In response to enquiries from NHS Borders and the Medicines Management Partnership

What is the clinical and cost effectiveness of rapid antigen detection tests (RADTs) for Group A Streptococcal (GAS) infection in patients with acute sore throat in primary care?

What is an evidence note?

Evidence notes are rapid reviews of the evidence on health technologies under consideration by decision makers within NHSScotland. They are intended to provide information quickly to support time-sensitive decisions. Information is available to the topic referrer within a 6-month period and final publication of the associated advice is usually complete within 6–12 months. Evidence notes are not comprehensive systematic reviews. They are based on the best evidence that Healthcare Improvement Scotland could identify and retrieve within the time available. Evidence notes do not make recommendations for NHSScotland, however the Scottish Health Technologies Group (SHTG) produces an Advice Statement to accompany all evidence reviews.

This evidence note is based upon a review of the published secondary clinical and cost effectiveness literature, and has been peer reviewed by experts across NHS Scotland.

Key points

- Summary estimates of sensitivity and specificity of rapid antigen detection tests (RADTs) for presence of Group A Streptococcal (GAS) bacteria were comparable across reviews, at around 85% and 95%, respectively. There was substantial heterogeneity around sensitivity.

- A systematic review identified three non-UK cluster randomised controlled trials (RCTs) conducted between 2005 and 2008 and reported that the use of RADTs reduces rates of antibiotic prescribing for acute pharyngitis when compared with usual care. There was some evidence of antibiotic prescribing for patients who had negative test results. The
Evidence note

Delayed prescribing strategy recommended as UK standard care may limit the applicability of these findings.

- In a UK RCT, the use of a clinical score (FeverPAIN) to guide primary care prescribing for patients with sore throat provided a modest benefit on patient-reported symptoms and reduced the rate of antibiotic use compared with delayed prescribing. The use of an RADT to guide prescribing in patients with a FeverPAIN score ≥3 did not result in additional benefits for these outcomes.

- Patients in the UK study reported the RADT to be an acceptable intervention, finding it reassuring in confirming their diagnosis and helping them avoid unnecessary exposure to antibiotics.

- One NHS-based economic evaluation comparing RADT use for patients with a high FeverPAIN score with both a delayed prescribing and a clinical scoring strategy (FeverPAIN) found the clinical scoring strategy was likely to be most cost-effective. This was consistent across outcome measures used (1 point change in symptom severity or quality-adjusted life years [QALYs]).

- Results of economic evidence from non-UK settings are inconsistent and not transferrable to NHSScotland.

- One UK service evaluation on the use of RADT for diagnosis of GAS infection in the pharmacy setting suggested a ‘test and treat’ pharmacy based service is feasible.

Literature search

A systematic search of the published literature was carried out between 7-13 November 2017 to identify primary studies, systematic reviews, health technology assessments and other evidence based reports. Databases used were: Medline, Cochrane, Embase, Cinahl and Web of Science. A separate search to identify literature on patient experience of rapid antigen detection tests was carried out on the 10-11 October 2017 and 9 November 2017. Databases used were: Medline, Web of Science and PsychInfo.

Key websites were searched for guidelines, policy documents, clinical summaries, patient stories and economic studies.

Concepts used in all searches included: rapid (streptococcal) antigen detection tests (RADTs) for sore throat, point of care tests (POCT), rapid strep test, rapid diagnostic test, Group A Streptococcus bacterial infections, Group A Streptococcus, Strep A / Group A β-haemolytic Streptococcus (GABH), Group A Streptococci (GAS). A full list of resources searched and terms used are available on request.
Introduction

Acute sore throat (including pharyngitis and tonsillitis) is a common reason for a person to consult with their GP and an indication for which antibiotic therapy is commonly prescribed. In a study conducted across 568 general practices in England in 2011, rates of antibiotic prescribing for sore throat in adults aged 18-59 ranged from 35% to 83% of cases in the lowest and highest 5% of practices, with the median practice prescribing antibiotics for 60% of those consulting for this symptom. There is also evidence that, in most cases, sore throat is self-limiting and that antibiotics provide only modest benefits in limiting symptom duration or risk of complications, which suggests that there may be an opportunity to reduce inappropriate prescribing. However, the effectiveness of antibiotics in reducing symptoms is increased in people with *Streptococci* bacteria growing in their throat.

