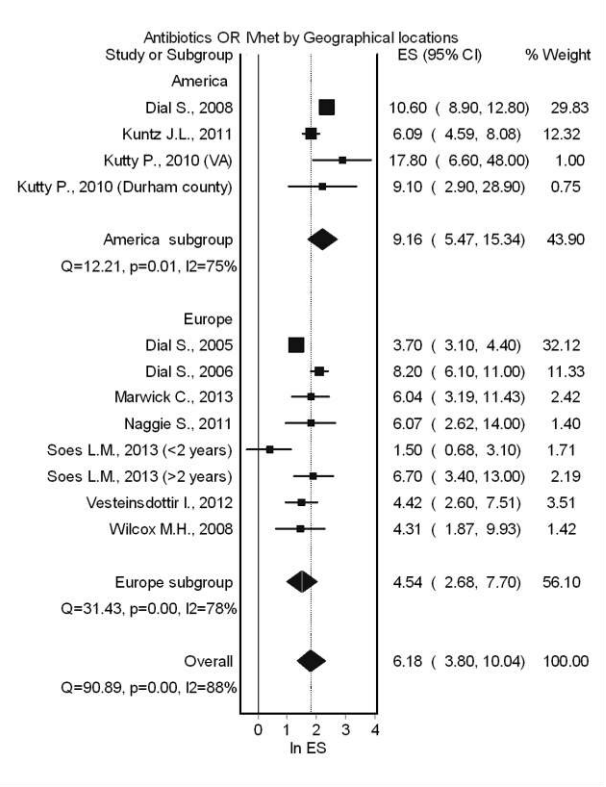



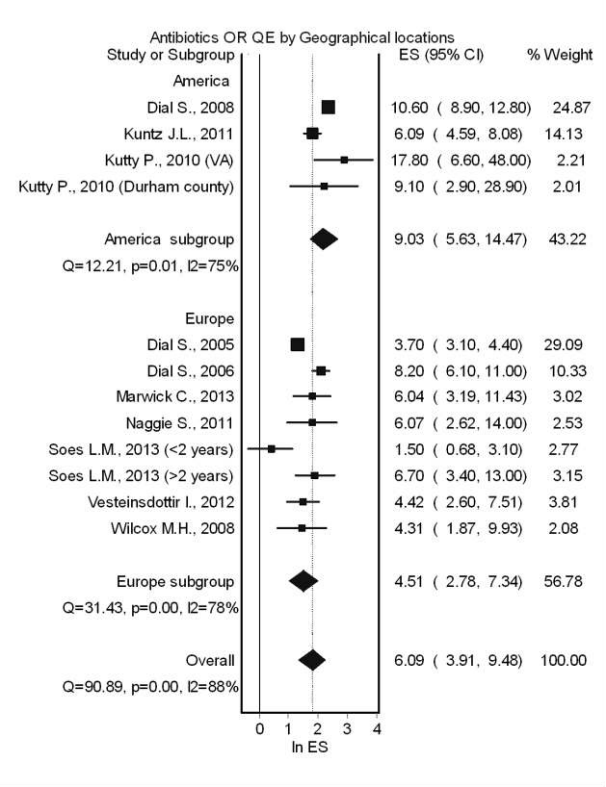



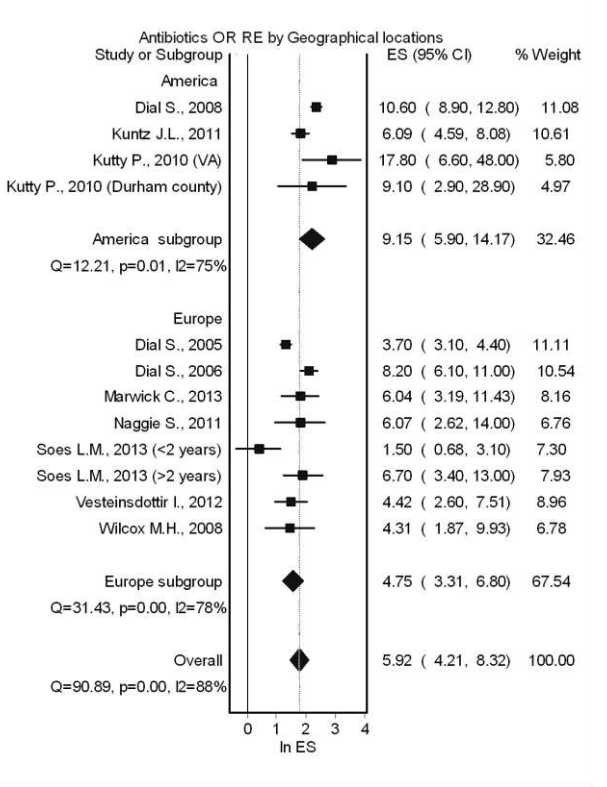




3.24.- Solid cancer

