NICE advice

BD MAX Enteric Bacterial Panel for identifying pathogens in contagious gastroenteritis

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Summary

The BD MAX Enteric Bacterial Panel (EBP) is an assay that detects common enteric bacterial pathogens (which can cause gastroenteritis) from stool samples in 2–3 hours; current standard culture methods take several days. Three fully-published diagnostic test accuracy studies suggested that the BD MAX EBP has higher sensitivity than culture-based methods for detecting bacterial pathogens in gastroenteritis. The cost of running each sample using the BD MAX EBP is £22.50, excluding VAT. The list price for the BD MAX System platform, on which several molecular diagnostic tests can also be run, is £85,000 excluding VAT.

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Likely place in therapy	Effectiveness and safety
• The BD MAX Enteric Bacterial Panel (EBP) is an assay using polymerase chain reaction (PCR) testing to detect bacterial pathogens in stool specimens from people with contagious gastroenteritis. • The BD MAX EBP would be used in microbiology laboratories, before, or instead of, bacterial culture methods, to test stool samples from people with suspected gastroenteritis in hospital and community settings. • If the test is negative, bacterial culture of the specimen is not normally indicated, but may be needed in some circumstances to test for other pathogens.	• Three fully-published diagnostic test accuracy studies were identified for the BD MAX EBP. Nine further studies were available as abstracts. • One manufacturer-sponsored study (Harrington et al. 2015) compared the BD MAX EBP to routine diagnostic culture in 4242 specimens from adults and children. • One study conducted in the UK (Biswas et al. 2014) investigated the diagnostic accuracy and laboratory turnaround time of 3 different PCR assays for detecting bacterial gastroenteritis compared with routine culture techniques in 434 specimens. • One study (Anderson et al. 2014) evaluated the performance of the BD MAX EBP in preserved stool specimens that were then artificially spiked with pathogen strains at different concentrations. • The results from these studies suggest that the BD MAX EBP had higher sensitivity than existing culture-based methods for detecting bacterial pathogens in gastroenteritis. Specificity was either equivalent or superior to culture methods. It was also reported to be substantially faster than those techniques.

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Technical factors	Cost and resource use
• The BD MAX EBP is run using the BD MAX System platform. Testing is automated, including cell lysis, nucleic acid extraction, PCR set-up, target amplification and detection. Results are available in 2–3 hours, compared with several days for standard bacterial culture methods. • The BD MAX EBP detects pathogens including *Salmonella* spp., *Campylobacter* spp. (*jejuni* or *coli*), *Shigellosis* disease-causing agents (*Shigella* spp. and enteroinvasive *Escherichia coli*) and Shiga-toxin-producing *E. coli*.	• The list price of each BD MAX EBP assay is £22.50 per sample, excluding VAT. • The list price for capital purchase of the BD MAX System is £85,000, excluding VAT. The manufacturer produces several different assays that can be run on this system. • No published evidence on resource consequences solely attributable to the BD MAX EBP was identified.

Introduction

Gastroenteritis is a transient illness characterised by the sudden onset of diarrhoea with or without vomiting. It can be caused by infection with bacteria, viruses or parasites. About 20% of the UK population develop gastroenteritis each year (NICE 2014) with an estimated 17 million cases annually in the UK (Tam et al. 2012).

Common bacterial pathogens causing gastroenteritis are *Campylobacter*, *Salmonella, E. coli* O157 and *Shigella sonnei*. Public Health England statistics (Public Health England 2015a) show that in England in 2014 there were:

- 58,722 positive laboratory reports of *Campylobacter*
- 6672 positive laboratory reports of *Salmonella*
- 1088 positive laboratory reports of *Shigella*
- 891 positive laboratory reports of *E. coli* O157.

Rarer bacterial pathogens include *Shigella boydii*, *Shigella dysenteriae* and *Shigella*

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flexneri. Public Health England statistics (Public Health England 2015b) show that in 2014 there were:

- 711 positive laboratory reports of *Shigella flexneri*
- 58 positive laboratory reports of *Shigella boydi*
- 29 positive laboratory reports of *Shigella dysenteriae.*

Polymerase chain reaction (PCR) is a molecular technique that involves the detection and amplification of DNA from clinical samples. In recent years multiplex real-time PCR has been developed to give rapid, quantitative detection of multiple pathogens from a single sample at the same time (Reddington et al. 2014). Different PCR-based systems are available, offering different tests with varying levels of automation. PCR-based detection of pathogens is faster than traditional bacterial culture techniques and in some cases offers greater sensitivity and specificity.

The increased sensitivity of PCR-based detection of pathogens compared with bacterial culture methods may partly reflect the detection of DNA after an acute infection has resolved. Antibiotic treatment may kill the bacteria, but the bacterial DNA can still be detected by PCR. Persistent detection can occur in chronic and convalescent carriers after an acute infectious episode (Health Protection Agency, now Public Health England, 2013). As such it is possible that increased detection of DNA may result in unnecessary treatment.