Lancefield Group A haemolytic *Streptococcal* (GAS) infection is the most common bacterial pathogen associated with sore throat. Many other pathogens can be associated with similar symptoms, including Group C and G beta haemolytic *streptococci*. An individual may be a carrier of GAS whilst presenting with a sore throat of viral origin. The most common viral agents are rhinovirus and coronavirus and adenovirus.

As well as causing sore throat, GAS infection can lead to suppurative complications such as quinsy, otitis media and acute sinusitis. Non-suppurative complications include acute rheumatic fever potentially leading to chronic rheumatic heart disease, scarlet fever, post-streptococcal glomerulonephritis and toxic shock syndrome.

Although serious GAS complications are rare in the UK, there is recent evidence of increasing incidence of scarlet fever and invasive GAS infection such as meningitis, toxic shock syndrome or necrotising fasciitis. Health protection agencies in both England and Scotland recommend ongoing vigilance.

There is variation in guideline recommendations around the use of rapid antigen detection tests (RADTs) to identify patients with GAS depending on the national context. Diagnosis is of greatest prominence in settings which have a pro-treatment approach, aiming to treat all identified cases.

In comparisons of recommendations from developed countries, those settings which did not recommend testing rationalised that the incidence of rheumatic fever is low and so the harms (both individual and societal) and costs associated with antibiotics are too great to be justified for prevention of rare complications. The high prevalence of streptococcal carriers (5%-20%) also supports this rationale. However, in many countries, RADTs are recommended and this is based on the fact that the complications, although rare, are very serious. Strategies for identifying infection are perceived to be necessary given that GAS throat infection is highly transmissible by droplet spread and, in the majority of patients, eradication of bacteria occurs 24-48 hours after the start of antibiotic treatment.
In the UK a delayed antibiotics strategy may be implemented\(^\text{10}\), where a prescription is offered on the basis that the antibiotics be accessed under particular clinical scenarios agreed between patient and healthcare professional, for example if no resolution of symptoms after 3-5 days or if symptoms seem to be becoming significantly worse within 24 hours. This strategy may differ from other contexts internationally which will influence interpretation of clinical outcomes of research studies.

Diagnosis of GAS pharyngitis in UK primary care is typically performed by clinical examination\(^\text{4}\) with or without the use of clinical scoring systems such as Centor or FeverPAIN. These are described as below:

<table>
<thead>
<tr>
<th>Centor(^\text{11})</th>
<th>FeverPAIN(^\text{12})</th>
</tr>
</thead>
<tbody>
<tr>
<td>One point given for each of:</td>
<td>One point given for each of:</td>
</tr>
<tr>
<td>1. Tonsillar exudate</td>
<td>1. Purulent tonsils (pus visible on tonsils)</td>
</tr>
<tr>
<td>2. Fever over 38°C by history</td>
<td>2. Fever in the last 24 hours</td>
</tr>
<tr>
<td>3. Absence of cough</td>
<td>3. Absence of cough or coryza (irritation and inflammation of the mucous membrane inside the nose)</td>
</tr>
<tr>
<td>4. Tender anterior cervical adenopathy</td>
<td>4. Rapid attendance (prior duration of illness ≤3 days)</td>
</tr>
<tr>
<td></td>
<td>5. Severe inflammation of pharynx/tonsils as assessed by doctor</td>
</tr>
</tbody>
</table>

Current NICE guidelines\(^\text{13}\) (Jan 2018) for antimicrobial prescribing for acute sore throat recommend the use of the FeverPAIN or Centor clinical scoring system to identify patients who may benefit from delayed or immediate antibiotic prescription, based on symptoms. The guideline was not focused on diagnosis.

