NICE advice

Point-of-care diagnostic testing in primary care for strep A infection in sore throat

Medtech innovation briefing
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Summary

- The 11 **technologies** described in this briefing are point-of-care tests for diagnosing group A beta-haemolytic streptococcus (strep A) throat infection.
- The **innovative aspects** are the fast turnaround time compared with laboratory culture of throat swabs, allowing potential use in primary care.
- The intended **use** would be in addition to clinical scoring systems, to increase diagnostic confidence of a suspected strep A infection and guide antibiotic prescribing for people presenting with sore throat in primary care and community pharmacies.
- The **main points from the evidence** summarised in this briefing are from 4 prospective studies, 1 pilot study and 1 systematic review, including 102,694 patients, of whom 3,552 were tested with the technologies described in this briefing. The evidence, which covers 5 of 11 tests included in the briefing, suggests that point-of-care tests are more helpful for diagnosing strep A infection than clinical scoring systems alone in people with acute sore throat.
- **Key uncertainties** around the technology are the lack of an established NHS care pathway for using strep A tests. There are also differences in diagnostic accuracy depending on the patient population tested.
- The **cost** of point-of-care strep A tests varies depending on the technology, from £0.80 per test with no additional costs to £50 per test with an additional reader cost of £17,339.27 (excluding VAT).

- The **resource impact** would initially be greater than standard care because of the additional test costs. This could be offset if their use led to better antimicrobial stewardship and helped to reduce antimicrobial resistance and improved patient education and satisfaction.

This briefing describes technologies that fulfil a similar purpose. During development, every effort was made to identify and include relevant technologies but others may not have been identified, or may have been excluded when important information was unavailable.

The technology

This briefing describes 11 tests that are designed to indicate the presence or absence of streptococcus (strep) A. The tests vary by diagnostic technique:

- Nine of the 11 are rapid antigen detection tests, 8 of which use lateral flow techniques (also known as immunochromatographic assays). A throat swab is taken and the sample is applied to an adsorbent pad on the end of the test strip. The sample from the throat swab migrates along the strip, which contains strep A antigen and causes a test line to appear if strep A is present. A control line shows technical success. Results are read by either visual inspection or by using a test reader.
- One of the rapid antigen detection tests uses a turbidimetric immunoassay, which is based on the change in optical properties in the presence of an antigen-antibody complex.
- The other 2 tests use nucleic acid amplification techniques, either polymerase chain reaction (PCR) or isothermal nucleic acid amplification of a specific segment of the strep A genome. Fluorescent probes label DNA during the PCR, producing fluorescent light, which is monitored by a reader. If fluorescence reaches a specific threshold, the test is considered positive. If the threshold is not reached during the set time (usually up to 15 minutes), the test is negative.

Regulatory information

All the technologies included in this briefing are CE marked as in-vitro diagnostic medical devices and are summarised in table 1. The focus of the briefing is their potential use in primary care.

Table 1 Summary of included point-of-care strep A tests

Technology	Device (company name)	Components	Method	Time to result

Rapid antigen detection test	Clearview exact strep A cassette (Abbott)	25 test kit	Lateral flow	5 minutes
Rapid antigen detection test	Clearview exact strep A dipstick (Abbott)	25 test kit	Lateral flow	5 minutes
Rapid antigen detection test	BD Veritor Plus system group A strep assay (Beckton Dickinson)	30 test kit	Lateral flow	5 minutes
		BD Veritor system analyser module		
Rapid antigen detection test	Strep A rapid test (Biopanda Reagents)	20 test cassettes	Lateral flow	5 minutes
		50 test strips		
Rapid antigen detection test	NADAL strep A (nal von minden GmbH)	40 test strips including controls	Lateral flow	5 minutes
		50 test strips (tube) including controls		
		20 test cassettes including controls		
		Positive control vial		
		Negative control vial		

