

Summary Statement Title:

Rapid diagnostic tests for bacterial intestinal pathogens in feces and food: Evidence and implications for public health

Review Quality Rating: 8 (strong)

Review on which this summary statement is based:

Abubakar, I., Irvine, L., Aldus, C.F., Wyatt, G.M., Fordham, R., Schelenz, S., Shepstone, L., Howe, A., Peck, M., Hunter, P.R. (2007). **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.** *Health Technology Assessment*, 11(36), 1-216.

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This is a summary statement written to condense the work of the authors of this systematic review, referenced above. The intent of this summary is to provide an overview of the findings and implications of the full review. For more information on individual studies included in the review, please see the review itself.

Review content summary

This systematic review of 87 primary studies aimed to assess the reliability, accuracy, and cost-effectiveness of 'rapid diagnostic tests' for bacterial intestinal pathogens in feces and food. It also aimed to address the feasibility of such tests being adopted more widely by microbiology laboratories. Retrospective and prospective study designs that compared rapid testing methods with established reference tests in patients suspected of having food borne illness were included. Tests had to be performed on human fecal samples or food. The outcome of interest was test accuracy. Studies had to report accuracy statistics (sensitivity and specificity), or provide the raw data necessary to calculate these statistics. Rapid testing methods include a variety of assays such as: a) highly specific nucleic acid-based methods (e.g., polymerase chain reaction [PCR]); b) antibody-based tests (e.g., enzyme-linked immunosorbent assay [ELISA], lateral flow, latex agglutination, immunomagnetic separation [IMS]); c) simple miniaturized biochemical assays; and d) physicochemical tests that measure bacterial metabolites (e.g., bioluminescence and fluorescence). Included studies evaluated nucleic acid-based method (32), antibody-based tests (28), and improvements to the traditional culture technique (5). The review focused on six bacterial food-borne pathogens: *Bacillus cereus*, *Campylobacter*, *Clostridium perfringens*, *Escherichia coli* O157, *Salmonella*, and *Staphylococcus aureus*. Almost all relevant studies evaluated tests for *Campylobacter*, *E. coli*, or *Salmonella*. Findings suggest that PCR assays for *Campylobacter*, *E. coli* O157, and *Salmonella* identify pathogens, and may possibly detect more than the number currently reported using culture methods. ELISA and latex agglutination appear to be effective in detecting *E.coli* O517. Due to publication bias it is possible these results are an overestimation of the true effect. Less is known about the benefits of testing for *B. cereus*, *C. perfringens* and *S. aureus* due to the absence of an appropriate reference standard, and the benefits of using immunological and PCR tests for testing more than one organism at a time.

Comments on this review's methodology

This review is methodologically strong. The authors formed a focused research question, and described criteria used to select primary studies. They conducted a comprehensive search strategy, which covered an adequate number of years. The authors did not describe the level of evidence of each primary study included in the review. Methodological quality was adequately assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool. The process for assessing methodological quality was not transparent. Studies reporting test accuracy were grouped according to the index test evaluated. The sensitivity, specificity and diagnostic odds ratio (DOR) (i.e., the odds of disease in positive tests relative to the odds of disease in negative tests) were calculated for each evaluation. To determine the appropriateness of pooling data, sensitivity and specificity were correlated. For highly correlated data, sensitivity and specificity estimates were combined using summary receiver operating characteristic (SROC) curves to summarize diagnostic accuracy across studies, otherwise separate pooled measures of sensitivity and specificity were presented. Area under the curve (AUC), which estimates the discriminative power of the test, was the main measure of diagnostic accuracy. Heterogeneity was calculated and appropriate models used. Where there was evidence of significant heterogeneity, narrative synthesis was used and a meta-analysis was not conducted. Where it was reasonable to assume that the underlying diagnostic accuracy was the same in all studies, and that any observed variation in sensitivity or specificity was due to sampling variation, a fixed-effect model was applied. Where heterogeneity existed, statistical analysis involved a random-effects model. Lastly, studies were weighted appropriately.

Why is this issue of interest to public health?

The rapid detection and identification of bacterial pathogens is an important intervention because infected cases, especially those who are infected with certain pathogens or particularly vulnerable, may require specific therapy and a delay in diagnosis may result in a delay in treatment, with consequential increases in morbidity.^{1,2} As well, delays in diagnosis may increase the

time period during which a case remains infectious in the community². Traditional methods of detection, such as cultures, are often time-consuming². PCR, which amplifies and detects pathogenic DNA/RNA, and immunoassays, which detect antigens or antibodies from pathogens, reduce the time needed for diagnosis of bacterial food poisoning (when compared with culture methods)². Unfortunately, these rapid detection methods are likely more expensive than culture methods². Initial costs of purchasing rapid methods equipment and training staff to familiarize them with new technologies are significant². Laboratories with a high volume of throughput may recover set-up costs quickly, but smaller laboratories may struggle to fund initial capital and training costs². However, costs may be offset by a reduction in technical staff costs associated with traditional labour-intensive culture methods². The potential for an increase in laboratory costs needs to be balanced against a possible reduction in overall costs².