The UK Clinical Knowledge summary on acute sore throat notes that\(^\text{14}\): If the diagnosis of GAS needs to be confirmed with certainty (such as in people at high risk of rheumatic fever, vulnerable people such as the very old or young, or people who are at risk of immunosuppression, or people with very severe symptoms), arrange a rapid antigen test for GAS. A negative antigen test in a person (particularly a child) with suspected GAS should be followed up with throat culture.

The gold standard for diagnosis of GAS presence is blood agar culture in a microbiology laboratory. Results from this are obtained in around 48 hours\(^\text{15}\).
This evidence note addresses the following questions:

- What is the evidence for the diagnostic accuracy of RADTs for GAS in adults and children presenting with acute sore throat?
- What is the evidence for the clinical and cost-effectiveness of the use of RADTs in patients with acute sore throat in primary care settings including community pharmacy?
- What is the evidence around patient experience of RADTs for diagnosis of GAS infection in acute sore throat?

**Health technology description**

Rapid antigen detection tests for GAS infection are typically marketed for ruling in or ruling out this infection in patients who present to ambulatory care settings with sore throat⁴.

RADTs involve the detection of a GAS-specific cell wall antigen and are based on the rapid formation of an antigen-antibody complex⁴. There are several formats for the tests such as dipstick tests and cassettes and tests vary in the number of steps which are involved¹². The tests are carried out on throat swabs and results are generally available in around 5 minutes.

**Epidemiology**

For children with sore throat, *Streptococci* are found in the throat in around 20-30% of cases. For adults the figure is lower at 5-15%¹⁶.

Most people who experience a sore throat do not seek help from their GP¹¹. In Scotland in 2005-2006, there were 313,150 GP consultations for any form of sore throat or tonsillitis, a rate of 58.3 per 1,000 population¹⁷.

**Diagnostic accuracy**

Three well conducted systematic reviews with meta-analyses were identified examining the diagnostic accuracy of RADTs for presence of GAS compared with gold standard of laboratory culture¹⁵, ¹⁸, ¹⁹. The reviews overlapped in terms of included studies. The time frame for study inclusion and key findings are outlined in Table 1. Summary estimates of sensitivity and specificity were comparable across reviews, at around 85% and 95%, respectively. The authors concluded that RADT specificity is sufficiently high to ensure against unnecessary use of antibiotics. Heterogeneity, around sensitivity in particular, was high as indicated by a wide prediction region around the pooled summary estimates. This was not explained by factors from sensitivity analysis of study level characteristics including test type, use of enrichment broth before laboratory culture, age of patients, clinical severity of sore throat or GAS prevalence¹⁵. Across included primary studies,
sensitivity ranged from 38.6% to 100%. The methodological quality of included studies was poor \(^\text{15}\) and there was evidence of publication bias\(^\text{19}\).

Assuming a prevalence of GAS of 20% in patients presenting with sore throat the diagnostic accuracy parameters described here would mean that for every 1,000 patients tested, 30 patients with GAS would not be picked up by the test and 40 would be incorrectly diagnosed as having GAS.

Table 1: Key findings of systematic reviews of diagnostic accuracy studies

<table>
<thead>
<tr>
<th>Publication/years of study inclusion</th>
<th>Number of participants / studies</th>
<th>Patient group</th>
<th>Summary sensitivity (95% CI)</th>
<th>Summary specificity (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen(^\text{15}) (1980-2015)</td>
<td>48,808 86 Studies</td>
<td>Paediatric(^\text{▲}) (≤21)</td>
<td>85.4% (82.7% to 87.8%)</td>
<td>95.8% (94.8% to 96.6%)</td>
</tr>
<tr>
<td>Stewart(^\text{19}) (2000-2012)</td>
<td>1,216 6 studies</td>
<td>Adult(*)</td>
<td>91% (87% to 94%)</td>
<td>93% (92% to 95%)</td>
</tr>
<tr>
<td></td>
<td>10,325 28 studies</td>
<td>Paediatric(*)</td>
<td>86% (85% to 87%)</td>
<td>96% (95% to 96%)</td>
</tr>
<tr>
<td>Lean(^\text{18}) (1996-2013)</td>
<td>21 studies</td>
<td>Adult and paediatric(^\text{▲})</td>
<td>84% (80% to 88%)</td>
<td>96% (94% to 97%)</td>
</tr>
<tr>
<td></td>
<td>14 studies</td>
<td>Paediatric (#)</td>
<td>85% (80% to 89%)</td>
<td>97% (95% to 98%)</td>
</tr>
</tbody>
</table>

