NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

DIAGNOSTICS ASSESSMENT PROGRAMME

Diagnostics consultation document

Rapid tests for group A streptococcal infections in people with a sore throat

The National Institute for Health and Care Excellence (NICE) is producing guidance on using the rapid tests for detecting group A streptococcal (strep A) infections in people with a sore throat in the NHS in England. The diagnostics advisory committee has considered the evidence and the views of clinical and patient experts.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence (the diagnostics assessment report and the corresponding erratum and addendum).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound, and a suitable basis for guidance to the NHS?

Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the recommendations may need changing to meet these aims. In particular, please tell us if the recommendations:

- could have a different effect on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology

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- could have any adverse effect on people with a particular disability or disabilities.

Please provide any relevant information or data you have about such effects and how they could be avoided or reduced.

Note that this document is not NICE's final guidance on the use of rapid tests for detecting strep A infections in people with a sore throat. The recommendations in section 1 may change after consultation.

After consultation, the committee will meet again to consider the evidence, this document and comments from the consultation. After considering the comments, the committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the diagnostics assessment programme manual.

Key dates:

Closing date for comments: 7 August 2019

Second diagnostics advisory committee meeting: 20 August 2019

1 Recommendations

1.1 Rapid tests for group A streptococcal infections in people with a sore throat are not recommended because their effect on antimicrobial prescribing and patient outcomes is likely to be limited. Therefore, they are unlikely to be a cost-effective use of NHS resources.

Why the committee made these recommendations

Unnecessary use of antibiotics can contribute to antimicrobial resistance, which is a public health concern. NICE's guideline on antimicrobial prescribing for acute sore throat aims to limit antibiotic use and reduce antimicrobial resistance. It advises that sore throat is self-limiting, and so in people who are otherwise healthy, antibiotics are usually not needed, whether the cause is bacterial or viral. So, it is uncertain whether there is a clinical need for rapid testing for strep A infections. Also, the diagnostic accuracy of the tests in routine clinical practice is uncertain and likely to be highly

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variable. There is no evidence to suggest that the rapid tests could reduce the rate of antibiotic prescribing or improve clinical outcomes in people with a sore throat.

The cost-effectiveness estimates for using rapid tests in people with a sore throat are high, so the tests are unlikely to be a cost-effective use of NHS resources. The model does not consider wider public health benefits, such as effects on antimicrobial stewardship or onward transmission rates. However, these are unclear and difficult to measure and are unlikely to change the interpretation of the cost-effectiveness estimates. Therefore, the rapid tests are not recommended for use in the NHS.

2 The diagnostic tests

Clinical need and practice

2.1 Sore throat is usually a self-limiting condition that lasts about a week. It is often caused by a virus but, in a few people, sore throat is caused by bacterial infection, usually group A streptococcus (strep A). Sore throat usually does not need antibiotic treatment, regardless of the cause (viral or bacterial). Most people get better without antibiotics and withholding antibiotics rarely leads to complications.

2.2 Unnecessary use of antibiotics can contribute to antimicrobial resistance. This is microorganisms' ability to withstand antimicrobial treatments such as antibiotics (that is, the antimicrobial treatments become ineffective). Addressing antimicrobial resistance is 1 of the key NHS priorities, described in the NHS 5-year plan for how the UK will contribute to containing and controlling antimicrobial resistance by 2040.

2.3 NICE's guideline on antimicrobial prescribing for acute sore throat was developed to help limit antibiotic use and reduce antimicrobial resistance. The guidance advises that sore throat is self-limiting. Also, it recommends using clinical scoring criteria such as Centor or FeverPAIN to help identify people who are more or most likely to benefit from an antibiotic. However, the guidance does not cover the potential use of rapid tests for strep A to

increase diagnostic confidence of strep A infection and guide antimicrobial prescribing.

2.4 The purpose of this assessment is to evaluate the clinical and cost effectiveness of using rapid tests to detect strep A infection in people with a sore throat aged 5 and over, to help appropriate prescribing of antibiotics. These tests are only intended for people who are identified as more or most likely to benefit from antibiotics by clinical scoring tools such as FeverPAIN or Centor.

The condition

2.5 Sore throat is characterised by inflammation of the pharynx (pharyngitis) or inflammation of the tonsils (tonsillitis). Symptoms of a sore throat include pain in the throat, fever and a headache. Other symptoms could also include nausea, vomiting, abdominal pain, muscle pain, scarlet fever and rashes.

2.6 The most common cause of bacterial infection is strep A, accounting for about 80% of bacterial infections. The remaining 20% of bacterial infections are usually caused by group C and G streptococcus. Strep A throat infections are more common in children than adults and the incidence of strep A infections is highest in winter and spring.

2.7 Most cases of strep A infection resolve without complications. However, rarely complications can develop, such as rheumatic fever (affecting the heart), post-streptococcal glomerulonephritis (affecting the kidneys), or necrotising fasciitis (a severe infection of soft tissue). Strep A can also cause scarlet fever and invasive group A strep infections. Invasive group A strep infections happen when the bacteria move from the throat into other parts of the body. This can lead to sepsis or streptococcal toxic shock syndrome. The risk of invasive group A strep infections is usually very low, but is higher in older people (aged over 75 years), in whom the risk of associated mortality is also higher.

The care pathway

2.8 The care pathway for assessing and treating a sore throat is outlined in NICE's guideline on antimicrobial prescribing for acute sore throat. Healthcare professionals should advise people with a sore throat that it usually gets better without treatment, and explain self-care measures.

2.9 Antibiotic prescribing for sore throat should be guided by the FeverPAIN or Centor clinical risk scoring tools, unless the patient is systemically very unwell, has symptoms and signs of a more serious illness or condition, or is at high risk of complications.

- People with a FeverPAIN score of 0 or 1, or a Centor score of 0, 1 and 2 are unlikely to benefit from an antibiotic. They should be offered advice on self-care without an antibiotic prescription.
- People with a FeverPAIN score of 2 or 3 might benefit from an antibiotic. 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).
- People with a FeverPAIN score of 4 or 5, or a Centor score of 3 or 4 are most likely to benefit from an antibiotic. For these people either an immediate or a back-up antibiotic prescription should be considered. This should take into account the risk of possible complications of untreated strep A and of possible adverse effects of antibiotics.

2.10 The purpose of the rapid tests is to increase diagnostic confidence of a suspected strep A infection and guide antimicrobial prescribing decisions. The tests are for people identified as more or most likely to benefit from antibiotics by clinical scoring tools. They have a faster turnaround time than laboratory culture of throat swabs. This could allow a prescribing decision in the initial consultation (but some tests might need confirmation of negative test results by laboratory culture). This may contribute to improved antimicrobial stewardship. The tests are suitable for all settings

where patients present with an acute sore throat. This includes both primary and secondary care, and community pharmacies.

The interventions

The assessment included 21 rapid tests for strep A, of which 17 tests use immunoassay detection methods (rapid antigen detection tests) and 4 use molecular methods (polymerase chain reaction [PCR] or isothermal nucleic acid amplification).

Rapid antigen detection tests

2.11 Of the rapid antigen detection tests, 16 use lateral flow (immunochromatographic and immunofluorescence) technology and 1 test (QuikRead Go Strep A test) is a turbidimetric immunoassay (see Table 1). Depending on the technology, the results of the lateral flow tests are read by visual inspection or by using a test reader device.

2.12 Several manufacturers recommend that negative rapid antigen detection test results are confirmed by microbiological culture of a throat swab.

