Technoleg Iechyd Cymru
Health Technology Wales

Topic Exploration Report

Topic explorations are designed to provide a high-level briefing on new topics submitted for consideration by Health Technology Wales. The main objectives of this report are to:

1. Determine the quantity and quality of evidence available for a technology of interest.
2. Identify any gaps in the evidence/ongoing evidence collection.
3. Inform decisions on topics that warrant fuller assessment by Health Technology Wales.

Topic:	**FebriDx point-of-care test for acute respiratory infection in patients attending Emergency Departments.**
Topic exploration report number:	TER238

Introduction and aims

FebriDx is a rapid point of care (POC), dual marker, immunoassay test. It has the potential to support effective patient triaging and cohorting in Emergency Departments to help prevent spread of infection and reduce hospital congestion. The test is performed on patients with symptoms of acute respiratory infection (ARI) (e.g. fever, cough, shortness of breath, sore throat). Patients who test viral negative can be cohorted in non-COVID-19 areas and thereby free up hospital resources for patients that may require isolation. Patients who test viral positive using FebriDx would continue to be isolated while awaiting a subsequent confirmatory PCR test. FebriDx can also distinguish between viral and bacterial acute respiratory infections (ARIs) and has the potential to ensure early identification of bacterial infections.

The test takes up to 10 minutes and uses a fingerstick sample collection and onboard transfer of the buffer solution. Raised levels of C-reactive protein (CRP) and myxovirus resistance protein A (MxA) in peripheral blood are detected. CRP is an acute-phase protein synthesised by the liver and a non-specific marker for acute inflammation. It is elevated within 4-6 hours of infection and peaks after 26 hours. MxA is an intracellular blood protein found in lymphocytes which is stimulated by the presence of type I interferon MxA levels remain low with bacterial infection but it is able to detect viral infection. Induction is 1-2 hours after infection and it peaks at 16 hours, remaining elevated in the presence of elevated interferon. POC CRP tests are considered to have potential in supporting decision-making over prescription of antibiotics for ARIs in primary care. The addition of MxA biomarker seeks to increase specificity by differentiating viral from bacterial infection.

The current reference standard for viral ARIs is PCR test. Adding FebriDx to the initial triage could result in more rapid identification of ARI-symptomatic, COVID-19-negative patients entering emergency departments than using PCR alone. These patients would otherwise require cohorting with COVID-19-positive patients if symptomatic. Symptomatic, viral positive patients would continue to be treated and cohorted as usual while awaiting PCR confirmatory testing.

FebriDx is CE-marked as in vitro diagnostic device. This device has previously been explored for acute upper respiratory tract infection in March 2019 (TER052).

Health Technology Wales researchers searched for evidence of the clinical and cost effectiveness of FebriDx to test for acute respiratory infections in emergency departments on 10-11/12/2020. As a NICE Medtech Innovation Briefing was published on 26 August 2020, the search was limited to studies published from June 2020 onwards (assuming a standard 11 weeks between the NICE literature search and publication).

Summary of evidence

Overview

A NICE Medtech Innovation Briefing on the use of FebriDx was published in August 2020, which was not specific to use in emergency departments. The evidence found suggested that FebriDx was effective with high sensitivity and specificity for both bacterial and viral infections. Three of the studies identified were based in emergency departments. Two of which were included in a subsequent meta-analysis, which found a pooled sensitivity and specificity of 92% and 86%, respectively (estimated prevalence of 41% for COVID-19). A budget impact analysis study was identified which found the cumulative annual cost of FebriDx to be less than a CRP POC test and no test (£237 million versus £290 million and £327 million respectively).

Only one new clinical study of FebriDx for patients attending emergency departments with suspected ARI not previously included in the NICE Medtech Innovation Briefing was identified. This was a pre-print (not yet peer-reviewed) on a retrospective cohort study of patients requiring admission to a medical ward from the emergency department in a UK hospital. In patients triaged to be 'possible' cases sensitivity of FebriDx was 91.1% and specificity was 90.0% (N=958; prevalence of COVID-19: 4.1%). Use of clinical triage plus FebriDx overall had a sensitivity and specificity of 92.6% and 86.4% respectively (in patients admitted and triaged) compared to 95.6% and 61.5% with clinical triage alone. Negative and positive predictive values (NPV and PPV) were 99.7% and 22.0% respectively compared to 99.7% and 9.3% with clinical triage alone. The addition of FebriDx enabled 826 patients who had been triaged as possible cases to be managed in 'non-COVID' areas.