Technology overview

This briefing describes the regulated use of the technology for the indication specified, in the setting described, and with any other specific equipment referred to. It is the responsibility of health care professionals to check the regulatory status of any intended use of the technology in other indications and settings.

About the technology

CE marking

The BD MAX Enteric Bacterial Panel (EBP) is manufactured by BD Diagnostics and received a CE mark in March 2013. The BD MAX System, which is a platform needed to run the

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panel, received a CE mark in April 2011. Both the EBP and the BD MAX System are classified as Annex III devices and are in compliance with the European directive for in vitro diagnostic medical devices (IVDD/98/79/EC).

Description

The BD MAX EBP is an assay to be used on the BD MAX System. The BD MAX System is a fully automated real-time polymerase chain reaction (RT-PCR) machine that can process up to 24 samples at a time.

The BD MAX EBP is an automated in vitro diagnostic test that uses RT-PCR for the direct qualitative detection of enteric bacterial pathogens. Targets include *Salmonella* spp., *Campylobacter* spp. (*jejuni* and *coli*), Shigellosis disease causing agents (*Shigella* spp. and enteroinvasive *E. coli* [EIEC]) and Shiga-toxin producing *E. coli* in stool specimens from symptomatic patients with suspected acute gastroenteritis, enteritis or colitis.

The BD MAX EBP kit comprises all the reagents and components needed for extraction and PCR set-up, including pipette tips. Kit components include:

- Unitised reagent strips (24 strips for 24 tests) that allow a single strip to be used for a single test, thereby minimising waste and disposables. The strip contains a single reaction tube, a waste receptacle, and wash, elution and neutralisation buffers specific to the test. The strip is placed into the BD MAX System rack and the extraction and master mix tubes are snapped into the unitised reagent strip.
- Extraction tubes (24 tubes for 24 tests), that contain magnetic beads and lytic enzymes needed to extract the sample. Extraction reagents are lyophilised and dried down for long-term storage at room temperature.
- Master mix (24 tubes for 24 tests) that contain primers and probes specific to the test and for the included Sample Processing Control. Reagents are lyophilised and dried down for long-term storage at room temperature.
- Septum caps (25 septum caps) that allow robotic pipetting through the cap with no need to de-cap for sample processing.
- Sample buffer tubes (24 tubes) that contain the buffer specific for the test.

Although the microfluidic cartridge is supplied separately from the BD MAX EBP kit; it is included in the price per test.

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To run a test, the stool sample is homogenised and added into the sample buffer tube. This tube is placed into the BD MAX System, along with the BD MAX EBP reagent strip and microfluidic cartridge. Automated cell lysis, DNA extraction, amplification and detection all take place in the BD MAX System. A qualitative result for each run of samples is given in under 3 hours. However, results are available in under 2 hours if a small number of samples is run. The results indicate whether the sample is positive or negative for each of the pathogens that the test is able to detect. A message reading 'unresolved', 'indeterminate', or 'incomplete' denotes test failure.

The manufacturer states that the results should not be used as the sole basis for diagnosis and treatment or for other patient management decisions. Positive results do not rule out co-infection with other organisms that are not intended to be detected by the test. In practice the test may be performed alongside culture methods and tests for other pathogens not tested for by the BD Max EBP.

A number of BD Max assay cartridges are available to run on the BD MAX System, and open system reagents can also be used for user-defined protocols. Assays other than the BD MAX EBP are beyond the scope of this briefing.

Other CE-marked devices that have a similar function to the BD MAX EBP include:

- BioMeuriex FilmArray Gastrointestinal Panel
- Luminex xTAG Gastrointestinal Pathogen Panel
- RIDAGENE Bacterial Stool Panel and EHEC/EPEC Panels
- FTD Bacterial Gastroenteritis (Fast Track Diagnostics).

Intended use

The BD MAX EBP is intended to identify common enteric bacterial pathogens in stool specimens from people with gastroenteritis.

Setting and intended user

The BD MAX EBP test is intended to be carried out in microbiology laboratories by appropriately trained staff. Stool samples collected from any care setting are sent to a local microbiology laboratory for testing.

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Current NHS options

Gastroenteritis is usually self-limiting. Therefore treatment normally only includes advice on rehydration to prevent serious dehydration, although in some cases antibiotic therapy, anti-diarrhoeal or antiemetic drugs are given according to the NICE clinical knowledge summary on gastroenteritis. Stool samples are sometimes analysed to identify the infectious agent causing the gastroenteritis and the clinical knowledge summary, which is designed for healthcare professionals providing primary healthcare, describes patient selection criteria for stool analysis:

- people who are systemically unwell
- people who have blood or pus in the stool
- people who have an impaired immune system
- people who have recently stayed in hospital or had recent antibiotic treatment
- people with diarrhoea that has occurred after travelling abroad to certain countries
- people with persistent diarrhoea in whom giardiasis is suspected
- where there is diagnostic uncertainty.