Rapid antigen detection test	NADAL strep A plus star mould format (nal von minden GmbH)	20 pack cassettes including controls 5 pack cassettes including controls	Lateral flow	5 minutes
Rapid antigen detection test	NADAL strep A scan test (nal von minden GmbH)	20 pack cassettes including controls Colibri reader Colibri USB and software	Lateral flow	5 minutes
Rapid antigen detection test	OSOM strep A test (Sekisui Diagnostics)	50 test pack	Lateral flow	5 minutes
Rapid antigen detection test	QuikRead Go strep A test kit (Orion Diagnostica; currently distributed in the UK and Ireland by Roche Diagnostics)	50 tests including controls QuikRead Go instrument	Turbidimetric immunoassay	<7 minutes
Molecular assay	Alere i strep A (Abbott)	24 test kit Alere i instrument	Isothermal nucleic acid amplification	<8 minutes
Molecular assay	Cobas Liat strep A assay (Roche Diagnostics)	Strep A assay box of 20	Polymerasechain reaction (PCR)	<15 minutes

		Liat analyser		
		Quality-control box of 3		

Other, similar technologies may be available but are not included in this briefing (for example, if they were not identified, or the company chose not to participate).

Innovations

Point-of-care strep A tests are designed to give a more accurate confirmation of the presence of bacterial infection than clinical evaluation, including clinical scoring systems. This is aimed at improving antibiotic prescribing in line with local guidelines, which may help to reduce antimicrobial resistance. The quick 'time to result' of the tests compared with laboratory testing aims to help treatment decisions to be made during a single GP or community pharmacy visit, without the need to wait for laboratory tests results.

Current care pathway

Most people with acute sore throat, whether caused by a bacterial or viral infection, usually get better within a week and do not need medical intervention. In cases when it is felt that a person may benefit from having an antibiotic, a GP or pharmacist prescriber should use the FeverPAIN or the Centor score to identify people with a bacterial infection. Using rapid antigen tests in addition to clinical scoring has so far not been found to give any added benefit when trialled in the UK (Little et al. 2014). The NICE antimicrobial prescribing guideline on acute sore throat does not make any recommendations about using point-of-care tests or throat cultures to confirm strep A infection.

According to NICE guidance, the outcome of clinical inquiry along with results from the FeverPAIN or Centor Score will lead to either: no antibiotic prescription; a back-up antibiotic prescription; or an immediate antibiotic prescription.

The following publications inform the care pathway:

- Acute sore throat (NICE antimicrobial prescribing guideline)
- Acute sore throat (NICE clinical knowledge summary)

- Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (NICE guideline)

Population, setting and intended user

The strep A point-of-care tests would be used in primary care (GP practices and community pharmacies) for people with acute sore throat and when a FeverPAIN score of 4 or 5 or a Centor score of 3 or 4 has shown that a strep A infection is likely and the health professional is considering prescribing antibiotics. They may also be used in primary care to help to support the decision not to prescribe antibiotics for people with a FeverPAIN score of 0 or 1 or a Centor score of 0, 1 or 2. The test would be used by a trained healthcare professional, most likely a GP or independent prescriber. Most companies offer training and support for healthcare professionals using their tests.

Costs

Technology costs

The cost of point-of-care streptococcus (strep) A tests varies widely depending on the type of technology and complexity of the technology. The costs range from £0.80 per test for a simple lateral flow test with no additional costs to £50 per test for the nucleic acid amplification tests with an additional reader cost of £17,339.27 (excluding VAT). The readers display results, eliminating interpretation and transcription errors. The readers for the nucleic acid amplification tests are also compatible with other molecular assays from the same companies.

Costs of standard care

Standard care is either self-management or a consultation with a primary care clinician. The unit costs of a GP consultation, excluding costs of antibiotic prescription, range from £3 to £4 per minute of patient contact (Personal Social Services Research Unit 2017). Using the doses in NICE's antimicrobial prescribing guideline on acute sore throat, and the January 2018 NHS Business Services Authority Electronic Drug Tariff, the cost of a course of antibiotics for treating sore throat ranges from £1.93 for a phenoxymethylpenicillin prescription for a child aged 1 to 11 months (125-mg/5-ml oral solution) to £3.20 for an adult (250-mg tablets).