Table 1 Summary of rapid antigen detection tests

Product (manufacturer)	Test format	LOD	Time to result[a] (minutes)	Results	Confirmation of negative result?
Clearview exact Strep A cassette (Abbott)	Cassette	5×10^4 organisms/test	5	Qualitative	Yes
Clearview exact Strep A dipstick (Abbott)	Test strip	5×10^4 organisms/test	5	Qualitative	Yes
BD Veritor plus system group A Strep (Beckton 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)[b]	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)[c]	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 bacteria/swab	5	Qualitative	Not known
Sofia Strep A FIA (Quidel)[d]	Cassette	1.86×10^4 to 9.24×10^3 CFU/test	5 to 6	Qualitative	Yes

Abbreviations: CFU/ml, colony forming units per millilitre; LOD, limit of detection.

[a] Read time (does not include sample preparation time).

[b] Needs BD Veritor Plus analyser.

[c] Needs QuikRead go instrument.

[d] Needs Sofia analyser.

Molecular tests

2.13 Of the molecular tests, 2 use isothermal nucleic acid amplification (Alere i Strep A and Alere i Strep A 2 tests) and 2 use PCR (Cobas Strep A assay and Xpert Xpress Strep A; see Table 2).

Table 2 Summary of molecular tests for rapid strep A detection

Product	Analyser	LOD	Time to result (minutes)[a]	Result	Confirmation of negative result?
Alere i Strep A (Abbott)	Alere i instrument	4 to 42 CFU/ml	Less than 8	Qualitative	Yes
Alere i Strep A 2 (Abbott)	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
Abbreviations: CFU/ml, colony forming units per millilitre; LOD, limit of detection.					
[a] Read time (does not include sample preparation time).					

The comparator

2.14 Antibiotic prescribing decisions using clinical judgement and a clinical scoring tool such as FeverPAIN or Centor, outlined in section 2.9.

Reference standard

2.15 The reference standard for assessing the accuracy of the rapid strep A tests is microbiological culture of throat swabs.

2.16 The reference standard is unlikely to be 100% accurate. Its accuracy may depend on the use of culture media and swabbing technique used to collect the sample.

3 Evidence

The diagnostics advisory committee (section 8) considered evidence on rapid tests for strep A in people with a sore throat from several sources. Full details of the evidence are in the committee papers.

Clinical effectiveness

3.1 The external assessment group (EAG) did a systematic review to identify evidence on the clinical effectiveness of rapid tests for detecting strep A infection in people with a sore throat. Evidence on the following outcomes was of interest:

- diagnostic performance
- effect on prescribing behaviours and clinical outcomes
- contribution to antimicrobial stewardship and onward transmission of infection.

3.2 The EAG found 38 studies that met the inclusion criteria:

- 35 studies reported test accuracy data, 12 reported antibiotic prescribing behaviours (9 studies reported both outcomes), and none reported clinical outcomes such as morbidity, mortality, or onward transmission rate.
- 26 studies reported in peer-reviewed journals (full-text articles), 3 in conference abstracts, 4 in Food and Drug Administration (FDA) documents, and 5 in unpublished manufacturers' data.

3.3 Across studies, the prevalence of strep A ranged from 15% to 49%. There were no clear demographic or clinical patterns accounting for this variation, and no identified differences between primary and secondary care settings.

3.4 Populations in most studies did not fit the scope for this assessment. Only 2 studies included people with a Centor score of 3 or more, or FeverPAIN score of 4 or more; the people who would have a rapid test in current

practice. Both studies reported antibiotic prescribing behaviours only. There were 2 test accuracy studies that reported outcomes separately by Centor score. All other studies enrolled people with lower clinical scores than those in the scope, or did not use clinical scores as an inclusion criterion.

3.5 The relevant subgroups in the review included children (aged 5 to 14), adults (aged 15 to 75) and older people (aged over 75). However, age group definitions varied between studies. Only 2 studies met the age criterion for children and 2 studies met the age criterion for adults defined in the topic scope. There were no studies reporting data for the older population (aged over 75).

3.6 The quality of all 26 published accuracy studies was assessed using QUADAS-2 criteria. All studies were considered at high risk of bias in at least 1 domain, and 13 studies were considered at high risk of bias in 2 or more domains. Studies reported in FDA documents or unpublished manufacturer data could not be quality assessed because of the lack of information. The main applicability issue was related to not using clinical scoring tools, described in section 3.4.

3.7 Of studies reporting antibiotic prescribing behaviours, the methodological quality of the 3 randomised controlled trials (RCTs) was fair, as assessed by the Cochrane risk of bias tool. No domains were considered at high risk of bias but 1 to 3 domains per study had unclear risk of bias. Of 9 cohort studies, 3 assessed hypothetical prescribing behaviours according to the prescribing guidelines and were not quality assessed. The remaining 6 cohort studies were assessed using the Joanna Briggs Institute Critical Appraisal Checklist for analytical cross-sectional studies. There was 1 study with unclear risk of bias in 1 domain, and 5 studies were at high risk of bias in 1 or more domains.

Evidence on diagnostic performance of rapid tests for strep A infections

3.8 Only 2 studies reported the diagnostic accuracy of the rapid tests in people who are more (FeverPAIN score of 2 or 3), or most (Centor score of 3 or 4, or a FeverPAIN score of 3 or 4) likely to benefit from antibiotics. Accuracy data from these 2 studies is in Table 3.

Table 3 Diagnostic accuracy of rapid tests in people who are more or most likely to benefit from antibiotics

Citation	Test	Population	Setting	Centor threshold	Sensitivity (95% confidence interval) %	Specificity (95% confidence interval) %
Humair et al. (2006)	Alere TestPack Plus Strep A	Adults with a Centor score of 2 or more	Primary care in Switzerland	Centor 3 or more	95% (89% to 98%)	94% (88% to 98%)
				Centor 2	80% (63% to 92%)	96% (91% to 99%)
Llor et al. (2011)	OSOM Strep A	Adults with a Centor score of 1 or more	Primary care in Spain	Centor 3 or more	92% (76% to 98%)	96% (89% to 99%)
				Centor 1 or 2	85% (55% to 98%)	93% (87% to 96%)

3.9 Most studies included either all patients with acute sore throat, without using the clinical scoring tools, or used these tools at a lower threshold than in UK practice. Across these studies (any population or healthcare setting), accuracy data were available for 18 of 21 tests:

- There were no accuracy data for 3 tests: Strep A Rapid Test Strip (Biopanda), Biosynex Strep A Cassette test, and Bionexia Strep A Plus Cassette test.
- Accuracy estimates for 8 tests (Strep A rapid test cassette [Biopanda], 5 NADAL Strep A tests, Alere i Strep A 2 tests and Xpert Xpress Strep A test) were only available from unpublished manufacturer data or FDA reports.
- Only 5 tests had data from 2 or more published studies (BD Veritor Plus System, GuickRead Go Strep A Kit, Alere i Strep A, OSOM

Strep A Strip, Alere TestPack Plus Cassette). Meta-analysis was possible for these tests.

3.10 Across studies, there was a wide variation in sensitivity (67.9% to 100%), and specificity (73.3% to 100%) of the rapid tests. There was a wide variation in accuracy estimates even for the same test. For example, the sensitivity of the Alere TestPack Plus cassette ranged from 73% (95% confidence interval [CI] 45% to 92%) to 96% (95% CI 91% to 99%). Its specificity ranged from 86% (95% CI 81% to 91%) to 100% (95% CI 96% to 100%) across 10 studies. Data from the manufacturer and FDA submissions consistently provided higher estimates of sensitivity and specificity than peer-reviewed studies.

3.11 Head-to-head comparison of the diagnostic accuracy of different tests was only reported in 4 studies. These studies suggested there is some variation in accuracy between tests. Because of the large degree of inter-study variability, it was not possible to compare the relative accuracy of different tests across different studies.

