13C-urea breath test for the diagnosis of Helicobacter pylori infection in children: a systemic review and meta-analysis
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CRD summary
This review concluded 13C-urea breath test was highly accurate for diagnosing Helicobacter pylori infection in children over six years, but performance was less clear in younger children. Accuracy could be improved by varying diagnostic threshold, pre-test meal and tracer dose. These conclusions reflect the data, but should be interpreted cautiously given limitations in the review methods and analyses.

Authors' objectives
To assess the performance of the 13C-urea breath test for diagnosis of Helicobacter pylori infection in children.

Searching
PubMed, EMBASE and LILACS were searched from December 1997 to May 2009. Search terms were reported and included methodological terms for test accuracy studies. Although searches were not restricted by language, only studies published in English or Spanish were included.

Study selection
Eligible studies assessed the diagnostic performance of the 13C-urea breath test, with H. pylori culture, histologic examination or rapid urease test as the reference standard. Studies were required to include at least 30 participants and report absolute numbers of true positive, true negative, false positive and false negative test results.

Approximately two thirds of the studies used H. pylori culture and histology as the reference standard and the remainder used histology and rapid urease test or histology alone.

The authors did not state how many reviewers selected studies for inclusion.

Assessment of study quality
The methodological quality of studies was assessed with criteria based on the STARD statement on the reporting of test accuracy studies. Criteria included use of an appropriate reference standard, reference standard confirmation in all or a random sample of participants, conduct of the 13C-urea breath test blind to the reference standard results and prospective recruitment of children with suspected H. pylori infection (avoidance of a case-control design).

The authors did not specify how many reviewers performed the quality assessment.

Data extraction
Data were extracted to calculate sensitivity and specificity, with 95% confidence intervals (CIs), for each study.

Data were extracted by one reviewer and a subset was independently extracted by a second reviewer.

Methods of synthesis
Pooled estimates of sensitivity, specificity, positive and negative likelihood ratios and diagnostic odds ratio, with 95% confidence intervals (CIs) were calculated using a fixed-effect model. A summary receiver operating characteristic curve was estimated with the Moses and Littenberg model.

Between study heterogeneity was assessed using Χ² and quantified using Ι². Potential sources of heterogeneity were explored using subgroup analyses.

Results of the review
Thirty one studies (4,037 children, median 99) were included in the review. Sixteen articles reported data for more than one 13C-urea breath test protocol, therefore 135 data sets were included in the analyses. All studies used a case-control design and prospective data collection. Twelve studies reported at least single-blind interpretation of the 13C-urea breath
test and reference standard result, the remainder reported no information on blinding.

**All studies** (135 data sets): The pooled estimate of sensitivity was 95.9% (95% CI 95.3 to 96.4%) and specificity was 95.7% (95% CI 95.3 to 96.0%). The pooled estimate of positive likelihood ratios was 17.4 (95% CI 14.6 to 20.7) and negative likelihood ratios was 0.06 (95% CI 0.05 to 0.07). There was significant between-study heterogeneity in all estimates.

**Children 6 or under years** (21 data sets): The pooled estimate of sensitivity was 95.0% (95% CI 91.5 to 97.4%) and specificity was 93.5% (95% CI 92.1 to 94.9%). The pooled estimate of positive likelihood ratios was 11.7 (95% CI 8.3 to 16.7) and negative likelihood ratios was 0.12 (95% CI 0.08 to 0.18). There was significant between-study heterogeneity in specificity and positive likelihood ratios.

**Children over 6 years** (11 data sets): The pooled estimate of sensitivity was 96.6% (95% CI 94.5 to 98.0%) and specificity was 97.7% (95% CI 96.6 to 98.6%). The pooled estimate of positive likelihood ratios was 42.6 (95% CI 22.2 to 81.9) and negative likelihood ratios was 0.04 (95% CI 0.03 to 0.06). There was significant between-study heterogeneity in the positive likelihood ratios.

The results of further subgroup analyses were reported for delta time, fasting time, type of meal, tracer dose and type of results reported. The highest accuracy results were given in the following subgroups: delta time of 20 minutes; fasting time of four hours; protocols that did not include a meal; use of a unique rather than body-weight-adjusted tracer dose; urea hydrolysis rate results.

**Authors’ conclusions**
The $^{13}$C-urea breath test was highly accurate for the diagnosis of *H. pylori* infection in children older than six years, but its performance was less clear in younger children. The accuracy of the test could be improved by varying the diagnostic threshold, pre-test meal and tracer dose.

**CRD commentary**
The review stated a clear objective and defined appropriate inclusion criteria. Several sources were searched for relevant articles. The use of search terms for test accuracy studies may have resulted in relevant studies being missed, and the restriction to inclusion of English and Spanish studies raised the possibility of language bias. Measures were taken to minimise error and/or bias in the data extraction process, but it was unclear whether similar measures were applied to study selection and data extraction. The meta-analytic methods used were broadly appropriate, though other summary receiver operating characteristic models (such as bivariate of hierarchical) were widely recommended. The authors do not appear to have considered the appropriateness (or otherwise) of pooling multiple data sets which may have been derived from the same patients. Meta regression could have provided a more informative investigation of sources of heterogeneity than the multiple separate subgroup analyses presented. The authors’ conclusions reflect the data, but should be interpreted cautiously given limitations in the review methods and analyses.

**Implications of the review for practice and research**
**Practice:** The authors stated that clinicians should consider using the $^{13}$C-urea breath test to diagnose *H. pylori* infection in children older than six years, but should be very cautious in interpreting results from children under six years (particularly those under two years). For the latter age group, and particularly in low prevalence populations, $^{13}$C-urea breath test results should be confirmed by another test.

**Research:** The authors did not specify any recommendations for future research.

**Funding**
The authors stated that they had no support or funding to report.

**Bibliographic details**

**PubMedID**
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.