For people at high risk of developing complications, throat culture may be requested. The national average cost of a microbiological diagnostic test is £8 (national schedule of reference costs for 2016/17).

Resource consequences

The point-of-care strep A tests would be an additional cost to standard care. However, should point-of-care tests be adopted in community pharmacy settings, it could lead to costs savings if fewer patients booked appointments to see their GP and fewer antibiotics were prescribed unnecessarily. It is estimated that each year, a quarter of the population in the UK visited their GP because of a respiratory tract infection. Of these, 27% of consultations were for sore throat (Gulliford et al. 2014). A recent feasibility study estimated that around 44% of patients would have opted to see their GP for a sore throat if freely allowed to do so (Thornley et al. 2016). It should be highlighted that there were substantial limitations of this feasibility study because it did not have a control arm and it is unlikely that a patient would get a GP appointment for a sore throat unless the symptoms lasted for more than 1 week.

A time and motion study suggests that point-of-care testing can be incorporated into community pharmacies with limited workflow disruption (Corn et al. 2017). No significant changes in facilities and infrastructure would be needed to adopt point-of-care strep A testing in primary care, particularly for the simple lateral flow technologies, which do not use a separate reader. If the tests were used in GP clinics, they could reduce unnecessary antibiotic use and provide an objective measure to reassure the patient that antibiotics are not needed. Unnecessary antibiotic use can cause drug-related adverse events and increase the prevalence of antibiotic-resistant organisms.

The Clearview cassette is currently used in 4 NHS sites in the UK and QuikRead Go is used in 3 NHS sites for diagnosing strep A. At these sites, the patients cover the full cost of the test and any antibiotics they are prescribed. No other point-of-care tests for strep A in this briefing were found to be in routine use in the NHS.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, 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, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

Streptococcus (strep) A infections are more common in children than in adults. According to the equality impact assessment for NICE's guideline on antimicrobial prescribing for acute sore throat,

streptococcus (strep) A infections in people with disorders of the immune system and children under 5 should be managed differently to the rest of the population.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the interim process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technologies. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

The most recent, highest-quality systematic review was selected from several overlapping reviews identified.

Published evidence

This briefing summarises 6 studies, including 102,694 patients, of whom 3,552 were tested using 5 of the 11 technologies included in this briefing. The technologies are: OSOM, Clearview Exact (type of test not specified), QuikRead Go, Liat streptococcus (strep) A assay and Alere i strep A tests. There were 4 prospective studies (n=1,206), 1 pilot study (n=367) and 1 systematic review (n=101,121 participants, including 1,979 tested with technologies included in this briefing). Only the pilot study was done in the UK. Most of the evidence comes from studies that use throat culture as the comparator. The sensitivity and specificity of these strep A tests ranged from 77–98% and 79–95% respectively, and there may be some variation in results between children and adults. The systematic review found the diagnostic accuracy was lower in children with strep A compared with those without (86% compared with 95% respectively).

Overall assessment of the evidence

The diagnostic accuracy of point-of-care tests compared with throat culture was high, with sensitivity and specificity generally being above 80% for the 5 tests in the included studies.

There is limited evidence on how point-of-care testing would compare to current practice for antibiotic prescribing and patient outcome, because patients are typically not followed up after a prescription has been issued. Antibiotic prescription data, with and without clinical scoring systems or point-of-care testing, would inform how many unnecessary prescriptions were avoided by using a particular intervention.

Only 1 study was done over the course of an entire year. Strep A is more common in the winter or early spring in temperate climates (NICE clinical knowledge summary on acute sore throat), so seasonal data cannot be extrapolated to the whole year.

Finally, only 1 study was done in the UK, which may limit the generalisability of clinical results, particularly to UK primary care. Most studies used the Centor score, rather than the FeverPAIN score.

Table 2 summarises the clinical evidence as well as its strengths and limitations.