The NICE guideline on diarrhoea and vomiting in children, which applies to children younger than 5 years presenting in any setting, recommends that microbiological investigation of stools should be done when:

- septicaemia is suspected
- there is blood or mucus in the stool
- the child is immunocompromised.

Microbiological stool investigations should be considered when:

- the child has recently been abroad
- the diarrhoea has not improved by day 7
- there is uncertainty about the diagnosis of gastroenteritis.

To enable the rapid detection and management of disease and epidemics, registered

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medical practitioners and laboratories in the UK have a statutory duty to notify their local health protection team when they diagnose certain 'notifiable' diseases (Public Health England 2010). This should be done orally, usually by telephone. It is recommended that this should always be done within 24 hours of the diagnosis. Urgent oral notification should be followed up by written notification within 7 days. Notifiable bacterial organisms associated with gastroenteritis include *Campylobacter* spp., *Salmonella, Shigella* and verocytotoxigenic *E. coli* (including *E. coli* O157).

Standards for microbiological investigations involving enteric pathogens are set out by the Standards Unit, which is part of Microbiology Services at Public Health England.

Microbiology laboratories testing faecal specimens look for a number of specific pathogens. The laboratory decides which pathogens to look for, based on a complex range of factors, including whether:

- the specimen is from a hospital patient or a person being treated in primary care
- an infectious disease outbreak is involved
- the patient lives in the UK or has travelled to the UK from their home abroad
- food poisoning is involved
- the patient has a compromised or suppressed immune system
- the patient is a child under the age of 5 years.

All diagnostic specimens (except when screening for a specific organism is requested) should be cultured using standard bacterial culture methods to identify *Campylobacter* spp., *Salmonella* and *Shigella* spp. and *E. coli* O157. Further tests may be added if necessary, and some specimens may need to go to a reference laboratory for strain-type identification (Public Health England 2014).

Usually, samples test negative because these pathogens are relatively rare, even among people with gastroenteritis. Bacterial culture is recognised as having less than 100% sensitivity. PCR has a higher sensitivity, and can detect very low levels of pathogens in the sample. Therefore, more pathogens can be found using PCR than conventional bacterial culture, although the clinical significance of these additional pathogens may sometimes be uncertain (Public Health England 2014).

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Some laboratories currently use PCR methods for detecting gastrointestinal pathogens. Guidance from Public Health England (2014) states that rapid diagnostic tests, such as PCR, should be considered for use, if available. In current practice, bacterial culture is done following a positive PCR result whereas a negative PCR test can avoid the need for bacterial culture of stool specimens.

The Health Protection Agency has produced guidance on the interpretation of PCR assays (Health Protection Agency, now Public Health England, 2013). If PCR was used to identify a notifiable infection, this should also be reported and local laboratories should confirm the result by culture when possible.

Identifying which enteric pathogen is causing gastroenteritis may not always result in a change of treatment but early detection or exclusion of pathogens, including the bacteria detected by BD MAX EBP, may reduce the length of stay or avoid the need for isolation. Identification may be used to monitor infectious diseases, for outbreak investigations, for epidemiological investigations and for surveillance. In some circumstances, such as for people with a compromised or suppressed immune system, pathogen identification may save lives because rapid identification of pathogens allows appropriate antibiotics to be given sooner. Early identification of pathogens may also prevent surgical intervention because gastroenteritis can mimic acute appendicitis.

Costs and use of the technology

The list price of the BD MAX EBP (including microfluidic cartridge) is £22.50 per test, excluding VAT.

The BD MAX EBP can only be run on the BD MAX System platform, which has a list price of £85,000, excluding VAT. A 1-year warranty is provided on the BD MAX System. From year 2, the typical cost of a fully comprehensive service agreement, including annual preventive maintenance, is 10% of the purchase price (£8500). According to the manufacturer, the technology has not been on the market long enough to estimate its lifespan, but if the equipment fails within a typical 5-year contract, the manufacturer would expect to replace it.

The BD MAX System can also be used to run other BD molecular diagnostic tests, which if used, may reduce the overall cost of adopting the BD MAX EBP test. Tests developed by other companies can also be run on the system. Examples include the Check-Direct CPE assays (Check-Points) for carbapenamases, currently distributed in the UK by Hain Life

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Sciences, and in vitro diagnostic tests produced by Diagenode. The BD MAX System is 'open', which makes possible for third parties to develop or optimise their tests to run on the system. Users can also put their own in-house developed assays on the system to fully automate their testing process.

Likely place in therapy

The BD MAX EBP is used at the same point in the patient pathway as culture-based methods for enteric pathogen identification. People would continue to give stool samples, according to the current criteria, at the same point in the clinical pathway in primary or secondary care.

Specialist commentator comments

One specialist commentator noted that a test that improves sensitivity and the speed of detection of potentially notifiable pathogens must be welcomed. However, because most of the pathogens detected by the BD MAX EBP do not have a specific treatment, the effect on the patient pathway is likely to be limited. Exceptions to this are outbreak settings or specific populations such as people with suppressed immune systems or the most seriously ill patients.

