Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Rapid antigen detection tests for group A streptococcal infections to treat people with a sore throat in the community pharmacy setting

1. Purpose of the evidence appraisal report

This evidence appraisal report (EAR) aims to identify and summarise evidence that addresses the following question: in people who present with an acute sore throat, what is the clinical and cost effectiveness of rapid antigen detection tests for diagnosing and managing suspected group A streptococcal infection in the community pharmacy setting?

EARs are based on rapid systematic literature searches, with the aim of published evidence identifying the best clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. This EAR is adapted from diagnostics guidance produced by the National Institute for Health and Care Excellence (NICE), "Rapid tests for group A streptococcal infections in people with a sore throat", published in 2019 NICE (2019). The EAR is reviewed by experts and by Health Technology Wales (HTW) multidisciplinary advisory groups before publication.

2. Health problem

Sore throat describes the symptom of pain at the back of the mouth (NICE 2019). It is a self-limiting condition that lasts about a week. Clinical descriptions of acute sore throat include pharyngitis (inflammation of the pharynx) and tonsillitis (inflammation of the tonsils). Symptoms of a sore throat include pain in the throat, fever and a headache. Other symptoms can also include nausea, vomiting, abdominal pain, muscle pain and rashes (NICE 2019). Sore throat is most often caused by viral infections, while bacterial infections and non-infectious causes, such as hay fever and chronic cigarette smoke, are less common. However, distinguishing between bacterial and viral infections (and hence the likely effectiveness of antibiotics) can be difficult due to the similarity of symptoms. The most common bacterial cause of sore throat is group A beta-haemolytic streptococcus (GABHS). Complications of GABHS sore throat are rare but can include scarlet fever; suppurative complications including otitis media, acute sinusitis and quinsy; rheumatic fever (affecting the heart); necrotising fasciitis (a severe infection of soft tissue) and acute glomerulonephritis (affecting the kidneys) (NICE 2018a).

Currently, healthcare professionals in the UK are recommended to advise people with a sore throat that it usually gets better without treatment and how to best manage symptoms with self-care (including oral analgesia, medicated lozenges and appropriate fluid intake) (NICE 2018b, NICE 2019). The likelihood of GABHS sore throat is assessed by clinical examination with

or without the use of clinical scoring systems, specifically Centor or FeverPAIN (Table 1). Unless the patient is systemically very unwell, has symptoms and signs of a more serious illness, or is at high risk of complications, antibiotic prescribing for sore throat is typically guided by these clinical scoring systems (Table 2). In both children and adults, the first-choice antibiotic for acute sore throat is phenoxymethylpenicillin, while, if the patient is allergic or intolerant to penicillin, alternative first choice antibiotics include either clarithromycin or erythromycin. Dosage and course length varies depending on age and, for clarithromycin use in children, weight (NICE 2018b, NICE 2019)

Table 1: Clinical scoring system criteria recommended by NICE

Centor criteria	FeverPAIN criteria
Tonsillar exudate	Fever > 38° C (during previous 24 hours)
Tender anterior cervical lymphadenopathy or lymphadenitis	Purulence (pus on tonsils)
History of fever (over 38°C)	Attend rapidly (within three days after onset of symptoms)
Absence of cough	Severely inflamed tonsils
	No cough or coryza (inflammation of mucus membranes in the nose)
Each of the Centor criteria score 1 point (maximum score of 4). A score of 0, 1 or 2 is thought to be associated with a 3 to 17% likelihood of isolating streptococcus. A score of 3 or 4 is thought to be associated with a 32 to 56% likelihood of isolating streptococcus.	Each of the FeverPAIN criteria score 1 point (maximum score of 5). Higher scores suggest more severe symptoms and likely bacterial cause. A score of 0 or 1 is thought to be associated with a 13 to 18% likelihood of isolating streptococcus. A score of 2 or 3 is thought to be associated with a 34 to 40% likelihood of isolating streptococcus. A score of 4 or 5 is thought to be associated with a 62 to 65% likelihood of isolating streptococcus.

Table 2: Antibiotic prescribing

Antibiotic prescribing	Centor/FeverPAIN scoring	Suggested treatment
Unlikely to benefit from an antibiotic	FeverPAIN score of 0 or 1, or a Centor score of 0, 1 or 2	They should be offered advice on self-care without an antibiotic prescription
Might benefit from an antibiotic	FeverPAIN score of 2 or 3	They may be offered advice on self-care or a back-up antibiotic prescription (to use if symptoms do not start to improve within 3 to 5 days or worsen rapidly or significantly at any time)
Most likely to benefit from an antibiotic	FeverPAIN score of 4 or 5, or a Centor score of 3 or 4	Either an immediate or a back-up antibiotic prescription should be considered. This should take into account the risk of possible complications of untreated group A streptococcus infections and of possible adverse effects of antibiotics

Most people with sore throat do not attend their general practitioner (GP). A Scottish survey found 31% of adults reported a severe sore throat in the previous year, with 38% of these people visiting their GP. An estimated 60 visits to the GP, per 1,000 patients per year, is due to sore throat while recurrent sore throat has an annual incidence of 1 in 10 in UK general practice. A Swedish study found approximately 50% of cases occurred in people between 5 and 24 years of age (NICE 2018a). The estimated number of GABHS pharyngitis cases in children worldwide is 450 million per year. GABHS is estimated to account for 20% to 40% of cases of pharyngitis in children, and 5% to 15%

of pharyngitis cases in adults (Cohen et al. 2016). Incidence of GABHS throat infections is highest in winter and early spring. Specifically, colonisation with GABHS peaks in school-aged children (up to 20%) during the winter months (NICE 2018a). It is unclear whether the Welsh population would differ from the populations described.

3. Health technology

The gold star method for measuring GABHS remains microbiological culture of throat swabs; however, this method is neither immediate nor does it take place at point-of-care (Cohen et al. 2016). Rapid antigen detection tests (RADT) were developed to provide an immediate, point-of-care indication about the presence or absence of GABHS (producing either a positive or negative result). They do not detect non-GABHS, for example, group C or F non-haemolytic streptococci, which may also cause tonsillitis and streptococcal-invasive infection with patients presenting with similar symptoms. These tests are intended for people who are identified as more or most likely to benefit from antibiotics by clinical scoring tools, to confirm the need for antibiotics (Cohen et al. 2016).

Immune RADTs detect a GABHS specific cell-wall antigen. There are three types of immune RADTs: including latex agglutination assays, enzyme immunoassays and optical immunoassays. RADT for GABHS is about 70% to 90% sensitive and 95% specific compared with throat culture. A positive test in the absence of symptoms, however, is considered to represent colonisation and is not clinically relevant (BMJ Best Practice 2019, NICE 2018a). More recently, molecular tests have been developed and measure the amplification of GABHS DNA, by either polymerase chain reaction (temperature cycling dependent) or isothermal reaction (New England BioLabs 2020). A number of factors may affect the result of a RADT, including type of test kit used, expertise of the healthcare practitioner performing the test, method of specimen collection, severity of the disease and GABHS prevalence. There is no test that can differentiate between a GABHS carrier and invasive infection, or between living and non-living GABHS (CADTH 2018). The comparator to RADTs (immune RADTs or molecular tests), as per current antimicrobial prescribing guidelines, is clinical judgement and a clinical scoring tool such as Centor or FeverPAIN (Table 1). There are a number of tests that measure presence or absence of GABHS being produced (Appendix 4), but only one product is currently being used in NHS Wales: OSOM Strep A Test (NICE 2018b, Sekisui Diagnostics 2019).

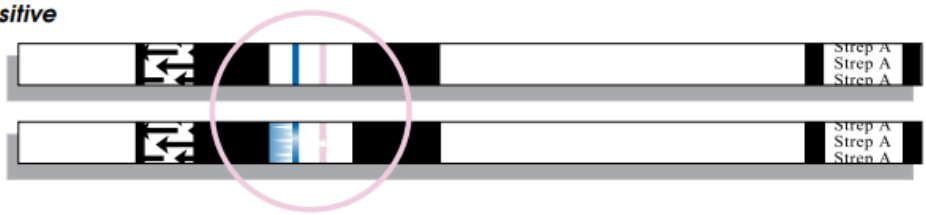
OSOM Strep A Test uses colour immunochromatographic dipstick technology, with antibodies coated on the nitrocellulose membrane (Sekisui Diagnostics 2019). Chemical extraction of the GABHS antigen is performed on the patient's throat swab. The test stick is placed within this mixture (containing the GABHS antigen) and the mixture migrates along the nitrocellulose membrane. If GABHS is present, it will interact with the anti-GABHS antibody that has colour particles attached, resulting in the production of a visible blue test line, indicating a positive result (Figure 1, taken from Sekisui Diagnostics).

Figure 1: Interpretation of OSOM Strep A Test results taken from Sekisui Diagnostics

INTERPRETATION OF TEST RESULTS

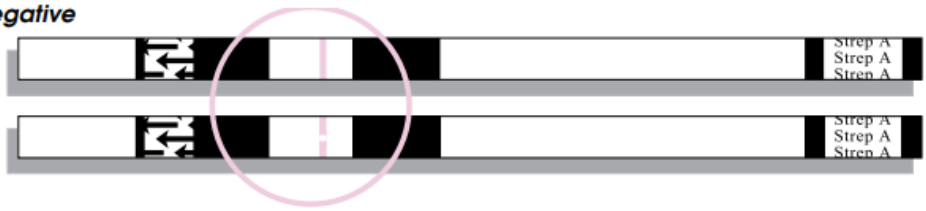
Note: A blue or red line which appears uneven in color density is considered a valid result. In cases of moderate or high positive specimens, some blue color behind the Test Line may be seen; as long as the Test Line and Control Line are visible, the results are valid.

Positive



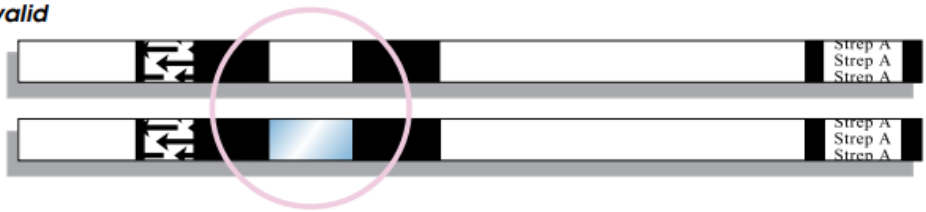
A blue Test Line and a red Control Line is a positive result for the detection of Group A Streptococcus antigen. *Note that the blue line can be any shade of blue and can be lighter or darker than the line in the picture.*

Negative



A red Control Line but no blue Test Line is a presumptive negative result.

Invalid



If no red Control Line appears or background color makes reading the red Control Line impossible, the result is invalid. If this occurs, repeat the test on a new Test Stick or contact Sekisui Diagnostics Technical Service.

4. Current guidance

Guidance from NICE diagnostics guidance (DG38) was published in 2019 and states that:

> *Rapid tests for strep A infections are not recommended for routine adoption for people with a sore throat. This is because their effect on improving antimicrobial prescribing and stewardship, and on patient outcomes, as compared with clinical scoring tools alone, is likely to be limited. Therefore, they are unlikely to be a cost-effective use of NHS resources* (NICE 2019).

However, use of RADT in the community pharmacy setting was not included:

> *The committee was aware that the rapid tests may be available in some community pharmacies. The EAG found no evidence on the diagnostic or clinical utility of rapid test accuracy when used in pharmacies, and therefore could not model this. Also, the committee noted that FeverPAIN had not been validated for use in pharmacies and that staff might need training to use clinical scoring tools. The committee concluded that it was not possible to assess the cost effectiveness of rapid tests for use in pharmacies.*

A Cochrane review was also published in June 2020 (Cohen et al. 2020b, Cohen et al. 2020a) which assessed randomised controlled trials (RCTs) comparing rapid tests with management on clinical grounds to guide the prescription of antibiotics for people with a sore throat in

ambulatory care settings (GP practices or emergency departments). The authors concluded that:

> *Rapid testing to guide antibiotic treatment for sore throat in primary care probably reduces antibiotic prescription rates by 25% (absolute risk difference), but may have little or no impact on antibiotic dispensing. More studies are needed to assess the efficacy and safety of rapid test-guided antibiotic prescribing, notably to evaluate patient-centred outcomes and variability across subgroups (e.g. adults versus children).*

Advice from the Scottish Health Technologies Group (SHTG) was published in 2018 and states that:

> *A systematic review of three non-UK cluster randomised controlled trials (RCTs) reported that the use of rapid antigen detection tests (RADTs) reduces rates of antibiotic prescribing. The delayed prescribing strategy recommended as UK standard care may limit the applicability of these findings.*
>
> *Based on one UK study in the context of delayed antibiotic prescribing, the use of a RADT for presence of Group A Streptococcal bacteria (GAS) in patients with acute sore throat in the general practice setting did not provide additional benefit in terms of symptom resolution or rates of antibiotic use when compared with use of a formal clinical scoring system. In this study, use of RADTs was not cost effective* (SHTG 2019).

5. Evidence search methods

The Population-Intervention-Comparator-Outcomes framework for the evidence appraisal (Appendix A) was developed following input from the Health Technology Wales (HTW) Assessment Group and Welsh experts.

A systematic literature search was undertaken between 15th January and 5th February 2020 and later updated on 9th September 2020. The search was adapted from those performed by SHTG, NICE and Cochrane and performed without a date restriction. The sift was then restricted from the year 2000 until present to exclude dated technologies and this decision was supported by Welsh expert input. The search strategy is available on request. Databases searched included Medline, Embase, and the Cochrane Library, as well as registers of clinical trials and selected key websites. Background guidance identified at the scoping stage was also assessed and included when relevant.

Identified studies were only included if the intervention was carried out in the community pharmacy setting. Patient safety and organisational issues were identified from the papers included in the clinical effectiveness section, and expert advice; no specific searches were undertaken.

Additionally, a separate patient experience literature review was undertaken, based on a dedicated search which aimed to identify and summarise the experiences, perspectives and opinions of patients. The search of key websites was undertaken on the 23rd to 27th March 2020. The three inclusion criteria applied were: patient experience of using RADT for group A streptococcal infections; patient experience of using RADT; and patient experiences of living with and treatment of sore throat and group A streptococcal infections. A full list of resources searched and terms used are available on request, as well as the detailed criteria used to select evidence for the appraisal.

6. Clinical effectiveness

This review found no published evidence which looked at the use of RADT in community pharmacy compared to other healthcare settings, or reported on the diagnostic accuracy of using RADT in community pharmacy. One study was in press at the time of the review, which used an ecological design to assess the effectiveness of RADT in community pharmacy. This is reported below.

A Cochrane Review by Cohen et al. (2020b) was identified which sought to assess the efficacy and safety of strategies based on rapid tests to guide antibiotic prescriptions for sore throat in primary care settings. The authors concluded that rapid testing in primary care probably reduces antibiotic prescription rates by 25% but may have little or no impact on antibiotic dispensing. Antibiotic dispensing refers to medicines accessed in pharmacies, while antibiotic prescriptions refer to medicines prescribed by healthcare providers). However, the trial identified which reports the number of participants with an antibiotic dispensed (reported as two separate parts as two different scoring systems were used), was based in general practices (Little et al. 2013). This review was therefore not included.

6.1 Studies comparing diagnosis and management using clinical scoring tools and point-of-care RADT carried out in the pharmacy setting, to screening and management in other care settings (based on clinical scoring tools or clinical judgement alone)

No published studies were identified that compared outcomes from RADT, following use of a clinical scoring tool, in a community pharmacy setting with those from use of a clinical scoring tool or clinical judgement in another care setting. A recent pilot in Wales introduced RADT in sore throat consultations with antibiotic supply across 56 community pharmacies, where pre-specified clinical criteria were met (Mantzourani et al. 2020). Patients aged ≥ 6 years presenting with acute sore throat were assessed using either FeverPAIN or Centor clinical scoring. Those with clinical scores of > 3 or > 2, respectively, were offered RADT in the pharmacy. Patients with a positive RADT were offered antibiotics. Of the 1,239 patients who underwent RADT (including 59 who did not meet the FeverPAIN or Centor criteria), 28.2% (n = 350) tested positive. No cultures were undertaken to enable calculation of diagnostic accuracy. Of all patients presenting with acute sore throat, 19.7% (n = 340) received antibiotics.

An ecological study design was employed to compare antibiotic prescribing between primary care cluster areas offering the service in community pharmacy and those not. There was a slight difference in the reduction of phenoxymethylpenicillin prescriptions between intervention areas and controls (-3.4% versus -3.8%) but no difference once pharmacy supplies were included. There was a similar reduction in prescriptions for oral broad-spectrum penicillins (-2.5% versus -3.4%). No increase in the monthly number of incidents of quinsy was detected. The average sore throat consultation rate in one practice (list size: 10,220) before and after introduction of the pilot in that area decreased from 0.71 per 1,000 patients to 0.36 per 1,000 patients.

6.2 Studies assessing diagnostic accuracy of point-of-care RADT (using microbiological culture as reference standard)

No studies were identified which reported on the diagnostic performance of point-of-care RADT undertaken in the community pharmacy setting, using microbiological culture as a reference standard. The NICE review (NICE 2019) previously assessed and reported the evidence base for

diagnostic performance in other care settings. This included a systematic review of the evidence base for 21 point-of-care tests for group A streptococcus infections. It was not possible to identify which test was the most accurate due to paucity of evidence and considerable heterogeneity. Only two studies reported diagnostic accuracy in the population of interest (patients with Centor/McIsaac scores ≥ 3 or FeverPAIN ≥ 4) (see Table 3).

Since this search (undertaken in March 2019), three more recent studies and a second systematic review have been published. Fraser et al. (2020) identified 26 studies reporting on the diagnostic accuracy of RADT in patients aged ≥ 5 years presenting to primary or secondary care. This included community pharmacy but no studies were identified for this setting. The authors found wide variation in the accuracy of the results and studies to be weak quality evidence. Meta-analysis was undertaken for five RADTs which are reported in Table 3. The same two studies were identified for the population with Centor/McIsaac scores ≥ 3 or FeverPAIN ≥ 4 as by NICE.

The three new studies did not restrict the patient population to those having undergoing clinical scoring and relied on clinical judgement. They may also have included patients < 5 years. One assessed the diagnostic accuracy of Orient Gene Strep A rapid test kit (a lateral flow immunoassay) in paediatric patients admitted for acute tonsillpharyngitis (Gumus et al. 2019). The second study (Kim et al. 2019) looked at diagnostic accuracy of three RADTs in children presenting to outpatient clinics in Korea. The third assessed the diagnostic accuracy of BD Veritor for children and adult samples from a range of different clinics (Bulut et al. 2020). Reported diagnostic accuracy fell within the relatively wide ranges previously found by the NICE review.

Table 3. Summary of findings

Study/ review	Population	Diagnostic accuracy
NICE (2019)	Patients aged ≥ 5 years presenting with sore throat	Sensitivity range: 67.9% to 100% Specificity range: 73.3% to 100%
	Patients aged ≥ 5 years presenting with sore throat and Centor/McIsaac ≥ 3 or FeverPAIN ≥ 4	Sensitivity range (2 studies): 92% to 95% Specificity range (2 studies): 94% to 96%
Gumus et al. (2019)	Paediatric patients admitted for acute tonsillpharyngitis	Orient Gene Strep A test: Sensitivity: 85.2%; specificity: 98%
Kim et al. (2019)	Children presenting to outpatient clinics in Korea	careUS Strep A Plus test: Sensitivity: 92.5% (95% CI: 83.4% to 97.5%); specificity: 97.0% (95% CI: 93.1% to 99.0%) SD Bioline test: Sensitivity: 71.6% (95% CI: 59.3% to 81.9%); specificity: 94.6% (95% CI: 90.1% to 97.5%) BD Veritor test: Sensitivity: 74.6% (95% CI: 62.5% to 84.4%); specificity: 92.9% (95% CI: 87.8% to 96.2%)
Bulut et al. (2020)	Children and adults presenting to clinics in Turkey	BD Veritor test: Sensitivity: 94.1%; specificity: 97.9%; PPV: 91.0%; NPV: 98.7%; accuracy: 97%
	Children aged 5-15 years presenting to clinics in Turkey	BD Veritor test: Sensitivity: 94.8%; specificity: 96.8%; PPV: 91.8%; NPV: 98.0%

Study/ review	Population	Diagnostic accuracy
Fraser et al. (2020)	Patients aged ≥ 5 years presenting with sore throat	BD Veritor test (2 studies): Sensitivity: 78% (95% CI: 67% to 87%); specificity: 90% (95% CI: 86% to 93%) QuikRead Go Strep A Kit (2 studies): Sensitivity: 87% (95% CI: 78% to 95%); specificity: 78% (95% CI: 71% to 85%) Aleri i Strep A test (3 studies): Sensitivity: 98% (95% CI: 95% to 100%); specificity: 96% (95% CI: 90% to 100%) OSOM Strep A Strip (5 studies): Sensitivity: 94% (95% CI: 89% to 98%); specificity: 95% (95% CI: 91% to 98%) Aleri TestPack Plus Cassette (10 studies): Sensitivity: 85% (95% CI: 79% to 90%); specificity: 96% (95% CI: 94% to 98%)

CI: confidence interval; NICE: National Institute for Health and Care Excellence

6.3 Ongoing trials

There were no ongoing studies identified from the literature search.

7. Economic evaluation

7.1 Health economic evidence review

The titles and abstracts of records identified in the search for this research question were screened and 13 health economic studies were deemed potentially relevant. The full texts of these studies were reviewed against the inclusion/exclusion criteria. Following consideration of the full texts, 11 studies were excluded from the review with most excluded for the use of RADT in a setting other than the community pharmacy setting. The remaining two studies were included in the review (Klepser et al. 2012, Lathia et al. 2018). All of the studies were only partially applicable to NHS Wales as they considered healthcare systems in other countries.

Klepser et al. (2012) describes a cost-utility analysis of RADTs for the diagnosis of group A streptococcus pharyngitis in the pharmacy setting. The analysis compared pharmacist-use of RADTs against six other strategies: RADT-use in walk-in clinics, physician observation, physician culture, physician empiric therapy, physician RADT and physician RADT with follow-up culture. The strategy of pharmacists using RADTs was found to be the least costly strategy overall. It was also found to be equally effective or more effective than most strategies and was therefore dominant. The two exceptions were physician culture and physician RADT with follow-up culture, which were both found to be more effective than a strategy of pharmacists using RADT. In comparison to pharmacy RADT, the incremental cost-effectiveness ratio (ICER) for physician culture was $6,042 (£4,780) per quality-adjusted life-daily (QALD) gained, while the ICER for physician RADT with follow-up culture was $40,745 (£32,233) per QALD gained. Both ICER values exceed the authors chosen threshold of $137 (£108) per QALD (selected as it reflects $50,000 [£39,555] per QALY) and would therefore not be deemed cost-effective.

A limited range of one-way sensitivity analyses were conducted in which adjusting the probability of false negatives with RADT was found to be the only aspect that changed the result. Probabilistic sensitivity analysis was not conducted.

Lathia et al. (2018) describes a cost-minimisation analysis which considered point-of-care strep throat testing in a pharmacy setting in comparison to usual care in a family physician's office, walk-in clinic or an emergency room. In comparison to usual care, the estimated cost savings per patient managed with point-of-care strep throat testing in a pharmacy setting was estimated to be $12.47 to $24.36 (£7.00 to £13.67).

7.2 De novo economic analysis

HTW developed an economic analysis to estimate the cost effectiveness of using RADT as part of a community pharmacy test-and-treat service for suspected group A streptococcal infection in comparison to standard GP assessment (see Appendix 5 for full details of analysis).

The economic analysis was based largely on an economic analysis conducted as part of NICE DG38 on 'Rapid tests for group A streptococcal infections in people with a sore throat' (NICE 2019). The NICE analysis considered the use of RADTs in primary and secondary care settings. The analysis was adapted to reflect the use of RADTs as part of an assessment in the community pharmacy setting.

Note that, in order to be able to develop such an analysis, an assumption needed to be made that pharmacists would be able to carry out the RADT testing with the same level of effectiveness as a physician. This assumption was considered reasonable by the HTW Assessment Group.

A decision tree analysis was developed to estimate the cost effectiveness of diagnostic strategies for suspected group A streptococcal infection. Two strategies were considered in the analysis:

1. Pharmacist test-and-treat service using RADT
2. Standard GP assessment

The analysis took the perspective of the UK NHS and personal social services (PSS). A time horizon of one year was considered, reflecting the maximum period over which outcomes are likely to differ between the strategies. Discounting of future costs and benefits was not considered due to the short time horizon.

The pharmacist test-and-treat service using RADT was found to be dominant (more effective and less costly than standard GP assessment). This result was driven primarily by the lower cost associated with an assessment at pharmacy in comparison to a GP assessment as well as a reduction in antibiotic prescription (and associated complications).

The result was found to be robust in the sensitivity analysis, with the conclusion of the analysis remaining unchanged in all modelled scenarios modelled. Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case were replaced with values drawn from distributions around the mean values and the model is run 10,000 times. At a threshold of £20,000 per quality-adjusted life-year (QALY), the pharmacist test-and-treat service using RADT was found to have a 100% probability of being cost effective.

8. Organisational Issues

Currently, patients with sore throat are encouraged to seek advice from community pharmacies in Wales through the national pharmacy Common Ailments Service (CAS) (Mantzourani et al. 2020). The CAS only supports provision of symptomatic treatments and does not supply antibiotics to patients, which results in many patients choosing to attend a GP practice instead. The sore throat test-and-treat pilot in Wales extended the CAS service to enable community pharmacies to undertake screening and provide medication using a service specification. Community pharmacies contracted to Cwm Taf Morgannwg University Health Board and Betsi Cadwaladr University Health Board signed a Service Level Agreement to provide the extended service. Antibiotics specified in a Patient Group Direction were supplied to patients by pharmacists following consultation and assessment in accordance with national antibiotic prescribing guidance. Patients not meeting the criteria for RADT or testing negative were still offered analgesics under the CAS.

Pharmacists received detailed training on throat examination, use of scoring tools and sampling using a throat swab. This involved half a day face-to-face training with an antimicrobial pharmacist on antimicrobial resistance, and half a day with a registered company on use of RADT and clinical training including recognising red flag symptoms. The antimicrobial resistance training may be replaced with an online webinar in future. A prerequisite of delivering the service was completion of the Health Education and Improvement Wales (HEIW) New Enhanced Services Accreditation process, and HEIW Sore Throat Test-and-Treat Training. Feedback from expert reviewers supported that appropriate training is available for pharmacists in Wales and that testing in pharmacies would be as, if not more, effective as in GP practices.

There are a number of wider intangible benefits to this approach not captured by the clinical and cost effectiveness outcomes. Unnecessary antibiotic prescribing contributes to the wider public health issue of antimicrobial resistance. Any reduction in unnecessary prescribing may have positive patient benefits through antibiotic stewardship and reduction in adverse effects, including *Clostridium difficile* infection. In the study by Mantzourani et al. (2020) all patients were offered education on the difference between viral and bacterial infection and on antimicrobial stewardship. The study also aimed to provide a more accessible, efficient and high-quality clinical pathway, better utilisation of pharmacist skills, and to free up GP time for more complex and urgent medical issues. The use of RADT in the community pharmacy could lead to appropriate substitution of provision by GPs to provision by pharmacists, potentially reducing demand on GP practices. It is estimated that an average size (list size of 7,000) GP practices in the UK has around 5,480 consultations for sore throat over 10 years, resulting in around 3,560 antibiotic prescriptions, and that around 80% of patients recover without treatment within 8 days (Gulliford et al. 2016, Spinks et al. 2013). However, any impact on demand would be dependent on a number of factors, including awareness and willingness of patients to present at a community pharmacy and referral of patients from GP practices to community pharmacies.

There are a number of potential issues which could impact on the delivery of a community service. For example, there is potential for milder cases to present to pharmacies with a lower prevalence of GABHS, which would impact on the diagnostic performance of the test. Use of self-administered RADTs (with pharmacist supervision) may prove less effective. This is particularly relevant for a service being delivered during the COVID-19 pandemic. Patient behaviour may also be impacted by COVID-19 and take-up of the community pharmacy service reduced. In addition, the clinical expertise of pharmacists may benefit from the delivery of the service, and this may reduce the additional benefit from RADT compared to standard assessment as their skills in clinical judgement grow.

9. Patient issues

No specific patient issues/perspectives were identified in the course of searching for clinical and cost-effectiveness evidence. However, a separate patient experience literature review was also undertaken, based on a dedicated search which aimed to identify and summarise the experiences, perspectives and opinions of patients. The review identified a qualitative study of GP, nurse practitioner and patient views about the use of streptococcus antigen detection tests in primary care carried out in the primary care setting using semi-structured face-to-face and telephone interviews (Little et al. 2014). Of the 51 participants, nine were patients: the other 42 comprised of GPs and nurse practitioners. Patient interviews lasted for half an hour and of the five main themes that were identified, the following three related specifically to patient issues:

- patients reported a feeling of reassurance about their diagnosis and treatment recommendations because of undergoing RADT;
- patients reported that they would still be inclined to initially wait and see if their sore throat resolved itself before going to the GP despite knowing that RADT was available, thereby indicating that provision of RADT might not necessarily increase visits to GP surgeries;
- patients reported that they would not want to take antibiotics unless it was necessary and they viewed RADT as a way to assist making that decision.

Two additional papers were published after the date of the initial patient experience literature search. (Mantzourani et al. 2020) undertook a survey of patient experiences and 510 responses were collected over a period of seven months. Surveys were received from patients of all ages including children and young adults. The review found that 98% of patients surveyed were satisfied with the service they received, 99% of patients were happy to return to a pharmaceutical setting for future treatment and the majority of patients reported that their confidence in managing their condition and service satisfaction was not dependent on having been supplied antibiotics. Other findings of note include:

- patient-reported behavioural intentions signify a potential shift in health-seeking behaviour towards a pharmacist-led service;
- patients surveyed stated they would recommend the service to others;
- patients surveyed were happy with the performance of the pharmacist and were reassured about their condition after having the test;
- the majority of patients agreed it was a more convenient service when compared to a GP appointment, although some obstacles were identified for some patients, such as availability of a qualified pharmacist able to deliver the test and accessibility to the pharmacy;
- the inclusion of the test increased patients' confidence in the treatment outcome.

Kirby&Mousa (2020) undertook a survey of patient satisfaction with a RADT pilot in community pharmacy in the USA. They used a collaborative pharmacy practice agreement between two community pharmacies and a physician at a nearby primary care clinic to provide testing and treatment for influenza or group A streptococcus (GAS) infection. It was unclear how many of the 38 individuals tested for GAS were followed up, but 100% and 73% of those aged < 18 and ≥ 18 years reported symptom resolution respectively. Six and 27% reported that they had required follow-up in primary care respectively. Average satisfaction with the service and likelihood of recommending it to others on a 5-point scale was 4.93 in both cases, for both those aged <18 and ≥ 18 years. The study was considered to be at high risk of bias.

These studies highlight the additional intangible benefits to patients of receiving RADT in community pharmacy settings, for example, convenience and reassurance.

10. Conclusions

Evidence for the clinical effectiveness of RADT in community pharmacy, and the wider benefits of this to the system, is currently limited. However, there is a demand for this service in Wales and where it is being put into practice, it would be beneficial to encourage studies of diagnostic accuracy and clinical effectiveness with patient-level controls. Robust research and evaluation is needed to inform the safety, effectiveness, costs and wider impacts of the service. The de novo economic analysis indicated that a pharmacist test-and-treat service was likely to be more effective and less costly than usual care. The conclusion of the analysis was found to be robust in deterministic sensitivity analysis and in probabilistic sensitivity analysis, RADT was found to have a 100% probability of being cost effective at a threshold of £20,000 per QALY.

11. Contributors

This topic was proposed by Andrew Evans, Chief Pharmaceutical Officer, Welsh Government.

The HTW staff and contract researchers involved in writing this report were:

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A range of clinical experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

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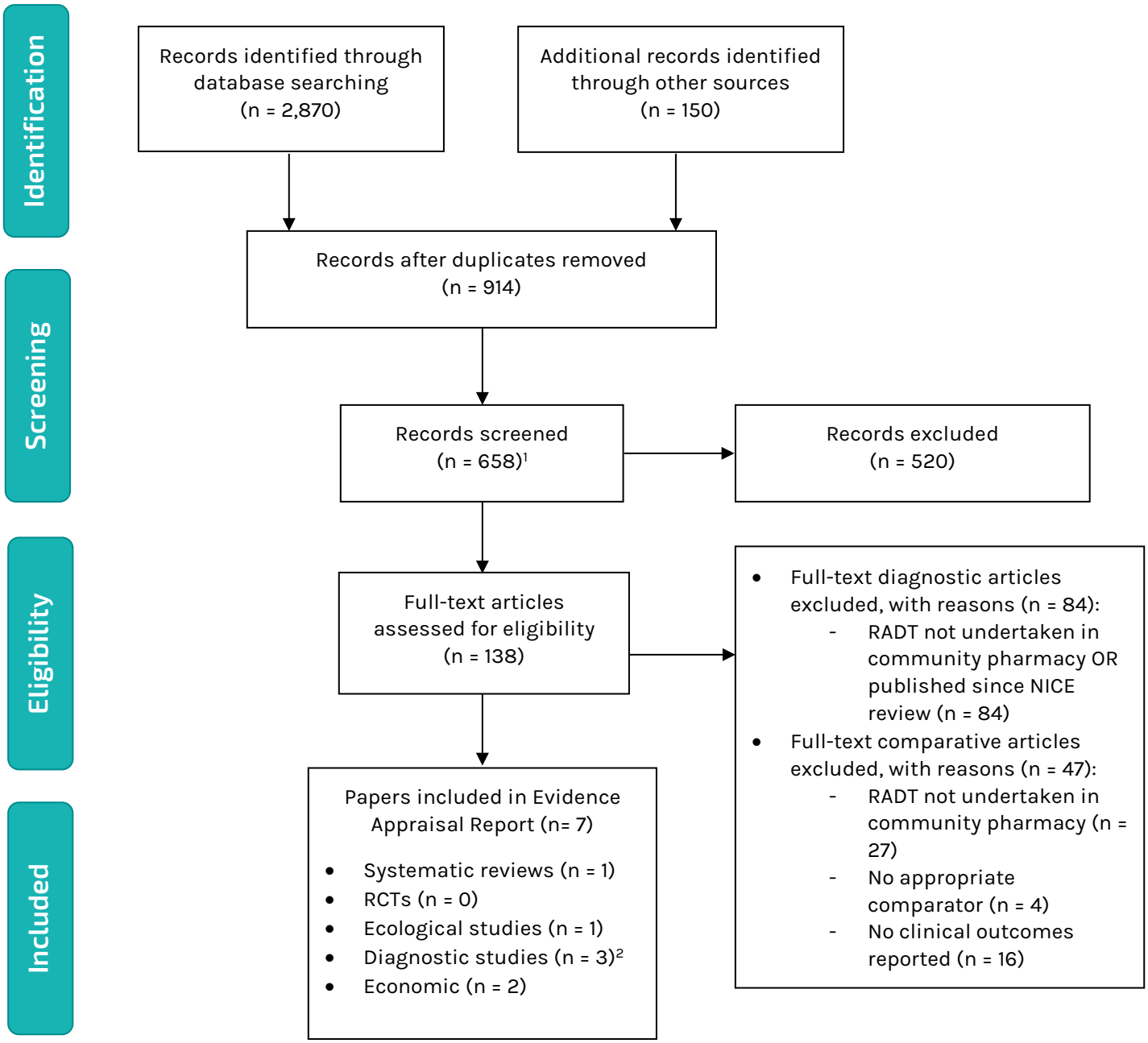
Appendix 1. PICO framework

Clinical effectiveness studies	
Population	People presenting with symptoms of an acute sore throat in whom group A streptococcal infection is suspected
Intervention	Diagnosis and management using clinical scoring tools and point-of-care RADT carried out in the community pharmacy setting
Comparison/ Comparators	Screening and management in other care settings, based on clinical scoring tools or clinical judgement alone
Outcome measures	Time to antimicrobial prescribing decision; changes to antimicrobial prescribing decision; number of appointments required per episode; number of delayed or immediate antibiotic prescriptions issued or dispensed; morbidity, either from infection complications or from antibiotic therapy; mortality; contribution to antimicrobial stewardship and onward transmission of infection; health-related quality of life; patient satisfaction with test and antimicrobial prescribing decision; healthcare professional satisfaction with test and antimicrobial prescribing decision; cost effectiveness or other measures of economic impact
Diagnostic accuracy studies	
Population	People presenting with symptoms of an acute sore throat
Intervention	Diagnosis of group A streptococcal infection using point-of-care RADT
Comparison/ Comparators	Diagnosis of group A streptococcal infection using microbiological culture of throat swabs
Outcome measures	Test accuracy (sensitivity, specificity, positive predictive value, negative predictive value), test success/failure rates, time diagnosis/test result

Appendix 2. PRISMA flow diagram outlining selection of papers for clinical and cost effectiveness (up to 7th September 2020)



[1] The search was limited to publications from 2000 onwards.
[2] Limited to diagnostic studies in community pharmacy or published since NICE review.

Appendix 3: Summary of included studies

Appendix Table 1: Mantzourani et al. (2020)

Descriptive details	PICO	Results & Conclusions	Observations & quality
Setting: 56 community pharmacies, Wales. **n = 1,725 patients** underwent sore throat consultations in community pharmacy Median age at consultation (IQR): 29.2 years (16-39) **Intervention period:** November 2018 to March 2019 **Study design:** ecological before-and-after.	**Population:** patients aged ≥6 years presenting with acute sore throat at a participating pharmacy. **Assessment:** patients were assessed with either FeverPAIN or Centor clinical scoring. Where FeverPAIN >3 or Centor >2 patients were offered RADT in the pharmacy. Patients with a positive RADT were offered antibiotics. **Comparator:** primary care clusters without a RADT available in community pharmacy. **Outcomes measured:** antibiotic prescriptions issued; average monthly sore throat consultation rates in a GP practice.	• Of 1,725 patients screened with clinical scoring, 1,239 received RADT. Of these, 350 tested positive and 340 were supplied with antibiotics. In addition, 528 patients received 804 analgesic items (89 patients received both antibiotics and analgesics). • There was a reduction in phenoxymethylpenicillin prescriptions in both intervention and control clusters, this was greater in control areas (-3.4% versus -3.8% respectively). Once pharmacy supplies were included, no difference was found (-3.4% versus -3.4%). • The reduction in oral broad-spectrum penicillin prescriptions was greater in control clusters (-2.5% versus -3.4%). • No increase in the monthly rate of quinsy was detected. • The average monthly sore throat consultation rates prior to the availability of RADT in community pharmacy were 0.71 per 100,000 in March 2018. This decreased to 0.36 per 100,000 in March 2019 post-intervention. **Conclusions:** "Data from the first 5 months of the service suggest that it may have a role in safely rebalancing uncomplicated sore throat management from general practice to community pharmacies while continuing to promote antibiotic stewardship."	• Comparison of antibiotic prescribing was conducted using an ecological, before and after study design comparing primary care cluster areas (population sizes between 50,000 and 100,000). • GP consultation data was only obtained from one GP practice (list size = 10,220). The practice was located adjacent to four community pharmacies providing RADT. • No cultures were obtained to enable diagnostic accuracy to be assessed. • Statistical significance of findings were not reported.

Appendix Table 2: NICE (2019)

Descriptive details	PICO	Results & Conclusions	Observations & quality
Setting: any healthcare setting. **n = 38 studies** (n = 29 for RADT) **Search undertaken:** March 2019 **Study design:** systematic review.	**Population:** patients aged ≥5 years presenting with symptoms of sore throat. **Assessment:** clinical judgement and a clinical scoring tool such as FeverPAIN or Centor where available. **Intervention:** 21 rapid tests for strep A were included; 17 used immunoassay detection methods (RADTs) and 4 used molecular methods **Reference standard:** throat culture. **Outcomes measured:** diagnostic performance; effect on prescribing behaviours and clinical outcomes; contribution to antimicrobial stewardship and onward transmission of infection.	• Only 2 studies reported diagnostic performance in patients with Centor >3. One of these looked at OSOM Strep A test. Sensitivity and specificity were 95% (89% CI 63% to 98%) and 94% (95% CI 88% to 98%), and 92% (95% CI 76% to 98%) and 96% (95% CI 89% to 99%) respectively. • Two studies looked at use of OSOM Strep A in patients with Centor score ≥2 and reported sensitivities of 96% (95% CI 76% to 100%) and 95% (95% CI 85% to 99%), and specificities of 97% (95% CI 90% to 100%) and 92% (95% CI 86% to 95%). A third study looked at the use of OSOM Strep A in patients with Centor score ≥1 and reported sensitivity of 90% (95% CI 78% to 97%) and 94% (95% CI 90% to 97%) respectively. • There was wide variation in sensitivity (67.9% to 100%) and specificity (73.3% to 100%) across the 21 rapid tests. • In the RCT which used OSOM Strep A, 44% of patients received an antibiotic prescription compared with 64% in the Centor clinical scoring alone group. • One RCT based in the UK for patients aged >3 years with sore throat in primary care, found 18% of patients who received FeverPAIN clinical scoring plus RADT were prescribed antibiotics compared to 16% of those with clinical scoring alone. • A before-and-after study in a UK paediatric emergency department found antibiotic prescribing rates decreased from 79% to 24% the following year, and 28% in the second year, after the introduction of the McIsaac clinical scoring tool followed by RADT. **Conclusions:** "The systematic review and the cost-effectiveness models identified uncertainties around the adoption of point-of-care tests within primary and secondary care settings. Although sensitivity and specificity estimates are promising, we have little information to establish the most accurate point-of-care test."	• All studies were considered at high risk of bias in at least 1 domain, and 13 were at high risk of bias in 2+ domains. • 1 RCT, 25 cohorts studies, and 9 of unclear design reported on test accuracy • 3 RCTs, cohort studies, and 1 before-and-after study reported on antibiotic prescribing rates

Appendix Table 3: Gumus et al. (2019)

Descriptive details	PICO	Results & Conclusions	Observations & quality
Setting: Single hospital, Turkey. **n = 250 patients** **Median age (range):** 6 years (1-18) **Intervention period:** January 2015 to March 2016 **Study design:** diagnostic.	**Population:** paediatric patients admitted to hospital for acute tonsillopharyngitis. **Assessment:** not reported. **Intervention:** Orient Gene Strep A rapid test kit (Zhuhai Encode Medical, China) **Reference standard:** throat culture. **Outcomes measured:** diagnostic accuracy.	• Sensitivity and specificity was 85.2% and 98% respectively. **Conclusions:** The Orient Gene Strep A rapid test kit is a test that can be used in the diagnosis of acute tonsillopharyngitis because the sensitivity of the kit is within acceptable limits (>80%).	• Limited details reported in the study. • An unclear number of the population do not meet the age criteria.

Appendix Table 4: Kim et al. (2019)

Descriptive details	PICO	Results & Conclusions
Setting: Single hospital, Korea. **n = 255 patients** **Median age (range):** 9.6 years (4-17) **Intervention period:** September to November 2015 **Study design:** diagnostic.	**Population:** patients suspected of having streptococcal pharyngitis (defined as the presence of a painful throat and inflammation of the throat or tonsils on physical examination). **Assessment:** clinical judgement. **Intervention:** (1) careUS Strep A Plus (rapid chromatographic immunoassay); (2) SD Bioline Strep A (chromatographic solid-phase immunoassay); and (3) BD Veritor system (lateral flow chromatographic immunoassay). **Reference standard:** throat culture. **Outcomes measured:** diagnostic accuracy.	See table below. **Conclusions:** Among the three RADTs evaluated, careUS Strep A Plus showed good performance in terms of sensitivity, specificity, accuracy and agreement with culture. It would be expedient to encourage the use of RADTs to obtain acceptable and fast results using simple equipment.
Observations & quality		• An unclear number of the population do not meet the age criteria.

RADT	Sensitivity % (95% CI)	Specificity % (95% CI)	Accuracy % (95% CI)	PPV (95% CI)	NPV (95% CI)	Kappa index (95% CI)	Kappa index p-value
Care US	92.5 (83.4 to 97.5)	97.0 (93.1 to 99.0)	95.7 (92.3 to 97.9)	92.5 (83.9 to 96.7)	97.0 (93.3 to 98.7)	0.896 (0.83 to 0.95)	<0.0001
SD Bioline	71.6 (59.3 to 81.9)	94.6 (90.1 to 97.5)	88.1 (83.2 to 91.9)	84.2 (73.5 to 91.1)	89.3 (85.1 to 92.4)	0.694 (0.58 to 0.79)	<0.0001
BD Veritor	74.6 (62.5 to 84.4)	92.9 (87.8 to 96.2)	87.7 (82.7 to 1.5)	80.7 (70.36 to 87.9)	90.2 (85.8 to 93.2)	0.690 (0.58 to 0.79)	<0.0001

CI: confidence interval

Appendix Table 5: Bulut et al. (2020)

Descriptive details	PICO	Results & Conclusions	Observations & quality
Setting: Single hospital, Turkey. **n = 12,391 patients** **Mean age (range):** 12.1 years (1-80) **Intervention period:** October 2017 to January 2019 **Study design:** diagnostic.	**Population:** preliminary diagnosis of pharyngitis. **Assessment:** not reported. **Intervention:** BD Veritor System rapid antigen test **Reference standard:** throat culture. **Outcomes measured:** diagnostic accuracy.	• For all samples: sensitivity: 94.1%; specificity: 97.9%; PPV: 91.0%; NPV: 98.7%; accuracy: 97% • Aged 5-15 years: sensitivity: 94.8%; specificity: 96.8%; PPV: 91.8%; NPV: 98.0% **Conclusions:** The test yielded high sensitivity and specificity and will contribute significantly to clinical diagnosis and management of tonsillopharyngitis.	• 25% of samples were from adult clinics – 1,603 from family medicine; 1,079 from emergency clinic; 215 from otolaryngology clinic; 104 from infection clinic; 75 from internal medicine clinic; and 39 from other clinics.

Appendix Table 6: Fraser et al. (2020)

<table>
<tr><th>Descriptive details</th><th>PICO</th><th>Results & Conclusions</th></tr>
<tr>
<td>Setting: primary care (general practice clinics, community pharmacies and walk-in centres) and secondary care (urgent care/walk-in centres and emergency departments)

No. studies: 38 of clinical effectiveness & 3 of cost-effectiveness

Search period: up to March 2019

Study design: systematic review and economic evaluation</td>
<td>Population: people aged ≥ 5 years presenting with sore throat symptoms

Studies: comparisons of point-of-care testing with antibiotic prescribing decisions, studies of test accuracy, or studies of cost-effectiveness.

Intervention: point-of-care tests for group A Streptococcus (including rapid antigen detection tests and molecular tests), preferably in those identified as being at high risk.

Comparator: antibiotic-prescribing decisions using clinical scoring tools for group A Streptococcus, such as FeverPAIN or Centor/modified Centor (McIsaac) alone

Reference standard: microbiological culture.

Outcomes measured: any patient-related outcome, test accuracy (the ability of a test to correctly differentiate between people who do and people who do not have a disease) or performance, prescribing behaviour and cost-effectiveness estimates.</td>
<td>In the population of interest (patients with Centor/McIsaac scores of ≥ 3 points or FeverPAIN scores of ≥ 4 points), point estimates were 0.829 to 0.946 for sensitivity and 0.849 to 0.991 for specificity. There was considerable heterogeneity, even for studies using the same point-of-care test, suggesting that is unlikely that any single study will have accurately captured a test's true performance.

Meta-analysis was undertaken for five RADTs:
<table>
<tr><th>RADT (no. studies)</th><th>Sensitivity % (95% CI)</th><th>Specificity % (95% CI)</th></tr>
<tr><td>QuikRead Go Strep A Kit (2)</td><td>87 (78 to 95)</td><td>78 (71 to 85)</td></tr>
<tr><td>OSOM Strep A Strip (5)</td><td>94 (89 to 98)</td><td>95 (91 to 98)</td></tr>
<tr><td>BD Veritor (2)</td><td>78 (67 to 87)</td><td>90 (86 to 93)</td></tr>
<tr><td>Aleri i Strep A (3)</td><td>98 (95 to 100)</td><td>96 (90 to 100)</td></tr>
<tr><td>Aleri TestPack Plus Cassette (10)</td><td>85 (79 to 90)</td><td>96 (94 to 98)</td></tr>
</table>
Conclusions:

There is some randomised controlled trial evidence to suggest that the use of rapid antigen detection tests may help to reduce antibiotic-prescribing rates. Although sensitivity and specificity estimates are promising, we have little information to establish the most accurate point-of-care test.</td>
</tr>
<tr><td>Observations & quality</td><td colspan="2">No studies were identified from pharmacy settings. Identified same studies as NICE (2019) for target population.</td></tr>
</table>

Appendix 4: Summary of tests measuring presence or absence of GABHS being produced, adapted from NICE guidance (NICE 2019)

Product (manufacturer)	Test format/analyser	Limit of detection	Time to result[a] (minutes)	Results	Confirmation of negative result?
Rapid antigen detection tests					
Clearview exact Strep A cassette (Abbott)[b]	Cassette	5 10^4 organisms/test	5	Qualitative	Yes
Clearview exact Strep A dipstick (Abbott)[c]	Test strip	5 10^4 organisms/test	5	Qualitative	Yes
BD Veritor plus system group A Strep (Becton Dickinson)	Cassette	1 10^5 to 5 10^4 CFU/ml	5	Qualitative	Yes
Strep A rapid test (Biopanda reagents)	Cassette	1E+05 organisms/swab	5	Qualitative	Yes
Strep A rapid test (Biopanda reagents)	Test strip	1E+05 organisms/swab	5	Qualitative	Yes
NADAL Strep A (nal von minden GmbH)	Test strip	1.5 10^5 organisms/swab	5	Qualitative	No
NADAL Strep A (nal von minden GmbH)	Cassette	1.5 10^5 organisms/swab	5	Qualitative	No
NADAL Strep A plus (nal von minden GmbH)	Cassette	1.5 10^5 organisms/swab	5	Qualitative	No
NADAL Strep A plus (nal von minden GmbH)	Test strip	1.5 10^5 organisms/swab	5	Qualitative	No
NADAL Strep A scan test (nal von minden GmbH)[d]	Cassette	1.5 10^5 organisms/swab	5	Qualitative	No
OSOM Strep A test (Sekisui diagnostics)	Test strip	Not known	5	Qualitative	Yes
QuikRead Go Strep A test kit (Orion Diagnostica)[e]	N/A	7 10^4 CFU/swab	Less than 7	Qualitative	Not known
Alere TestPack Plus Strep A (Abbott)	Cassette	Not known	5	Qualitative	Yes (if symptoms persist)
Bionexia Strep A plus (Biomerieux)	Cassette	1 10^4 organisms/swab	5	Qualitative	Not known
Bionexia Strep A dipstick (Biomerieux)	Test strip	Not known	5	Qualitative	Not known
Biosynex Strep A (Biosynex)	Cassette	1 10^5 bacterial/swab	5	Qualitative	Not known
Sofia Strep A FIA (Quidel)[f]	Cassette	1.86 10^4 to 9.24 103 CFU/test	5 to 6	Qualitative	Yes

Product (manufacturer)	Test format/analyser	Limit of detection	Time to result[a] (minutes)	Results	Confirmation of negative result?
Molecular tests					
Alere i Strep A (Abbott)[g]	Alere i instrument	4 to 42 CFU/ml	Less than 8	Qualitative	Yes
Alere i Strep A 2 (Abbott)[h]	Alere i instrument	Not known	Less than 6	Qualitative	No
Cobas Strep A assay (Roche Diagnostics)	Cobas Liat analyser	5 to 10 CFU/ml	Less than 15	Qualitative	No
Xpert Xpress Strep A (Cepheid)	GeneXpert System	Not known	18 or more	Not known	Not known

[a] Read time (does not include sample preparation time)
[b] Replaced by Clearview Strep A cassette 2
[c] Replaced by Clearview Strep A dipstick 2
[d] Needs BD Veritor Plus analyser
[e] Needs QuikRead go instrument
[f] Needs Sofia analyser
[g] Replaced by ID NOW Strep A 2 test
[h] Rebranded to ID NOW Strep A 2

CFU: colony forming units; ml: millilitres

Appendix 5: Cost-effectiveness analysis

1. Background and objective

An economic analysis was developed to estimate the cost effectiveness of using RADT as part of a pharmacy test-and-treat service for suspected group A streptococcal infection in comparison to standard GP assessment.

The economic analysis was based largely on an economic analysis conducted as part of NICE Diagnostic Guidance 38 (NICE DG38) on 'Rapid tests for group A streptococcal infections in people with a sore throat' (NICE 2019). The NICE analysis considered the use of RADTs in primary and secondary care settings. The analysis was adapted to reflect the use of RADTs as part of an assessment in the community pharmacy setting.

2. Methods

2.1 Model structure

A decision tree analysis was developed using Microsoft Excel to compare the cost effectiveness of diagnostic strategies for suspected group A streptococcal infection. The analysis took the perspective of the UK NHS and personal social services (PSS). A time horizon of one year was considered, reflecting the maximum period over which outcomes are likely to differ between the strategies. Discounting of future costs and benefits was not considered due to the short time horizon.

A simplified version of the decision tree is shown in Figure 1 and the two strategies considered in the analysis are briefly described below:

1. Pharmacist test-and-treat service using RADT

   Pharmacist undertakes initial assessment using FeverPain or Centor risk score. If risk score is sufficiently high (Centor score $\geq$ 3 or FeverPAIN score $\geq$ 4), then assessment with RADT will be offered. Patients with a positive RADT result will be offered antibiotics. Patients with a negative RADT result or patients with a clinical risk score below the threshold for testing will not be offered antibiotics. Patients not offered antibiotics are advised to return for re-assessment if symptoms persist or seek medical attention sooner if symptoms worsen rapidly or significantly. Re-assessment at repeat consultations were included in the analysis and were assumed to follow the same system as the original consultation.

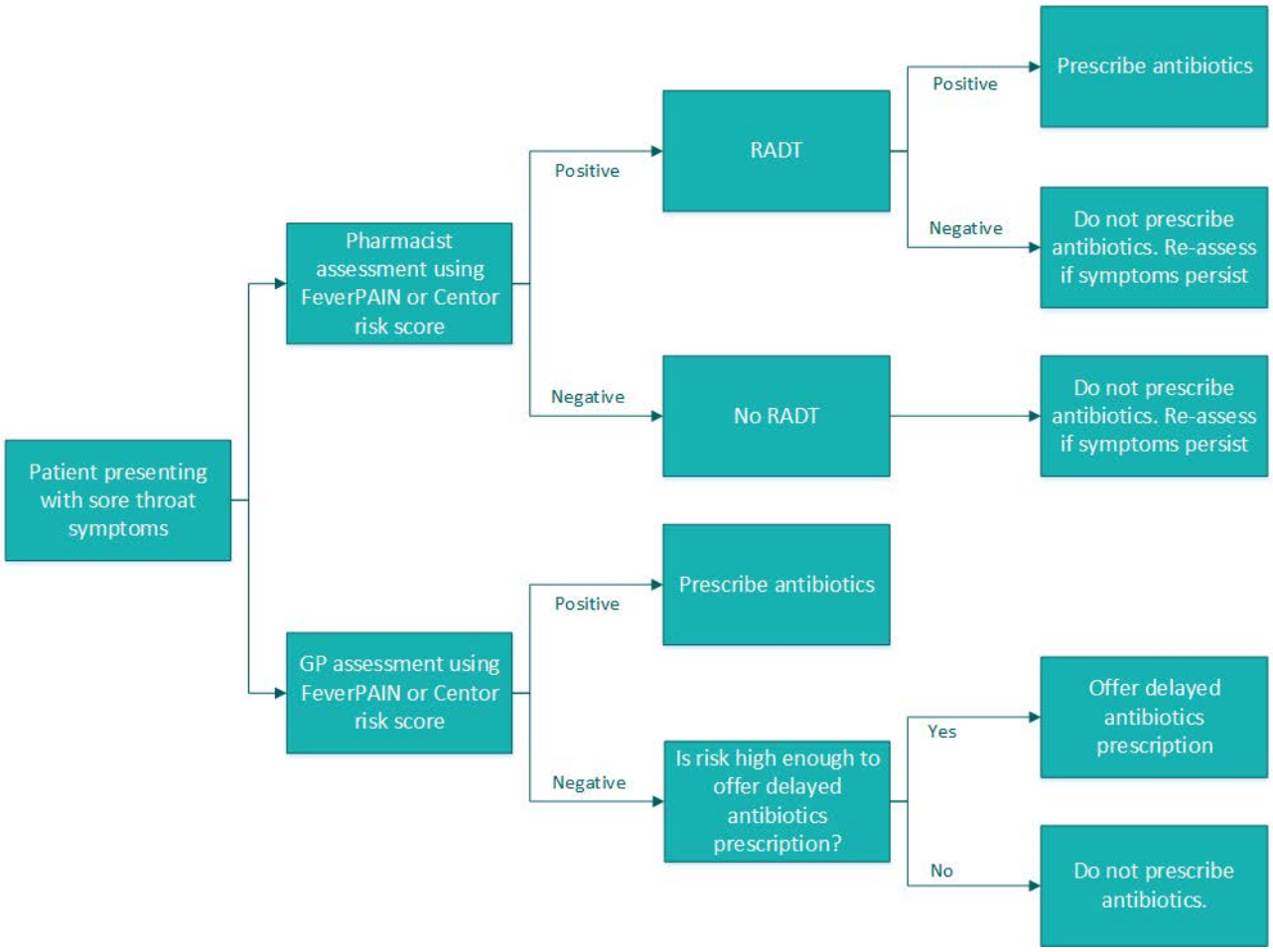
2. Standard GP assessment

   GP undertakes initial assessment using FeverPain or Centor risk score. If risk score is sufficiently high (Centor score $\geq$ 3 or FeverPAIN score $\geq$ 4), then patients will be offered antibiotics. Patients with a clinical risk score below the threshold for immediate antibiotic prescription will either not be offered antibiotics or will be offered a delayed prescription of antibiotics to collect after three to five days if symptoms don't improve.

Some further considerations were incorporated in the analysis based on outcomes from a recent pilot of a pharmacist test-and-treat service using RADT in Wales (Mantzourani et al. 2020). Mantzourani et al. (2020) showed that pharmacists sometimes made judgement calls whereby they would decide to offer RADT even in situations where it is not indicated based on the clinical risk score assessment. In addition, pharmacists referred some patients to see their GP if they were concerned about another condition or if RADT was indicated but it was not possible to complete. The model structure was adapted to allow for these real-world complexities to be

incorporated. The probability of these events occurring are described in the clinical data section below.

Figure 1: Modelled decision tree



2.2 Clinical data

2.2.1 Prevalence and accuracy data

The prevalence of group A streptococcal infection in patients presenting with a sore throat was estimated to be 22.8% for adults and 30.2% for children. These estimates were sourced from the economic analysis conducted as part of NICE DG38 (NICE 2019). NICE derived the estimate of 22.8% for adults from Little et al. (2013), which reported 136 cases of group A streptococcal infection amongst 597 patients aged ≥ 5 years old presenting in UK primary care settings. NICE reported that there were no clear UK estimates for prevalence in children and instead estimated a median value of 30.2% from three non-UK studies of children in primary care.

The diagnostic accuracy of GP or pharmacist assessment using a clinical risk score was estimated using the accuracy of the Centor risk score presented in NICE DG38, based on meta-analysis of 12 studies reported by Aalbers et al. (2011). Table 1 shows estimates of the diagnostic accuracy of the Centor risk score for group A streptococcal infection at various threshold levels.

Table 1. Diagnostic accuracy of Centor risk score for group A streptococcal infection

Threshold for infection	Sensitivity	Specificity	Source
Centor score ≥ 1	95%	18%	Aalbers et al. (2011)
Centor score ⩾2	79%	55%	Aalbers et al. (2011)
Centor score ⩾3	49%	82%	Aalbers et al. (2011)
Centor score = 4	18%	95%	Aalbers et al. (2011)

In the base case analysis, it was assumed that a Centor score threshold of 3 would be used to guide decision making. When used as part of a pharmacy assessment, patients with a Centor score ≥ 3 would be offered RADT testing whereas those with a Centor score < 3 would not be offered antibiotics. When used as part of a GP assessment, patients with a Centor score ≥ 3 would be offered antibiotics, whereas those with a Centor score < 3 would either not be offered antibiotics or be offered a delayed antibiotics prescription. Using a Centor score ≥ 3 as the threshold for infection results in a sensitivity of 49% and a specificity of 82%. Alternative Centor score thresholds were considered in sensitivity analysis.

Note that FeverPAIN could not be considered in the analysis because there are no data available in a format suitable for utilisation in the economic model (i.e. sensitivity and specificity based on FeverPAIN thresholds).

No data were available on the diagnostic accuracy of RADT when undertaken by community pharmacists. Therefore, diagnostic accuracy was sourced from data on the use of RADT in primary or secondary care under the assumption that pharmacists would be able to carry out the RADT testing with the same level of effectiveness as a physician.

The diagnostic accuracy of RADT was estimated based on accuracy data presented for a range of RADTs in NICE DG38 (NICE 2019). Average sensitivity and specificity were estimated for the adult and child population based on accuracy estimates presented in NICE DG38. Estimates were only included in the calculation of the average if they were based on published, peer-reviewed, studies (the NICE report also included accuracy data from abstracts as well as manufacturer submitted data, but these have been excluded from the calculation). An average sensitivity of 87% and specificity of 93% was estimated for the adult population, while an average sensitivity of 84% and specificity of 95% was estimated for the child population.

Table 2 and Table 3 show the diagnostic accuracy data of RADTs for the adult and child population, respectively.

Table 2. Diagnostic accuracy of RADT for group A streptococcal infection in adults

Population	Sensitivity (95% CI)	Specificity (95% CI)	Source
Clearview extract strep A cassette (Abbott)	68% (54% to 80%)	95% (92% to 97%)	1 study included in NICE DG38
Clearview extract strep A dipstick - test strip (Abbott)	68% (54% to 80%)	95% (92% to 97%)	1 study included in NICE DG38
BD Veritor Plus system group A strep Assay cassette (Beckton Dickinson)	78% (67% to 87%)	90% (86% to 93%)	2 studies included in NICE DG38
OSOM Strep A test - test strip (Sekisui diagnostics)	92% (76% to 98%)	96% (89% to 99%)	3 studies included in NICE DG38
QuikRead Go Strep A test kit (Oriom Diagnostica)	100% (85% to 100%)	79% (60% to 92%)	1 study included in NICE DG38

Population	Sensitivity (95% CI)	Specificity (95% CI)	Source
Alere TestPack Plys Strep A - cassette (Abbott)	95% (89% to 98%)	94% (88% to 98%)	1 study included in NICE DG38
Sofia Strep A FIA (Quidel)	85% (81% to 89%)	95% (93% to 97%)	1 study included in NICE DG38
Alere i Strep A (Abbott)	95% (74% to 100%)	97% (92% to 99%)	1 study included in NICE DG38
Cobas Strep A Assay on Liat system (Roche Diagnostics)	98% (93% to 100%)	93% (90% to 96%)	1 study included in NICE DG38
Average	**87%**	**93%**	
Note: NICE DG38 includes diagnostic accuracy data for additional tests but these have been excluded from the table as they were based on data submitted by the manufacturer or data from abstracts			
CI: confidence interval; DG: diagnostics guidance: NICE: National Institute for Health and Care Excellence			

Table 3. Diagnostic accuracy of RADT for group A streptococcal infection in children

Population	Sensitivity (95% CI)	Specificity (95% CI)	Source
Clearview extract strep A cassette (Abbott)	68% (54% to 80%)	95% (92% to 73%)	1 study included in NICE DG38
Clearview extract strep A dipstick - test strip (Abbott)	68% (54% to 80%)	95% (92% to 97%)	1 study included in NICE DG38
BD Veritor Plus system group A strep Assay cassette (Beckton Dickinson)	76% (61% to 88%)	94% (89% to 97%)	1 study included in NICE DG38
OSOM Strep A test - test strip (Sekisui diagnostics)	94% (89% to 98%)	95% (91% to 98%)	1 study included in NICE DG38
QuikRead Go Strep A test kit (Oriom Diagnostica)	80% (56% to 94%)	91% (72% to 99%)	1 study included in NICE DG38
Alere TestPack Plys Strep A - cassette (Abbott)	86% (79% to 91%)	99% (97% to 100%)	1 study included in NICE DG38
Sofia Strep A FIA (Quidel)	85% (81% to 89%)	95% (93% to 97%)	1 study included in NICE DG38
Alere i Strep A (Abbott)	98% (95% to 100%)	96% (89% to 100%)	3 studies included in NICE DG38
Cobas Strep A Assay on Liat system (Roche Diagnostics)	98% (93% to 100%)	93% (90% to 96%)	1 study included in NICE DG38
Average	**84%**	**95%**	
Note: NICE DG38 includes diagnostic accuracy data for additional tests but these have been excluded from the table as they were based on data submitted by the manufacturer or data from abstracts			
CI: confidence interval; DG: diagnostics guidance: NICE: National Institute for Health and Care Excellence			

While the base case analysis uses average accuracy data across all RADTs, alternative estimates were applied in the sensitivity analysis. This includes a scenario based on accuracy data for the OSOM Step A test, which is known to be the test used in the recent pilot of a pharmacist test-and-treat service using RADT in Wales (Mantzourani et al. 2020).

2.2.2 Delayed prescription and repeat consultations

Some patients undergoing standard assessment via GP consultations were assumed to be offered a delayed prescription of antibiotics. This is an option for patients with a Centor score below the threshold for antibiotic prescription (< 3 in the base case). The proportion of patients that are offered a delayed prescription as well as prescription use was estimated from NICE DG38 (NICE 2019). NICE DG38 estimated proportions based upon prescribing behaviour of GPs reported in the PRISM trial.

The probability of a delayed prescription given a negative clinical score was estimated to be 51.1%, based on 91 out of the 178 patients with a FeverPAIN score < 4 in the in the clinical score arm of the PRISM trial that were offered a delayed prescription (under the assumption that a Centor score < 3 is equivalent to a FeverPAIN score < 4). Of those offered a delayed antibiotic prescription, 45.7% were assumed to use it based on PRISM data showing that 75 out of 164 patients offered a delayed antibiotic prescription went on to use it.

Some of the patients in whom RADT wasn't indicated following pharmacist assessment using a clinical risk tool were assumed to have a re-assessment due to the persistence of symptoms. The proportion of patients that might have a re-assessment was estimated using data on delayed antibiotic prescription in combination with the proportion that go on to use it. This was considered to be a reasonable approximation under the assumption that those that go on to use the prescription were likely to have had persistent symptoms. Therefore, 23.4% of patients that did not require a RADT were assumed to have a re-assessment (estimated as 0.511 multiplied by 0.457).

Similarly, some patients with a negative RADT result were assumed to have a re-assessment due to the persistence of symptoms. The proportion of patients that might have a re-assessment in this case was estimated in a similar manner to the above, except that a different estimate for delayed antibiotic prescription was applied. In the economic analysis conducted as part of NICE DG38, it was estimated that 27.6% of patients with a negative RADT result receive a delayed antibiotic prescription (based on 48 out of 174 patients offered a delayed prescription following a positive clinical score in the PRISM trial). This value was used in combination with the proportion of patients offered a delayed antibiotic prescription that go on to use it (45.7%). Therefore, 12.6% of patients with a negative RADT were assumed to have a re-assessment (estimated as 0.276 multiplied by 0.457).

2.2.3 Clinical judgement and further GP contact

As noted above, some real-world considerations were incorporated in the analysis based on outcomes from a recent pilot of a pharmacist test-and-treat service using RADT in Wales (NICE 2019). It was assumed that RADT would be offered to 10.8% of patients with a Centor score < 3. This was based on evidence from Mantzourani et al. (2020), which showed that pharmacists made a judgement call to offer RADT to 59 of the 545 people (10.8%) in whom RADT was not indicated based on the clinical risk score assessment and/or a direct request by a GP.

In addition, it was assumed that pharmacists would refer 9.7% of people to see their GP. This was based on evidence from Mantzourani et al. (2020), which showed that pharmacists referred 167 of 1,725 patients to GPs (9.7%). A further three patients were referred by pharmacists to dentists, but this was not incorporated in the analysis as it may reflect a referral for a complication (such as an abscess) and this is already incorporated in the analysis. Therefore, it was not included to avoid the risk of doubling counting the cost of a complication.

Further GP contact following the pharmacist assessment was also incorporated in the analysis based on evidence from Mantzourani et al. (2020). It was assumed that 2.6% of patients with a

negative RADT and 8.3% of patients with a positive RADT would have a GP consultation, based on a reported 23 out of the 889 people with a negative RADT and 29 out of the 350 people with a positive RADT that went on to see their GP in Mantzourani et al. (2020). It was further assumed that 2.9% of patients that did not undergo a RADT assessment would have a GP consultation, based on a reported 14 out of the 486 people that did not require a RADT that went on to see their GP in Mantzourani et al. (2020).

2.2.4 Complications

Complications relating to group A streptococcal infection were incorporated in the analysis using estimates applied in the economic analysis conducted as part of NICE DG38. The NICE analysis based the complication estimates on data presented in Little et al. (2013), a large cohort study of UK patients presenting in primary care with sore throat. The probability of complications for patients with a treated infection was estimated to be 1.3%, based on 78 complications reported among 5,932 treated patients. The probability of complications for patients with an untreated infection was estimated to be 1.5%, based on 75 complications reported among 4,974 untreated patients.

Little et al. (2013) did not report rates for rare non-suppurative complications such as acute rheumatic fever. Therefore, in-line with an assumption made by the NICE analyst, it was assumed that only 0.01% of complications would be non-suppurative.

The probability of penicillin-induced complications was also based on estimates applied in the economic analysis conducted as part of NICE DG38 as well as a previous economic evaluation of diagnostic and treatment strategies for adults with streptococcal pharyngitis (Neuner et al. (2003)). It was therefore assumed that 2% of patients prescribed antibiotics will develop penicillin-induced rash and 0.1% will develop penicillin-induced anaphylaxis or sepsis.

The complication rates applied in the analysis are presented in Table 4.

Table 4: Complication rates

Complication	Probability	Source
Complications relating to group A streptococcal infection		
Probability of complications with treated infection	1.3%	Little et al. (2013)
Probability of complications with untreated infection	1.5%	Little et al. (2013)
Proportion of complications that are non-suppurative	0.01%	Assumption made in NICE (2019)
Penicillin-induced complication		
Probability of developing rash	2%	Neuner et al. (2003)
Probability of anaphylaxis or sepsis	0.01%	Neuner et al. (2003)

2.3 Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. Where possible, all costs were estimated in 2019 prices.

2.3.1 Consultation costs

The cost of a GP consultation was sourced from unit costs estimates from the Personal Social Services Research Unit (PSSRU). The PSSRU reports that a typical GP consultation lasting 9.22 minutes costs £39.23 (including direct care staff costs and qualification costs).

The cost of a consultation at a community pharmacy test-and-treat service using RADT was estimated based upon the fee listed within the service specification for the Community Pharmacy Sore Throat Test-and-Treat (STTT) Service. The report specifies that an activity payment of £135.83 will be made for every 10 patients managed using the STTT service. For simplicity, this was converted into a per-patient fee for use in the economic analysis (equal to £13.58 per patient).

The service specification states that this fee will be charged in addition to any reimbursement for the cost of any medication prescribed (described in treatment cost section below) as well as the cost of equipment and consumables. Therefore, the cost of equipment and consumables used as part of all consultations (£0.89) was incorporated based on estimates provided by the lead researcher involved in the recent pilot of the pharmacy test and treat service using RADT in Wales (Mantzourani et al. 2020).

2.3.2 Investigation costs

The cost of RADT was estimated based on costs presented in NICE DG38. NICE (2019) presented costs for a range of RADTs from different manufacturers, with costs ranging from £0.64 for the Biopanda's Strep A rapid test strip to £64.63 for Cobas Strep A Assay on Liat system supplied by Roche Diagnostics. Test cost estimates were primarily based on costs submitted by the respective manufacturer. The list of NICE costs was supplemented with data provided by the lead researcher involved in the pilot of the pharmacy test and treat service using RADT in Wales (Mantzourani et al. 2020). This data showed that the cost of the test used in the service (OSOM Step A test) was £1.80 per test.

For the purpose of the base case analysis, an average cost per test was estimated based on all of the RADT cost data in NICE DG38 as well as the cost of the OSOM Strep A test. The resulting average cost per test was £7.61. The cost of additional equipment required to undertake the test, such as the cost of a tongue depressor and disposable apron, was estimated to be £0.27 based on data provided by the lead researcher involved in the pilot of the pharmacy test-and-treat service using RADT in Wales. Thus, the total cost for the test and associated equipment was estimated to be £7.88. Alternative cost estimates were applied in sensitivity analysis, including a scenario where the cost estimate is based only upon OSOM Strep A (in which case, the total cost was £2.07).

The cost of a confirmatory swab culture for patients with a negative RADT result was estimated in-line with NICE DG38. A cost of £7.58 was applied based on the cost associated with microbiology in NHS Reference costs 2018/19.

2.3.3 Treatment costs

The cost associated with the prescription of antibiotics was estimated using costs from the British National Formulary (BNF). It was assumed that a ten-day, four-times-daily course of phenoxymethylpenicillin 250mg or 500mg would be prescribed. The cost of the regimen was estimated based upon a drug tariff price of £1.28 for a 28 pack, which resulted in a cost of £1.83 for the 250mg dose and £3.66 for the 500mg dose. An average of the two regimens was calculated, resulting in an estimated cost of £2.74.

The cost associated with the prescription of paracetamol was also estimated using costs from the BNF. It was assumed that a 32-tablet pack of paracetamol 500mg would be prescribed at a cost of £1.06 (based on drug tariff price listed in the BNF). This is in-line with the assumption made in the economic analysis conducted in NICE DG38.

2.3.4 Complication costs

The cost of managing complications relating to group A streptococcal infection were incorporated based on sources and assumptions made in NICE DG38 (NICE 2019). The cost of treating group A streptococcal infection related abscess was estimated at £1,913 based on the cost of a tonsillectomy in people aged 4 years and over (CA60C) reported in NHS Reference Costs 2018/19. The cost of treating acute rheumatic fever was estimated to be £2,346 based on the cost for Other Acquired Cardiac Conditions with CC Score 6 to 8 (EB14C) in NHS Reference Costs 2018/19.

The cost of managing complications relating to the adverse effects of penicillin were incorporated based on sources and assumptions made in NICE DG38. People with a penicillin-induced rash were assumed to require an additional GP consultation (£39.23) and be switched to clarithroymycin 250mg-500mg, twice-daily for five days. The cost of clarithroymycin 250mg twice-daily for five days was estimated to be £1.19 based on a drug tariff price of £1.67 for a pack of 14 tablets from the BNF. The cost of clarithroymycin 500mg twice-daily for five days was estimated to be £1.95 based on a drug tariff price of £2.73 for a pack of 14 tablets from the BNF. An average of the 250mg and 500mg regimens was calculated for the purpose of the analysis, resulting in an average cost of £1.57.

NICE DG38 estimated that the cost of penicillin-induced anaphylaxis or sepsis was £1,744 based on a 2017 study on the cost of sepsis, which estimated that 93,973 adults would need treatment for sepsis in UK hospitals at annual total cost £163,949,055. This value was inflated to 2019 prices, resulting in an estimated cost of £1,810.

2.3.5 Training costs

Pharmacists are likely to receive training before offering the test-and-treat service using RADT. Researchers involved in the pilot of the service in Wales provided estimates of training time (Mantzourani et al. 2020). It was estimated that two half-day training sessions would be required for each pharmacist, with one face-to-face session and another session delivered virtually (webinar). However, the cost of the training sessions is not known and it's also not known whether the cost of the community pharmacist's time would be reimbursed by the NHS.

Training costs were not considered in the base case analysis because of this uncertainty and also the potential for the analysis to be distorted by a 'one-off' cost in the set-up of the service. However, training costs were considered in sensitivity analysis in three scenarios. In one scenario, it was assumed that there would be no training fee but that pharmacist time would be reimbursed at a rate equivalent to that of NHS pharmacists in the community setting. In another scenario, it was assumed that pharmacist time would not be reimbursed but the NHS would pay a fee for the training session (based on an assumed fee of £250). In the third scenario it was assumed that pharmacist time would be reimbursed and the NHS would pay a fee for the training session.

In the scenarios in which it was assumed that pharmacist time was reimbursed, costs were estimated using unit costs from the PSSRU 2019. A cost of £49.50 per hour of pharmacist time was estimated (including oncosts, travel and overheads) based on the average cost of a band 6 or band 7 scientific or professional staff worker based in the community setting. As the training cost is a one-off cost, the cost needs to be spread across all the RADT test and treat service

consultations that an individual pharmacist is likely to undertake (to give a training cost per consultation). This was estimated based on data from the pilot, which reported 1,725 consultations in 52 community pharmacies over the five-month period of the study (Mantzourani et al. 2020). Based on this, it was estimated that there could be 74 RADT test and treat service consultations per pharmacy per year. The number of community pharmacists per pharmacy was estimated from a report from the International Pharmaceutical Federation (2017), which estimated a median number of 2.23 community pharmacists per pharmacy in high-income countries. Thus, there could be 33 RADT test and treat service consultations per community pharmacist per year. It was assumed that each pharmacist might be involved in the service for an average of three years. This approximation aims to account for many possibilities, such as pharmacists changing jobs, retiring or receiving refresher training sessions. Spreading the training cost over the likely consultations that a pharmacist may undertake over a three-year period, results in an estimated cost of £3.73 per consultation.

2.4 Health-related quality of life

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining life year estimates with quality of life (QoL) values associated with being in a particular health state. Mortality is not considered in this analysis because it is not anticipated that there would be survival differences between the two strategies. Therefore, differences in QALYs will be entirely driven by differences in QoL.

The source and approach taken to the estimation of QoL values was based upon the economic analysis conducted as part of NICE DG38.

Baseline QoL for adults was assumed to be 0.863, which is equal to the mean QoL for the general UK population (Kind et al. 1998). Baseline QoL for children was assumed to be 0.940 which is equal to the mean QoL for the general UK population aged under 25 years old (Kind et al. 1998). Note that this was the lowest age band available in the study. Based on the general trend of lower ages having higher QoL, it is possible that this value underestimates QoL in children. However, this would not be anticipated to have any meaningful influence on the results of the economic analysis as the result is driven by differences in strategies and this value is applied equally in both strategies.

QoL decrements associated with infection and complications were sourced from NICE DG38, which itself sourced values from previously published economic evaluations of diagnostic and management strategies for adults with pharyngitis.

Losses of 0.15 and 0.25 quality-adjusted life days were reported for treated and untreated sore throat infections. These estimates translate into QoL decrements of 0.000411 (0.15/365) for a treated infection and 0.000685 (0.25/365) for an untreated infection. A loss of 5 quality-adjusted life days was reported for peritoncillar abscess, equivalent to a QoL decrement of 0.0037 (5/365). A loss of 76.5 quality-adjusted life days was reported for rheumatic fever, equivalent to a QoL decrement of 0.209 (76.5/365). A loss of nine quality-adjusted life days was reported for penicillin-induced anaphylaxis or sepsis, equivalent to a QoL decrement of 0.025 (9/365). A loss of 0.65 quality-adjusted life days was reported for penicillin-induced rash, equivalent to a QoL decrement of 0.0017 (0.65/365).

QALYs were calculated by subtracting the QoL decrements associated with any events that occur within the modelled from the baseline QoL estimates, with QoL decrements assumed to be additive. For example, the total QALYs associated with an adult with a treated infection without complications would be equal to 0.862589 (calculated as *0.863-0.000411)* whereas the total QALYs

associated with an adult with a treated infection with a penicillin induced rash would be equal to 0.860808 (calculated as *0.863-0.000411-0.001781).*

Table 5 presents the QoL values applied in the economic analysis.

Table 5. Quality of life values

Health state	QoL value	Source
Baseline QoL for adults	0.863	Kind et al. 1998 (UK population norm for adults)
Baseline QoL for children	0.940	Kind et al. 1998 (UK population norm for children)
QoL decrements		
Untreated infection	0.000685	Neuner et al. (2003)
Treated infection	0.000411	Neuner et al. (2003)
Penicillin induced rash	0.001781	Neuner et al. (2003)
Penicillin induced anaphylaxis (sepsis)	0.024658	Neuner et al. (2003)
Abscess	0.013699	Neuner et al. (2003)
Rheumatic fever	0.209589	Neuner et al. (2003)
QoL: quality of life		

3. Results

3.1 Base case results

The base case results of the analysis are shown in Table 6 and Table 7 for the adult and child population, respectively. The results of the analysis are similar in both populations with pharmacy assessment using RADT found to be marginally more effective and less costly than GP assessment. Therefore, pharmacy assessment using RADT was found to be dominant as it was both more effective and less costly than GP assessment.

Table 6. Base case results for the adults (presented on a per-patient basis)

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
GP assessment	£47.68	-	0.86282	-	-
Pharmacy assessment using RADT	£34.08	-£13.60	0.86283	0.000004	Dominant
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; RADT: rapid antigen detection test					

Table 7. Base case results for children (presented on a per-patient basis)

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
GP assessment	£49.69	-	0.86277	-	-
Pharmacy assessment using RADT	£36.26	-£13.43	0.86277	0.0000005	Dominant

Diagnostic strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; RADT: rapid antigen detection test					

3.2 Deterministic sensitivity analysis results

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the deterministic sensitivity analyses are presented in Table 8.

It can be seen that the results of the analysis are relatively insensitive to changes in the majority of input parameters. In the majority of scenarios, the conclusion of the base case analysis remains unchanged with pharmacy assessment using RADT found to be less costly and more effective than GP assessment. In other instances, pharmacy assessment with RADT was found to be less effective and less costly than GP assessment. In such cases, the interpretation of the ICER result changes as it represents the amount of money saved for each QALY that is lost and therefore values above £20,000 per QALY can be considered cost effective. In all instances where this scenario occurred, the ICER value was above £20,000 per QALY indicating that pharmacy assessment with RADT can be considered cost effective as the savings outweigh the minor reduction in quality of life.

Table 8. Deterministic sensitivity analysis results

Modelled scenario	ICER result (cost per QALY)	
	Adults	Children
Base case	Dominant	Dominant
Prevalence of group A streptococcal infection = 10%	Dominant	Dominant
Prevalence of group A streptococcal infection = 20%	Dominant	Dominant
Prevalence of group A streptococcal infection = 30%	Dominant	Dominant
Prevalence of group A streptococcal infection = 40%	£6,895,062*	£3,944,054*
RADT sensitivity = 70%	£13,907,699*	£2,575,363*
RADT sensitivity = 80%	Dominant	£13,789,274*
RADT specificity = 70%	Dominant	£9,762,813*
RADT specificity = 80%	Dominant	£21,949,360*
Centor score threshold of ≥1	Dominant	Dominant
Centor score threshold of ≥2	Dominant	Dominant
Centor score threshold of 4	Dominant	£5,808,351*
RADT cost based on OSOM Strep A test only	Dominant	Dominant
RADT accuracy based on OSOM Strep A test only	Dominant	Dominant
RADT cost and accuracy based on OSOM Strep A test only	Dominant	Dominant
No repeat consultations	Dominant	£5,096,700*
No pharmacist judgement calls	Dominant	£7,209,499*
No GP contact following pharmacy consultation	Dominant	Dominant

Modelled scenario	ICER result (cost per QALY)	
	Adults	Children
Complications related to group A streptococcal infection doubled	Dominant	£49,756,354*
Penicillin induced complication rates doubled	Dominant	Dominant
All complication rates doubled	Dominant	Dominant
Cost of managing anaphylaxis or sepsis increased by 50%	Dominant	Dominant
Cost of managing anaphylaxis or sepsis increased by 50%	Dominant	Dominant
All complication costs increased by 50%	Dominant	Dominant
All complication costs decreased by 50%	Dominant	Dominant
Training cost based on reimbursement of pharmacist time	Dominant	Dominant
Training cost based on training fee of £250 per pharmacist	Dominant	Dominant
Training cost based on reimbursement of pharmacy time and training fee of £250 per pharmacist	Dominant	Dominant
QoL decrements increased by 50%	Dominant	Dominant
QoL decrements rates increased by 100%	Dominant	Dominant

3.3 Threshold analysis results

A threshold analysis was conducted to assess the uncertainty around the cost of training. The total training cost required for pharmacy assessment using RADT to no longer be cost-effective was estimated (using a threshold of £20,000 per QALY). It was found that pharmacy assessment using RADT in adult and child populations was no longer cost-effective if the training cost exceeds £1,169 and £1,153, respectively.

3.4 Probabilistic sensitivity analysis results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case were replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are shown using ICER scatterplots and cost-effectiveness acceptability curves (CEAC). The ICER scatter plots show the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC graphs show the probability of each strategy being considered cost effective at the various cost-effectiveness thresholds on the x axis.

Figure 2 and Figure 3 show the ICER scatterplot for the adult and child population, respectively. In both populations, it can be seen that all of the results reside in the bottom half of the graph, indicating that the pharmacy assessment strategy with RADT is always less costly than GP assessment. The results appear to be roughly split in half between those that reside the south-east quadrant (indicating that pharmacy assessment strategy with RADT is less costly and more effective than GP assessment) and those that reside in the south-west quadrant (indicating that pharmacy assessment strategy with RADT is less costly and less effective than GP assessment).

Figure 2. ICER scatterplot for pharmacy assessment using RADT in comparison to GP assessment in adult population

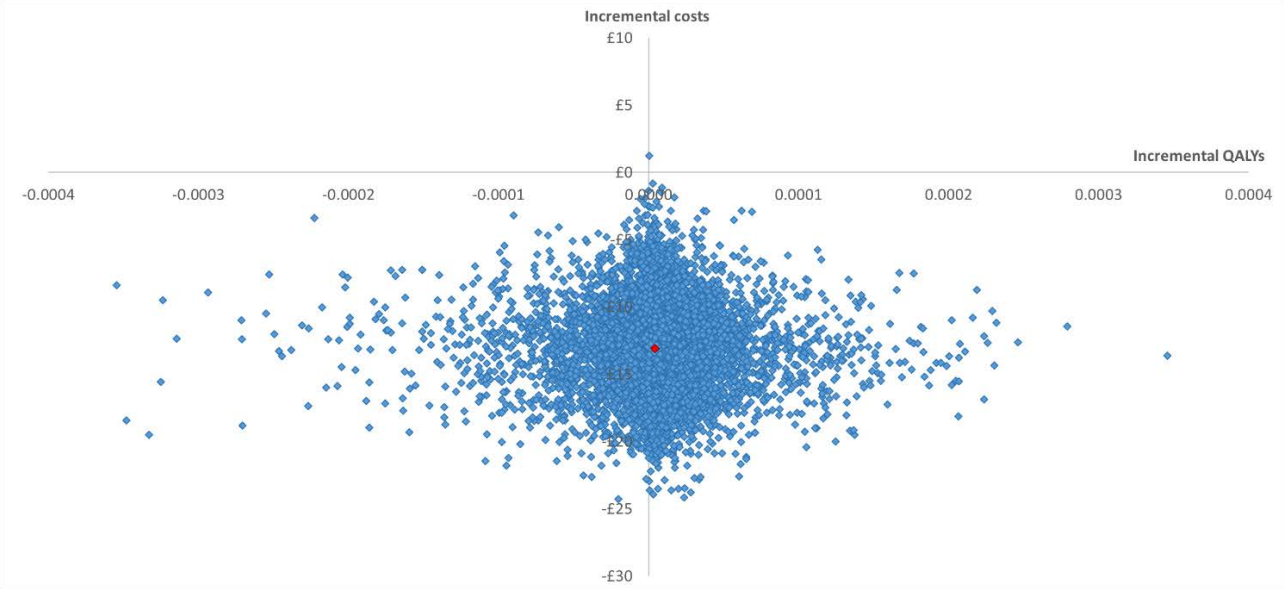


Figure 3. ICER scatterplot for pharmacy assessment using RADT in comparison to GP assessment in child population

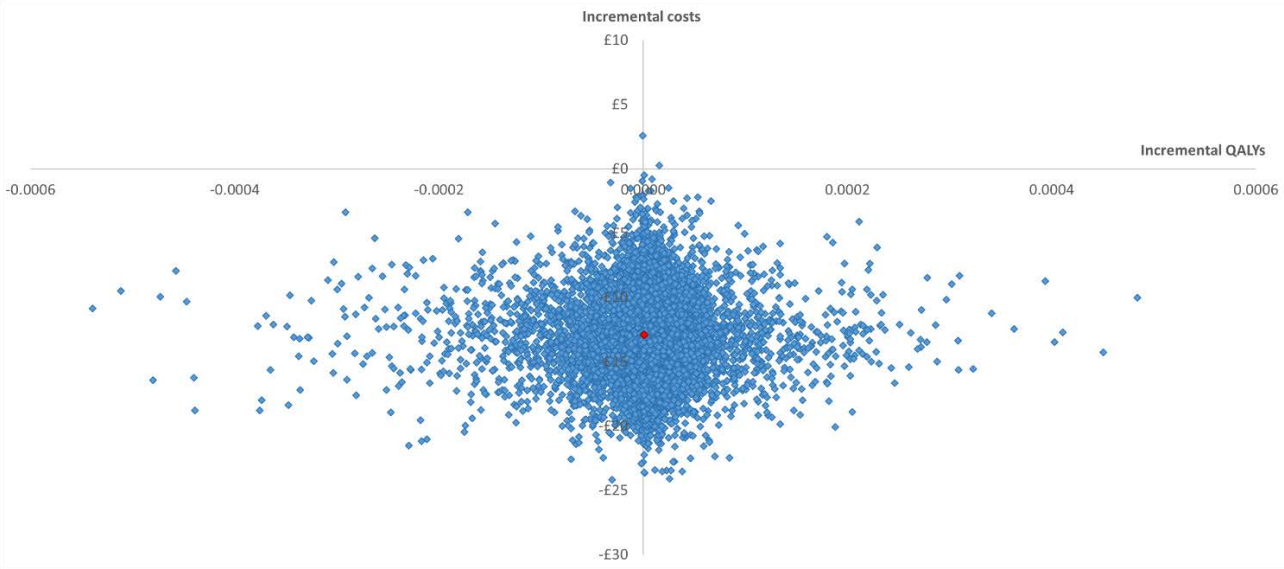


Figure 4 and Figure 5 show the CEACs for the adult and child population, respectively. In both populations, it can be seen that the probability of the pharmacy assessment strategy with RADT being cost effective is high and that it remains high across all cost-effectiveness thresholds. At a threshold of £20,000 per QALY, the pharmacy assessment strategy with RADT was found to have a 100% probability of being cost effective in both adults and children.

To explore the uncertainty around training costs, the probabilistic sensitivity analysis was re-run with training costs incorporated. In this scenario, at a threshold of £20,000 per QALY, the pharmacy assessment strategy with RADT was found to have a 81% and 80% probability of being cost-effective in adults and children, respectively.

Figure 4. CEACs for pharmacy assessment using RADT in comparison to GP assessment in adult population

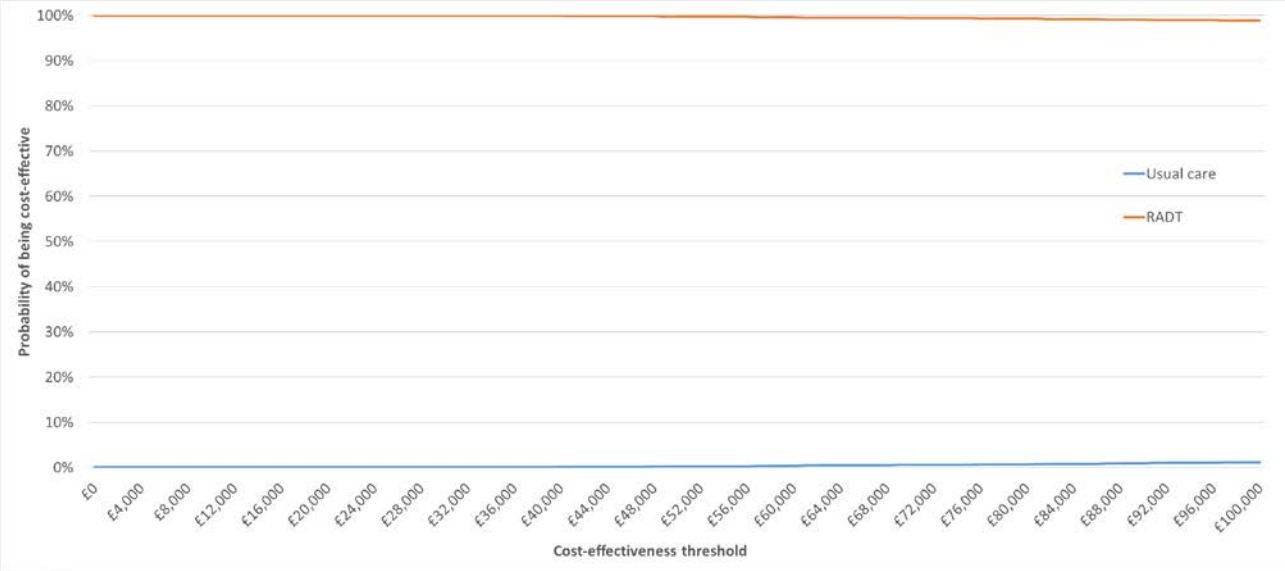


Figure 5. CEACs for pharmacy assessment using RADT in comparison to GP assessment in child population