A meta-analytic evaluation of the polymerase chain reaction for the diagnosis of HIV infection in infants

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Authors' objectives
To evaluate the sensitivity and specificity of the polymerase chain reaction (PCR) for the diagnosis of human immunodeficiency virus (HIV) infection in infants.

Searching
Studies published during or before 1991 were located by searching 17 databases, including MEDLINE. The search strategy is available from the authors on request. For studies between 1992 and 1994, the search was restricted to MEDLINE. The bibliographies of retrieved articles and conference proceedings were also searched. From the searches, only articles written in English were considered for inclusion.

Study selection
Study designs of evaluations included in the review
All study designs were included. Studies with 10 or fewer patients were specifically excluded.

Specific interventions included in the review
Studies using PCR on peripheral blood mononuclear cells, and DNA (not RNA) amplification were eligible for inclusion in the review.

Reference standard test against which the new test was compared
No inclusion criteria were specified in relation to the reference standard. However, the authors stated that a positive result on viral culture, persistence of HIV antibody past 15 months, or definitive clinical evidence of HIV infection, (as defined by the Centre for Disease Control and Prevention,) were accepted as evidence of infection.

Participants included in the review
Studies of infants or children (less than 13 years) were eligible for inclusion in the review. Where studies contained data from children and adults, only data from the children were used.

Outcomes assessed in the review
Studies reporting data to calculate the sensitivity and specificity of PCR were eligible for inclusion in the review.

How were decisions on the relevance of primary studies made?
Two independent investigators assessed the studies for relevance using defined inclusion criteria.

Assessment of study quality
Studies were assessed on the basis of the following: the adequacy of PCR; the adequacy of the reference test; the consistency in applying the reference test; whether PCR was interpreted blinded to other test results and clinical information; the adequacy of the description of the clinical population; the appropriateness of obtaining the study sample; and the adequacy of the sample size. Two reviewers, blind to all information except the methods section, assessed the studies according to prospectively developed validity criteria. For each criterion, a score of 0, 1 or 2 was assigned to indicate that the design failed, partially met, or fully satisfied the criteria. A weighted combination of the 7 validity criteria was used to determine the overall appropriateness of the design of each study for evaluating the performance of PCR, as rated on a 4-point scale (1 = poor, 4 = well suited).

Data extraction
Two investigators independently abstracted the data from each study. The data for calculating the sensitivity and
specificity of PCR were extracted. Also extracted were details of the reference test used, the criteria used to interpret the PCR and reference test results, PCR protocol, length of follow-up, population characteristics, date of study initiation and publication, location of study and author affiliations.

The sensitivity and specificity were calculated based on the number of participants rather than the number of samples. The results were stratified according to participant age: studies of patients aged 30 days or younger, and studies of patients aged older than 30 days or all ages.

**Methods of synthesis**

How were the studies combined?
The estimates of sensitivity and specificity were combined in a summary receiver operating characteristic (ROC) curve. After determining that the ROC curve could be represented by a common odds ratio, the Mantel-Haenszel estimator was used to develop a summary ROC curve. A summary ROC curve was developed from both the upper and lower estimates of sensitivity and specificity. The Subgroups were also compared using the upper estimate of sensitivity and specificity.

How were differences between studies investigated?
Differences between the studies were investigated by subgroup analysis.

**Results of the review**
Thirty-two studies were included. There were 565 HIV-infected children, 1,011 uninfected children, 11 children whose PCR results were indeterminate, and 209 children whose infection status was indeterminate.

The median sensitivity was 91.6% (range: 31 to 100) and the median specificity was 100% (range: 50 to 100). The summary ROC curve based on all 32 included studies indicted that PCR has a maximum joint sensitivity and specificity between 93.2 and 94.9%.

The subgroup analysis indicated that the joint sensitivity and specificity was significantly higher (P=0.04) in older infants (98.2%) than in neonates (aged 30 days or less; 93.3%). For infants at low risk of perinatal transmission (probability of transmission, 8.3%), the positive predictive value for PCR was 55.8% in neonates and 83.2% in older infants. A negative PCR result reduced the probability of HIV infection to less than 3%.

Study quality was rated one (lowest rating) in 25 studies, two in 6 studies, and three in 1 study. No study received the highest quality rating of four.

**Authors' conclusions**
PCR is one of the best tests available for the diagnosis of HIV infection in neonates and infants, but it is not definitive. Therefore, PCR should be interpreted with the aid of careful clinical follow-up examinations. The sensitivity and specificity of PCR was lower in neonates than in older infants, resulting in a low positive value; however, negative tests are informative. Delaying the use of PCR until after the neonatal period, or repeating PCR on independent samples obtained 30 to 60 days later, will reduce test errors.

**CRD commentary**
This was a well-written and concise report. The research question was relatively well defined by inclusion criteria relating to the test and population. However, there remained some ambiguity with respect to the reference standard.

The literature search up to 1991 appeared thorough, although the restriction of the search between 1992 and 1994 to MEDLINE alone and the restriction to English language publications was disappointing. The authors believed that by searching the single database they reduced unnecessary duplication between searches; however, it is likely that some studies were not located, particularly those published in non-U.S. journals. No attempt to identify unpublished data was reported and the possible extent of publication bias was not assessed, although the authors highlighted this deficiency.
There were limited details of the characteristics of the participants, which makes it difficult to assess the generalisability of the review's findings. The statistical methods used to pool the studies were described clearly and inferences were correctly drawn.

**Implications of the review for practice and research**

**Practice:** The variability in test performance between the studies highlighted the need for clinicians to be familiar with the performance characteristics of PCR in the laboratory performing the assay for their institution. The interpretation of PCR results in neonates requires special care. The range of post-test probabilities reported suggested that a single PCR test is not sufficient to diagnose or exclude HIV, and that PCR is more informative when delayed until after the first month of life.

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

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