Table 2 Summary of selected studies

Cohen et al. (2017)	
Study size, design and location	Cochrane systematic review in children and young adults (aged 21 years or under) with sore throat. There were 98 studies: 101,121 participants, of which 1,979 used technologies included in this briefing (n=630 Clearview Exact strep A; n=1,349 OSOM strep A).
Intervention and comparator(s)	Intervention: Various RADTs including 2 tests included in this briefing: Clearview Exact strep A and OSOM strep A. Comparator: Throat culture.
Key outcomes	The primary outcome was diagnostic accuracy of rapid antigen testing. There was substantial heterogeneity in sensitivity across studies, whereas specificity was more stable. RADT specificity is sufficiently high to ensure against unnecessary use of antibiotics. Based on the results, 86% of children with strep A infection would be correctly diagnosed with the rapid test, whereas 14% would be false negatives and not have antibiotic treatment. 95% of children without strep A infection would be correctly identified with the rapid test, whereas 5% would be misdiagnosed as having strep A infection and have unnecessary antibiotics.

Strengths and limitations	High-quality systematic review with multiple reviewers, quality assessment of included studies and statistical analysis. The review only included studies on children and young adults and did not consider any molecular methods for diagnosing strep A. The overall methodological quality of included studies was poor, mainly because many studies were at high risk of bias for patient selection and because of the reference standard used. The population only contained people aged 21 years or below, because prevalence is higher in children than in adults.
Bura et al. (2017)	
Study size, design and location	202 adults (aged 18–44) in a prospective case-control study in Poznan, Poland. Two arms: 101 had sore throat, 101 were an age- and sex-matched healthy control group.
Intervention and comparator(s)	Intervention: OSOM Strep A RADT test. Comparator: Centor score, throat culture.
Key outcomes	In young adults with sore throat with CS 2–4, beta-HS are responsible for a minority of cases. The RADT had a sensitivity of 95.7% and specificity 97.4% in patients, when compared with throat culture. The RADT sensitivity in identifying GAS was significantly higher than that of CS alone ($p<0.001$). The final decision on antibiotic therapy was made by a GP and antibiotics were prescribed in 45% of patients with negative RADT results. An economic analysis presented the cost per patient for appropriate antibiotic therapy. This was calculated as €6.81 per patient with CS 3–4, in line with NICE's antimicrobial prescribing guidance on acute sore throat.
Strengths and limitations	The study was done over 1 year, so seasonal effects did not skew results. There was a comparatively small number of participants and no assessment of patient outcomes, including assessment of therapeutic decisions without an RADT.
Stefaniuk et al. (2017)	

Study size, design and location	96 children and adults (all aged 14 years or over) in a prospective study in Warsaw, Poland.
Intervention and comparator(s)	Intervention: QuikRead Go strep A RADT test. Comparator: Physical examination findings, Centor score, throat culture.
Key outcomes	The sensitivity of RADT was 91% and specificity was 83%, with some variation between age groups. The sensitivity and specificity were higher in children than adults (children/adults: sensitivity 91%/77%; specificity 89%/79%). When the QuikRead Go strep A test results were positive, doctors prescribed antibiotics in 98% of cases; when negative, they issued antibiotic treatment in 20% of cases. The research shows that GPs consider quick tests reliable and are willing to use them in their practice.
Strengths and limitations	There were a comparatively small number of participants, in only 1 clinical site. The study was performed from March to May, but GAS prevalence changes depending on the season, so the results cannot be extrapolated over a full year.
Wang et al. (2017)	
Study size, design and location	427 children and adults (adults in this study were aged 21 years or over) in a prospective multicentre study in 5 sites, US.
Intervention and comparator(s)	Intervention: Cobas Liat strep A PCR assay. Comparator: Throat culture, site-standard diagnostic method (RADT and/or diagnostic culture). None of the RADTs in the comparator group are included in scope of this briefing.
Key outcomes	The Cobas Liat strep A assay had a high sensitivity (97.7%) and specificity (93.3%) compared with reference culture. The sensitivity of the Cobas Liat strep A assay was found to be greater than that of RADTs in the comparator group (Consult strep A, Quidel QuickVue dipstick, and McKesson strep A dipstick). There was a 15-minute turnaround time, showing that POC testing does not always present a trade-off between time and accuracy.