3.12 There were 3 studies that enrolled both adults and children, with separate accuracy data for each age group, allowing for a within-study comparison. These studies showed no clear trends in the diagnostic accuracy of the rapid tests between different age groups. In addition, there were 7 studies that enrolled adults only and 10 studies that enrolled children only. All other studies enrolled a mixed population of adults and children or did not report the age group.

3.13 No studies compared the diagnostic accuracy of the rapid tests in different healthcare settings. A total of 10 studies were done in primary care and 14 in secondary care; healthcare setting was not reported in the remaining studies. There were no studies done in a pharmacy setting.

3.14 Conflicting results between the rapid tests and microbiological culture of throat swabs were resolved using polymerase chain reaction (PCR) in

4 studies. A large proportion of conflicting results (both false positive and false negative) tested positive with PCR. This suggests that the reference standard used in this assessment is not 100% accurate, and may be under or overestimating the accuracy of rapid tests.

3.15 Rapid test failure rates were generally low, as reported in 5 studies:

- Alere i Strep A: 0% and 2.8% (2 studies).
- Alere TestPack Plus Strep A: 0.3% and 1.3% (2 studies).
- Sofia Strep A FIA: 4.7% (1 study).

The EAG noted that these differences could be because of environmental factors such as staff training rather than issues with the tests.

Evidence on antibiotic prescribing behaviours

3.16 The 3 RCTs reporting on antibiotic prescribing showed a decrease in antibiotic prescribing with the rapid tests:

- In a UK study of adults and children aged 3 years or more with acute sore throat in primary care (Little et al. 2013), the rate of immediate prescribing was 10% (21 of 207 patients) in the control (delayed antibiotic) group, 16% (33 of 211 patients) in the clinical scoring tool (FeverPAIN) group, and 18% (38 of 213 patients) in the FeverPAIN plus rapid strep A (Alere TestPack Plus Strep A) test group. The rate of delayed prescribing was 79%, 41% and 23%, respectively. The rate of immediate or delayed prescriptions was lower with the rapid strep A test compared with the clinical scoring group, but the reported use of antibiotics was comparable between the groups (35% and 37% respectively, compared with 46% in the control group). Data on reported antibiotic use was only available for 80% of enrolled patients so should be interpreted with caution.
- In a Spanish study of adults in primary care (Llor et al. 2011), 44% of people who had the OSOM Strep A test as well as the Centor tool had

an antibiotic prescription, compared with 64% of people in the Centor only group.

- In a Canadian study of adults in primary care (Worrall et al. 2007), antibiotics were prescribed for 58% of patients in the control group (usual care), 55% of people in the sore throat decision rules group (STDR; modified Centor), 27% of people in the rapid test group (Clearview Exact Strep A), and 38% of patients in the STDR plus rapid test group.

3.17 The before-and-after study by Bird et al. (2018) assessed antibiotic prescribing rates before and after introducing the McIsaac clinical scoring tool and a rapid strep A test (Bionexia Strep A) in a UK paediatric emergency department. After introducing this strategy, antibiotic prescribing rates decreased from 79% at baseline (October to November 2014) to 24% in the first year (August to November 2015) and 28% in the second year (September to November 2016). However, random annual fluctuations and seasonality could have confounded the results.

Cost effectiveness

Systematic review of cost-effectiveness evidence

3.18 The EAG found 3 cost-effectiveness studies for the rapid strep A tests. However, 2 of these studies only reported cost per person and did not report enough information for full data extraction and critical appraisal of the models. The economic evaluation by Little et al. (2014) was considered high quality according to the consolidated health-economic evaluation reporting standards checklist.

3.19 Little et al. (2014) did an economic analysis alongside an RCT (reported in Little et al. 2013). The RCT was based in UK primary care clinics, and included both adults and children aged 3 years or more with acute sore throat. Patients were randomised to targeted antibiotic use according to:

- delayed prescribing

- FeverPAIN clinical scoring tool
- rapid strep A test (Alere TestPack Plus Strep A; used with FeverPAIN tool).

3.20 The economic analysis was from the NHS perspective and the time horizon was short (14 and 28 days), so long-term effects were not captured. The analysis included a cost-effectiveness analysis (cost per change in symptom severity) and a cost-utility analysis (cost per quality-adjusted life year [QALY]). QALYs were calculated using the mean EQ-5D scores from the 14-day diary records, and were adjusted for differences in baseline characteristics.

3.21 In the cost-utility analysis, the delayed prescribing group was dominated by the FeverPAIN group for both time frames. The incremental cost-effectiveness ratio (ICER) for the rapid test compared with FeverPAIN was £74,286 per QALY gained for the 14-day time frame and £24,528 per QALY gained for the 28-day time frame. At £30,000 per QALY gained, the probabilities of each strategy being cost effective were 28%, 38% and 35% for delayed prescribing, FeverPAIN clinical score and the rapid test, respectively, for the 28-day time frame.

Economic analysis

3.22 The study by Little et al. (2014) included only 1 of the 21 rapid tests relevant to this assessment. Also, it only considered a primary care setting, and did not assess adults and children separately. Therefore, the EAG constructed 4 de novo economic models to assess the cost effectiveness of all relevant rapid tests in people with acute sore throat:

- adults in primary care
- adults in secondary care
- children in primary care
- children in secondary care.

3.23 Economic assessment for older people or for the pharmacy setting was not possible because of the lack of evidence.

Model structure

3.24 A decision tree was created to simulate the potential care pathways associated with using rapid tests and clinical scoring tools, compared with using clinical scoring tools only (current practice), in people with acute sore throat.

3.25 The economic analysis was from the UK NHS and personal social services perspective. A 1-year time horizon was used to see the effect of rare but serious complications of strep A infection on costs and outcomes (a shorter time frame of 14 days was used in sensitivity analyses). No discounting was applied to costs and benefits because of the short time horizon.

Model inputs

3.26 A prevalence of 22.6% was used for adults, based on the study by Little et al. (2014). The study enrolled patients aged 3 years or older in UK primary care. For children, an estimate of 30.2% was assumed, based on the median of 3 non-UK studies of children in primary care.

3.27 The accuracy estimates for the Centor clinical scoring tool were taken from the meta-analysis by Aalbers et al. (2011). It focused on Centor to predict strep A pharyngitis in adults (15 years or older) in primary care. At the Centor threshold of 3 or more, the sensitivity was estimated as 49% (95% CI 38% to 60%), and specificity as 82% (95% CI 72% to 88%). There were no studies reporting the accuracy of FeverPAIN clinical scoring tool so it could not be modelled.

3.28 The accuracy estimates for the rapid strep A tests were from the systematic literature review done by the EAG. The sensitivity of the rapid tests ranged from 68% to 100%, and the specificity from 79% to 100% (see Table 4 and Table 5). The estimates of accuracy based on

unpublished manufacturers' data or FDA reports were consistently higher than the estimates from the published peer-reviewed studies. Therefore, the economic models based solely on manufacturers' test accuracy data should be interpreted with caution.