\(^\text{▲}\) Enzyme immunoassays (not optical immunoassay methods)
\(*\) Immunochromatographic assay methods (high quality studies only)
\(^\text{▲}\) Lateral flow/ immunochromatographic assay (calculated for test types with more than three studies)
\(#\) Lateral flow/ immunochromatographic assay

Clinical effectiveness

Outcomes of interest relating to the clinical utility of RADTs include rates of antibiotic prescribing (appropriate and inappropriate), rates of antibiotic use, symptom severity and duration, complication rates (eg quinsy, otitis media, acute rheumatic fever) and healthcare resource use\(^3\). No data were identified comparing outcomes around antimicrobial resistance, infection transmission or rates of invasive disease.
Primary care setting

RADT versus usual care

A systematic review examined whether RADTs improve antibiotic prescribing for uncomplicated acute respiratory tract infections. Based on a literature search to February 2015, the review identified 3 cluster RCTS, conducted between 2005 and 2008, which evaluated the utility of RADT, with or without back-up culture, compared with usual care. All were conducted in outpatient settings among primary care physicians and were methodologically appraised in the review as fair quality. The use of RADTs reduced rates of antibiotic prescribing for acute pharyngitis. In each case the difference was statistically significant; 64.1% to 43.8% (p<0.001), 58.2% to 26.7% (p<0.001) and 72.2% to 33.7% (p=0.004).

One of the trials assessed appropriateness of antibiotic prescribing according to results of microbial culture. The study was conducted in Catalonia and was an unblinded cluster RCT of adults (n=543) presenting to primary care centres (n=20) with acute pharyngitis. GPs allocated to the usual care group prescribed antibiotics in 64.1% of cases whilst those with access to RADT prescribed in 43.8% of cases, p<0.001. Inappropriate prescribing (93% of instances as antibiotics with negative culture, 7% of instances where no antibiotic with positive culture) was identified in 26.9% of cases in the intervention group and 60% of cases in the control group (p<0.001). There was no statistically significant difference in rate of full clinical recovery at the 3rd week between those treated with and those not treated with antibiotics (81.4% vs 86.1%). One finding of this study was that physicians did not appear to trust the results of RADT, with antibiotics prescribed in over 30% of cases where RADT was negative.

One poorly reported RCT conducted in Southwest Poland also reported high rates of prescribing for patients with negative RADT test. This trial, published in 2017, compared the rate of antibiotic prescribing for children with pharyngitis (aged 2-15 years, n=1,307) between clinics randomised to diagnosis using the OSOM Strep A test (Sekisui Diagnostics) or by interview and physical examination only. The rate of antibiotic prescribing at first visit was not significantly different between the groups (44.9% intervention vs 50.1% control, p>0.05). In this study 21% of patients with a negative RADT result were prescribed an antibiotic; this was hypothesised to relate to the physician perception of risk of false negative results.

RADT applied according to a clinical scoring systems versus usual care or clinical score alone

A RCT which formed part of a Health Technology Assessment on Primary Care Streptococcal Management (PRISM) provided information directly relevant to UK primary care practice. This study forms the basis of the NICE guideline recommendation to use a clinical scoring system to identify patients who may benefit from delayed or immediate antibiotic prescription.
Study participants (≥3 years, mean age 29 years, n=631) presenting with sore throat were recruited by general practitioners or practice nurses and randomised to one of three intervention groups. These offered different treatment strategies for targeting antibiotic use; delayed antibiotics (control), use of a clinical scoring system (FeverPAIN) to guide no, immediate or delayed antibiotic prescribing, or use of RADT (IMI TestPack® Plus Strep A (Inverness Medical, Bedford, UK) targeted by high clinical score (≥3) to guide antibiotic prescribing. The primary outcome was symptom control (severity and duration). Patient-reported rates of antibiotic use were also recorded. The trial was pragmatic in that, although clinicians were asked to use the intended strategy, there was flexibility in terms of what could be agreed with the patient. Intended strategy was undertaken in 83% of consultations. Blinding of patients and those collecting data was done where possible but due to the type of interventions and the nature of medical note-taking full blinding was not possible. Self-report information was available for around 78-81% of study participants across the three arms.