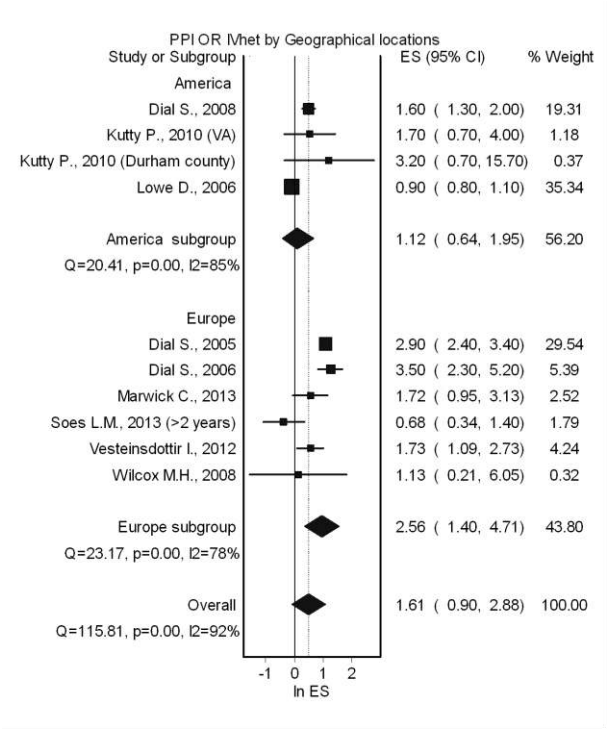
**Appendix 4.-** Sensitivity analysis

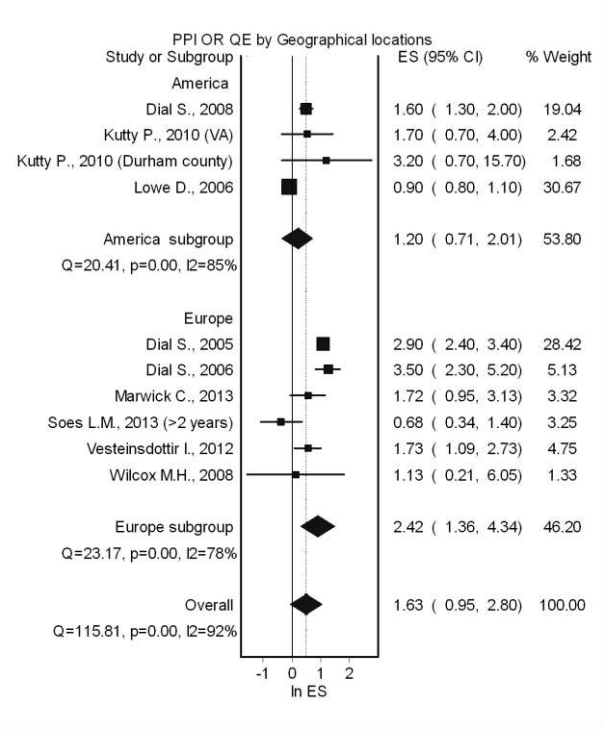