One specialist commentator stated that early detection or exclusion of a bacterial gastrointestinal pathogen can reduce the length of time spent in hospital and can help to avoid unnecessary investigations in people with gastrointestinal symptoms. They also felt that there may be some small infection control benefits from diagnosing bacterial gastroenteritis early. The commentator noted that a greater benefit may be seen from a rapid test that excludes all causes of infective diarrhoea, including viruses and parasites, rather than bacterial alone. A second commentator agreed that a rapid test for detecting viral gastroenteritis may be more useful.

Two specialist commentators noted that the BD MAX EBP used alone would not, or would very rarely, shorten the time the patient spent in isolation because the test does not detect all known pathogens or the most common pathogens. One specialist commentator stated that additional tests, including bacterial cultures, may be needed to provide a final comprehensive result and these cultures can delay clinical decisions. This commentator also noted that they would prefer PCR panels that detect a larger range of pathogens.

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Two specialist commentators noted that the automated nature of the test means that it could be done by lower grades of laboratory staff, if biomedical scientists give appropriate training and help with data checking and trouble-shooting. Therefore, although whole-time equivalent staff numbers may not change, there is potential for savings through skill mix revision. A commentator noted that a disadvantage of BD MAX EBP (as with any PCR-based technology) is that there is no means of providing antibiotic sensitivity data when using this technique. With increasing antibiotic resistance this information is essential to ensure appropriate antibiotic stewardship.

Equality considerations

NICE is committed to promoting equality and eliminating unlawful discrimination. In producing guidance, NICE aims to comply fully with all legal obligations to:

- promote race and disability equality and equality of opportunity between men and women
- eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

Identification of enteric pathogens is recommended for people who have a compromised or suppressed immune system. This may include people who are considered to have a long-term condition if that condition has a substantial effect on daily activities to the extent that it causes disability. Disability resulting from long-term conditions is a protected characteristic under the 2010 Equality Act.

Evidence review

Clinical and technical evidence

Regulatory bodies

A search of the Medicines and Healthcare Products Regulatory Agency website revealed no manufacturer Field Safety Notices or Medical Device Alerts for this device. No reports

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of adverse events were identified from a search of the US Food and Drug Administration (FDA) database: Manufacturer and User Device Facility Experience (MAUDE).

Clinical evidence

A literature search and information from the manufacturer identified 12 publications. Three diagnostic test accuracy studies were published in full and are described in detail in this briefing (Harrington et al. 2015; Biswas et al. 2014; Anderson et al. 2014). The other 9 articles were available only as abstracts or conference proceedings and brief summaries are included (Ashman et al. 2013; Beucher et al. 2014; Buchan et al. 2013; Chapin et al. 2013; McAulay et al. 2014; Mortensen et al. 2014; Perry et al. 2014; Porter et al. 2014; Rebec et al. 2013).

Fully-published studies

The study by Harrington et al. (2015) was a cross-sectional multicentre study funded and conducted by the manufacturer, BD Diagnostic Systems. The objective was to evaluate the BD MAX Enteric Bacterial Panel (EBP) compared with routine diagnostic culture for detecting *Salmonella*, *Shigella*, *Campylobacter* (*coli* and *jejuni*) and Shiga-like toxin genes *stx1* and *stx2* from Shiga-toxin-producing organisms (bacterial species not specified). Testing took place in 6 clinical laboratories in the USA and 1 in Canada, using samples collected from sites in the USA, Canada and Mexico.

The study included 4242 soft or diarrhoeal stool specimens from adults and children whose samples were submitted for routine analysis for bacterial stool pathogens. Of these, 3457 were prospective samples, 1345 of which were unpreserved and 2112 were preserved. The remaining 785 samples were retrospective; 321 were unpreserved and 464 were preserved. To increase the number of positive samples of the rarer Shiga-like toxin genes (*stx1* and *stx2*) from Shiga-toxin-producing organisms (bacterial species not specified), retrospective samples were included. These samples had previously been identified as positive for Shiga toxin using enzyme immunoassay (EIA) methods. Where possible these were paired with 1 or more culture-negative specimens from the same time period.

The primary outcome was positive percentage agreement (PPA) and negative percentage agreement (NPA) with culture or EIA results, rather than sensitivity and specificity because bacterial culture is not a true gold standard. Samples that gave different results between the BD MAX EBP and culture or EIA were tested with an alternative polymerase chain

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reaction (PCR) method (PCR methods have greater sensitivity than culture). This PCR result was then used as the reference standard where BD MAX EBP was positive but culture or EIA negative.

The overview and results of this study are summarised in tables 1 and 2 respectively. For prospective samples, the PPA ranged from 80% to 100% and the NPA ranged from 98.2% to 99.7%. For retrospective samples, the PPA ranged from 97% to 100% and the NPA ranged from 99.5% to 100%.