Table 4 Test accuracy data used in the economic model for adults in primary care

Test name (manufacturer)	Sensitivity (95% confidence interval), %	Specificity (95% confidence interval), %	Data source
Clearview Exact Strep A cassette (Abbott)	68 (54 to 80)	95 (92 to 97)	1 abstract
Clearview Exact Strep A dipstick (Abbott)	68 (54 to 80)	95 (92 to 97)	1 abstract
BD Veritor Plus system group A Strep Assay cassette (Beckton Dickinson)	78 (67 to 87)	90 (86 to 93)	2 published studies
Strep A rapid test cassette (Biopanda Reagents)	95 (90 to 98)	98 (96 to 99)	1 unpublished study[1]
Strep A rapid test dipstick (Biopanda Reagents)	95 (90 to 98)	98 (96 to 99)	No data[2]
NADAL Strep A test strip (nal von minden GmbH)	98 (92 to 100)	98 (94 to 99)	1 unpublished study[1]
NADAL Strep A cassette (nal von minden GmbH)	98 (92 to 100)	98 (94 to 99)	1 unpublished study[1]
NADAL Strep A plus cassette (nal von minden GmbH)	98 (92 to 100)	98 (94 to 99)	1 unpublished study[1]
NADAL Strep A plus test strip (nal von minden GmbH)	98 (92 to 100)	98 (94 to 99)	1 unpublished study[1]
NADAL Strep A scan test cassette (nal von minden GmbH)	98 (92 to 100)	98 (94 to 99)	1 unpublished study[1]
OSOM Strep A test strip (Sekisui Diagnostics)	92 (76 to 98)	96 (89 to 99)	3 published studies
QuikRead Go Strep A test kit (Orion Diagnostica)	100 (85 to 100)	79 (60 to 92)	1 published study
Alere TestPack Plus Strep A cassette (Abbott)	95 (89 to 98)	94 (88 to 98)	1 published study
Bionexia Strep A plus - cassette (Biomerieux)			No data
Bionexia Strep A dipstick – test strip (Biomerieux)	85 (74 to 92)	91 (84 to 95)	1 abstract
Biosynex Strep A cassette (Biosynex)			No data
Sofia Strep A FIA (Quidel)	85 (81 to 89)	95 (93 to 97)	1 published study
ALERE i Strep A (Abbott)[4]	95 (74 to 100)	97 (92 to 99)	1 published study
ALERE i Strep A 2 (Abbott)[5]	98 (96 to 100)	93 (91 to 95)	1 FDA Report
Cobas Strep A assay on Liat system (Roche Diagnostics)	98 (93 to 100)	93 (90 to 96)	1 published study
Xpert Xpress Strep A (Cepheid)	100 (99 to 100)	94 (92 to 96)	1 unpublished study[1] and 1 FDA report

[1] Unpublished manufacturer data.

[2] Assumed the same accuracy as the cassette version of the test.

Table 5 Test accuracy data used in the economic model for children in primary care

Test name (manufacturer)	Sensitivity (95% confidence interval), %	Specificity (95% confidence interval), %	Data source
Clearview Exact Strep A cassette (Abbott)	68 (54 to 80)	95 (92 to 97)	1 abstract
Clearview Exact Strep A dipstick (Abbott)	68 (54 to 80)	95 (92 to 97)	1 abstract
BD Veritor Plus system group A Strep Assay cassette (Beckton Dickinson)	76 (61 to 88)	94 (89 to 97)	1 published study
Strep A rapid test cassette (Biopanda Reagents)	95 (90 to 98)	98 (96 to 99)	1 unpublished study[1]
Strep A rapid test dipstick (Biopanda Reagents)	95 (90 to 98)	98 (96 to 99)	No data[2]
NADAL Strep A test strip (nal von minden GmbH)	98 (92 to 100)	98 (94 to 99)	1 unpublished study[1]
NADAL Strep A cassette (nal von minden GmbH)	98 (92 to 100)	98 (94 to 99)	1 unpublished study[1]
NADAL Strep A plus cassette (nal von minden GmbH)	98 (92 to 100)	98 (94 to 99)	1 unpublished study[1]
NADAL Strep A plus test strip (nal von minden GmbH)	98 (92 to 100)	98 (94 to 99)	1 unpublished study[1]
NADAL Strep A scan test cassette (nal von minden GmbH)	98 (92 to 100)	98 (94 to 99)	1 unpublished study[1]
OSOM Strep A test strip (Sekisui Diagnostics)	94 (89 to 98)	95 (91 to 98)	1 published study
QuikRead Go Strep A test kit (Orion Diagnostica)	80 (56 to 94)	91 (72 to 99)	1 published study
Alere TestPack Plus Strep A cassette (Abbott)	86 (79 to 91)	99 (97 to 100)	1 published study
Bionexia Strep A plus - cassette (Biomerieux)			No data
Bionexia Strep A dipstick – test strip (Biomerieux)	85 (74 to 92)	91 (84 to 95)	1 abstract
Biosynex Strep A cassette (Biosynex)			No data
Sofia Strep A FIA (Quidel)	85 (81 to 89)	95 (93 to 97)	1 published study
ALERE i Strep A (Abbott)[4]	98 (95 to 100)	96 (89 to 100)	3 published studies
ALERE i Strep A 2 (Abbott)[5]	98 (96 to 100)	93 (91 to 95)	1 FDA Report
Cobas Strep A assay on Liat system (Roche Diagnostics)	98 (93 to 100)	93 (90 to 96)	1 published study
Xpert Xpress Strep A (Cepheid)	100 (99 to 100)	94 (92 to 96)	1 unpublished study[1] and 1 FDA report

[1] Unpublished manufacturer data.

[2] Assumed the same accuracy as the cassette version of the test.

3.29 Treatment-related probabilities and complication rates used in the model are in Table 6.

Table 6 Treatment-related probabilities and complication rates

Description of parameter	Mean	Standard error[a]
GP practice		
Proportion attending repeat GP consultation following group A streptococcal infection	0.142	0.007
Antibiotic prescribing probabilities		
Probability immediate prescription if Centor score is 3 or higher, or positive test	1.00	–
Probability delayed prescription if Centor score is below 3 (current practice arm)	0.51	0.026
Probability delayed prescription if negative test (intervention arm)	0.267	0.014
Probability antibiotics used given delayed prescription	0.46	0.023
Probability antibiotics used given immediate prescription	1.0	–
Complication rates following group A streptococcal infection		
Probability of complication if antibiotics given (treated infection)	0.013	0.0005
Probability of complications if no antibiotics given (untreated infection)	0.015	0.0007
Proportion of complications that are non-suppurative (that is, rheumatic fever)	0.0001	–
Adverse effects of penicillin		
Penicillin-induced rash	0.02	–
Penicillin-induced anaphylaxis	0.0001	–
[a] Standard error derived assuming upper and lower bound equal to 10% of the mean estimate.		

3.30 The health impact of each pathway was expressed in QALYs. These were calculated by subtracting the disutilities associated with treated and untreated strep A infection, complications of strep A infection and adverse effects of penicillin (see Table 7) over 1 year from the mean baseline utilities. The mean baseline utilities in the model were based on a general UK population: 0.863 for adults and 0.94 for people under 25 years (Kind et al. 1998). The latter is the closest age group to children and therefore was used as a baseline utility in the paediatric models. Mean disutilities were based on published literature (Neuner et al. 2003; reported as quality-adjusted life days), by converting quality-adjusted life days to utility decrements.

Table 7 Utility decrements associated with strep A infection and complications

	Mean quality-adjusted life days lost	Mean utility decrement used in the model[1]	Standard error[2]
Utility decrement associated with strep A infections			
Untreated infection	0.25	0.000685	0.00005
Treated infection	0.15	0.000411	0.00003
Utility decrement associated with strep A infection complications			
Peritonsillar abscess	5	0.0137	0.0007
Rheumatic fever	76.5	0.209	0.011
Utility decrement associated with adverse effects of penicillin			
Penicillin-induced anaphylaxis	9	0.025	0.0013
Penicillin-induced rash	0.65	0.0017	0.0001

[1] Calculated by converting quality-adjusted life days to utilities.

[2] Standard error derived assuming upper and lower bound equal to 10% of the mean estimate.

3.31 Costs were calculated using 2017/18 prices. The total costs for each strategy (current practice and rapid tests) include GP consultations, antimicrobial therapy, and managing strep A infection-related complications and adverse effects of penicillin (see Table 8).