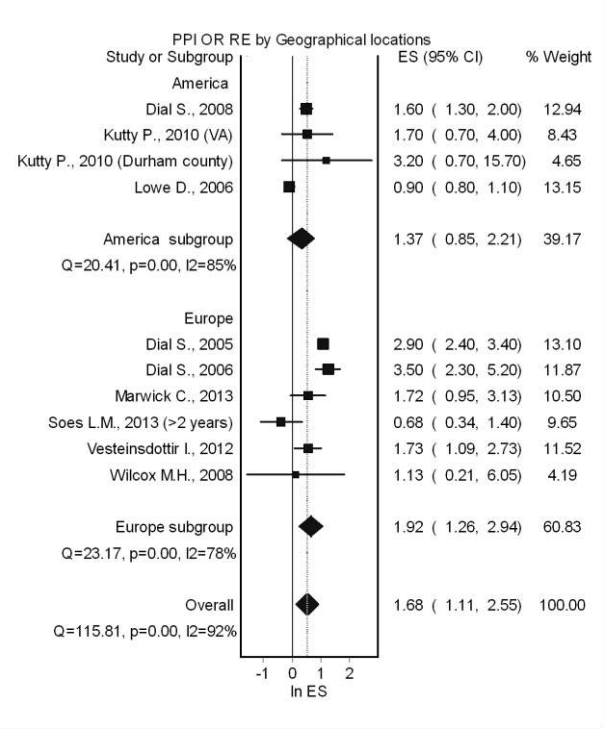



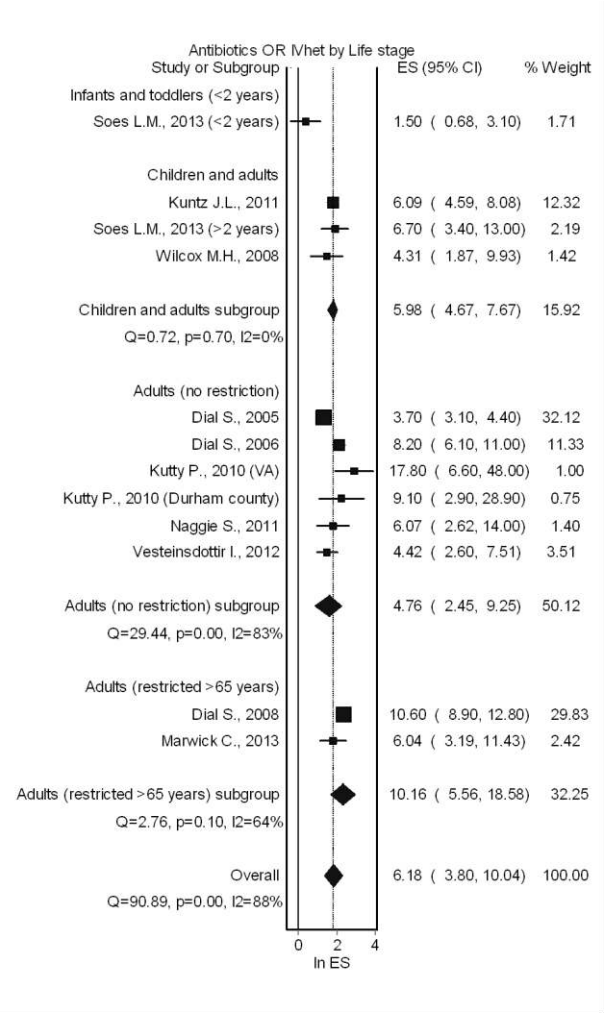

4.1.- Antimicrobials by location

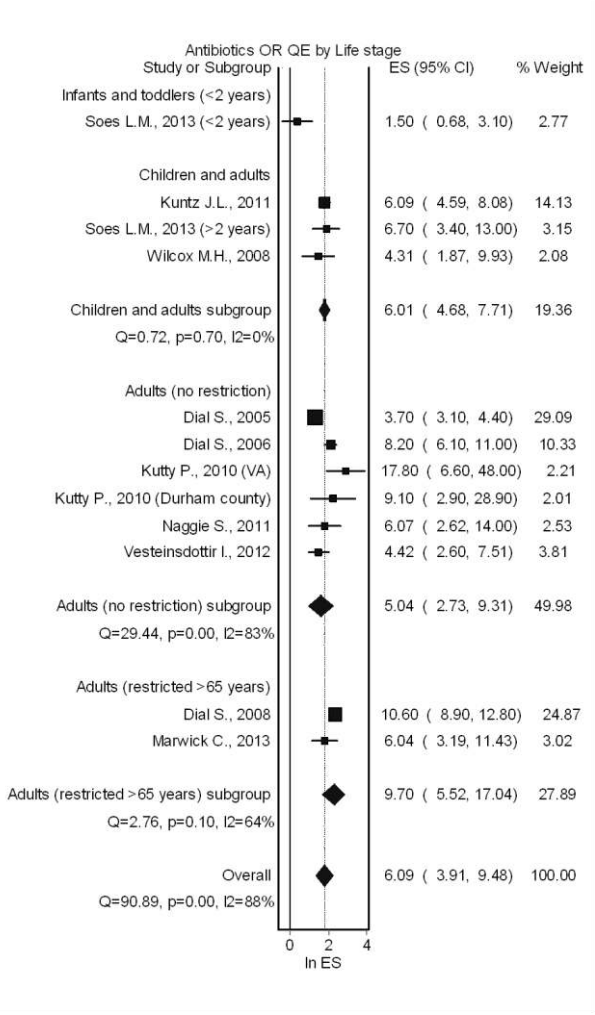