Of discrepant results, 6 were positive by culture but not by the BD MAX EBP (1 *Campylobacter*, 5 *Salmonella*). A number of samples were positive by BD MAX EBP but negative by culture or EIA (see table 2 for details).

The authors concluded that the BD MAX EBP showed superior sensitivity compared with conventional methods and excellent specificity for the detection of bacterial pathogens in stool specimens.

Table 1 Overview of the Harrington et al. (2015) study

Study component	Description
Objectives/ hypotheses	To evaluate the BD MAX EBP assay compared with routine diagnostic culture for detecting *Salmonella* spp., *Shigella* spp., *C. coli*, and *C. jejuni* and enzyme immunoassay for Shiga toxins.
Study design	Cross-sectional, multicentre study.
Setting	Clinical laboratories, 6 in the USA and 1 in Canada. Study developed and supported by the manufacturer.

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Inclusion/ exclusion criteria	Soft or diarrhoeal stool specimens from adults and children submitted for routine analysis for bacterial stool pathogens. Prospective and retrospective specimens in either a clean dry container or preserved in Cary–Blair transport medium. To increase the number of possible positive samples of the rarer pathogen Shiga toxin, retrospective samples of positive samples for Shiga toxin EIA were also included if frozen at −20˚C. Where possible these were paired with one or more culture negative specimens from the same time period. Formed stools or rectal swabs were excluded.
Primary outcomes	PPA and NPA rather than sensitivity or specificity because no true reference method is available. Reference standard: Standard culture methods for the laboratory. EIA for Shiga toxins. Samples with discrepant results for the BD MAX EBP and culture or EIA were tested with an alternative PCR method, which was then used as the reference standard if BD MAX EBP was positive but culture negative.
Statistical methods	PPA and NPA with 95% confidence intervals. Chi–square or Fisher's exact test to compare PPA and NPA between preserved and unpreserved specimens.
Conclusions	The BD MAX EBP showed superior sensitivity compared with conventional methods and excellent specificity for the detection of bacterial pathogens in stool specimens.
Abbreviations: EIA, enzyme immunoassay; PCR, polymerase chain reaction; PPA, positive percentage agreement; NPA, negative percentage agreement.	

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Table 2 Summary of results from the Harrington et al. (2015) study

Patients included	4242 specimens from adult and paediatric patients. 3457 prospective samples collected between December 2012 and September 2013: 1345 were unpreserved and 2112 were preserved. 785 retrospective samples collected between 2007 and 2013: 321 unpreserved and 464 preserved. The age distribution of patients was as follows: <1 year 3.7% 1–4 years 10.3% 5–12 years 11.5% 13–18 years 10.5% 19–65 years 48.6% >65 years 15.3%. Approximately 25% of specimens were from children <12 years. No further details regarding the patient spectrum are provided. Prevalence of each target pathogen in the sample of prospective specimens (based on culture or EIA methods): *Campylobacter*: 1.5% *Salmonella*: 1.2% *Shigella*: 0.8% Shiga toxin: 0.4%. Prevalence of each target pathogen in the sample of prospective specimens (based on culture, EIA and PCR methods): *Campylobacter*: 2.3% *Salmonella*: 2% *Shigella:* 1.1% Shiga toxin: 0.8%.

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Primary outcome	**Prospective specimens** PPA *Campylobacter*: 97.8% *Salmonella:* 87.2% *Shigella:* 100% Shiga toxins: 80%. NPA *Campylobacter:* 98.2% *Salmonella:* 99.1% *Shigella:* 99.7% Shiga toxins: 99.3%.	**Retrospective specimens** PPA *Campylobacter:* 97.0% *Salmonella:* 99.4% *Shigella:* 98.9% Shiga toxins: 100%. NPA *Campylobacter*: 99.5% *Salmonella:* 99.8% *Shigella:* 100% Shiga toxins: 100%.
	Of discrepant results: Six were positive by culture but negative by the BD MAX EBP of which 1 grew *Campylobacter* and 5 grew *Salmonella* not detected by BD MAX EBP or alternative PCR. Two samples were positive for Shiga toxin EIA and negative by the BD MAX and alternative PCR. Samples that were positive by the BD MAX EBP but negative by culture or EIA: *Campylobacter*: 51 (of which 22 were positive with alternative PCR) *Salmonella*: 26 (of which 19 were positive with alternative PCR) *Shigella*: 10 (of which 9 were positive with alternative PCR) Shiga toxins: 17 (of which 9 were positive with alternative PCR).	
Abbreviations: EIA, enzyme immunoassay; PCR, polymerase chain reaction; PPA, positive percentage agreement; NPA, negative percentage agreement.		