There was no routine RADT testing arm. Appropriateness of prescribing was not measured by reference to microbial culture.

Key findings are set out in Table 2. The use of FeverPAIN improved symptoms (severity or pain and difficulty swallowing) in days 2-4 after general practice consultation compared with control when adjusted for baseline severity of symptoms and fever during the previous 24 hours. The benefit was equivalent to one person in three rating symptoms ‘slight’ rather than ‘moderately bad’. The addition of RADT resulted in no additional benefits compared with FeverPAIN alone. Resolution of symptoms was statistically significantly faster in the clinical score group compared with ‘delayed prescribing’ control; this is equivalent to saving a day of moderately bad symptoms. The rates of no, immediate and delayed prescribing are noted in Table 2. The rate of participants reporting use of antibiotics in their self-report diaries were lower in the FeverPAIN only group (37%) and the FeverPAIN plus RADT group (35%) compared with the control group (46%). This was statistically significant for both comparisons. The trial report notes that there were no suppurative complications (otitis media, sinusitis, quinsy or cellulitis) in the follow up period which ranged from one month to 2 years. However, it was confirmed with the study author that this point was made in error. As correctly reported in the study economic analysis, two individuals in the control group experienced quinsy and there was one case of otitis media in the RADT group (P.Little, personal communication 24 January, 2018).

There was no statistically significant difference between study groups in medicalisation measured as belief in need to see the doctor for future sore throat episodes.

The views of both healthcare practitioners and patients on the use of RADT was collected in a nested qualitative study described in a later section of this Evidence Note.
Table 2: Findings of RCT in PRISM HTA\textsuperscript{12} – symptom severity and antibiotic use in different treatment strategies

<table>
<thead>
<tr>
<th>Outcomes for patients completing diaries</th>
<th>Delayed antibiotics (control)</th>
<th>Clinical score</th>
<th>Clinical score + RADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean severity (seven-point scale) of sore throat and difficulty swallowing on days 2–4 (standard deviation)</td>
<td>3.11 (1.49)</td>
<td>2.88 (1.52)</td>
<td>2.83 (1.62)</td>
</tr>
<tr>
<td>Adjusted mean difference</td>
<td>−0.33 (95% CI −0.64 to −0.02) p = 0.039</td>
<td>−0.30 (95% CI −0.61 to 0.004) p = 0.053</td>
<td></td>
</tr>
<tr>
<td>Median duration of symptoms rated moderately bad or worse (interquartile range)</td>
<td>5 (3 to 7)</td>
<td>4 (2 to 6)</td>
<td>4 (2 to 7)</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>1</td>
<td>1.30 (95% CI 1.03 to 1.63) p = 0.028</td>
<td>1.11 (90% CI 0.88 to 1.40) p = 0.372</td>
</tr>
</tbody>
</table>

Antibiotic outcomes

<table>
<thead>
<tr>
<th>Antibiotic strategy</th>
<th>No offer of antibiotics</th>
<th>Immediate antibiotics</th>
<th>Delayed antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>21/207 (10%)</td>
<td>21/207 (10%)</td>
<td>164/207 (79%)</td>
<td></td>
</tr>
<tr>
<td>33/211 (16%)</td>
<td>91/211 (43%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>126/213 (59%)</td>
<td>38/213 (18%)</td>
<td>48/213 (23%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antibiotic use</th>
<th>75/164 (46%)</th>
<th>60/161 (37%)</th>
<th>58/164 (35%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic use risk ratio</td>
<td>1</td>
<td>0.71 (95% CI 0.50 to 0.95) p = 0.018</td>
<td>0.73 (95% CI 0.52 to 0.98) p = 0.033</td>
</tr>
</tbody>
</table>