Strengths and limitations	The study was done from December to April, but GAS prevalence changes depending on the season, so the results cannot be extrapolated over a full year. The number of children (412) was much greater than the number of adults (15) tested. The same RADT was not used at each site, and diagnostic culture was not executed at all sites.
Cohen et al. (2015)	
Study size, design and location	481 children and adults in a prospective multicentre study in 10 sites, US.
Intervention and comparator(s)	Intervention: Alere i strep A nucleic acid isothermal amplification test (NAAT). Comparator: Throat culture (real-time PCR analysis to back up discordant findings).
Key outcomes	Alere i strep A had sensitivity of RADT (95.9%) and specificity (94.6%), with slight variation in children and adults. With PCR adjudication, increased average sensitivity (98.7%) and specificity (98.5%), with slight variation in children and adults, showing that using the Alere i strep A may remove the need for back-up testing on negative results. The test could easily be performed by non-laboratory staff in several clinical settings.
Strengths and limitations	The study was performed from January to March, but GAS prevalence changes depending on the season, so the results cannot be extrapolated over a full year. Specific reasons for 14 invalid results were not identified. The number of children (355) was greater than the number of adults (126) tested.
Thornley et al. (2016)	
Study size, design and location	367 patients in a pilot service evaluation of strep A screening in 35 pharmacies, UK.
Intervention and comparator(s)	Intervention: Centor score, OSOM strep A test, antibiotic treatment. Comparator: None (patients were asked what they would have done without the test).

Key outcomes	A test-and-treat service was introduced into pharmacies to assess the feasibility of RADTs in this setting. The study found it was feasible to deliver this screening and treatment service to people aged 12 years and over. 48.8% of patients with a low risk of strep A infection said they would have accessed their GP if the pharmacy test-and-treat service had not been available. Around two-thirds of patients (218/367) who would have otherwise seen their GP scored 1 or 2 on the Centor questionnaire. There is therefore potential to reduce the demand on GP appointments.
Strengths and limitations	To understand the true effect of this service, a comparative study would need to be done with a full health economic analysis. The sample size is relatively small and the study was done during the winter months, so cannot be extrapolated over a full year. Asking patients what they would have done without the intervention does not reflect real-world practice, when a request for a GP appointment for a sore throat may not be granted immediately.
Abbreviations: beta-HS, beta-haemolytic streptococcus; CS, Centor score; GAS, group A beta-haemolytic streptococcus; PCR, polymerase chain reaction; POC, point-of-care; RADT, rapid antigen detection test.	

Recent and ongoing studies

- In vitro diagnostic device for the detection of strep A. ClinicalTrials.gov identifier: NCT02068469. Status: completed. Device: Liat strep A assay (Roche).
- Rapid strep testing in children with recent streptococcal pharyngitis. ClinicalTrials.gov identifier: NCT03055728. Status: recruiting.
- An NHS community pharmacy referral service (CPRS) was established as a pilot project in the North East of England. The CPRS pilot aimed to better manage illness in people contacting NHS 111 with low-acuity conditions, including sore throat, by referring them to a community pharmacy. The pilot was scheduled to run from 4 December 2017 to 31 March 2018 and was intended to reduce pressure on the primary and urgent care system, particularly demand for GP out-of-hours services. The CPRS pilot service specification does not explicitly refer to point-of-care diagnostic tests as a rule-out strategy, but strep A testing could fit into such a pathway in future.

Specialist commentator comments

Comments on this technology were invited from clinical specialists working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

All 5 specialists were familiar with this technology and 1 had used it before.

Level of innovation

All of the specialists agreed that although the technology is not innovative as such, its use in addition to a clinical scoring system has the potential to change patient behaviour, and manage expectation or demand for GP appointments. If used in primary care, it could reduce unnecessary antibiotic prescribing.

The specialists agreed that this technology is not widely used in the NHS.