The UK-based study by Biswas et al. (2014) investigated the diagnostic accuracy and laboratory turnaround time of 3 PCR assays for the identification of bacterial pathogens in cases of gastroenteritis. In this cross-sectional study, funded by the National Institute for Health Research, the BD MAX EBP was compared with the RIDAGENE Bacterial Stool Panel and EGEC/EPEC Panels (made by R-Biopharm AG) and the FTD Bacterial Gastroenteritis (made by Fast Track Diagnostics). The study took place in a single laboratory at a London teaching hospital in the UK. Unpreserved diarrhoeal stool samples submitted for routine

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bacterial culture between November 2013 and February 2014 were included. Samples came from both hospital inpatients and people in the community. The reference standard for a true positive was either a positive culture, or 2 out of 3 PCR methods positive for a pathogen. The primary outcomes were sensitivity, specificity, positive predictive value and negative predictive value.

There were 434 samples collected, of which 318 were prospectively collected and 116 were retrospective culture-positive samples. The results are presented in tables 3 and 4.

PCR led to the detection of an additional 9 cases of *Campylobacter* and 4 cases of *Shigella*. The reported laboratory turnaround time was 163 minutes, with 20 minutes hands-on time, compared with 66.5 hours for bacterial culture methods. It is not clear from the paper whether these figures represent the average time per test. The authors concluded that PCR panels were more sensitive than culture-based methods, allowing faster detection of a larger number of infectious people. Of the 3 PCR systems the BD MAX System was the fastest, needed the least hands-on time and appeared to have slightly better performance characteristics in terms of sensitivity, specificity, positive predictive value and negative predictive value than the alternatives.

Table 3 Overview of the Biswas et al. (2014) study

Study component	Description
Objectives/ hypotheses	To investigate the diagnostic accuracy and laboratory turnaround time of 3 PCR assays for the detection of bacterial gastroenteritis. The assays included: BD MAX EBP RIDAGENE Bacterial Stool Panels FTD Bacterial Gastroenteritis
Study design	Cross-sectional
Setting	UK single-centre laboratory study. NIHR-funded.

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Inclusion/ exclusion criteria	Unpreserved diarrhoeal stool samples submitted for routine bacterial culture between November 2013 and February 2014.
Primary outcomes	Sensitivity and specificity. Reference standard true positive if either culture or 2 out of the 3 PCR methods tested positive.
Statistical methods	Sensitivity, specificity, PPV, NPV
Conclusions	PCR panels are more sensitive than culture-based methods allowing faster detection of a larger number of infectious people. The BD MAX EBP was fastest of all methods and required the least hands-on time. The BD MAX EBP appeared to have slightly greater performance characteristics than the other PCR panels.
Abbreviations: EIA, enzyme immunoassay; NIHR, National Institute for Health Research; PCR, polymerase chain reaction; PPV, positive predictive value; NPV, negative predictive value.	

Table 4 Summary of results from the Biswas et al. (2014) study

Patients included	434 samples: 318 prospectively collected and 116 retrospective culture-positive samples. This was described as a mostly community- or outpatient-based patient cohort.

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Results	**Prevalence of pathogens in the prospective samples** *Campylobacter*: 5.3% *Shigella*: 4.4% *Salmonella*: 1.3% Shiga-toxin-producing *E. Coli*: 0.3%. **BD MAX EBP — prospective samples only** *Campylobacter:* Sensitivity 100% (95% CI 80.5 to 100) Specificity 100% (95% CI 98.8 to 100) PPV 100% (95% CI 80.5 to 100) NPV 100% (95% CI 98.8 to 100). *Shigella*: Sensitivity 100% (95% CI 76.8 to 100) Specificity 100% (95% CI 98.8 to 100) PPV 100% (95% CI 76.8 to 100) NPV 100% (95% CI 98.8 to 100). *Salmonella*: Sensitivity 100% (95% CI 39.8 to 100) Specificity 99.7% (95% CI 98.2 to 100) PPV 80% (95% CI 28.4 to 99.5) NPV 100% (95% CI 98.8 to 100). **All samples (prospective and retrospective)** NB: Sensitivity and specificity only presented in paper. *Campylobacter*: Sensitivity 92.1% (95% CI 85 to 96.5) Specificity 100% (95% CI 98.9 to 100). *Shigella*: Sensitivity 94.4% (95% CI 81.3 to 99.3) Specificity 100% (95% CI 99.1 to 100). *Salmonella*: Sensitivity 75% (95% CI 50.9 to 91.3)

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	Specificity 100% (95% CI 99.1 to 100). Shiga-toxin-producing *E. Coli*: Sensitivity 100% (95% CI 25 to 100) Specificity 99.5% (95% CI 98.3 to 100). PCR led to the detection of an additional 9 cases of *Campylobacter* and 4 cases of *Shigella*. Laboratory turnaround time: BD MAX EBP: 163 minutes (with 20 minutes hands-on time) Culture methods: 66.5 hours.
Abbreviations: CI, confidence interval;EIA, Enzyme Immunoassay; NPA, negative percentage value; PCR, Polymerase Chain Reaction; PPV, positive predictive value.	