Another RCT\textsuperscript{23} identified in the previously mentioned systematic review\textsuperscript{21} compared antibiotic prescription, guided by a four item clinical score adapted from the Centor criteria plus RADT (Clearview\textsuperscript{®} Exact Strep A dipstick, Wampole Laboratories), with usual clinical practices, RADT only and clinical score only. In this cluster study of 37 practices (n=533 adult participants), conducted in Canada in 2005, the use of the RADT either alone or in combination with a clinical score led to lower antibiotic prescribing rates compared with usual care or the use of a clinical score alone (26.7%, 38.2%, 58.2%, 55.3% respectively). The study did not examine symptoms or duration of illness. The systematic review authors pooled the findings of this study and the UK RCT\textsuperscript{12} for the comparison of clinical score plus RADT versus clinical score alone (36% vs 47% odds ratio 0.70 95% CI 0.50 to 0.98) finding that the inclusion of the RADT had a benefit on antibiotic prescribing rate. The review states that this gives moderate strength evidence that the combination is better than the decision rule alone. However, given the different clinical contexts, different study methodologies (cluster vs individual patients randomised), different clinical score and usual care interventions, as well as the difference in outcomes (antibiotic prescribing /antibiotic use) the validity of this pooled estimate is uncertain.
Community pharmacy setting

A non-comparative feasibility study evaluated screening and treatment for GAS pharyngitis in a UK community pharmacy setting (35 pharmacies) using the Centor clinical score followed by use of a RADT to guide an offer of antibiotics by the pharmacist under the authority of a Patient Group Direction (PGD)\textsuperscript{24}. Patients (n= 367 with data available) aged over 12 years of age enquiring about a sore throat were enrolled in the study. The cost to the patient was £7.50 for the RADT and £10 for antibiotic. In this setting, 40% of participants had the RADT. Of these 75.8% tested negative and 24.2% were positive for GAS and had antibiotics supplied (n=36). There was no control arm so the effect of the intervention on rates of antibiotic prescription or use could not be identified. Fifty six patients were referred to their GP. Study authors concluded that it was feasible to offer a test and treat service in the community pharmacy setting.

Another feasibility study, undertaken in the the US, demonstrated the ability and capacity of pharmacists to provide screening, testing and treatment for GAS pharyngitis according to a collaborative practice agreement with primary care providers. It was suggested that this led to increased access to care outside of normal office hours but the applicability of the study to the UK setting is likely to be limited\textsuperscript{25}. A similar pilot of a Canadian experience was presented as a conference abstract\textsuperscript{26}.

Experiences of using RADT

A qualitative study - conducted within an RCT on the use of RADT as part of a strategy for GAS detection in primary care used semi-structured interviews to explore key issues for patients and healthcare practitioners\textsuperscript{12}. Thematic analysis (constant comparison analysis) was conducted and themes which emerged were agreed across the team of three qualitative researchers.

Patient experiences

Nine patients were interviewed. Three themes emerged:

- Patients reported feeling reassured about their diagnosis and treatment as a result of having the RADT.
- They reported that provision of the test in their GP practice would not influence their decision to attend with symptoms of sore throat.
- Patients would prefer not to have antibiotics unless they were needed and believed the test helped with clarifying this.
Healthcare practitioner experiences

Forty two health care practitioners were interviewed. Of these, 29 were GPs and 13 were nurse practitioners. Qualitative analysis of the data revealed five main themes as shown in Table 3. As well as commenting on the RADT, practitioners also had a view on the use of clinical scores and this is included in the table. Healthcare practitioners found the tests useful and easy to operate especially as they gained experience within the trial. Although there were concerns about the cost and time implications of using an RADT it was felt that RADTs and clinical scores could be helpful for inexperienced practitioners. The issue of conflict of opinion between test results and clinical findings came up as part of concerns around accuracy of diagnosis and may reflect the issue of antibiotics being prescribed for patients with a negative RADT as discussed earlier.