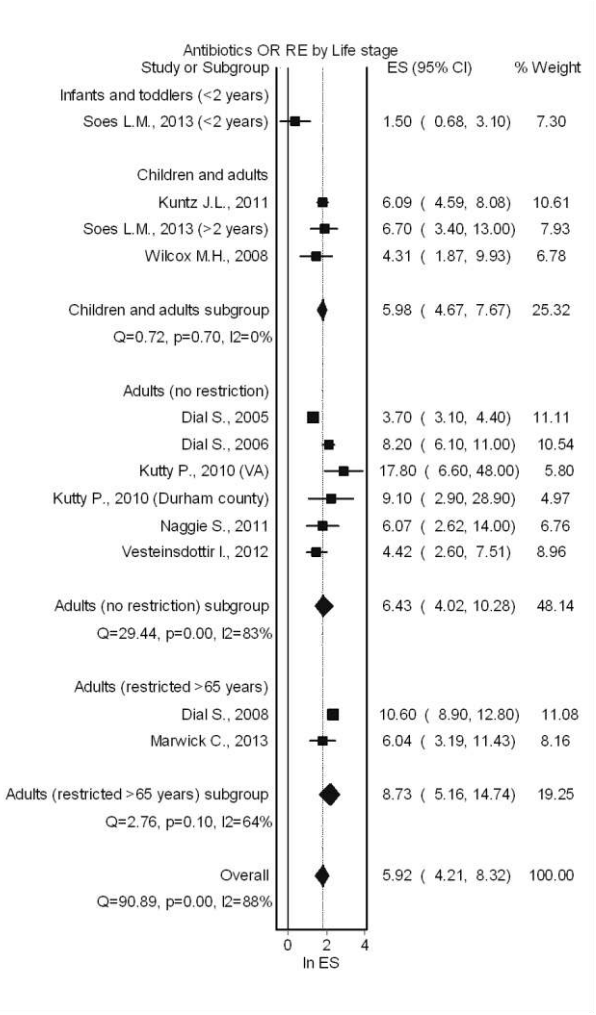



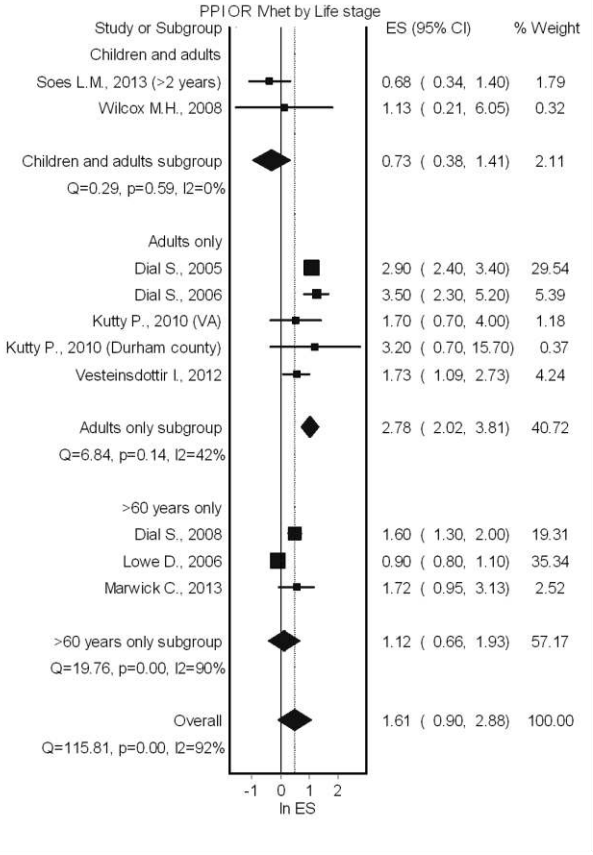

4.2.- Proton pump inhibitors by location

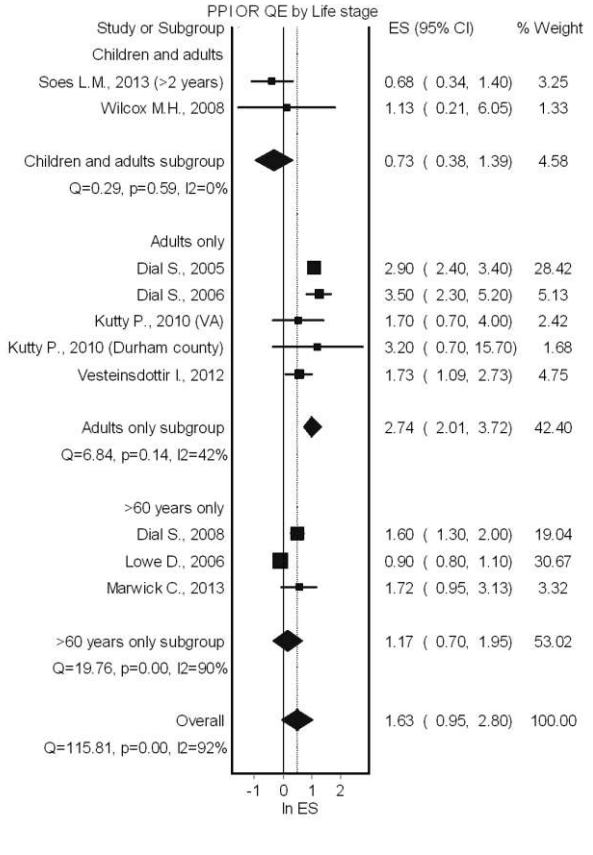