Table 8 Treatment costs (2017/18 price year)

Treatment costs	Mean	Standard error	Source
Antibiotics (phenoxymethylpenicillin 250 mg, 28-tablet pack)	£0.91	£0.046	BNF 72 (2017)
Pain relief (paracetamol 500 mg, 32-tablet pack)	£0.74	£0.037	BNF 72 (2017)
GP consultation (9.22 minutes)	£37.4	£1.91	Personal social services research unit costs 2017
Treatment costs, penicillin-induced rash (switch to erythromycin 500 mg)	£10.00	£0.51	BNF 72 (2017)
Treatment costs, penicillin-induced anaphylaxis[a]	£1,744.64	£89.01	Derived from Hex et al. 2017
Treatment costs, abscess (tonsillectomy)	£1,571.28	£80	2017 NHS reference costs
Treatment costs, acute rheumatic fever	£1,772.44	£90.43	2017 NHS reference costs

[a] Based on expert opinion, costs of penicillin-induced anaphylaxis were assumed to be equivalent to the initial cost of treating sepsis, as derived from Hex et al. 2017.

3.32 Cost data were available for 14 of the 21 rapid tests in this assessment (see Table 9). The cost of testing also accounted for:

- Additional GP time needed to process the test, ranging from 5 to 12 minutes depending on the test.
- Apportioned cost of analyser or test cassette reader (that is, cost of analyser or reader adjusted for its average life span and the average number of samples analysed).
- Cost of the microbiological culture of throat swabs (£8 per sample) to confirm negative test results, when needed.

Table 9 Test costs

Test ID	Test name	Cost	Test process time	Throat culture[1]
1	Clearview Exact Strep A cassette (Abbott)	£2.72	5	Yes
2	Clearview Exact Strep A dipstick (Abbott)	£1.92	5	Yes
3	BD Veritor Plus system group A Strep Assay cassette (Beckton Dickinson)	Not known		
4	Strep A rapid test cassette (Biopanda Reagents)	£0.82	5	Yes
5	Strep A rapid test dipstick (Biopanda Reagents)	£0.64	5	Yes
6	NADAL Strep A test strip (nal von minden GmbH)	£1.20	5	No
7	NADAL Strep A cassette (nal von minden GmbH)	£1.40	5	No
8	NADAL Strep A plus cassette (nal von minden GmbH)	£1.50	5	No
9	NADAL Strep A plus test strip (nal von minden GmbH)	£1.30	5	No
10	NADAL Strep A scan test cassette (nal von minden GmbH)	£1.96	5	No
11	OSOM Strep A test strip (Sekisui Diagnostics)	Not known		
12	QuikRead Go Strep A test kit (Orion Diagnostica)	£4.34	5	Assumed yes[2]
13	Alere TestPack Plus Strep A cassette (Abbott)	£2.70	5	Assumed no[3]
14	Bionexia Strep A plus cassette (Biomerieux)	Not known		
15	Bionexia Strep A dipstick (Biomerieux)	Not known		
16	Biosynex Strep A cassette (Biosynex)	Not known		
17	Sofia Strep A FIA (Quidel)	Not known		
18	ALERE i Strep A (Abbott)[4]	Not known		
19	ALERE i Strep A 2 (Abbott)[5]	£22.94	5	No
20	Cobas Strep A assay on Liat system (Roche Diagnostics)	£64.63	6	No
21	Xpert Xpress Strep A (Cepheid)	£4.25	12	Assumed yes[2]

[1] Confirmatory microbiological culture of throat swabs for negative results of rapid tests is needed, as specified in the information for use documents.

[2] Not known whether confirmatory test is needed, assumed that it is.

[3] Confirmatory testing warranted only if symptoms persist.

[4] This test has been replaced by ID NOW Strep A 2 test.

[5] Rebranded to ID NOW Strep A 2.

Base-case assumptions

3.33 The model was created for adults in primary care and then adapted for children and secondary care:

- In current practice, antibiotic prescribing (immediate, delayed or no prescribing) is based on the Centor score.

- In the rapid test cohort, people with Centor score of 3 or more are offered the rapid test. Antibiotic prescribing decisions (immediate, delayed or no prescribing) are based on the test results.
- Of people offered delayed prescription, 46% use their prescription.
- There are 1.3% to 1.5% of people with strep A infection who develop complications, depending whether or not they had antibiotics.
- People who take antibiotics are at risk of penicillin-related adverse effects (2% have penicillin-induced rash and 0.01% have penicillin-induced anaphylaxis).
- When recommended by manufacturers, negative results for rapid strep A tests were followed up with a microbiological culture or throat swabs to confirm the results.

3.34 The model for adults in secondary care was adapted from the adult primary care model by excluding the cost of the initial GP consultation. Also, it was assumed that all rapid tests could be done in the standard time allocated for secondary care appointments. The accuracy of rapid tests was assumed to be the same as in primary care (because of the lack of specific data in secondary care) except for 3 tests for which the sensitivity estimates from secondary care were available: OSOM Strep A test (94%), QuikRead Go Strep A test kit (87%) and the Alere TestPack Plus Strep A (90%). All other assumptions and inputs are the same as in the primary care model.

3.35 The model for children in primary care was adapted from the corresponding adult model by adjusting the prevalence of strep A infections from 22.6% to 30.2%, and using the accuracy estimates from studies in children whenever these were available (see Table 5). The costs of treating peritonsillar abscess and related complications in children were assumed to be lower than in adults (£1,420.50 compared with £1,571.28), based on the NHS reference costs for both age groups.

3.36 The test accuracy data for children in secondary care were assumed to be the same as in primary care (because of the lack of specific data in secondary care), except for 3 tests for which the accuracy estimates from secondary care were available: OSOM Strep A test (test strip; sensitivity: 94%, specificity: 97%), QuikRead Go Strep A test kit (sensitivity: 87%, specificity: 78%), and Alere TestPack Plus Strep A (sensitivity: 77%, specificity: 97%).

Economic analysis results

Base-case results

3.37 In the base-case adult primary care model, current practice dominated (that is, current practice was more effective and cheaper than the testing strategy) 2 tests: the Clearview Exact Strep A cassette and dipstick. The ICERs for the remaining 12 tests ranged from £1,353,677 to £6,059,081 per QALY gained, compared with current practice (see Table 10). Costs and QALYs were multiplied by 1,000 because of the very small incremental QALYs.

3.38 The results of the base-case adult secondary care were aligned with the adult primary care model, but the ICERs were much lower (see Table 11).

3.39 In both models for children, current practice dominated 4 tests: the Clearview Exact Strep A cassette and dipstick, QuikRead Go Strep A test kit and Alere TestPack Plus Strep A cassette (see Table 11). In the children's primary care model, the ICERs for the remaining 10 tests ranged from £1,762,306 to £7,893,857 per QALY gained, compared with current practice. In the children's secondary care model, the ICERs for the remaining 10 tests ranged from £65,122 to £5,723,279 per QALY gained, compared with current practice.