Table 3. Themes identified in analysis of qualitative interviews with health care practitioners

<table>
<thead>
<tr>
<th>Theme</th>
<th>Subthemes - Benefits</th>
<th>Subthemes - Concerns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Practicalities</td>
<td>• Reduces antibiotic prescribing</td>
<td>• Time concerns</td>
</tr>
<tr>
<td></td>
<td>• Easy to use</td>
<td>• Cost concerns</td>
</tr>
<tr>
<td></td>
<td>• Useful for inexperienced staff</td>
<td></td>
</tr>
<tr>
<td>Accuracy of diagnosis</td>
<td>• Confirmation of diagnosis</td>
<td>• Conflict of opinion (between test result and clinical findings)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Identification of carriers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Alternative bacteria not detected</td>
</tr>
<tr>
<td>Patient outcomes</td>
<td>• Reassurance for patient</td>
<td>• Concerns around medicalisation</td>
</tr>
<tr>
<td></td>
<td>• Education tool for patient</td>
<td></td>
</tr>
<tr>
<td>Experience of using clinical scores (final 11 interviewees)</td>
<td>• Useful for inexperienced practitioners</td>
<td>• Unnecessary for experienced practitioners</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Time-consuming</td>
</tr>
<tr>
<td>RADT trial participation</td>
<td>Trial participation increases positive views of RADT</td>
<td>Concerns that practitioners not involved in trial would be reluctant to use the RADT</td>
</tr>
<tr>
<td></td>
<td>Concerns that practitioners not involved in trial would be reluctant to use the RADT</td>
<td></td>
</tr>
</tbody>
</table>

Safety

No safety issues around the use of RADTs were identified within the literature examined for this evidence note. The PRISM HTA suggested that the throat swab would involve some minor discomfort for patients (and in some, gagging and vomiting).
Cost effectiveness

One UK-based economic evaluation was identified\(^\text{12}\). A within-trial analysis for an RCT was conducted comparing a RADT strategy versus a control strategy of delayed prescribing, and versus a strategy whereby antibiotics were prescribed according to the number of criteria met on the FeverPAIN clinical score algorithm.

The perspective for the economic evaluation was NHS and Personal and Social Services. The setting was Primary Care (general practitioner or nurse practitioner). Resources used (including those resulting from complications of the illness or treatment) were gathered from the trial and unit costs applied using routine data sources\(^\text{27, 28}\). Outcome data of change in symptom severity score at 2-4 days (cost-effectiveness analysis) and QALY data (cost-utility analysis) were calculated from EQ-5D data collected during the trial at baseline and at 14 days.

The results indicate the clinical scoring algorithm dominated (i.e. it had lower costs and improved outcomes) the other interventions and had the highest probability of being the most cost effective treatment. Delayed prescribing was dominated, but the incremental cost effectiveness ratio for the RADT strategy ranges from £24,528 to £74,286 depending on the follow up period for outcome measurement (14 or 28 days) and methods used to derive QALYs at each time point. Bootstrapping methods were used to further consider this variation. The results indicate that across willingness-to-pay (WTP) thresholds of zero to £50,000 per QALY gained, delayed prescribing consistently had the lowest probability of being the most cost effective of the three strategies, whereas the clinical scoring algorithm (FeverPAIN) had the highest probability of being the most cost-effective of the three strategies. However, it should be noted that as WTP increases, the difference in the probabilities between RADT and clinical scoring as being the most cost-effective strategy diminishes. Using QALY data at 28 days, the probability of FeverPAIN being the most cost-effective strategy was 38% compared with RADT alongside FeverPAIN at 35%. Using the data at 14 days, the probability of FeverPAIN being the most cost-effective strategy was 40% compared with RADT alongside FeverPAIN at 35%. Nevertheless, despite the uncertainty around these results, the choice of FeverPAIN as the most clinically and cost-effective of the three strategies remained consistent within the economic evaluation.