In Canada, approximately 11 to 13 million cases of food-borne illness are reported annually.¹ While most of these illnesses are self-limiting² and the majority of those affected fully recover, adverse effects include pain, bloody diarrhea (as in the case of *E. coli* 0157:H7), septicemia and meningitis^{1, 3}. Chronic health problems (e.g., chronic arthritis, Guillian–Barré syndrome, and hemolytic uremic syndrome leading to kidney failure) occur in 2-3% of cases^{1, 2}. The annual cost related to these illnesses, and related deaths, is between 12 and 14 billion dollars¹.

Evidence and implications

In the evidence table below, evidence points are not weighted or ranked according to strength.

What's the evidence?	Implications for practice and policy:
<p>1. Campylobacter (13studies, 6 included in meta-analysis)</p> <p>1.1. Nucleic acid-based test methods</p> <p>1.1.1. PCR for the 16s rRNA gene (6 studies, 4495 samples) PCR correctly identified an abnormal test result 98.7% of the time. The true identification rate ranged from 98.4% to 98.9%. The modified charcoal cefoperazone desoxycholate agar was used as the reference test [Area under curve (AUC) 0.987, 95% CI 0.984 to 0.989). Publication bias detected</p> <p>1.2. Antibody-based tests</p> <p>1.2.1. ProSpecT immunoassay (Alexon-Trend) (4 studies, 2078 samples) This test correctly identified an abnormal test result 86.2% of the time. The true identification rate ranged from 56% to 100% of the time (AUC 0.862, 95% CI 0.568 to 1.000).</p>	<p>1. Campylobacter</p> <p>1.1. The PCR immunoassay test for Campylobacter appears to be very accurate. However, given publication bias was detected it is possible these results are an overestimation of the true effect.</p> <p>1.2. Further studies are needed to make firm recommendations about whether or not to use nucleic acid based test methods or antibody based test methods for detecting campylobacter</p>
<p>2. Salmonella (22 studies, 7 included in meta-analysis)</p> <p>2.1. Nucleic acid-based test methods</p> <p>2.1.1. PCR (7 studies, 2134 samples) The PCR test correctly identified an abnormal test result 99.5% of the time. The true identification rate ranged from 98.5% to 100% of the time (AUC 0.995, 95%CI 0.985 to 1.000). DOC 406.16 (50.87 to 3243.00) Publication bias detected</p> <p>2.2. Non-molecular-based methods</p> <p>2.2.1. Wampole Bactigen, latex agglutination test (4 studies) Diagnostic Odds Ratio (DOR) 264.3, 95% CI 116.9 to 597.6</p> <p>2.2.2. Wellcolex Colour agar latex agglutination test (3 studies) DOR 2951, 95% CI 710.9 to 12000</p> <p>2.2.3. AutoMicrobic Enteric Pathogen Screen cards, biochemical ID test (3studies) DOR 365.49 (30.21 to 4421.06)</p> <p>2.2.4. MUCAP, improved culture test (4 studies) DOR 543.77 (95.47 to 3097.20)</p>	<p>2. Salmonella</p> <p>2.1. The PCR test for Salmonella appears to be very accurate however due to publication bias it is possible these results are an overestimation of the true effect.</p> <p>2.2. Further studies are needed to make firm recommendations about whether or not to use nucleic acid based test methods or non-molecular-based methods for detecting salmonella.</p>
<p>3. E. Coli 0157 & other shiga toxin-producing E. Coli (27 studies)</p> <p>3.1. Nucleic acid-based test methods</p> <p>3.1.1. PCR (10 studies) The PCR test correctly identified an abnormal test result 99.6% of the time. The true identification rate ranged from 99% to 100% of time (AUC 0.996, 95% CI 0.990 to 1.000).</p>	<p>3. E. Coli</p> <p>3.1. The PCR test for E. Coli appears to be very accurate however, due to publication bias it is possible these results are an overestimation of the true effect.</p> <p>3.2. The Verocytotoxin-producing Escherichia coli (VTEC)-Screen also appears to be effective in detecting E.Coli.</p>