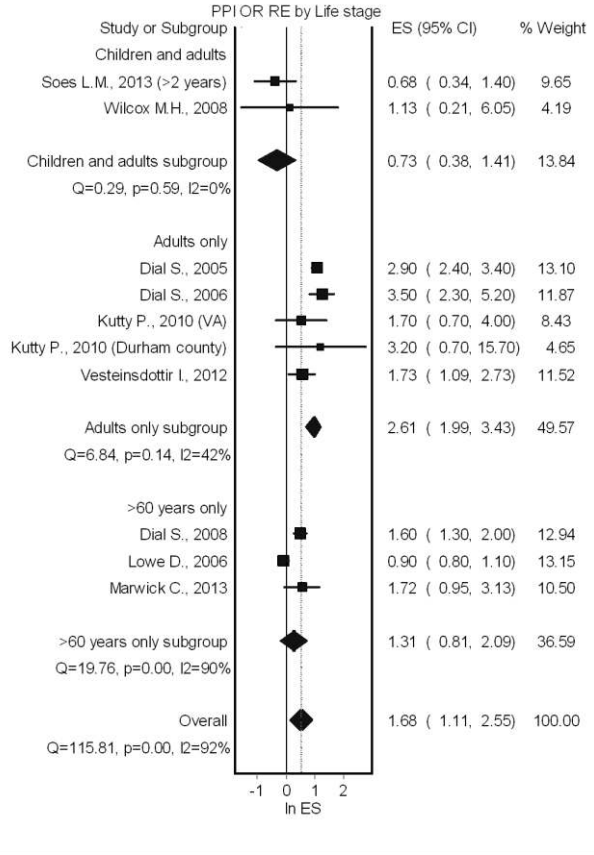




4.3.- Antimicrobials by life stage




4.4.- Proton pump inhibitors by life stage