In the RADT intervention group in the RCT, the rapid test was used among those with FeverPAIN scores of three or more. The authors note that varying the scoring thresholds at which a RADT might be used could alter the health economic modelling results but suggest that a more widespread use of the tests would likely not be acceptable to clinicians and may be an even less efficient use of resources.

Three additional cost-effectiveness analyses were identified, from out with an NHS setting. Two were European-based\(^\text{29, 30}\) and one was a US-study, which had used a societal perspective but provided sufficient data to consider multiple payer perspectives (Medicaid and Private) in addition to this\(^\text{31}\). These studies were considered further on account of having compared at least one RADT strategy with an explicit clinical algorithm for identifying patients who require an antibiotic prescription for
sore throats. However, the transferability of the results to the UK setting is unclear for several reasons. Firstly, transferability of data across different healthcare systems is widely known to be problematic in general\textsuperscript{32, 33}. Secondly, none of the non-UK studies had used the same (FeverPAIN) algorithm as the clinical scoring strategy, but had instead used either the Centor scoring system\textsuperscript{30}, or a modified version of it\textsuperscript{29, 31}. Therefore only two of the criteria used in the scoring systems are consistent across all the identified cost-effectiveness studies (absence of a cough and presence of tonsillar exudates).

Each of the studies came to different conclusions around which strategy was the likely most cost-effective strategy for their healthcare system. For Humair and colleagues\textsuperscript{30} this was testing everyone with a rapid test, and for Giraldez-Garcia and colleagues\textsuperscript{29} it was performing RADT in patients triaged as scoring ‘high’ with the clinical algorithm. For the US study, no strategy was consistently the best option\textsuperscript{31}. This could indicate the importance of both the model perspective and structural assumptions, or may reflect how sensitive the results are to the currently available data on RADT. Of note is that RADT sensitivity parameters varied from 0.856 to 0.95, as did specificity from 0.78 to 0.973 across the studies. The study by Humair and colleagues\textsuperscript{30} found that results were not sensitive to changes in the diagnostic accuracy of RADT whereas the study by Giraldez-Garcia\textsuperscript{29} and colleagues found that the diagnostic accuracy of RADT affected whether or not testing everyone with RADT or first triaging RADT according to the clinical algorithm was the most effective strategy. Where other univariate sensitivity analyses had been reported, there was inconsistency in whether or not the cost of antibiotics, and the cost of RADT affected results. No model reported disease prevalence as influencing results.

**Conclusion**

The findings of this evidence review highlight different perspectives around clinical effectiveness, cost-effectiveness and patient acceptability of RADTs which are challenging to integrate into an overall conclusion.

Use of RADTs reduces rates of antibiotic prescribing for acute sore throat in primary care. However, one RCT from UK primary care suggests that, in the context of delayed prescribing, using the 5-item FeverPAIN clinical score to guide prescribing may be similarly effective in reducing antibiotic use and controlling sore throat symptoms when compared with the addition of RADT for patients with FeverPAIN scores ≥3. The evidence base on the cost-effectiveness of RADTs is inconclusive.

RADTs seem to be acceptable to patients, providing reassurance around diagnosis and helping them in their aim of avoiding unnecessary antibiotics. Healthcare professionals identified both potential benefits of the tests and concerns around their use.
Identified research gaps

Long term studies investigating potential medicalisation effects of RADT use for self-limiting sore throat such as increased belief in need to consult with a general practitioner.

Evidence on the impact on RADTs on the rate of serious GAS compilations is currently lacking, and further research should be encouraged.

Equality and diversity

Healthcare Improvement Scotland is committed to equality and diversity in respect of the nine equality groups defined by age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion, sex, and sexual orientation.

The process for producing evidence notes has been assessed and no adverse impact across any of these groups is expected. The completed equality and diversity checklist is available on www.healthcareimprovementscotland.org

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To propose a topic for an evidence note, email shtg.hcis@nhs.net

References can be accessed via the internet (where addresses are provided), via the NHS Knowledge Network www.knowledge.scot.nhs.uk, or by contacting your local library and information service.

A glossary of commonly used terms in Health Technology Assessment is available from htaglossary.net.
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