A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food

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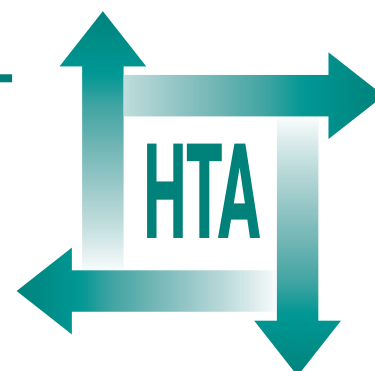
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Executive summary

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Executive summary

Background

Technological advances have increased the speed of diagnostic testing for many diseases. However, for bacterial food poisoning, stool culture, which can take up to 1 week, is still the only method routinely used for diagnosis in most UK microbiology laboratories.

The principle methodologies emerging for the rapid diagnosis of food poisoning are immunoassays, which detect antigens or antibodies from pathogens, and polymerase chain reaction (PCR), a commonly used technique to amplify and detect pathogenic DNA/RNA. Both techniques may significantly reduce the detection time for pathogens in faecal or food samples, compared with traditional culture methods.

This systematic review focused on the use of rapid tests for six bacterial food-borne pathogens: *Salmonella*, *Campylobacter*, *Escherichia coli* O157, *Clostridium perfringens*, *Staphylococcus aureus* and *Bacillus cereus*. Diagnostic accuracy was assessed, and an economic model was subsequently developed, assessing costs and cost-effectiveness of PCR and immunoassays, compared with culture.

Methods

Standard systematic review methods were applied. Literature was identified from electronic databases and further handsearching. Study findings were extracted using a predesigned and piloted tool in duplicate to avoid errors. The methodological quality of studies was assessed using a standard tool.

Data synthesis

Sensitivity, specificity and diagnostic odds ratios were presented in forest plots. Studies within clinically appropriate groups were subjected to meta-analysis. Evidence for heterogeneity was assessed using a χ^2 test and the I^2 statistic. Where correlation between sensitivity and specificity was evident (measured using Spearman's ρ), a summary receiver operating characteristic (SROC) curve was generated. Area under the curve (AUC) was the main measure of diagnostic accuracy. In the absence of correlation, pooled estimates of sensitivity and specificity were presented. Evidence of publication bias was examined using funnel plots of log odds ratios.

Results

The electronic search identified 1853 studies, 87 of which were included in this review. The quality of studies was variable for studies included in meta-analysis; however, in studies discussed narratively (principally for toxin-inducing pathogens), reporting was generally poor.

Clinical effectiveness
Campylobacter
SROC analysis was performed on six studies, evaluating PCR for the 16s rRNA gene. Combining 4495 samples, AUC was 0.987 [95% confidence interval (CI) 0.984 to 0.989]. Four studies (2078 samples) evaluated the ProSpecT immunoassay (Alexon-Trend), and reported an overall AUC of 0.862 (95% CI 0.568 to 1.000).

Salmonella
Identified test methods included PCR, Wellcolex Colour agar, MUCAP test, Wampole Bactigen and AutoMicroBic identification system. Combining 2134 samples (from seven studies), the AUC value for PCR was 0.995 (95% CI 0.985 to 1.000); however, publication bias was evident. Other tests exhibited very high diagnostic odds ratios (DORs), ranging from 264 (95% CI 116.9 to 597.6) (Wampole Bactigen) to 2951 (95% CI 710.9 to 12000) (Wellcolex Colour).

E. coli
SROC analysis for PCR assays showed very high diagnostic accuracy (AUC 0.996, 95% CI 0.990 to 1.000); however, publication bias was evident, compared with VTEC-Screen reverse passive latex agglutination (RPLA) results (AUC 0.994, 95% CI 0.982 to 1.000), which was not affected by publication bias. The Premier enterohaemorrhagic *Escherichia coli* (EHEC) immunoassay had high pooled sensitivity and specificity values (0.935 and 0.997, respectively), which were not correlated. Other entrohaemorrhagic *E. coli* tests evaluated included ProSpecT, Duopath Verotoxin, ImmunoCard Stat and RidaScreen Verotoxin.

A very limited number of studies evaluated rapid diagnostic methods against an appropriate reference standard for *C. perfringens*, *B. cereus* and staphylococcal food poisoning. Therefore, it was not possible to assess effectiveness using statistical methods.

Although traditional culture is the logical reference test to use, on many occasions the rapid test outperformed culture, detecting more positive cases of food-borne illness. Immunological and PCR tests may be useful for 'multiplexing', thereby providing simultaneous speciation or characterisation.

Cost-effectiveness
Cost estimates for each test method were derived from published sources, contact with manufacturers and discussion with laboratory staff. A decision analytic model was developed to assess their cost-effectiveness and the sensitivity of these results to changes in various parameters in the model was assessed.

Evidence about the relative costs of implementing rapid diagnostic methods in practice is sparse and highly uncertain. The isolation rate of the reviewed pathogens is low in laboratories. This implies that the provision of routine tests can be very expensive. At the baseline, testing one sample for *Campylobacter*, *Salmonella* and *E. coli* will cost £18.85 with PCR, £15.66 with immunoassays and £15.01 by culture methods. The most sensitive parameter in the decision analytic model is the isolation rate for each pathogen. Adoption of rapid tests in combination with routine culture is unlikely to be cost-effective; however, as the cost of rapid technologies decreases, total replacement with rapid technologies may be feasible. With multiplex PCR tests, if multiple pathogens could be simultaneously detected in the same reaction tube, molecular diagnosis may prove very cost-effective; however, there are insufficient published evaluations of these assays at present.

Conclusions

Evidence from this systematic review suggests that rapid diagnostic assays, especially PCR, for

Salmonella, *Campylobacter* and *E. coli* O157 are highly accurate. Less is known about the benefits of testing for toxin-producing pathogens and the significance of additional positives detected by these assays. It is unclear whether the additional benefits derived from early diagnosis and more sensitive detection can justify the large set-up costs of rapid tests, particularly if they remain diagnostic adjuncts to culture. Any decisions regarding the use of these assays must consider the speed of diagnosis (including transportation and reporting delays), effect on clinical outcome and costs of implementation simultaneously.

Implications for research
The effectiveness and cost-effectiveness of emerging tests for more than one organism at a time, such as multiplex PCR and DNA microarrays technologies, require further investigation.

Substantial evidence suggests that rapid assays may be more sensitive than culture methods. Attempting to evaluate diagnostic tests in the absence of a true gold standard creates methodological challenges.

Implications for practice
The feasibility of conversion to rapid methods is dependent on localised considerations, including the community prevalence rates for specific pathogens, the skill base and subsequent training costs for laboratory staff and spare capacity available to ensure adequate laboratory space for new equipment. Although these tests show good promise for the future, further studies are needed to assess their immediate use in practice.

Publication

NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer-reviewed by a number of independent expert referees before publication in the widely read monograph series *Health Technology Assessment*.

> **Criteria for inclusion in the HTA monograph series**
> Reports are published in the HTA monograph series if (1) they have resulted from work for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.
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> Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned by the HTA Programme as project number 03/40/03. The contractual start date was in April 2005. The draft report began editorial review in May 2006 and was accepted for publication in January 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.