The study by Anderson et al. (2014) was a cross-sectional study in a single laboratory in the USA that aimed to evaluate the performance of the BD MAX EBP in detecting *Salmonella*, *Campylobacter jejuni*, *Shigella* and Shiga-toxin-producing *E. coli* in preserved stool specimens. The organisms tested for included 4 unique strains each of *Salmonella, Campylobacterjejuni, Shigella* and enterohaemorrhagic *E. coli* (a total of 16 strains). The study used Cary–Blair-preserved stool specimens (specimens preserved in Cary–Blair transport medium, a transport medium for Gram-negative and anaerobic organisms) that had previously tested negative for enteric pathogens by routine culture and the BD MAX EBP. These negative samples were mixed with known concentrations of different species of bacteria. The total number of samples in this study is unclear although it appears to be 1 sample per bacterial species at each concentration level. The reference standard was the known true result of these artificially produced samples.

The BD MAX EBP demonstrated 100% sensitivity for all bacteria tested at the following concentrations of bacteria in the sample: 10^7 colony-forming units (CFU)/ml, 10^6 CFU/ml and 10^5 CFU/ml. The results of this study are summarised in tables 5 and 6.

For all of the bacterial species and concentrations tested, the BD MAX EBP was as sensitive as culture methods. At lower concentrations BD MAX EBP was more sensitive than culture methods. The authors concluded that the BD MAX EBP has a higher sensitivity at low levels of concentration for enteric pathogens compared with culture.

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Table 5 Overview of the Anderson et al. (2014) study

Study component	Description
Objectives/ hypotheses	To evaluate the performance of the BD MAX EBP in detecting 16 strains in total of *Salmonella,Campylobacter jejuni* and *coli*, *Shigella* and Shiga-toxin-producing *E. coli* in preserved stool specimens.
Study design	Cross-sectional.
Setting	Single-centre laboratory study, USA.
Inclusion/ exclusion criteria	Cary–Blair-preserved stool samples, negative for enteric pathogens by routine culture methods and the BD MAX EBP that were artificially spiked with pathogen strains at the following levels of concentration: 10^7 CFU/ml 10^6 CFU/ml 10^5 CFU/ml 10^4 CFU/ml 10^3 CFU/ml.
Primary outcomes	Sensitivity. Reference standard determined by known true result of artificially produced samples.
Statistical methods	Sensitivity %
Conclusions	The BD MAX EBP has a higher sensitivity at low levels of concentration for enteric pathogens compared with culture.
Abbreviations: CFU/ml, colony forming unit/millilitre; EIA, enzyme immunoassay; PCR, polymerase chain reaction.	

Table 6 Summary of results from the Anderson et al. (2014) study

Patients included	Cary–Blair-preserved specimens from clinical patients negative for enteric pathogens by routine stool culture and BD MAX EBP artificially spiked with pathogens at a range of concentrations.

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Primary outcome results	At the following concentrations: 10^7 CFU/ml;10^6 CFU/ml 10^5 CFU/ml; the BD MAX EBP demonstrated 100% sensitivity for all organisms tested. At 10^4 CFU/ml the sensitivity of the BD MAX EBP was: *Campylobacter*: 100% Shiga-toxin-producing *E. coli*: 87.5% *Salmonella*: 68.8% *Shigella*: 100%. At 10^3 CFU/ml the sensitivity of the BD MAX EBP was: *Campylobacter*: 100% Shiga-toxin-producing *E. coli*: 13.3% *Salmonella*: 43.8% *Shigella*: 81%. For all pathogens at all concentrations the BD MAX EBP was as sensitive as culture methods. At lower concentrations the BD MAX EBP was more sensitive than culture methods.
Abbreviations: CFU/ml, colony forming unit/millilitre; EIA, enzyme immunoassay; PCR, polymerase chain reaction.	

Studies available as abstracts

Seven abstracts reported cross-sectional studies of the diagnostic performance of the BD MAX EBP compared with culture or enzyme immunoassay methods in a total of 4569 samples (Ashman et al. 2013; Beucher et al. 2014; Buchan et al. 2013; Chapin et al. 2014; McAulay et al. 2014; Porter et al. 2014; Rebec et al. 2013). These studies, including 1 in which stool samples from children were tested (Beucher et al. 2014), all reported that the BD MAX EBP was more sensitive than conventional methods.

One abstract (Perry et al. 2014) reported a study comparing the BD MAX EBP with the Luminex xTAG Gatrointestinal Pathogen Panel (GPP) for the detection of *Campylobacte*r, *Salmonella,Shigella* and Shiga toxin-producing *E coli* using artificially spiked samples. The authors concluded that the BD MAX EBP demonstrated superior limits of detection compared with the Luminex xTAG GPP.

One abstract (Mortensen et al. 2014) reported the results of a time-motion study

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comparing the use of the BD MAX EBP with conventional culture techniques in a US hospital-based laboratory. Following the processing of 86 samples, the average time to report for routine culture was 44 hours 37 minutes compared with 7 hours and 6 minutes for the BD MAX EBP, which represented an average reduction of turnaround time of 85%.

Recent and ongoing studies

No ongoing or in-development trials on BD MAX EBP for gastroenteritis were identified.