Table 10 Base-case cost-effectiveness results: adult primary care model

Test	Mean costs[1]	Mean quality-adjusted life years[1]	Incremental costs[1]	Incremental quality-adjusted life years[1]	Incremental cost-effectiveness ratio versus current practice
Current practice[2]	£49,147	859.82458955	£0	0.0000000	–
Clearview Exact Strep A cassette (Abbott)[3]	£56,180	859.82063008	£7,033	−0.0039595	Dominated
Clearview Exact Strep A dipstick (Abbott)[3]	£55,980	859.82063008	£6,833	−0.0039595	Dominated
Strep A rapid test cassette (Biopanda Reagents)[4]	£55,442	859.82769587	£6,295	0.0031063	£2,026,496
Strep A rapid test dipstick (Biopanda Reagents)[4,5]	£55,397	859.82769587	£6,250	0.0031063	£2,012,006
NADAL Strep A test strip (nal von minden GmbH)[4]	£54,394	859.82846603	£5,248	0.0038765	£1,353,677
NADAL Strep A cassette (nal von minden GmbH)[4]	£54,444	859.82846603	£5,298	0.0038765	£1,366,577
NADAL Strep A plus cassette (nal von minden GmbH)[4]	£54,469	859.82846603	£5,323	0.0038765	£1,373,029
NADAL Strep A plus test strip (nal von minden GmbH)[4]	£54,419	859.82846603	£5,273	0.0038765	£1,360,126
NADAL Strep A scan test cassette (nal von minden GmbH)[4]	£54,584	859.82846603	£5,438	0.0038765	£1,402,700
QuikRead Go Strep A test kit (Orion Diagnostica)	£56,083	859.82810269	£6,936	0.0035131	£1,974,319
Alere TestPack Plus Strep A cassette (Abbott)	£54,781	859.82751669	£5,634	0.0029271	£1,924,717
ALERE i Strep A 2 (Abbott)[4,6]	£59,837	862.82824206	£10,691	0.00365250	£2,926,915
Cobas Strep A assay on Liat system (Roche Diagnostics)	£71,277	859.82824206	£22,131	0.0036525	£6,059,081
Xpert Xpress Strep A (Cepheid)[4]	£63,323	859.82854357	£14,177	0.0039540	£3,585,436

Notes: Cost-effectiveness analyses were not done for 7 tests that had no cost data (Bionexia Strep A plus cassette and Biosynex Strep A cassette had neither costs nor accuracy data available).

[1] Per 1,000 individuals.

[2] Clinical scoring based on Centor 3 or higher plus clinical assessment.

[3] Based on the accuracy data presented in a conference abstract only.

[4] Based on the accuracy data from the FDA or manufacturer's data.

[5] Assumed equal accuracy to the cassette version of this test.

[6] Rebranded to ID NOW Strep A 2.

Table 11 Base-case cost-effectiveness results: other models

Test	Incremental cost-effectiveness ratio versus current practice		
	Adults secondary care	Children primary care	Children secondary care
Current practice[2]	–	-	–
Clearview Exact Strep A cassette (Abbott)[3]	Dominated	Dominated	Dominated
Clearview Exact Strep A dipstick (Abbott)[3]	Dominated	Dominated	Dominated
Strep A rapid test cassette (Biopanda Reagents)[4]	£392,342	£2,992,743	£517,066
Strep A rapid test dipstick (Biopanda Reagents)[4,5]	£377,852	£2,970,792	£495,115
NADAL Strep A test strip (nal von minden GmbH)[4]	£44,184	£1,762,306	£65,122
NADAL Strep A cassette (nal von minden GmbH)[4]	£57,085	£1,779,026	£81,845
NADAL Strep A plus cassette (nal von minden GmbH)[4]	£63,537	£1,787,386	£90,205
NADAL Strep A plus test strip (nal von minden GmbH)[4]	£50,636	£1,770,666	£73,482
NADAL Strep A scan test cassette (nal von minden GmbH)[4]	£93,211	£1,825,846	£128,662
QuikRead Go Strep A test kit (Orion Diagnostica)	£12,700,432	Dominated	Dominated
Alere TestPack Plus Strep A cassette (Abbott)	£335,358	Dominated	Dominated
ALERE i Strep A 2 (Abbott)[4,6]	£1,537,126	£3,817,336	£2,008,522
Cobas Strep A assay on Liat system (Roche Diagnostics)	£4,391,332	£7,893,857	£5,723,279
Xpert Xpress Strep A (Cepheid)[4]	£504,287	£4,396,205	£574,900

Notes: Cost-effectiveness analyses were not done for 7 tests that had no cost data (Bionexia Strep A plus cassette and Biosynex Strep A cassette had neither costs nor accuracy data available).

[1] Per 1,000 individuals.

[2] Clinical scoring based on Centor 3 or higher plus clinical assessment.

[3] Based on the accuracy data presented in a conference abstract only.

[4] Based on the accuracy data from the FDA or manufacturer's data.

[5] Assumed equal accuracy to the cassette version of this test.

[6] Rebranded to ID NOW Strep A 2.

Probabilistic sensitivity analysis

3.40 The results of the probabilistic sensitivity analysis mirrored the results of the deterministic base-case analysis in all models.

3.41 The probability of a rapid test being cost effective was 0 in all 4 models, regardless of the rapid test used.

Deterministic sensitivity analyses

3.42 A range of scenario analyses was done. For the adult primary care model, none produced ICERs that were around or below £30,000 per QALY gained, compared with current practice.

3.43 For the adult secondary care model, changing the rate of penicillin-induced anaphylaxis from 0.01% (Neuner et al. 2003) to 0.64% (Van Howe and Kusnier 2006), resulted in 6 rapid tests dominating current practice (that is, testing was cheaper and more effective than current practice). These were the 5 NADAL tests and Alere TestPack Plus Strep A. The ICERs for 4 tests (2 Clearview Exact Strep A tests and 2 Strep A rapid tests from Biopanda) decreased to around or below £30,000 per QALY gained, compared with current practice.

3.44 In addition, for the adult secondary care model, the ICERs for the 5 NADAL tests decreased to around or below £30,000 per QALY gained, compared with current practice, for the following assumptions:

- changing the Centor threshold for starting antibiotics and testing to 2 or more (ICERs: £30,230 to £69,690 per QALY gained)
- changing the Centor threshold for starting antibiotics and testing to 1 or more (ICERs: £22,220 to £56,190 per QALY gained)
- lowering the prevalence of strep A infection to 10% (ICERs: £20,628 to £53,506 per QALY gained)
- doubling the rate of penicillin-related rash to 4% (ICERs: £8,913 to £32,557 per QALY gained)

- doubling the utility decrement of penicillin-induced rash (ICERs: £21,309 to £44,953 per QALY gained).

3.45 For the children's primary care model, no scenario analyses produced ICERs that were around or below £30,000 per QALY gained.

3.46 The scenario analyses for the children's secondary care model largely mirrored scenario analyses for the adult secondary care model, except that changing Centor threshold for starting antibiotics and testing to a score of 2 or more had no major effect on the ICERs.

3.47 In addition, several analyses favoured testing strategies, and all or some of the tests dominated by current practice in base-case analyses were no longer dominated. However, the ICERs were around or above £100,000 per QALY gained:

- doubling the complication rate of treated strep A infection to 2.6%
- halving the complication rate of untreated strep A infection to 0.75% (children's primary care model only)
- halving the utility decrement of untreated strep A infection
- doubling the utility decrement of treated strep A infection
- changing the accuracy estimates to the lower confidence limits for both the rapid test and Centor clinical scoring tool (children's primary care model only).

3.48 Several scenario analyses favoured current practice. In all 4 models, doubling the utility decrement associated with untreated strep A infection resulted in an additional 2 to 4 tests being dominated by current practice, compared with base-case results. These tests were the Strep A rapid test cassette and the test strip from Biopanda (all models), the Alere TestPack Plus Strep A cassette (adult primary and secondary care models) and the QuikRead Go Strep A test kit (adult secondary care model). In the adult secondary care model, the following assumptions also resulted in additional tests being dominated by current practice:

- increasing the prevalence rate to 35.9%
- halving the complication rate of treated strep A infection to 0.65%
- doubling the complication rate of untreated strep A infection to 3%
- halving the rate of penicillin-related rash to 1%
- halving the utility decrement of treated strep A infection
- halving the utility decrement of penicillin-induced rash
- doubling the utility decrement of an abscess.