Potential patient impact

There were differences in opinion among the specialists about the groups of people that would particularly benefit from this technology. Although 1 specialist thought that the test would benefit anyone with a sore throat, another thought it would most benefit those at low risk of streptococcus (strep) A who currently have antibiotic treatment. Conversely, 1 specialist stated that the tests would only benefit children aged 3 to 15 years when strep A sore throat is prevalent; 1 thought it would be of greatest benefit to adults. One specialist added that the whole population could benefit from increased elimination of group A streptococcus from the community as its spread would be reduced.

Four specialists believed that the main benefit lies in avoiding unnecessary antibiotic use. One specialist added that it would also reduce the spread of group A streptococcus in the community. Another commentator suggested that using point-of-care strep A tests could lead to better diagnosis and potentially avoid tonsillectomy and rheumatic disease.

One specialist thought that the greatest patient impact is in shifting care from GPs to community pharmacies, citing that the use of the technology within the community pharmacies could help to support self-care. Additionally, the accessibility of community pharmacies (opening hours, locations, and no need for appointments) makes accessing healthcare easier, supporting wider social value.

Potential system impact

Four specialists stated that there could be cost savings in the long term, if all costs including indirect cost, future cost and opportunity cost are considered. The savings could also depend on who pays for the test. The savings are likely to be through reducing unnecessary demand on GP appointments and urgent and emergency care services, increase in patient self-care, and reduced antibiotic use. The importance of close collaboration and information exchange between community pharmacists and GPs, and clear and consistent messages to patients and healthcare professionals in current care pathways, were highlighted.

Two specialists highlighted that the technology should only be used after clinical scoring systems such as FeverPAIN and Centor, because it would not be an efficient use of resources if used for every patient. Three specialists considered this technology to have the potential to improve antibiotic stewardship by reducing unnecessary antibiotic use.

All specialists stated that there would need to be staff training on using the technology and taking throat swabs. If the technology were implemented in community pharmacies, there would need to be a large public information programme to promote participating sites so people know to access them. Clinical commissioning groups would need to approve care pathways and patient group directions to permit prescription and supply of medicines for symptomatic relief and antibiotics to patients.

General comments

All of the specialists thought that these tests would be an addition to the current standard care, with 1 specialist adding that its place in the care pathway would be to replace current care.

One specialist stated that this technology is slightly more invasive than standard care, because it uses throat swabbing. One specialist thought some tests may be easier to use in practice than others, although all specialists agreed that the usability issues were minor.

All specialists thought that more research would be needed to address uncertainties in the evidence. Two wanted to see more evidence that access to testing in pharmacies would have an appreciable effect on demand in traditional primary care settings. One suggested patient satisfaction assessment should be done, whereas 1 suggested a pilot scheme would be useful in at least 2 areas with different baseline antibiotic use. In such a scheme, the change in the baseline would be evaluated with other relevant outcomes such as GP consultation and urgent and

emergency care presentations related to sore throat symptoms. One specialist suggested a larger scale crossover study of screening in pharmacy, with GP care as a control, is needed.

Specialist commentators

The following clinicians contributed to this briefing:

- Dr Tha Han, consultant in public health medicine, London Borough of Enfield. Did not declare any interests.
- Professor Tracey Thornley, senior manager contract framework and outcomes, Boots. Employed by Boots UK, although most work is on behalf of the community pharmacy sector.
- Professor Jonathan Cooke. Honorary professor, Manchester Pharmacy School, visiting professor in the infectious diseases and immunity section, Imperial College London. Did not declare any interests.
- Professor Michael Moore. Professor of primary care research, Southampton University. Part-owner through share ownership of a community pharmacy. Salaried doctor in primary care. NICE pneumonia guideline development group member, advisory committee on antimicrobial prescribing, resistance and healthcare-associated infection member, head of department of primary care and population sciences at University of Southampton. Multiple grants and awards PhD studentships.
- Professor Peter Wilson. Consultant microbiologist, University College London Hospitals NHS Foundation Trust. Advisory panel for 3M on cleaning. Lectures for Merck Sharp & Dohme on antibiotic development. Sits on the drug safety monitoring board for Roche for biologic treatments.

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