One study of FebriDx in symptomatic and asymptomatic patients is due to report imminently in the US. It is not clear if subgroup analysis for those presenting to emergency departments will be available. A second study of FebriDx in Australian emergency departments is due to report in 2022.

Technology Assessments

NICE published a Medtech Innovation Briefing on the use of FebriDx in August 2020 (MIB224).(1) They identified 43 diagnostic accuracy studies, of which two were in COVID-19 (Clark et al. 2020; Karim et al. 2020), four feasibility studies and one clinical evaluation. The evidence suggested that FebriDx is effective with high sensitivity (>80%) and specificity (>90%) when identifying bacterial and viral infections in adults. The emerging evidence suggested that it could help with early detection of viral infections, such as COVID-19. Uncertainties highlighted were that there was only one published study exclusively in children and one published study for people with suspected COVID-19. There was also limited follow-up evidence of effects on antibiotic use. In addition to standard care, FebriDx was estimated to cost £12.75 (excluding VAT). Published evidence was found to suggest that FebriDx could save

costs by reducing antibiotic use and avoiding associated complications. NICE identified six other CE-marked devices with some of the same functions as FebriDx, however, none included a viral biomarker and all need bench-top analysers.

NICE also published as Medtech Innovation Briefing on the use of FebriDx in primary care in 2017.(2) This was updated and replaced by MIB224.

Systematic reviews

One systematic review of FebriDx in acute hospital settings, not yet peer-reviewed, by Unwin et al. (2020) was identified.(3) This identified and included the two studies by Clark et al. (2020) and Karim et al. (2020).(11,12) Meta-analyses of these two studies found a pooled sensitivity of 92% and specificity of 86% compared with PCR (estimated prevalence of COVID-19: 40.5%).

One ongoing systematic review of POC tests to differentiate between bacterial and viral infections in children and adults presenting to primary and secondary care with ARIs was identified.(5) The analysis will be stratified by age and healthcare setting with an anticipated completion date of July 2020.

Primary studies

Cost-effectiveness studies

Schneider et al. (2020) conducted a budget impact analysis to assess POC testing options for identifying patients with an ARI who may benefit from antibiotics in a UK outpatient setting.(4) The authors compared FebriDx to a standalone CRP POC test, a hypothetical POC test which met a target product profile (TPP), and no POC test. Diagnostic accuracy was taken from the study by Shapiro et al. (2018) and FebriDx was costed at £11.25 (which is lower than the NICE estimated cost of £12.75).(8,1) The cumulative annual cost of FebriDx was estimated to be £237,614,489 compared to £290,295,065, £147,805,881 and £326,500,346 for CRP, TPP and no test respectively.

Clinical effectiveness studies

One retrospective cohort study was shared as a pre-print (not yet peer reviewed) by the Topic Proposer. This included patients who required admission to a medical ward from the emergency department in a UK hospital (N=3,433).(12) FebriDx was used for patients who were clinically assessed as a possible COVID-19 case (but not in those assessed to be unlikely or likely cases) (N=958). The reference standard was PCR and prevalence of COVID-19 was estimated to be 4.1% in possible cases. Use of FebriDx in possible cases following clinical triage had a sensitivity of 91.1% and specificity of 90.0%. Use of clinical triage plus FebriDx overall had a sensitivity and specificity of 92.6% and 86.4% respectively (in patients admitted and triaged). Clinical triage alone had a sensitivity and specificity of 95.6% and 61.5% respectively. NPV and PPV were 99.7% and 22.0% respectively for clinical triage plus FebriDx compared to 99.7% and 9.3% with clinical triage alone. The addition of FebriDx enabled 826 patients who had been triaged as possible cases to be managed in 'non-COVID' areas.

No further studies of FebriDx in patients attending emergency departments with suspected ARI, published since the NICE Medtech Innovation Briefing, were identified from literature.

Key clinical studies previously included by NICE MIB224

The study by Clark et al. (2020) was a non-randomised, pre- and post-implementation study of 251 results from 266 adults with suspected COVID-19 presenting at hospitals in the UK between March and April 2020.(11) The reference standard was PCR. Sensitivity for detection of viral infection was 93% (95% CI 87% to 97%) and specificity was 86% (95% CI 79% to 92%). Overall accuracy was 90% (95% CI 52% to 72%), PPV was 63% (95% CI 52% to 72%) (assuming 20% prevalence), and NPV was 99% (95% CI 96% to 99%). Several patients with a positive result had a negative PCR but radiological features of COVID-19 and were considered true positives. It was noted by NICE that the reference standard was likely to be suboptimal. It was also noted that the results could not be applied to people who are immune-compromised or to children.

Karim et al. (2020) undertook a prospective observational cohort study of 48 patients presenting to emergency departments in UK hospitals with symptoms of ARI suspected to be COVID-19.(10) The reference standard was PCR and clinical assessment. Of 35 patients considered positive for ARI, 30 had a positive PCR and 5 a clinical assessment suggesting ARI (5/35). One patient had a negative PCR for SARS-CoV-2 but other viral infection could not be excluded. Therefore, sensitivity of FebriDx was 100% for COVID-19 positive patients and 97% for all viral infection. SARS-CoV-2 was detected by PCR in 31/34 patients with a diagnosis of COVID-19 based on clinical and/or radiological assessment (meeting the case definition for Probable COVID-19).The specificity for both FebriDx and PCR in COVID-19 positive patients was 100%. At the time this study was assessed by NICE it had not been peer-reviewed.

Shapiro et al. (2018) undertook a cross-sectional, observational cohort study of 223 people attending emergency departments and urgent care settings in the US with a history of fever in the previous 72 hours and clinical signs and symptoms of an upper respiratory tract infection.(8) FebriDx was compared with PCR, culture and clinical override. For bacterial infection, FebriDx was found to have an overall sensitivity of 95% and specificity of 94% with a PPV of 76% and NPV of 99%. For viral detection, FebriDx was found to have a sensitivity of 90% and specificity of 76% with a PPV of 83% and NPV of 85%.

Ongoing trials

One trial was identified which is due for completion in December 2020.(6) This is an observational study of individuals presenting to emergency departments, urgent care centres and primary care in the US with new onset fever and respiratory symptoms. The estimated enrolment is 2,000 participants. FebriDx will be compared in symptomatic and asymptomatic cohorts.

A second trial looking at the NPV of FebriDx in patients presenting to an Australian Emergency Department with suspected COVID-19 was registered in October 2020.(7) The estimated last date of data collection is May 2022.

Areas of uncertainty

There is some evidence to support diagnostic accuracy of FebriDx in emergency department settings and one recent study reports the reduction in patients who requiring cohorting as COVID-19 positive patients by introducing FebriDx. The evidence uses PCR as the reference

standard and there is some uncertainty around its accuracy. There is a lack of good quality studies comparing FebriDx against other POC tests for ARIs in emergency departments.

Conclusions

There is evidence of diagnostic accuracy of FebriDx when used in emergency departments for ARIs from at least three studies. One recent study reports a reduction in patients who require cohorting as COVID-19 positive patients through the use of FebriDx in emergency departments. There is also some evidence to suggest that FebriDx may result in a lower annual cost than a CRP POC test or no test based on a reduction in unnecessary antibiotic prescribing (one study).

Brief literature search results

Resource	Results
HTA organisations	
Healthcare Improvement Scotland	We did not identify any relevant evidence from this source.
Health Technology Assessment Group	We did not identify any relevant evidence from this source.
Health Information and Quality Authority	We did not identify any relevant evidence from this source.
EUnetHTA	We did not identify any relevant evidence from this source.
International HTA Database	We did not identify any relevant evidence from this source.
UK guidelines and guidance	
SIGN	We did not identify any relevant evidence from this source.
NICE	1. https://www.nice.org.uk/advice/mib224/chapter/Summary Medtech Innovation Briefing (MIB224), 26 August 2020 2. https://www.nice.org.uk/advice/mib114 FebriDx for C-reactive protein and Myxovirus resistance protein A testing in primary care. Medtech innovation briefing [MIB114] Published date: 31 July 2017. Updated and replaced by NICE medtech innovation briefing 224
Secondary literature and economic evaluations	
https://www.epistemonikos.org/en/	3. Unwin et al. (2020). FebriDx point-of-care test in patients with suspected COVID-19: a pooled diagnostic accuracy study. https://www.epistemonikos.org/en/documents/1f039a3de217410298af36956dd8a5d445b3e8c8
https://www.tripdatabase.com/	We did not identify any relevant evidence from this source.
Cochrane library	We did not identify any relevant evidence from this source.
Medline	4. Schneider et al. (2020). Application of a simple point-of-care test to reduce UK healthcare costs and adverse events in outpatient acute respiratory infections. https://pubmed.ncbi.nlm.nih.gov/32259465/
Primary studies	
https://www.epistemonikos.org/en/	We did not identify any relevant evidence from this source.
https://www.tripdatabase.com/	We did not identify any relevant evidence from this source.
Cochrane library	We did not identify any relevant evidence from this source.
Medline	We did not identify any relevant evidence from this source.
Ongoing primary or secondary research	
PROSPERO database	5. Carlton et al. PROSPERO 2020. A systematic review of novel point-of-care tests to differentiate viral from bacterial infections to guide antibiotic prescribing. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=178973
Clinicaltrials.gov	6. ClinicalTrials.gov identifier: NCT02018198. Status: recruiting, estimated study completion date: December 2020. Indication: acute respiratory tract infections. https://www.clinicaltrials.gov/ct2/show/NCT02018198?term=FebriDx&draw=2&rank=1 FebriDx DISRUPT acute respiratory infection trial in acute respiratory infection: an evaluation of FebriDx point-of-care test.
https://www.epistemonikos.org/en/	7. ACTRN12620001029987p Negative predictive value of the FebriDx host response point-of-care test in patients presenting to a single Australian Emergency Department with suspected COVID-19. https://www.epistemonikos.org/en/documents/c7b21d3ff92bea3f6c34273cd1d92d51403fa562

Other	
Evidence provided by the Topic Proposer	8. Shapiro NI, Self WH, Rosen J, Sharp SC, Filbin MR, Hou PC, et al. A prospective, multi-centre US clinical trial to determine accuracy of FebriDx point-of-care testing for acute upper respiratory infections with and without a confirmed fever. Ann Med. 2018;50(5):420-29. https://doi.org/10.1080/07853890.2018.1474002 9. Self WH, Rosen J, Sharp SC, Filbin MR, Hou PC, Parekh AD, et al. Diagnostic accuracy of FebriDx: A rapid test to detect immune responses to viral and bacterial upper respiratory infections. J Clin Med. 2017;6(10):94. 10. Karim N, Ashraf MZ, Naseem M, et al. Utility of the FebriDx point-of-care test for rapid triage and identification of possible coronavirus disease 2019 (COVID-19). Int J Clin Pract. 2020;e13702. doi: 10.1111/ijcp.13702 11. Clark TW, Brendish NJ, Poole S, et al. Diagnostic accuracy of the FebriDx host response point-of-care test in patients hospitalised with suspected COVID-19. J Infect. 2020;Epub ahead of print. doi: 10.1016/j.jinf.2020.06.051 AND Clark et al. (2020). Real-World Diagnostic Accuracy of a Host Response Point-of-Care Test in Hospitalised Patients with Suspected COVID-19 https://www.epistemonikos.org/en/documents/d49bc705143de73ee8cb5c83cf7fd268e4b60eb9 12. Houston H, Gupta-Wright A, Deas G et al. Use of the FebriDx point-of-care assay as part of a triage algorithm for medical admissions with possible COVID-19. Preprint (not certified by peer review. https://doi.org/10.1101/2021.01.05.21249154

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Concepts used:	FebriDx; myxovirus