CRD summary
The authors concluded that proton pump inhibitors were associated with a moderate increase in the risk of developing Clostridium difficile, but the observational nature of the evidence did not permit causality to be established. These conclusions reflect the evidence, but the uncertain causality and variation between studies mean that the actual risk of infection with proton pump inhibitors remains unclear.

Authors' objectives
To assess the association between proton pump inhibitor therapy and the risk of Clostridium difficile infection.

Searching
Five electronic databases, including MEDLINE and The Cochrane Library, were searched for articles published in any language between 1990 and October 2010. Search terms were reported. Reference lists from included studies and relevant reviews were manually screened.

Study selection
Eligible for inclusion were observational studies (including cross-sectional, case-control, and cohort studies) assessing the association between proton pump inhibitors and the risk of Clostridium difficile (C. difficile) infection in adults over the age of 18 years. Studies presenting data based on C. difficile episodes, rather than the number of patients, were excluded.

The included studies were conducted in the USA, Canada, the UK (four studies), or South Korea. Where reported, the mean age of participants ranged from 56.6 to 82.3 years. Most studies were of hospitalised patients. Comparison groups did not receive proton pump inhibitors.

Two reviewers independently screened studies for inclusion; discrepancies were resolved by referral to a third reviewer.

Assessment of study quality
Two reviewers independently assessed study quality, based on five criteria; clear identification of study population, clear definition of outcome and outcome assessment, identification of important confounders, independent assessment of outcomes, and selective loss during follow-up. Disagreements between reviewers were resolved by referral to a third reviewer.

Data extraction
Two reviewers independently extracted the outcome data to calculate odds ratios and 95% confidence intervals. Disagreements were resolved by referral to a third reviewer. Primary study authors were contacted for further information, where necessary.

Methods of synthesis
A DerSimonian and Laird random-effects model was used to combine the odds ratios and 95% confidence intervals. Statistical heterogeneity was assessed using Cochran Q and I²; I² over 50% indicated significant heterogeneity.

Subgroup and sensitivity analyses were performed, based on study design and antibiotic use. Studies were categorised into three antibiotic-use groups: studies with a percentage of antibiotic use that was greater than the overall median; studies with percentage use that was less than or equal to the median; and studies for which antibiotic use data were unavailable.

Publication bias was assessed using funnel plots.
Results of the review
Twenty-nine articles reporting 30 studies (five cohort and 25 case-control; 202,965 participants) were included in the review. All studies clearly identified their population, and defined the outcome and outcome assessment. Twenty-two adjusted for important confounders; none independently assessed the outcome; and none had a selective loss of patients during follow-up.

Proton pump inhibitors statistically significantly increased the risk of C. difficile (OR 2.15, 95% CI 1.81 to 2.55; 30 studies), but there was evidence of significant statistical heterogeneity (I²=87%).

Subgroup and sensitivity analyses by study design and antibiotic use showed similar results.

There was no evidence of publication bias in the funnel plot.

Authors' conclusions
Proton pump inhibitors were associated with a moderate increase in the risk of developing C. difficile, compared with no therapy, but the observational nature of the evidence did not permit causality to be established.

CRD commentary
The review question and supporting inclusion criteria were clearly stated. A satisfactory search of relevant sources was undertaken, but attempts do not appear to have been made to locate unpublished data, which means that potentially relevant evidence may have been missed. Each stage of the review process was performed in duplicate, thereby minimising the potential for reviewer error and bias. Study quality was assessed and fully reported. A large amount of evidence was presented and appropriate methods were used to assess and explore statistical heterogeneity.

The authors’ conclusions reflect the findings, but the observational nature of the evidence, and the significant variation between studies, mean that the actual risk of C. difficile with proton pump inhibitors remains unclear.

Implications of the review for practice and research
Practice: The authors stated that physicians should not stop prescribing proton pump inhibitors for medical indications clearly established in the literature, but the moderate increase in the risk of developing C. difficile was a significant health problem and should curb the indiscriminate use of these medications.

Research: The authors did not state any implications for research.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.