<p>Publication bias detected</p> <p>3.2. Antibody-based test methods(12 studies)</p> <p>3.2.1. Verocytotoxin-producing Escherichia coli (VTEC)-Screen Reverse Passive Latex Agglutination (RPLA) (5 studies) The VTEC test correctly identified an abnormal test result 99.4% of the time. The true identification rate ranged from 98.2% to 100% of the time (AUC 0.994, 95% CI 0.982 to 1.000). Publication bias not detected</p> <p>3.2.2. Premier Escherichia coli (EHEC) immunoassay High pooled sensitivity and specificity values (0.935 and 0.997, respectively), which were not correlated.</p>	<p>3.3. The Premier Escherichia coli (EHEC) immunoassay also appears to be very accurate however, due to publication bias, these results are likely to be an overestimation of true effect.</p> <p>3.4. Further studies are needed to make firm recommendations about whether or not to use nucleic acid based test methods or antibody -based methods for detecting <i>E.coli</i>.</p>
<p>4. Other pathogens</p> <p>4.1. <i>Clostridium perfringens</i></p> <p>4.2. <i>Bacillus cereus</i></p> <p>4.3. <i>Staphylococcus aureus</i></p> <p>A very limited number of studies evaluated rapid diagnostic methods against an appropriate reference standard for <i>C. perfringens</i>, <i>B. cereus</i> and <i>staphylococcal</i> food poisoning. Therefore, it was not possible to assess effectiveness using statistical methods.</p>	<p>4. Other pathogens</p> <p>4.1. Additional high quality research is needed to determine the effectiveness of these rapid detection methods.</p>
<p>5. Methodological Issues of included primary studies</p> <p>5.1. Rapid diagnostic test not compared against a true gold standard because rapid assay may be more sensitive than culture</p> <p>5.2. Majority of studies were retrospective</p> <p>5.3. Poor reporting of any detailed information related to</p> <p>5.3.1. Test results</p> <p>5.3.2. Assessment and interpretation blinding</p> <p>5.3.3. Study participants</p> <p>5.3.4. Assessment reliability and validity</p> <p>5.3.5. Full diagnostic accuracy information</p> <p>5.4. Lack of subgroup analyses</p> <p>5.5. Length of time between reference and index testing</p> <p>5.6. Publication bias</p> <p>5.7. Limited number of current studies</p>	<p>5. Program Evaluation and Research</p> <p>5.1. Additional high quality research should be undertaken to add to the body of knowledge in this area and address the deficits in study design, methodological quality, and reporting identified.</p> <p>5.2. 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.</p>
<p>General Implications</p> <ul style="list-style-type: none"> Evidence suggests that rapid assays may be effective methods to detect intestinal pathogens. However, the feasibility of introducing these methods depends upon many local factors that include: community prevalence rates for specific pathogens, skill base and related training costs for laboratory staff, costs associated with required space and equipment changes. Attempting to evaluate diagnostic tests in the absence of a true gold standard creates methodological challenges and this review suggests that rapid assays may be more sensitive than culture methods, which have been the primary method for diagnosis in microbiology laboratories. Furthermore, only a limited number of studies have evaluated rapid diagnostic methods against an appropriate reference standard for <i>C. perfringens</i>, <i>B. cereus</i> and <i>staphylococcal</i> food poisoning. Immunological and PCR tests that detect more than one organism as a time (i.e., multiplexing) may be useful; however, further investigation is required. 	
<p>Legend: CI – Confidence Interval; OR – Odds Ratio; RR – Relative Risk **please see the health-evidence.ca glossary of terms (found under 'How to Use This Site') for definitions</p>	

Cost benefit or cost-effectiveness information

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 (CAD\$ 40.13) with PCR, £15.66 (CAD\$ 33.34) 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.

References used to outline issue

1. Canadian Food Inspection Agency. (2006). Causes of food borne illness. Retrieved from <http://www.inspection.gc.ca/english/fssa/concen/causee.shtml>
2. Abubakar, I., Irvine, L., Aldus, C.F., Wyatt, G.M., Fordham, R., Schelenz, S., Shepstone, L., Howe, A., Peck, M., Hunter, P.R. (2007). 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. *Health Technology Assessment*, 11(36), 1-216.
3. Health Canada. (2006). *Guidelines for Canadian Drinking Water Quality: Guideline Technical Document — Bacterial Waterborne Pathogens — Current and Emerging Organisms of Concern*. Water Quality and Health Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario. Retrieved from http://www.hc-sc.gc.ca/ewh-sem/alt_formats/hecs-sesc/pdf/pubs/water-eau/pathogens-pathogenes/pathogens-pathogenes-eng.pdf

Other quality reviews on this topic

- Campbell, M.E., Gardner, C.E., Dwyer, J.J., Isaacs, S.M., Krueger, P.D., & Ying, J.Y. (1998). Effectiveness of public health interventions in food safety: A systematic review. *Canadian Journal of Public Health*, 1, 197-202
- Effective Public Health Practice Project. (2001). The effectiveness of food safety interventions. Hamilton, ON
- Ejemot R.I., Ehiri J.E., Meremikwu M.M., Critchley J.A. (2008). Hand washing for preventing diarrhoea. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD004265. DOI: 10.1002/14651858.CD004265.pub2.
- Riben, P.D., Mathias, R.G., Campbell, E., & Wiens, M. (1994). The evaluation of the effectiveness of routine restaurant inspections and education of food handlers: Critical appraisal of the literature. *Canadian Journal of Public Health*, 1 suppl., S56-S60.

Related links

- Canadian Food Inspection Agency <http://www.inspection.gc.ca/english/toce.shtml>
- Centers for Disease Control and Preventions <http://www.cdc.gov/>
- National Collaborating Centre for Infectious Diseases <http://www.nccid.ca/en/home>
- Public Health Agency of Canada: Infectious Diseases <http://www.phac-aspc.gc.ca/id-mi/index-eng.php>

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