Costs and resource consequences

The BD MAX EBP is currently in use in a number of NHS trusts. According to the manufacturer there are currently 31 BD MAX Systems installed across 27 NHS trusts in the UK, processing a variety of infectious disease assays. Of those sites, 13 are using the BD MAX EBP routinely, and several others have submitted business cases to use the panel.

Using the technology could eliminate the need for culture of stool specimens to detect the pathogen included in the panel, if specimens are negative on PCR testing. This could lead to a reduction in culture tests and in the time needed for trained scientists to carry out these tests.

The automated nature of the test means that it could be carried out by lower grades of laboratory staff than is needed for bacterial culture, provided that biomedical scientists train them and help with data checking and trouble-shooting. Therefore, there is potential for savings through revision of skills mix.

No published evidence on resource consequences solely attributable to the BD MAX EBP was identified.

Strengths and limitations of the evidence

From the perspective of evaluation of the BD MAX EBP as a diagnostic test, there is no clear reference standard and relevant studies have used composite reference standards incorporating both culture and molecular results. This issue applies to the evaluation of any diagnostic method to detect bacterial pathogens in gastroenteritis and is not specific to the BD MAX EBP.

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The study by Harrington et al. (2015) was a large diagnostic study that included samples from a variety of patients across a range of ages. There is little information about other patient characteristics. It is unclear whether all consecutive samples submitted to the laboratory were included or whether the included samples were randomly selected. As with all studies, the reference standard was imperfect, and in this study the PCR method used to resolve discrepant results was not described. The study did not describe whether staff were blinded to the status of samples or the order and timescale of testing. Although blinding should not affect the qualitative result offered by the BD MAX EBP, it might impact upon culture interpretation.

The study by Biswas et al. (2014) was an independent study that received no financial support from the manufacturer. It was conducted in a laboratory at a London hospital and received samples from inpatients and people in the community, so this might be reflective of standard use in a UK hospital. The sample size was small, resulting in few numbers of positive samples and some imprecise estimates of diagnostic accuracy. It is not clear whether all consecutive samples submitted to the laboratory were included or whether the included samples were randomly selected. The order of testing was unclear, nor was it clear whether technicians were blinded to the status of the samples throughout. As in the other studies, the reference standard was imperfect. However, in this study, PCR results, including the BD MAX EBP, were included to determine true positives. This may have reduced the problems associated with an imperfect reference standard, but could also introduce a risk of incorporation bias which might overestimate the sensitivity of the test.

The study by Anderson et al. (2014) was very small, although the exact number of samples tested was unclear. It offers experimental evidence of the sensitivity of the BD MAX EBP for detecting different bacterial concentrations, but all samples were artificially produced by mixing stool samples with bacteria, resulting in lower clinical relevance. No negative samples were tested, so no conclusions can be drawn regarding specificity. The study was materially funded by the manufacturer.

The evidence presented in the included abstracts broadly concurs with the findings of the 3 fully-published papers. Studies available only as abstracts may not have been fully peer-reviewed, may be more susceptible to a publication bias, and the limited information presented precludes critical appraisal.

Relevance to NICE guidance programmes

The use of the BD MAX EBP is not currently planned into any NICE guidance programme.

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Search strategy and evidence selection

Search strategy

The electronic databases OVID Medline, EMBASE, Scopus and CENTRAL were searched using the search term "BD MAX", which was found to be most sensitive in pilot searches. The manufacturer was contacted and invited to highlight relevant studies.

Evidence selection

Studies were included if they specifically evaluated the BD MAX System Enteric Bacterial Panel. Studies evaluating other assays for the BD MAX System were excluded. The reference lists of included papers were hand searched for possible studies. Studies published as full papers in peer-reviewed journals and relevant abstracts were included in the full briefing. The following criteria were used for study selection.

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Population

Patients with gastroenteritis where identification of a pathogen from a stool sample is required.

Intervention

In vitro diagnostic test to identify commonly encountered enteric bacterial pathogens: BD Max System Enteric Bacterial Panel.

Comparator

Standard methods to identify commonly encountered enteric bacterial pathogens: culture methods (agar plate and enhanced).

Other quantitative platforms and assays to identify commonly encountered enteric bacterial pathogens.

Outcomes

- Test characteristics.
- Frequency of identification of a bacterial pathogen.
- Time to gain a test result.
- Resource required to gain a test result.
- Impact on the patient pathway, including isolation unit/barrier nursing days.

Initial search screening identified 12 publications.

About this briefing

Medtech innovation briefings summarise the published evidence and information available for individual medical technologies. The briefings provide information to aid local decision-making by clinicians, managers and procurement professionals.

Medtech innovation briefings aim to present information and critically review the strengths

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and weaknesses of the relevant evidence, but contain no recommendations and **are not formal NICE guidance**.

Development of this briefing

This briefing was developed for NICE by Birmingham and Brunel Consortium. The interim process & methods statement sets out the process NICE uses to select topics, and how the briefings are developed, quality-assured and approved for publication.

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