4 Committee discussion

Clinical need and practice

Antimicrobial resistance is a growing public health concern

4.1 A clinical expert explained concerns about the global increase in bacteria developing resistance to antibiotics (antimicrobial resistance). Data from the UK's 5-year action plan for antimicrobial resistance 2019 to 2024 estimate that 700,000 people die every year globally because of infections caused by resistant strains of bacteria and this number will increase if no action is taken. The report notes that no new classes of antibiotics have been developed since the 1980s. Tackling antimicrobial resistance has been 1 of the key UK public health priorities for several years, and the use of antibiotics is gradually reducing. From 2014 to 2017, antibiotic use decreased by 7.3%, from 23.4 to 21.7 defined daily doses per 1,000 inhabitants per day. A key aim of the UK's 5-year action plan for antimicrobial resistance is to implement diagnostic tests that can guide antimicrobial prescribing decisions. The committee noted that rapid tests for strep A have been promoted for this purpose.

Sore throat is usually a self-limiting condition and clinical need for the rapid tests is unclear

4.2 A clinical expert explained that sore throat is a common condition that is usually self-limiting, that is, it usually resolves without any antibiotic treatment. Usually a sore throat is caused by a virus and so treatment with

antibiotics is not needed. The committee was aware of NICE's guideline on antimicrobial prescribing for acute sore throat. This highlights that treatment with antibiotics only reduces symptom duration by around 16 hours. However, the committee noted that this guideline covers all bacterial infections of the throat, and it was not clear what the treatment effect of antibiotics would be in people with a confirmed strep A infection. Antibiotics could reduce the risk of some complications of strep A, but these are usually either very rare or not serious. The committee heard that antibiotics are often prescribed because of the perceived clinical need or patient and carers' expectations to have treatment. Clinical experts explained that NICE's guideline on antimicrobial prescribing for acute sore throat focuses on measures of self-care and advises that antibiotics should only be considered for people who are most likely to benefit from them. Delayed prescribing is an option for most people who need antibiotics; that is, when antibiotics are only dispensed if symptoms do not improve within a few days of the person visiting their GP. Full implementation of this guideline is anticipated to reduce the use of antibiotics in people with a sore throat. The committee concluded that in people who are otherwise healthy, antibiotics are usually not needed for a sore throat, therefore the clinical need for rapid testing for strep A infections is unclear.

People with a sore throat may have different testing needs and preferences

4.3 A patient expert explained about the needs of patients and carers when they are seeking medical advice on a sore throat, and making a decision about whether to have antibiotics or whether to self-care. Patients would value information on what the results of the rapid strep A tests mean, how reliable they are, what the test involves and whether this information influences a treatment decision. The patient expert noted that it could be more difficult to explain the test procedure or take a throat swab in younger children and in people with cognitive impairment or learning difficulties. Therefore this could be challenging to do routinely in a standard appointment. They noted that some people with sore throat may

appreciate point-of-care testing and almost immediate results, whereas others may prefer the samples being sent for laboratory processing because this may be seen as more reliable. The committee concluded that patients and carers seeking advice for sore throat may have different testing needs and preferences, and treatment expectations.

Clinical effectiveness

Most accuracy studies are not applicable to NHS practice

4.4 The committee discussed the available data on the diagnostic accuracy of the rapid tests for strep A in people with a sore throat. It noted that although 26 accuracy studies were identified by the external assessment group (EAG), most included a broad population and only 2 reported data separately for people with a high clinical score (Centor score of 3 or more). The rapid tests for strep A are most likely to be useful for people with a high clinical score. The committee noted that the prevalence of strep A is higher in people with high clinical scores than in people with low clinical scores or in an unselected population of people with a sore throat. Therefore, it concluded that studies in unselected populations or populations with lower clinical scores may not be applicable to NHS practice.

The accuracy of the rapid tests in routine clinical practice is uncertain and likely to be very variable

4.5 The committee discussed the accuracy data available for each of the tests. It noted that no data were available for 3 of the tests (Strep A Rapid Test Strip from Biopanda, Biosynex Strep A Cassette test, and Bionexia Strep A Plus Cassette test). The EAG highlighted the high level of uncertainty in the estimates of rapid test accuracy because of the limited evidence available and the high variability between the studies. The committee noted that some tests only had accuracy data from studies done under ideal conditions such as in unpublished manufacturer studies, which is unlikely to be repeatable in routine clinical practice. This is

because the rapid tests' performance is linked to the quality of sampling and processing the sample. A clinical expert commented that positive test results are usually correct, but negative results could be related to absence of strep A infection, poor test sensitivity, or poor sampling technique. The committee also noted the imperfect accuracy of the reference standard (microbiological culture of throat swabs), which is subject to similar limitations. Laboratory polymerase chain reaction (PCR) tests have higher sensitivity than microbiological culture of throat swabs, but the clinical significance of this is unclear. For example, laboratory PCR tests could detect strep A carriers rather than infection, resulting in false positive results. The committee noted that the imperfect reference standard could under or overestimate the accuracy of the rapid tests but that the size of either bias was not known. Overall, the committee concluded that the performance of the rapid tests in routine clinical practice is uncertain and difficult to predict, and is likely to vary from practice to practice.

Rapid tests (used with clinical scoring tools) are unlikely to improve clinical outcomes compared with the use of clinical scoring tools alone

4.6 The committee reviewed the available evidence on the clinical effectiveness of using the rapid tests for people with suspected strep A throat infections. There was no evidence available on clinical outcomes such as morbidity, mortality, or onward transmission rate. The committee noted that severe complications of strep A are rare and there is no evidence to suggest that the rapid tests would reduce the risk of them happening. There were only 3 randomised controlled studies (RCTs) that reported antibiotic prescribing behaviours with or without rapid testing. The committee discussed the study by Little et al. (2013), done in UK primary care. The rate of delayed prescribing was lower in the rapid test group (23%) compared with the clinical score only group (43%). However, the reported use of antibiotics appeared similar in both groups (35% and 37%, respectively) and the level of immediate prescribing was also similar in both groups (18% and 16%, respectively). The EAG explained that data

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on reported antibiotic use was only available for 80% of enrolled patients so should be interpreted with caution. Also, a clinical expert commented that symptom severity and time to symptom resolution were comparable between these 2 groups (although the 2 groups were not formally tested for a difference). The committee concluded that the clinical benefit of the rapid tests was uncertain. The only study (Little et al. 2013) providing some evidence on this suggested there may be no benefit of rapid testing (used with the clinical scoring tool), compared with the use of clinical scoring tools alone.

Cost effectiveness

There is no evidence to assess the cost effectiveness of the rapid tests in pharmacies

4.7 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 in the pharmacy setting, and therefore could not model this. Also, the committee noted that FeverPAIN had not been validated in the pharmacy setting 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 in the pharmacy setting.

The accuracy inputs for the rapid tests are highly uncertain

4.8 The committee noted that test accuracy inputs for 9 of 14 rapid tests for which cost-effectiveness analysis was possible were from unpublished manufacturer data. This is likely to overestimate the accuracy of tests in routine clinical practice. Most accuracy estimates were from studies that were not applicable to NHS practice (see sections 4.4 to 4.5) because they did not use the tests with clinical scoring tools, or included unselected populations who did not necessarily have high scores from clinical scoring tools. The committee therefore concluded that the incremental cost-effectiveness ratios (ICERs) produced by the model

were highly uncertain because of bias in the data used to model the accuracy of the rapid tests.

The costs of using the tests in routine practice are likely to be underestimated in the model

4.9 The committee discussed the estimated costs of the tests and of the staff time for running the tests in the model. It raised concerns about the Xpert Xpress Strep A test cost, which was much lower than the costs of the other 3 molecular tests. The EAG explained that the test costs also included analyser or test cassette reader costs (when this equipment is needed). For all tests except Xpert Xpress Strep A, it was assumed that 2 tests per day would be done in a medium-sized GP practice, based on expert opinion. For the Xpert Xpress Strep A test, it was assumed that 28 tests per day would be run, resulting in a lower cost per test and therefore more favourable ICERs. Clinical experts commented that the time to process the rapid tests in routine clinical practice is likely underestimated in the model.They explained that the time included appears to account only for the time for the test read-out, and not for the time needed to prepare the test and take the throat swab. The total time necessary to run the test would depend on the experience of the healthcare professional doing the test. This could vary considerably between practices depending on their set-up for point-of-care testing. The time needed to take the throat swab might also be longer for certain populations, for example younger children. The committee concluded that including a more realistic estimate of test processing time would further increase the costs and ICERs for the rapid tests.

Penicillin-induced anaphylaxis is very rare

4.10 The committee considered the adverse events in the model and noted that the rate of penicillin-induced anaphylaxis had a big effect on the ICERs in scenario analyses. Clinical experts advised that the rate of penicillin-related anaphylaxis, when penicillin is taken orally, is very low (about 1 in a million). Therefore, the rate assumed in the base-case

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scenario (0.01%) is more appropriate than the rate assumed in the scenario analyses (0.64%), but could even overestimate the rate of penicillin-related anaphylaxis in the UK. Clinical experts also noted that the costs of sepsis are not generalisable to the treatment costs of penicillin-induced anaphylaxis, as had been assumed by the EAG. The committee concluded that penicillin-induced anaphylaxis is rare, and that the results of the scenario analyses which included a higher rate were unrealistic.

The model predicts a decrease in antibiotic use, but this might not be replicated in NHS practice

4.11 The committee recalled that one of the suggested benefits of the tests was providing a more targeted approach to antibiotic prescribing (see section 4.1). It discussed the antibiotic use predicted by the model for both current practice and for the rapid tests (used with clinical scoring tools). The model predicted a 15% decrease in the absolute rate of antibiotic use with rapid tests, compared with current practice. This was based on predicted treatment decisions related to the Centor score or the rapid test results (see Table 6). The committee questioned the external validity of this prediction because the study by Little et al. (2013) suggested similar antibiotic use between people who had the rapid test (with the clinical scoring tool), or the clinical scoring tool only (see section 4.6). It also recalled that the recent publication of NICE's guideline on antimicrobial prescribing for acute sore throat is expected to reduce antibiotic prescribing in sore throat further (see section 4.1). Clinical experts also advised that the FeverPAIN clinical scoring tool is more discriminative for strep A than the Centor tool. Therefore, the potential clinical benefits of the rapid tests compared with FeverPAIN could be even lower. The committee concluded that the predicted decrease in antibiotic use associated with the rapid tests might not be replicated in NHS practice.

The model does not account for all complications of strep A but this is appropriate because they are very rare

4.12 The committee noted that the model does not capture all complications of strep A and discussed the effect of excluding those that are more serious. Clinical experts advised that the risk of serious complications, such as invasive strep A or sepsis, is very low and therefore unlikely to have a major effect on the model results. They explained that the rate of serious complications is higher in people over 75 years, and the risk of associated mortality is higher for these people. Therefore, modelling serious complications could be important. However, modelling the use of rapid tests for people over 75 was not possible because of the lack of data for the model. For the children and adult models, the committee concluded that excluding the more severe complications was unlikely to have a big effect on the results.

Wider public health benefits are not captured in the model

4.13 The committee noted that the wider public health benefits of the rapid tests, such as contribution to antimicrobial stewardship or effect on onward transmission rate, are not captured in the model. The committee discussed the risk of onward transmission of untreated strep A infection to other household members, in particular, the risk of onward transmission leading to invasive strep A infection. It noted that although this risk exists, it is very small. The committee also noted that currently the public health impact (health effects and costs) of reduced antibiotic use has not been quantified. The model predicts a 15% reduction in the absolute rate of antibiotic use with the rapid tests (with clinical scoring tools), compared with clinical scoring tools only. However, this has minimal effect on the total cost of the pathway because penicillin costs are very low. The only differences in costs and quality-adjusted life years (QALYs) related to antibiotic prescribing are those of managing less severe strep A complications and side effects of penicillin. The committee discussed that although bacterial resistance to penicillin is not thought to be as great a

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problem as resistance to other classes of antibiotics such as macrolides (for example, erythromycin) or cephalosporins, there is very limited evidence to quantify this. Therefore, further research on the contribution of different classes of antibiotics to antimicrobial resistance, and to quantify the wider effect of antimicrobial stewardship, is needed (see section 5.1). The committee concluded that this evidence will be important for developing tests to improve prescribing decisions, which have the greatest impact on reducing antimicrobial resistance.

The rapid tests for strep A are unlikely to be a cost-effective use of NHS resources

4.14 The model predicted very small incremental costs and even smaller incremental QALYs. This resulted in ICERs between £1 million and £6 million per QALY gained, compared with current clinical practice, for most rapid tests (adult primary care model). The committee noted that there is uncertainty about the model inputs and the most plausible ICERs. However, all sensitivity analyses suggested that the rapid tests are unlikely to be a cost-effective use of NHS resources. The committee recalled the uncertain clinical role of the rapid tests in the context of NICE's recent guidance on antimicrobial prescribing for acute sore throat. The guidance advises that sore throat is self-limiting, and so in people who are otherwise healthy, antibiotics are usually not needed. The committee noted that the diagnostic accuracy of the tests in routine clinical practice is uncertain and likely to be highly variable. Also, there was no evidence to suggest that the rapid tests could reduce the rate of antibiotic prescribing or improve clinical outcomes in people with a sore throat. Therefore, the committee concluded that the most plausible ICERs for the rapid tests were too high, and their effect on wider public health benefits too uncertain (see section 4.13), to recommend routine adoption.

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5 Recommendations for further research

5.1 The committee recommended that further research is needed to measure the wider public health impact and the costs of antimicrobial stewardship associated with different classes of antibiotics used in different healthcare settings. This will help to inform the development of technologies to guide more targeted use of antibiotics and wider UK antimicrobial resistance policy.

6 Implementation

NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the developing specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 5 into its guidance research recommendations database and highlight these recommendations to public research bodies.

7 Review

NICE reviews the evidence 3 years after publication to ensure that any relevant new evidence is identified. However, NICE may review and update the guidance at any time if significant new evidence becomes available.

Mark Kroese

Chair, diagnostics advisory committee

July 2019

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8 Diagnostics advisory committee members and NICE project team

Committee members

This topic was considered by the diagnostics advisory committee, which is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the test to be assessed. If it is considered there is a conflict of interest, the member is excluded from participating further in that assessment.

The minutes of each committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Additional specialist committee members took part in the discussions for this topic:

Specialist committee members

Mrs Gillian Cross

Trainee advanced practitioner, Salford Primary Care Together

Mr Keith Howell

Clinical pharmacist, Northgate Medical Practice

Prof Michael Moore

Professor of primary care research, University of Southampton

Dr Mitul Patel

Consultant microbiologist, Birmingham Women's and Children's NHS Foundation Trust

Mrs Carole Pitkeathley

Lay specialist committee member

Mr Mohammed Rafiq

Clinical pharmacist, Pembroke Surgery

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Dr Derren Ready

Clinical scientist, Public Health England

NICE project team

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Ewa Rupniewska

Topic lead

Rebecca Albrow

Technical adviser

Donna Barnes

Project manager

ISBN: