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Title: Rapid Tests for Group A Streptococcal infections in people with sore throat

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The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

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Contributions of authors:
Rachel Court (Information specialist) developed the search strategy and undertook searches. Hannah Fraser (Research Associate), Sian Taylor-Phillips (Associate Professor), Chidozie Nduka (Senior Research Fellow), Christopher Stinton (Senior Research Fellow) and Bex Willans (Academic Foundation 2 doctor) conducted the clinical effectiveness systematic review, this included: screening and retrieving papers, assessing against the inclusion criteria, appraising the quality of papers and abstracting data from papers for synthesis. Daniel Gallacher (Research Fellow) conducted the meta-analyses and contributed to both the clinical and cost-effectiveness sections. Felix Achana (Senior Research Fellow) contributed to the cost-effectiveness review and undertook the health economic modelling. Paramjit Gill (Professor of General Practice) provided clinical guidance and helped

develop the model structures. Hema Mistry (Associate Professor) provided project management, conducted the cost-effectiveness review and supervised the economic analysis. All authors were involved in writing draft and final versions of the report

The following errors in this report have been identified. Corrections are supplied in the attached pages:

1. Pages 13, 18
   Fourteen out of 21 tests were evaluated and not 13
   Corrected pages 13 and 18 are copied below

2. Pages 31, 33
   Footnote corrected in Tables 1 and 2, to highlight information came from the NICE medtech briefing document
   Corrected pages 31 and 33 are copied below

3. Pages 161-162
   Fourteen out of 21 tests were evaluated and not 13 and removal of VAT from test prices
   Corrected pages 161-162 are copied below

4. Pages 166-177
   Updated results to take into account application of confirmatory testing only for negative results for which tests required it (as per table 1 and 2 of the final scope)
   Corrected pages 166-177 is copied below

5. Pages 179-189
   Updated results to take into account application of confirmatory testing only for negative results for which tests required it (as per table 1 and 2 of the final scope)
   Corrected pages 179-189 is copied below

6. Pages 191-197
   Updated results to take into account application of confirmatory testing only for negative results for which tests required it (as per table 1 and 2 of the final scope)
   Corrected pages 191-196 is copied below

7. Pages 198-200
   Updated results to take into account application of confirmatory testing only for negative results for which tests required it (as per table 1 and 2 of the final scope)
   Corrected pages 198-200 is copied below

8. Pages 202-213
   Updated results to take into account application of confirmatory testing only for negative results for which tests required it (as per table 1 and 2 of the final scope). Plus updated summary of economic modelling.
   Corrected pages 202-2013 is copied below

9. Pages 218, 221
   Fourteen out of 21 tests were evaluated and not 13
   Corrected pages 218, 221 are copied below

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possible to identify which test is the most accurate due to the paucity of evidence. There was considerable heterogeneity, even for studies performing the same point-of-care test, suggesting that is unlikely any single study will have accurately captured a tests true performance. There is some randomised control trial (RCT) evidence to suggest the use of rapid antigen detection tests may help reduce antibiotic prescribing rates, but there was no evidence on the effect of using molecular technologies. Sensitivity and specificity estimates for each test in each age group and care setting combination were obtained from published literature where available, or from manufacturer documentation if no other sources were available, using meta-analyses where appropriate. Any apparent differences in test accuracy may not be attributable to the tests, and may have been caused by known differences in the studies, latent characteristics, or chance.

Fourteen of the 21 tests for which relevant data were available in final economic modelling; however, there was considerable uncertainty about the cost-effectiveness of the different point-of-care tests for suspected Strep A in both primary and secondary care settings. Uncertainties in the model include parameter inputs and assumptions that increase the cost of testing, and the penalty for antibiotic over-prescriptions. While there is potential for cost-effectiveness in both primary and secondary care settings, key parameter inputs and modelling assumptions need to be confirmed and model findings remain uncertain.

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.

Future work

Further research is needed to understand the test accuracy of point-of-care tests within the proposed NHS pathway and within comparable settings and patient groups. Future work which considers head-to-head test accuracy studies or randomised controlled trials using multiple point-of-care tests in relevant populations would provide relevant comparator information and help to determine the value of point-of-care testing.

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Word count: 713

Fourteen of the twenty-one tests listed in the NICE scope had relevant data on test accuracy and costs, to be included in the final economic modelling. In the base-case analysis, which included adult patients seen in primary care with suspected GAS infection, the economic model found considerable uncertainty about the cost-effectiveness of the different point-of-care tests for suspected GAS infection. This finding was also seen in the other economic models which were adapted (adult patients seen in the hospital, children seen in primary care and children seen in the hospital). Important uncertainties in the model include parameter inputs and assumptions that increase the (i) cost of testing (acquisition cost of test, additional clinician time for administering and processing test results, and cost of confirmatory throat culture for those testing negative) and ii) penalty for antibiotic over-prescription/unnecessary antibiotic use (acquisition cost of antibiotic and probabilities for penicillin-induced anaphylaxis and rash).

Discussion and Conclusions

Main findings

The systematic review and cost-effectiveness model identify uncertainties around the adoption of point-of-care tests within the NHS. The available evidence is heterogeneous in populations studied, design, methods and analysis. Although sensitivity and specificity estimates are promising, we have little information on the best point-of-care test to use. While there is potential for the point-of-care tests to be cost-effectiveness in both primary and secondary care settings, key parameter inputs and modelling assumptions need to be confirmed and model findings remain uncertain.

Strengths and limitations

Strengths of the work include a robust and comprehensive systematic review (literature search, data extraction and analysis) strategy and the building of a *de novo* decision tree model to assess cost-effectiveness.

No studies on point-of-care use in a pharmacy setting or in the elderly population were retrieved. Additionally, no study matched the proposed pathway of care and treatment for patients with acute streptococcal pharyngitis, which would entail evaluating the test accuracy of a combined strategy of sore throat clinical scores at the recommended NICE thresholds (Centor/McIsaac ≥3 or FeverPAIN ≥4) and point-of-care tests in the age groups defined in the scope.

Although the economic model represented the clinical care pathway in the NHS, practice and management will vary from site to site (within and across both primary care and secondary care settings). The modelling may have underestimated the costs as we did not take into account the

Product	Test format and supply	Method	Limit of Detection	Description of results	Time to result (minutes)[a]
				test region (T). Read by visual inspection	
Biosynex Strep A - cassette (Biosynex)	Not reported	Lateral flow (immunochromatographic)	$1x10^5$ bacteria/swab	Positive results are indicated by 2 lines: one in the control region (C) and the other in the test region (T). Read by visual inspection	5
Sofia Strep A FIA (Quidel)	25 cassettes, including positive and negative control vials	Lateral flow (immunofluorescence)	Strain Bruno [CIP 104226]: $1.86x10^4$ CFU/test Strain CDC-SS-1402: $9.24x10^3$ CFU/test Strain CDC-SS-1460: $2.34x10^4$ CFU/test	Analysed using the Sofia analyser which interprets the immunofluorescent signal using on-board method-specific algorithms. Results are displayed on screen as positive, negative or invalid.	5-6

CFU/ml Colony forming units per millimetre

Clearview Exact Strep A cassette and Clearview Exact Strep A dipstick – test strip (both from Abbott) have been updated and replaced with the Clearview Exact 2

a This information was obtained from NICE medtech innovation briefing 145.[15]

Product	Test supply and format	Method	Analyser	Limit of Detection	Description of results	Time to result (minutes)[a]
Xpert Xpress Strep A (Cepheid)	Each kit contains sufficient reagents to process 10 specimens or quality control samples	Polymerase chain reaction	GeneXpert system	Strain: ATCC BAA-946 ATCC 19615 9–18 CFU/mL in a transport medium or 3–6 CFU/test.	Results displayed digitally	≥18

CFU/ml Colony forming units per millimetre

*The Alere i and Alere i Strep A 2 have now been replaced with the ID NOW Strep A 2.

a This information was obtained from NICE medtech innovation briefing 145.[15]

available for 14 (66.7 %) of the 21 tests considered in the NICE scope. The majority of the costs were provided by the manufacturers (submitted directly to NICE in response to a request for information) and ranged from £0.64 per test for the Biopanda's Strep A rapid test strip to £64.63 (2017/2018 prices) for Cobas Strep A Assay on Liat system supplied by Roche Diagnostics. Unit costs for Abbott's Clearview Exact Strep A tests were obtained from the NHS supply chain catalogue at £1.92 per test for the Clearview Strep A dipstick - test strip and £2.72 for the cassette version.[84] The duration of additional GP time for processing test results were estimated based on information provided in the manufacturer's submission and ranged from 5-12 minutes. Costs associated with additional GP time for processing test results are included in the base-case analysis. The cost of confirmatory swab culture following negative test result are calculated as part of the costs associated with modelled pathways in the intervention arm except for the Alere TestPack Plus Strep A - cassette (Abbott), ALERE i Strep A 2 (Abbott), Cobas Strep A assay on Liat system (Roche Diagnostics) and all 5 NADAL tests supplied by nal von minden GmbH. Details of costing methods are given in the next section.

Table 28: Test costs

Test ID	Test Name	Cost	Test process time	Source
1	Clearview Exact Strep A cassette (Abbott)	£2.72	5	NHS Supply chain catalogue (NPC =HHH2552)[84]
2	Clearview Exact Strep A dipstick – test strip (Abbott)	£1.92	5	Medisave UK Ltd.[85]
3	BD Veritor Plus system group A Strep Assay - cassette (Beckton Dickinson)			Test cost not available
4	Strep A rapid test - cassette (Biopanda Reagents)	£0.82	5	Manufacturer's submission*
5	Strep A rapid test – test strip (Biopanda Reagents)	£0.64	5	Manufacturer's submission*
6	NADAL Strep A - test strip (nal von minden GmbH)	£1.20	5	Manufacturer's submission*
7	NADAL Strep A - cassette (nal von minden GmbH)	£1.40	5	Manufacturer's submission*
8	NADAL Strep A plus - cassette (nal von minden GmbH)	£1.50	5	Manufacturer's submission*
9	NADAL Strep A plus - test strip (nal von minden GmbH)	£1.30	5	Manufacturer's submission*
10	NADAL Strep A scan test - cassette (nal von minden GmbH)	£1.96	5	Manufacturer's submission*
11	OSOM Strep A test – test strip (Sekisui Diagnostics)			Test cost not available
12	QuikRead Go Strep A test kit (Orion Diagnostica)	£4.34	5	Manufacturer's submission*
13	Alere TestPack Plus Strep A - cassette (Abbott)	£2.70	5	Manufacturer's submission*
14	Bionexia Strep A plus - cassette (Biomerieux)			Test cost not available
15	Bionexia Strep A dipstick – test strip (Biomerieux)			Test cost not available
16	Biosynex Strep A - cassette (Biosynex)			Test cost not available
17	Sofia Strep A FIA (Quidel)			Test cost not available
18	ALERE i Strep A (Abbott)			Test cost not available
19	ALERE i Strep A 2 (Abbott)	£22.94	5	Test cost not available
20	Cobas Strep A Assay on Liat system (Roche Diagnostics)	£64.63	6	Manufacturer's submission*
21	Xpert Xpress Strep A (Cepheid)	£4.25	12	Manufacturer's submission*

*submitted directly to NICE in response to a request for information

4.2.11 Adult primary care model: base-case analysis results

The base-case cost-effectiveness results for adults treated in primary care are presented in Table 30 for 14 of the 21 tests for which test accuracy and cost data were available. The rate at which incremental QALYs accrued over the one-year modelled time horizon was small, thus estimates of simulated costs and QALYs were multiplied by 1,000 to aid clarity in presentation of incremental estimates in the result tables and texts. The mean simulated costs under base-case assumptions was £49,147 per 1,000 individuals treated in primary care under usual care practice and ranged from £54,394 per 1000 individuals in the test group using the NADAL Strep A - test strip (nal von minden GmbH) to £71,277 per 1,000 individuals using the Cobas Strep A Assay on Liat system, Roche Diagnostics. The corresponding estimated mean QALYs were 859.825 per 1,000 individuals under usual care practice and ranged between 859.821 QALYs per 1,000 individuals in the intervention group using Abbott's Clearview Exact Strep A cassette or test strip to 859.829 QALYs per 1,000 individuals using Cepheid's Xpert Xpress Strep A tests. In terms of incremental cost-effectiveness, the base-case estimates suggest usual care was cheaper and generated marginally more QALYs than (and therefore dominated) both cassette and strip versions of Abbott's Clearview Exact Strep A test. Incremental cost-effectiveness ratios (ICERs) for the remaining twelve tests suggest testing was more costly and more effective than usual care with ICERs range from £1,353,677 per QALY gained for nal von minden GmbH's NADAL Strep A test strip to £6,059,081 per QALY gained for Roche Diagnostics's Cobas Strep A Assay on Liat system compared with usual care.

Table 30: Adult primary care model: Base-case cost-effectiveness results

TestID	Test Name	Mean costs / 1000 individuals	Mean QALYs / 1000 individuals	Inc. Costs / 1000 individuals	Inc. QALYS / 1000 individuals	ICER versus usual care
	Usual care (Clinical scoring based on Centor ≥3 plus clinical assessment)	£49,147	859.82458955	£0	0.0000000	-
1	Clearview Exact Strep A cassette (Abbott)	£56,180	859.82063008	£7,033	-0.0039595	Dominated
2	Clearview Exact Strep A dipstick – test strip (Abbott)	£55,980	859.82063008	£6,833	-0.0039595	Dominated
3	BD Veritor Plus system group A Strep Assay - cassette (Beckton Dickinson)					
4	Strep A rapid test - cassette (Biopanda Reagents)	£55,442	859.82769587	£6,295	0.0031063	£2,026,496
5	Strep A rapid test – test strip (Biopanda Reagents)*	£55,397	859.82769587	£6,250	0.0031063	£2,012,006
6	NADAL Strep A - test strip (nal von minden GmbH)	£54,394	859.82846603	£5,248	0.0038765	£1,353,677
7	NADAL Strep A - cassette (nal von minden GmbH)	£54,444	859.82846603	£5,298	0.0038765	£1,366,577
8	NADAL Strep A plus - cassette (nal von minden GmbH)	£54,469	859.82846603	£5,323	0.0038765	£1,373,029
9	NADAL Strep A plus - test strip (nal von minden GmbH)	£54,419	859.82846603	£5,273	0.0038765	£1,360,126
10	NADAL Strep A scan test - cassette (nal von minden GmbH)	£54,584	859.82846603	£5,438	0.0038765	£1,402,700
11	OSOM Strep A test – test strip (Sekisui Diagnostics)					
12	QuikRead Go Strep A test kit (Orion Diagnostica)	£56,083	859.82810269	£6,936	0.0035131	£1,974,319
13	Alere TestPack Plus Strep A - cassette (Abbott)	£54,781	859.82751669	£5,634	0.0029271	£1,924,717
14	Bionexia Strep A plus - cassette (Biomerieux)					
15	Bionexia Strep A dipstick – test strip (Biomerieux)					
16	Biosynex Strep A - cassette (Biosynex)					
17	Sofia Strep A FIA (Quidel)					
18	ALERE i Strep A (Abbott)					
19	ALERE i Strep A 2 (Abbott)	£59,837		£10,691		£2,926,915
20	Cobas Strep A Assay on Liat system (Roche Diagnostics)	£71,277	859.82824206	£22,131	0.0036525	£6,059,081
21	Xpert Xpress Strep A (Cepheid)	£63,323	859.82854357	£14,177	0.0039540	£3,585,436

[1]Test accuracy data for Biopanda Reagents Strep A rapid test – test strip not available, assumed the strip has same test accuracy as the cassette version of the test

Note: Missing cost-effectiveness estimates are for the tests where either test accuracy or cost data were not available

4.2.12 Adult primary care model: probabilistic sensitivity analyses

Table 31 below presents probabilistic estimates for adults presenting in primary care. The probabilistic estimates were very similar to the deterministic base-case results with ICERs indicating that usual care dominated two (the Clearview Exact Strep A cassette and the Clearview Exact Strep A dipstick – test strip supplied by Abbott) of the fourteen tests considered in the economic modelling. Base-case probabilistic ICERs for the remaining twelve tests ranged from £1,495,402 per QALY gained for NADAL Strep A plus - test strip supplied by nal von minden GmbH to £6,498,666 per QALY gained for Cobas Strep A Assay on Liat system supplied by Roche Diagnostics. The probability for testing to be cost-effective was zero under the base-case assumptions and model inputs regardless of the point-of-care test used in comparison to usual care.

Table 31: Adult primary care model: Probabilistic sensitivity analysis results

TestID	Test Name	Mean costs / 1000 individuals	Mean QALYs / 1000 individuals	Inc. Costs / 1000 individuals	Inc. QALYS / 1000 individuals	ICER versus usual care	Probability of cost-effectiveness at £20,000 per QALY
	Usual care (Clinical scoring based on Centor ≥3 plus clinical assessment)	£49,295	861.0209476	£0	0.0000000		1
1	Clearview Exact Strep A cassette (Abbott)	£56,387	861.0168718	£7,092	-0.0040758	Dominated	0
2	Clearview Exact Strep A dipstick – test strip (Abbott)	£56,183	861.0169652	£6,888	-0.0039824	Dominated	0
3	BD Veritor Plus system group A Strep Assay - cassette (Beckton Dickinson)						
4	Strep A rapid test - cassette (Biopanda Reagents)	£55,636	861.0239908	£6,341	0.0030432	£2,083,738	0
5	Strep A rapid test – test strip (Biopanda Reagents)*	£55,590	861.0239997	£6,295	0.0030521	£2,062,510	0
6	NADAL Strep A - test strip (nal von minden GmbH)	£54,582	861.0244537	£5,288	0.0035061	£1,508,134	0
7	NADAL Strep A - cassette (nal von minden GmbH)	£54,634	861.0243797	£5,339	0.0034321	£1,555,613	0
8	NADAL Strep A plus - cassette (nal von minden GmbH)	£54,658	861.0244709	£5,363	0.0035233	£1,522,258	0
9	NADAL Strep A plus - test strip (nal von minden GmbH)	£54,607	861.0245002	£5,313	0.0035526	£1,495,402	0
10	NADAL Strep A scan test - cassette (nal von minden GmbH)	£54,775	861.0244341	£5,480	0.0034865	£1,571,686	0
11	OSOM Strep A test – test strip (Sekisui Diagnostics)						
12	QuikRead Go Strep A test kit (Orion Diagnostica)	£56,273	861.0244144	£6,978	0.0034668	£2,012,942	0
13	Alere TestPack Plus Strep A - cassette (Abbott)	£54,968	861.0237881	£5,673	0.0028405	£1,997,326	0
14	Bionexia Strep A plus - cassette (Biomerieux)						
15	Bionexia Strep A dipstick – test strip (Biomerieux)						
16	Biosynex Strep A - cassette (Biosynex)						
17	Sofia Strep A FIA (Quidel)						
18	ALERE i Strep A (Abbott)						
19	ALERE i Strep A 2 (Abbott)	£60,056	861.0244146	£10,761	0.0034670	£3,103,806	0
20	Cobas Strep A Assay on Liat system (Roche Diagnostics)	£71,565	861.0243746	£22,271	0.0034270	£6,498,666	0
21	Xpert Xpress Strep A (Cepheid)	£63,581	861.0248804	£14,286	0.0039328	£3,632,549	0

[1]Test accuracy data for Biopanda Reagents Strep A rapid test – test strip not available, assumed the strip has same test accuracy as the cassette version of the test

4.2.13 Adult primary care model: exploratory sensitivity analyses

Exploratory analyses were conducted to test the robustness of the economic base-case estimates for adults presenting in primary care with suspected GAS. The base-case ICERs are highly sensitive to various modelling assumptions and input values. In the sections that follow, sensitivity analysis results are presented only for those tests where the ICER is sensitive to the alternative modelling assumptions and parameter inputs (as indicated by changes in the direction of incremental costs or incremental QALYs compared with usual care).

4.2.13.1 Adult primary care model - Prevalence of GAS and clinical score threshold for starting antibiotics (usual care arm) and testing (intervention arm)

In the base-case, a cut-off of three points on the Centor scale was used as threshold for starting antibiotic treatment with scores ≥3 indicating positive GAS infection. Changing this threshold to a score ≥2 had minimal impact on the base-case cost-effectiveness estimates. However, a threshold of ≥1 for initiating point-of-care testing in primary care (equivalent to a test all approach) favoured testing and changed the QALY difference from incremental QALY loss (-0.00396 per 1,000 individuals) to incremental QALY gain (0.00346 per 1,000 individuals) for Clearview Exact Strep A test cassette (Abbott) and Clearview Exact Strep A dipstick - test strip (Abbott) compared with usual care (Table 32). The corresponding ICERs changed from these two tests being dominated in the base-case to £7,071,480 and £6,875,048 per QALY gained for the cassette and dipstick versions respectively when compared with usual care.

The cost-effectiveness estimates were also sensitive to the prevalence GAS among adults presenting in primary care. Increasing the prevalence rate from 22.6% (base-case model) to 35.9% (upper estimate from studies included in systematic review of test accuracy studies) generally favoured usual care (results not shown here); however, whilst decreasing the prevalence to 10% (the value used in the Neuner 2003 study[75]) favoured the intervention arm (i.e. testing). In the majority of cases, the ICERs did not changed substantially to influence interpretation of cost-effectiveness, but the ICERs for Clearview Exact Strep A dipstick - test strip and Clearview Exact Strep A test - cassette (Abbott) changed from being dominated (less effective and more costly) to being more effective and more costly at 10% prevalence rate (Table 32).

Table 32: Adult primary care model: Deterministic sensitivity analyses - Centor threshold for starting antibiotic therapy and prevalence of GAS

Test	Base case			Sensitivity analysis		
	Inc. Costs per 1000 individuals	**Inc. QALYs per 1000 individuals**	**ICER**	**Inc. Costs per 1000 individuals**	**Inc. QALYs per 1000 individuals**	**ICER**
SA#2 - changed Centor threshold for starting antibiotics from ≥3 to ≥1						
Clearview Exact Strep A cassette (Abbott)	£7,033	-0.00396	Dominated	£24,462	0.00346	£7,071,480
Clearview Exact Strep A dipstick - test strip (Abbott)	£6,833	-0.00396	Dominated	£23,783	0.00346	£6,875,048
SA#5 - Changed GAS prevalence from 22.6% (base-case) to 10% (Neuner 2003[75])						
Clearview Exact Strep A cassette (Abbott)	£7,033	-0.00396	Dominated	£6,092	0.00131	£4,638,696
Clearview Exact Strep A dipstick - test strip (Abbott)	£6,833	-0.00396	Dominated	£5,923	0.00131	£4,510,168

4.2.13.2 Adult primary care model - Complications rates in treated and untreated GAS infection

Only ICERs for Clearview Exact Strep A dipstick - test strip (Abbott) and Clearview Exact Strep A dipstick – cassette (Abbott) were sensitive to modelled rates of complications (peritoncillar abscess, quinsy and cellulitis as the probabilities used in the model represented all these complications as shown Table 33). In the base-case analysis, GAS related complications rates were set to 1.5% for untreated infection and 1.3% for treated GAS infection based on UK primary care data published by Little et al (2013b).[81] Halving and doubling the complications rates in the untreated group did not influence ICERs substantially but doubling complications in the treated infection to 2.6% favoured testing. The ICER for the Clearview Exact Strep A dipstick - test strip (Abbott) and Clearview Exact Strep A cassette (Abbott) changed from being dominated in the base-case by usual care to £3,935,182 and £4,062,173 per QALY gained compared with usual care respectively (Table 33).

Table 33: Adult primary care model: Deterministic sensitivity analyses – Complications following GAS infection

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	**Inc. QALYs per 1000 individuals**	**ICER**	**Inc. costs per 1000 individuals**	**Inc. QALYs per 1000 individuals**	**ICER**
SA#10 - Doubled complications in treated GAS to 2.6%						
Clearview Exact Strep A cassette (Abbott)	£7,033	-0.00396	Dominated	£6,399	0.00158	£4,062,173
Clearview Exact Strep A dipstick - test strip (Abbott)	£6,833	-0.00396	Dominated	£6,199	0.00158	£3,935,182

4.2.13.3 Adult primary care model - Side-effects of penicillin

Cost-effectiveness estimates were most sensitive to modelled rates of penicillin-induced anaphylaxis. In the base-case, penicillin-induced anaphylaxis were set to 0.01% probability (Table 26) and utility decrement of 9 quality-adjusted life-days lost (Table 27) based on figures reported in the Neuner et al. 2003 study[75] with £1,744 in treatment costs (Hex et al. 2017)[88] reflecting the rare but serious nature of this event. Changing the rate of penicillin-induced anaphylaxis from 0.01% to 0.64% as reported in Van Howe and Kusnier (2006)[76] favoured testing – the ICER for Clearview Exact Strep A dipstick - test strip (Abbott) and Clearview Exact Strep A cassette (Abbott) changed from being dominated by usual care in the base-case to £3,935,182 and £4,062,173 per QALY gained compared with usual care. When the rate of mild penicillin rash was doubled from 2 to 4%, the ICER for Clearview Exact Strep A dipstick - test strip (Abbott) and Clearview Exact Strep A cassette (Abbott) changed from being dominated by usual care in the base-case to £288,702 and £299,305 per QALY gained compared with usual care, respectively (see Table 34).

Table 34: Adult primary care model: Deterministic sensitivity analyses – Exploring impact of complications of penicillin

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	**Inc. QALYs per 1000 individuals**	**ICER**	**Inc. costs per 1000 individuals**	**Inc. QALYs per 1000 individuals**	**ICER**
SA#16 - Doubled rates of mild penicillin reaction (rash) to 4%						

Clearview Exact Strep A cassette (Abbott)	£7,033	-0.00396	Dominated	£6,399	0.00107	£4,062,173
Clearview Exact Strep A dipstick - test strip (Abbott)	£6,833	-0.00396	Dominated	£6,199	0.00107	£3,935,182
SA#17 - Changed rates of anaphylaxis from 0.01% (Neuner 2003[75]) to 0.64% (Van Howe and Kusnier 2006[76])						
Clearview Exact Strep A cassette (Abbott)	£7,033	-0.00396	Dominated	£5,647	0.01887	£299,305
Clearview Exact Strep A dipstick - test strip (Abbott)	£6,833	-0.00396	Dominated	£5,447	0.01887	£288,702

4.2.13.4 Adult primary care model - Assume testing within standard general practice consultation time

The base-case analysis assumes the typical general practice consultation duration of 9.22 minutes on average[86] is not sufficient to administer and process test concurrently with usual consultation activities. Consequently, 5–12 minutes (depending on test) of additional clinician time was added when calculating test costs to account for longer consultation during testing in primary care. Excluding the additional cost of clinician time favoured testing but only the ICERs for the 5 Nadal tests fell below £100,000 per QALY gained compared with usual care (Table 35).

Table 35: Adult primary care model: Deterministic sensitivity analyses – Exploring impact of excluding additional clinician time to administer and process test results

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#22 - Assume testing within standard GP time						
NADAL Strep A - test strip (nal von minden GmbH)	£5,248	0.00388	£1,353,677	£171	0.00388	£44,184
NADAL Strep A - cassette (nal von minden GmbH)	£5,298	0.00388	£1,366,577	£221	0.00388	£57,085
NADAL Strep A plus - cassette (nal von minden GmbH)	£5,323	0.00388	£1,373,029	£246	0.00388	£63,537
NADAL Strep A plus - test strip (nal von minden GmbH)	£5,272	0.00388	£1,360,126	£196	0.00388	£50,636
NADAL Strep A scan test - cassette (nal von minden GmbH)	£5,438	0.00388	£1,402,700	£361	0.00388	£93,211

4.2.13.5 Adult primary care model - Utility decrement, Strep A sore throat and related complications

The base-case estimates were sensitive to changes in disutility associated with GAS sore throat and related complications. Decreasing the utility decrement associated with untreated GAS by half, favoured testing, whilst doubling it favoured usual care (see Table 36). All other testing scenarios involving doubling the utility decrements for treated GAS infection and penicillin-induced rash produced ICERs favourable to testing (key result changes are presented below).

Table 36: Adult primary care model: Deterministic sensitivity analyses - Utility decrement, Strep A sore throat and related complications

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#27 - Halved the utility decrement, untreated GAS						
Clearview Exact Strep A cassette (Abbott)	£7,033	-0.00396	Dominated	£7,033	0.00667	£1,054,577
Clearview Exact Strep A dipstick - test strip (Abbott)	£6,833	-0.00396	Dominated	£6,833	0.00667	£1,024,581
SA#28 - Doubled utility decrement, untreated GAS						
Strep A rapid test - cassette (Biopanda Reagents)	£6,295	0.00311	£2,026,496	£6,295	-0.0002	Dominated
Strep A rapid test - test strip (Biopanda Reagents)	£6,250	0.00311	£2,012,006	£6,250	-0.0002	Dominated
Alere TestPack Plus Strep A - cassette (Abbott)	£5,634	0.00293	£1,924,717	£5,634	-0.0004	Dominated
SA#30 - Doubled utility decrement, treated GAS						
Clearview Exact Strep A cassette (Abbott)	£7,033	-0.00396	Dominated	£7,033	0.00879	£799,685
Clearview Exact Strep A dipstick - test strip (Abbott)	£6,833	-0.00396	Dominated	£6,833	0.00879	£776,939
SA#36 - Doubled utility decrement, penicillin-induced rash						
Clearview Exact Strep A cassette (Abbott)	£7,033	-0.00396	Dominated	£7,033	0.00107	£6,554,023
Clearview Exact Strep A dipstick - test strip (Abbott)	£6,833	-0.00396	Dominated	£6,833	0.00107	£6,367,600

4.2.14 Adult secondary care model: base-case analysis results

The primary care adult model (section 4.2.2) was adapted to model adult patients presenting with suspected GAS infection in secondary care settings (urgent care/walk-in centres and emergency departments). The modelled pathways remain the same as the adult primary care model depicted in Figure 12 to Figure 14. Sensitivity and specificity of the clinical score at the specified Centor score ≥ 3 for a positive GAS infection were left unchanged as in the adult primary care model (Table 23) as were the modelled pathway probabilities (Table 26) and health-state utility values (Table 27). However, the two models differ in the way treatment and testing costs are calculated. The secondary care model assumes the care pathways associated with suspected cases of GAS infections are presenting for the first time in secondary care and have not received any treatment in primary care. The cost of the initial GP consultation included in the adult primary care model is therefore excluded from the cost. The model does however account for patients attending a GP consultation (and the associated costs) following hospital discharge at a rate equal to the proportion attending repeat GP consultations in the primary care model (14.2% based on figures reported in Little et al 2013b[81]). Additionally, we assume that point-of-care testing within secondary care settings can be performed within the standard allocated time for most hospital-based appointments, such that no additional time is required for administering and processing test results.

Test accuracy estimates were obtained from our systematic review and remained broadly the same as those used to inform the adults in primary care model (Table 24) except for three tests (OSOM Strep A test strip, QuikRead Go Strep A test kit and the Alere TestPack Plus Strep A – cassette). Table 37 presents test accuracy estimates used in adult secondary care model for these three point-of-care tests. Estimates of sensitivity changed from 92% in primary care to 94% in secondary care for OSOM Strep A test strip, from 100% in primary care to 87% in secondary care for QuikRead Go Strep A test kit and from 95% in primary to 90% in secondary care for the Alere TestPack Plus Strep A – cassette. Estimates of specificity for the three tests however remain broadly unchanged across primary and secondary care settings.

Table 37: Adult secondary care model: Test accuracy of point-of-care tests used in economic model*

Test Name Manufacturer	Sensitivity (95% CI)	Specificity (95% CI)	Assumed distribution	Data source
OSOM Strep A test – test strip (Sekisui Diagnostics)	0.94 (0.89, 0.98)	0.95 (0.91, 0.98)	Normal (logit)	5 studies (Bura 2017; Llor 2009; Llor 2011; Rogo 2011; Weinzierl 2018)
QuikRead Go Strep A test kit (Orion Diagnostica)	0.87 (0.78, 0.95)	0.78 (0.71, 0.85)	Normal (logit)	2 studies (Azrad 2019; Stefaniuk 2017)
Alere TestPack Plus Strep A – cassette (Abbott)	0.90 (0.86, 0.94)	0.95 (0.92, 0.96)	Normal (logit)	1 study (Rosenberg 2002) and 1 abstract (Valverde 2018)

*Only tests with secondary care accuracy estimates that are different from those used to inform the adult primary care model are presented in this table

Table 38 presents the cost-effectiveness results for adults in a secondary care setting. As with the adult primary care model, only 14 of the 21 tests that have test accuracy and costs data have been included in this analysis. The pattern and direction of cost-effectiveness in the secondary care adult model is similar to what has been observed in the adult primary care model although the ICERs were generally lower in secondary care model.

Two tests (Abbotts's Clearview Exact Strep A cassette and Clearview Exact Strep A dipstick – test trip) generated fewer QALYs than usual care and produced ICERs indicating being dominated by usual care (i.e. were less effective and more costly). The remaining 12 tests all generated marginally more QALYs than usual care. The ICERs ranged from £44,184 per QALY gained for NADAL Strep A - test strip (nal von minden GmbH) to £12,700,432 per QALY gained for the QuikRead Go Strep A test kit supplied by Orion Diagnostica.

Table 38: Adult secondary care model: Base-case cost-effectiveness results

TestID	Test Name	Mean costs / 1000 individuals	Mean QALYs/ 1000 individuals	Inc. Costs / 1000 individuals	Inc. QALYS / 1000 individuals	ICER
	Usual care (Clinical scoring based on Centor ≥3 plus clinical assessment)	£49,147	859.82458955	£0	0.0000000	
1	Clearview Exact Strep A cassette (Abbott)	£51,103	859.82063008	£1,957	-0.0039595	Dominated
2	Clearview Exact Strep A dipstick - test strip (Abbott)	£50,903	859.82063008	£1,757	-0.0039595	Dominated
3	BD Veritor Plus system group A Strep Assay - cassette (Beckton Dickinson)					
4	Strep A rapid test - cassette (Biopanda Reagents)	£50,365	859.82769587	£1,219	0.0031063	£392,342
5	Strep A rapid test - test strip (Biopanda Reagents)*	£50,320	859.82769587	£1,174	0.0031063	£377,852
6	NADAL Strep A - test strip (nal von minden GmbH)	£49,318	859.82846603	£171	0.0038765	£44,184
7	NADAL Strep A - cassette (nal von minden GmbH)	£49,368	859.82846603	£221	0.0038765	£57,085
8	NADAL Strep A plus - cassette (nal von minden GmbH)	£49,393	859.82846603	£246	0.0038765	£63,537
9	NADAL Strep A plus - test strip (nal von minden GmbH)	£49,343	859.82846603	£196	0.0038765	£50,636
10	NADAL Strep A scan test - cassette (nal von minden GmbH)	£49,508	859.82846603	£361	0.0038765	£93,211
11	OSOM Strep A test - test strip (Sekisui Diagnostics)					
12	QuikRead Go Strep A test kit (Orion Diagnostica)	£51,136	859.82474622	£1,990	0.0001567	£12,700,432
13	Alere TestPack Plus Strep A - cassette (Abbott)	£49,713	859.82627789	£566	0.0016883	£335,358
14	Bionexia Strep A plus - cassette (Biomerieux)					
15	Bionexia Strep A dipstick - test strip (Biomerieux)					
16	Biosynex Strep A - cassette (Biosynex)					
17	Sofia Strep A FIA (Quidel)					
18	ALERE i Strep A (Abbott)					
19	ALERE i Strep A 2 (Abbott)	£54,761	859.82824206	£5,614	0.0036525	£1,537,126
20	Cobas Strep A Assay on Liat system (Roche Diagnostics)	£65,186	859.82824206	£16,039	0.0036525	£4,391,332
21	Xpert Xpress Strep A (Cepheid)	£51,141	859.82854357	£1,994	0.0039540	£504,287

[1]Test accuracy data for Biopanda Reagents Strep A rapid test – test strip not available, assumed the strip has same test accuracy as the cassette version of the test

Note: Missing cost-effectiveness estimates are for the tests where either test accuracy or cost data were not available

Table 39: Adult secondary care model: Probabilistic sensitivity analysis results

TestID	Test Name	Mean costs / 1000 individuals	Mean QALYs / 1000 individuals	Inc. Costs / 1000 individuals	Inc. QALYS / 1000 individuals	ICER versus usual care	Probability of cost-effectiveness at £20,000 per QALY
	Usual care (Clinical scoring based on Centor ≥3 plus clinical assessment)	£49,182	860.0288998	£0	0.0000000		1
1	Clearview Exact Strep A cassette (Abbott)	£51,128	860.0249274	£1,947	-0.0039724	Dominated	0
2	Clearview Exact Strep A dipstick – test strip (Abbott)	£50,924	860.024949	£1,743	-0.0039508	Dominated	0
3	BD Veritor Plus system group A Strep Assay - cassette (Beckton Dickinson)						
4	Strep A rapid test - cassette (Biopanda Reagents)	£50,416	860.0319673	£1,234	0.0030675	£402,358	0
5	Strep A rapid test – test strip (Biopanda Reagents)*	£50,370	860.0319912	£1,188	0.0030914	£384,360	0
6	NADAL Strep A - test strip (nal von minden GmbH)	£49,358	860.0323456	£177	0.0034458	£51,324	0
7	NADAL Strep A - cassette (nal von minden GmbH)	£49,408	860.0324406	£226	0.0035408	£63,963	0
8	NADAL Strep A plus - cassette (nal von minden GmbH)	£49,433	860.0324859	£251	0.0035860	£70,042	0
9	NADAL Strep A plus - test strip (nal von minden GmbH)	£49,382	860.032473	£201	0.0035731	£56,186	0
10	NADAL Strep A scan test - cassette (nal von minden GmbH)	£49,550	860.0324781	£368	0.0035783	£102,876	0
11	OSOM Strep A test – test strip (Sekisui Diagnostics)						
12	QuikRead Go Strep A test kit (Orion Diagnostica)	£51,187	860.0289465	£2,005	0.0000467	£42,951,995	0
13	Alere TestPack Plus Strep A - cassette (Abbott)	£49,754	860.0306084	£573	0.0017086	£335,098	0
14	Bionexia Strep A plus - cassette (Biomerieux)						
15	Bionexia Strep A dipstick – test strip (Biomerieux)						
16	Biosynex Strep A - cassette (Biosynex)						
17	Sofia Strep A FIA (Quidel)						
18	ALERE i Strep A (Abbott)						
19	ALERE i Strep A 2 (Abbott)	£54,870	860.0323487	£5,688	0.0034488	£1,649,300	0
20	Cobas Strep A Assay on Liat system (Roche Diagnostics)	£65,430	860.0322608	£16,248	0.0033610	£4,834,450	0
21	Xpert Xpress Strep A (Cepheid)	£51,204	860.0328714	£2,022	0.0039715	£509,167	0

[1]Test accuracy data for Biopanda Reagents Strep A rapid test – test strip not available, assumed the strip has same test accuracy as the cassette version of the test

4.2.16 Adults secondary care model: exploratory sensitivity analyses

Exploratory analyses were conducted to test the robustness of the economic base-case estimates for adults presenting in secondary care with suspected GAS infection. The base-case ICERs are highly sensitive to various modelling assumptions and input values. In the sections that follow, sensitivity analysis results are presented only for those tests where the ICER is sensitive to the alternative modelling assumptions and parameter inputs (as indicated by changes in the direction of incremental costs or incremental QALYs compared with usual care).

4.2.16.1 Adults in secondary care - Centor threshold for starting antibiotics and testing

In the base-case secondary care model, Centor score ≥3 was used as an indication for starting antibiotic treatment in the usual care arm and to initiate testing using a point-of-care test in the intervention arm. Changing this threshold to Centor score ≥2 favoured testing and produced ICERs for the NADAL's tests ranging between £30,230 and £69,690 per QALY gained compared with usual care (Table 40). Using a threshold of ≥1 also favoured testing. The ICER for Clearview exact Strep A dipstick - test strip (Abbott) and Clearview Exact Strep A cassette (Abbott) changed from being dominated by usual care to £1,890,627 and £2,087,056 per QALY gained in comparison to usual care, respectively (Table 40). The ICERs for NADAL's tests reduced further to between £22,220 and £56,190 per QALY gained in comparison to usual care. ICERs for the other tests remained well above £100,000 per QALY gained in these scenario analyses.

Table 40: Adult secondary care model: Deterministic sensitivity analyses - Centor threshold for starting antibiotics

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#1 - Changed Centor threshold from ≥ 3 (base case) to ≥2						
NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	£307	0.01015	£30,230
NADAL Strep A - cassette (nal von minden GmbH)	£221	0.00388	£57,085	£412	0.01015	£40,614

NADAL Strep A plus - cassette (nal von minden GmbH)	£246	0.00388	£63,537	£465	0.01015	£45,807
NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	£359	0.01015	£35,422
NADAL Strep A scan test - cassette (nal von minden GmbH)	£361	0.00388	£93,211	£707	0.01015	£69,690
SA#2 - Changed Centor threshold from ≥ 3 (base case) to ≥1						
Clearview exact Strep A cassette (Abbott)	£1,957	-0.00396	Dominated	£7,220	0.00346	£2,087,056
Clearview exact Strep A dipstick - test strip (Abbott)	£1,757	-0.00396	Dominated	£6,540	0.00346	£1,890,627
NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	£422	0.019	£22,220
NADAL Strep A - cassette (nal von minden GmbH)	£221	0.00388	£57,085	£592	0.019	£31,159
NADAL Strep A plus - cassette (nal von minden GmbH)	£246	0.00388	£63,537	£677	0.019	£35,629
NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	£507	0.019	£26,690
NADAL Strep A scan test - cassette (nal von minden GmbH)	£361	0.00388	£93,211	£1,068	0.019	£56,190

4.2.16.2 Adults in secondary care - Prevalence of GAS

Changing the prevalence of GAS infection in secondary care from 22.6% base-case value to 35.9% (upper value reported in studies included in the test accuracy systematic review) was less favourable to testing with usual care dominating QuikRead Go Strep A test kit (Orion Diagnostica) and Alere TestPack Plus Strep A - cassette (Abbott) in comparison to base-case results (Table 41). In contrast, a lower prevalence of disease was more favourable to testing with ICERs for Clearview Exact Strep A dipstick - test strip (Abbott) and Clearview Exact Strep A cassette (Abbott) changing from being dominated by usual care to £1,248,775 and £1,377,303 per QALY gained, respectively in comparison to usual care (Table 41). ICERs for the NADAL's tests decreased to between £20,628 and £53,506 per QALY gained in comparison to usual care. ICERs for all other tests did not change substantially to suggest change in the direction of cost-effectiveness in comparison to usual care.

Table 41: Adult secondary care model: Deterministic sensitivity analyses - Prevalence of GAS

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#4 - Changed Strep A prevalence from 22.6% to 35.9%						
NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	£246	0.00282	£87,196
NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	£275	0.00282	£97,522
QuikRead Go Strep A test kit (Orion Diagnostica)	£1,990	0.00016	£12,700,432	£2,120	-0.00241	Dominated
Alere TestPack Plus Strep A - cassette (Abbott)	£566	0.00169	£335,358	£711	-0.00055	Dominated
SA#5 - Changed Strep A prevalence from 22.6% to 10%						
Clearview exact Strep A cassette (Abbott)	£1,957	-0.00396	Dominated	£1,809	0.00131	£1,377,303
Clearview exact Strep A dipstick - test strip (Abbott)	£1,757	-0.00396	Dominated	£1,640	0.00131	£1,248,775
NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	£101	0.00488	£20,628
NADAL Strep A - cassette (nal von minden GmbH)	£221	0.00388	£57,085	£143	0.00488	£29,280
NADAL Strep A plus - cassette (nal von minden GmbH)	£246	0.00388	£63,537	£164	0.00488	£33,606
NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	£122	0.00488	£24,954
NADAL Strep A scan test - cassette (nal von minden GmbH)	£361	0.00388	£93,211	£261	0.00488	£53,506

4.2.16.3 Adults in secondary care - Complication rates

In the base case analysis, GAS related complications rates were set to 1.5% for untreated infection and 1.3% for treated infection based on UK primary care data published by Little et al (2013b).[81] Halving complications in the treated group to 0.65% and doubling the rate in the untreated group to 3% were less favourable to testing with usual care dominating QuikRead Go Strep A test kit (Orion Diagnostica) and Alere TestPack Plus Strep A - cassette (Abbott). On the other hand, doubling the complications rates in the treated group to 2.6% and halving the rate in the untreated group to 0.75% favoured testing. The ICER for the Clearview Exact

Strep A dipstick - test strip (Abbott) and Clearview Exact Strep A cassette (Abbott) changed from being dominated by usual care in the base-case to £712,813 and £839,805 per QALY gained respectively (Table 42). ICERs for the NADAL tests ranged between £31,184 and £83,041 per QALY gained in the scenarios that favoured testing. ICERs for all other tests were much lower in comparison to the base-case estimates but still remained well above £100,000 per QALY gained in comparison to usual care.

Table 42: Adult secondary care model: Deterministic sensitivity analyses – complications following GAS sore throat

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	**Inc. QALYs per 1000 individuals**	**ICER**	**Inc. costs per 1000 individuals**	**Inc. QALYs per 1000 individuals**	**ICER**
SA#9 - Halved complications, treated infection to 0.65%						
NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	£191	0.0037	£51,597
NADAL Strep A - cassette (nal von minden GmbH)	£221	0.00388	£57,085	£241	0.0037	£65,100
NADAL Strep A plus - cassette (nal von minden GmbH)	£246	0.00388	£63,537	£266	0.0037	£71,853
NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	£216	0.0037	£58,350
QuikRead Go Strep A test kit (Orion Diagnostica)	£1,990	0.00016	£12,700,432	£2,119	-0.00097	Dominated
SA#10 - Doubled complications in treated infection to 2.6%						
Clearview exact Strep A cassette (Abbott)	£1,957	-0.00396	Dominated	£1,323	0.00158	£839,805
Clearview exact Strep A dipstick - test strip (Abbott)	£1,757	-0.00396	Dominated	£1,123	0.00158	£712,813
NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	£132	0.00422	£31,184
NADAL Strep A - cassette (nal von minden GmbH)	£221	0.00388	£57,085	£182	0.00422	£43,028
NADAL Strep A plus - cassette	£246	0.00388	£63,537	£207	0.00422	£48,948

(nal von minden GmbH)						
NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	£157	0.00422	£37,104
NADAL Strep A scan test - cassette (nal von minden GmbH)	£361	0.00388	£93,211	£322	0.00422	£76,191
SA#11 - Halved complications, untreated infection to 0.75%						
NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	£148	0.00408	£36,415
NADAL Strep A - cassette (nal von minden GmbH)	£221	0.00388	£57,085	£198	0.00408	£48,684
NADAL Strep A plus - cassette (nal von minden GmbH)	£246	0.00388	£63,537	£223	0.00408	£54,820
NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	£173	0.00408	£42,551
NADAL Strep A scan test - cassette (nal von minden GmbH)	£361	0.00388	£93,211	£338	0.00408	£83,041
SA#12 - Doubled complications, untreated infection to 3%						
NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	£217	0.00348	£62,404
NADAL Strep A - cassette (nal von minden GmbH)	£221	0.00388	£57,085	£267	0.00348	£76,786
NADAL Strep A plus - cassette (nal von minden GmbH)	£246	0.00388	£63,537	£292	0.00348	£83,978
NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	£242	0.00348	£69,596
QuikRead Go Strep A test kit (Orion Diagnostica)	£1,990	0.00016	£12,700,432	£2,287	-0.00244	Dominated
Alere TestPack Plus Strep A - cassette (Abbott)	£566	0.00169	£335,358	£795	-0.00031	Dominated

4.2.16.4 Adults in secondary care - Adverse effects of penicillin

Cost-effectiveness estimates were most sensitive to adverse-effects of penicillin. Halving the mild/uncomplicated side-effects of penicillin (rash) to 1.0% favoured usual care, whilst doubling it favoured testing (Table 43). The Clearview exact Strep A cassette (Abbott) and Clearview exact Strep A dipstick - test strip (Abbott) are no longer dominated by usual care under this scenario. ICERs for the NADAL tests ranged between £8,913 and £32,557 per QALY gained compared with usual care. In the base-case, penicillin-induced anaphylaxis were set to 0.01% probability (Table 26) and utility decrement of 9 quality-adjusted life-days lost (Table 27) based on figures reported in Neuner et al. 2003 study[75] with £1,744 in treatment costs (Hex et al. 2017)[88]. Changing the rate of penicillin-induced rash from 0.01% to 0.64% as reported in Van Howe and Kusnier (2006)[76] favoured testing with Alere TestPack Plus Strep A - cassette (Abbott) and all 5 NADAL tests dominating usual care (Table 43). ICERs for the remaining 12 tests ranged from £18 per QALY gained for Strep A rapid test - test strip (Biopanda Reagents) to £57,598 per QALY gained for QuikRead Go Strep A test kit (Orion Diagnostica).

Table 43: Adult secondary care model: Deterministic sensitivity analyses – adverse effect of penicillin

	Base case			Sensitivity analysis		
Test	**Inc. costs per 1000 individuals**	**Inc. QALYs per 1000 individuals**	**ICER**	**Inc. costs per 1000 individuals**	**Inc. QALYs per 1000 individuals**	**ICER**
SA#15 - Halved prob mild penicillin reaction (rash) to 1%						
QuikRead Go Strep A test kit (Orion Diagnostica)	£1,990	0.00016	£12,700,432	£2,034	-0.00169	Dominated
Alere TestPack Plus Strep A - cassette (Abbott)	£566	0.00169	£335,358	£618	-0.00046	Dominated
SA#16 - Doubled rates of mild penicillin reaction (rash) to 4%						
Clearview exact Strep A cassette (Abbott)	£1,957	-0.00396	Dominated	£1,836	0.00107	£1,711,314
Clearview exact Strep A dipstick - test strip (Abbott)	£1,757	-0.00396	Dominated	£1,636	0.00107	£1,524,891
NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	£72	0.00804	£8,913
NADAL Strep A - cassette (nal von minden GmbH)	£221	0.00388	£57,085	£122	0.00804	£15,136
NADAL Strep A plus - cassette (nal von minden GmbH)	£246	0.00388	£63,537	£147	0.00804	£18,246

NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	£97	0.00804	£12,024
NADAL Strep A scan test - cassette (nal von minden GmbH)	£361	0.00388	£93,211	£262	0.00804	£32,557
Alere TestPack Plus Strep A - cassette (Abbott)	£566	0.00169	£335,358	£463	0.00599	£77,328
SA#17 – changed penicillin-induced anaphylaxis from 0.01% (Neuner 2003[75]) to 0.64% (Van Howe and Kusnier 2006[76])						
Clearview Exact Strep A cassette (Abbott)	£1,957	-0.00396	Dominated	£571	0.01887	£30,270
Clearview Exact Strep A dipstick - test strip (Abbott)	£1,757	-0.00396	Dominated	£371	0.01887	£19,668
Strep A rapid test - cassette (Biopanda Reagents)	£1,219	0.00311	£392,342	£45	0.02243	£2,024
Strep A rapid test - test strip (Biopanda Reagents)	£1,174	0.00311	£377,852	£0	0.02243	£18
NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	-£975	0.02275	Dominant
NADAL Strep A - cassette (nal von minden GmbH)	£221	0.00388	£57,085	-£925	0.02275	Dominant
NADAL Strep A plus - cassette (nal von minden GmbH)	£246	0.00388	£63,537	-£900	0.02275	Dominant
NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	-£950	0.02275	Dominant
NADAL Strep A scan test - cassette (nal von minden GmbH)	£361	0.00388	£93,211	-£785	0.02275	Dominant
QuikRead Go Strep A test kit (Orion Diagnostica)	£1,990	0.00016	£12,700,432	£973	0.0169	£57,598
Alere TestPack Plus Strep A - cassette (Abbott)	£566	0.00169	£335,358	-£618	0.0212	Dominant
Xpert Xpress Strep A (Cepheid)	£1,994	0.00395	£504,287	£903	0.02192	£41,202

Note that of the tests with ICERs in the region of £30,000/QALY, only the Alere TestPack Plus and QuikRead Go tests used test accuracy data from published peer-reviewed studies. See Table 15 for more information.

4.2.16.5 **Adults in secondary care - Cost of testing in secondary care**

In the base-case, the cost of confirmatory throat culture following a negative test result was applied to 6 of the 14 tests considered in the analyses (Clearview Exact Strep A cassette

(Abbott), Clearview Exact Strep A dipstick – test strip (Abbott), Strep A rapid test - cassette (Biopanda Reagents), Strep A rapid test – test strip (Biopanda Reagents), QuikRead Go Strep A test kit (Orion Diagnostica), Xpert Xpress Strep A (Cepheid)). Excluding confirmatory throat-culture favoured testing. The ICER for Strep A rapid test - cassette and test strip supplied by Biopanda Reagents from £392,342 and £377,852 to £26,452 and £11,963 per QALY gained compared with usual care respectively (Table 44)).

Table 44: Adult secondary care model: Deterministic sensitivity analyses - Exclude cost of confirmatory throat culture given negative test result

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	**Inc. QALYs per 1000 individuals**	**ICER**	**Inc. costs per 1000 individuals**	**Inc. QALYs per 1000 individuals**	**ICER**
SA#20 - Assume no swab culture in those with a negative test result						
Strep A rapid test - cassette (Biopanda Reagents)	£1,219	0.00311	£392,342	£82	0.00311	£26,452
Strep A rapid test - test strip (Biopanda Reagents)	£1,174	0.00311	£377,852	£37	0.00311	£11,963

4.2.16.6 Adults in secondary care - Utility decrement, Strep A sore throat and related complications

The base-case estimates were sensitive to changes in disutility associated with GAS related complications (Table 45). Decreasing the utility decrement associated with treated infection (for two tests) and the utility decrement for penicillin-induced rash by a half, doubling the decrement associated with untreated infection (for four tests) and doubling the decrement for abscess each favoured usual care; producing ICERs suggesting that usual care dominated testing (see Table 45 for specific tests) in comparison to the base-case assumptions. Halving the utility decrement for untreated infection and doubling the decrements for treated infection and penicillin-induced rash all favoured testing. Clearview exact Strep A cassette (Abbott) and Clearview exact Strep A dipstick - test strip (Abbott) where no longer dominated by usual care when the utility decrement associated with penicillin-induced rash was doubled whilst the NADAL tests produced ICERs ranging from £21,309 to £44,953 per QALY gained compared with usual care.

Table 45: Adult secondary care model: Deterministic sensitivity analyses - Utility decrement, Strep A sore throat and related complications

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#27 - Halved utility decrement, untreated infection						
Clearview exact Strep A cassette (Abbott)	£1,957	-0.00396	Dominated	£1,957	0.00667	£293,426
Clearview exact Strep A dipstick - test strip (Abbott)	£1,757	-0.00396	Dominated	£1,757	0.00667	£263,430
NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	£171	0.00454	£37,720
NADAL Strep A - cassette (nal von minden GmbH)	£221	0.00388	£57,085	£221	0.00454	£48,734
NADAL Strep A plus - cassette (nal von minden GmbH)	£246	0.00388	£63,537	£246	0.00454	£54,242
NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	£196	0.00454	£43,228
NADAL Strep A scan test - cassette (nal von minden GmbH)	£361	0.00388	£93,211	£361	0.00454	£79,575
SA#28 - Doubled utility decrement, untreated infection						
Strep A rapid test - cassette (Biopanda Reagents)	£1,219	0.00311	£392,342	£1,219	-0.00022	Dominated
Strep A rapid test - test strip (Biopanda Reagents)	£1,174	0.00311	£377,852	£1,174	-0.00022	Dominated
NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	£171	0.00255	£67,224
NADAL Strep A - cassette (nal von minden GmbH)	£221	0.00388	£57,085	£221	0.00255	£86,852
NADAL Strep A plus - cassette (nal von minden GmbH)	£246	0.00388	£63,537	£246	0.00255	£96,668
NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	£196	0.00255	£77,040
QuikRead Go Strep A test kit (Orion Diagnostica)	£1,990	0.00016	£12,700,432	£1,990	-0.00848	Dominated
Alere TestPack Plus Strep A - cassette (Abbott)	£566	0.00169	£335,358	£566	-0.00495	Dominated
SA#29-Halved utility decrement, treated infection						
NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	£171	0.00348	£49,248

NADAL Strep A - cassette (nal von minden GmbH)	£221	0.00388	£57,085	£221	0.00348	£63,627
NADAL Strep A plus - cassette (nal von minden GmbH)	£246	0.00388	£63,537	£246	0.00348	£70,818
NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	£196	0.00348	£56,439
QuikRead Go Strep A test kit (Orion Diagnostica)	£1,990	0.00016	£12,700,432	£1,990	-0.00243	Dominated
Alere TestPack Plus Strep A - cassette (Abbott)	£566	0.00169	£335,358	£566	-0.0003	Dominated
SA#30 - Doubled utility decrement, treated infection						
Clearview exact Strep A cassette (Abbott)	£1,957	-0.00396	Dominated	£1,957	0.00879	£222,505
Clearview exact Strep A dipstick - test strip (Abbott)	£1,757	-0.00396	Dominated	£1,757	0.00879	£199,759
NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	£171	0.00467	£36,648
NADAL Strep A - cassette (nal von minden GmbH)	£221	0.00388	£57,085	£221	0.00467	£47,349
NADAL Strep A plus - cassette (nal von minden GmbH)	£246	0.00388	£63,537	£246	0.00467	£52,700
NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	£196	0.00467	£42,000
NADAL Strep A scan test - cassette (nal von minden GmbH)	£361	0.00388	£93,211	£361	0.00467	£77,313
Alere TestPack Plus Strep A - cassette (Abbott)	£566	0.00169	£335,358	£566	0.00567	£99,787
SA#32-Doubled utility decrement, abscess						
QuikRead Go Strep A test kit (Orion Diagnostica)	£1,990	0.00016	£12,700,432	£1,990	-0.00019	Dominated
SA#35-Halved utility decrement, penicillin-induced rash						
QuikRead Go Strep A test kit (Orion Diagnostica)	£1,990	0.00016	£12,700,432	£1,990	-0.00169	Dominated
Alere TestPack Plus Strep A - cassette (Abbott)	£566	0.00169	£335,358	£566	-0.00046	Dominated
SA#36 - Doubled utility decrement, penicillin-induced rash						
Clearview exact Strep A cassette (Abbott)	£1,957	-0.00396	Dominated	£1,957	0.00107	£1,823,596
Clearview exact Strep A dipstick - test strip (Abbott)	£1,757	-0.00396	Dominated	£1,757	0.00107	£1,637,173

NADAL Strep A - test strip (nal von minden GmbH)	£171	0.00388	£44,184	£171	0.00804	£21,309
NADAL Strep A - cassette (nal von minden GmbH)	£221	0.00388	£57,085	£221	0.00804	£27,531
NADAL Strep A plus - cassette (nal von minden GmbH)	£246	0.00388	£63,537	£246	0.00804	£30,642
NADAL Strep A plus - test strip (nal von minden GmbH)	£196	0.00388	£50,636	£196	0.00804	£24,420
NADAL Strep A scan test - cassette (nal von minden GmbH)	£361	0.00388	£93,211	£361	0.00804	£44,953
Alere TestPack Plus Strep A - cassette (Abbott)	£566	0.00169	£335,358	£566	0.00599	£94,521

4.2.17 Children primary care model: base-case results

The primary care adult model (section 4.2.2) was adapted to model children presenting with suspected GAS infection in a primary care setting. The modelled pathways remain the same as the adult primary care model depicted in Figure 12 to Figure 14. The prevalence of GAS changed from 22.6% in the adult primary care model to 30.2% - median prevalence in our systematic review of test accuracy studies among children in primary care settings (see Table 25). Sensitivity and specificity of the clinical score at the specified Centor score ≥3 for a positive GAS infection were left unchanged (see estimates displayed in Table 23) as well as the modelled pathway probabilities (see Table 26) and health-state utility values (see Table 27). Test accuracy estimates were obtained from our systematic review and remained broadly the same as those used to inform the adults in primary care model (Table 24) except for five tests (BD Veritor Plus system group A Strep Assay - cassette supplied by Beckton Dickinson, OSOM Strep A test - test strip supplied by Sekisui Diagnostics, QuikRead Go Strep A test kit by Orion Diagnostica and Alere TestPack Plus Strep A - cassette and ALERE i Strep A both supplied by Abbott) – see Table 24 for further detail.

Table 46: Children primary care model - Base-case cost-effectiveness results

TestID	Test Name	Mean costs / 1000 individuals	Mean QALYs / 10,000 individuals	Inc. Costs / 10,000 individuals	Inc. QALYS / 10,000 individuals	ICER versus usual care
	Usual care (Clinical scoring based on Centor ≥3 plus clinical assessment)	£50,185	939.77019917	£0	0.0000000	
1	Clearview Exact Strep A cassette (Abbott)	£57,773	939.76305927	£7,588	-0.0071399	Dominated
2	Clearview Exact Strep A dipstick – test strip (Abbott)	£57,554	939.76305927	£7,369	-0.0071399	Dominated
3	BD Veritor Plus system group A Strep Assay - cassette (Beckton Dickinson)					
4	Strep A rapid test - cassette (Biopanda Reagents)	£56,899	939.77244279	£6,715	0.0022436	£2,992,743
5	Strep A rapid test – test strip (Biopanda Reagents)*	£56,850	939.77244279	£6,665	0.0022436	£2,970,792
6	NADAL Strep A - test strip (nal von minden GmbH)	£55,952	939.77347194	£5,768	0.0032728	£1,762,306
7	NADAL Strep A - cassette (nal von minden GmbH)	£56,007	939.77347194	£5,822	0.0032728	£1,779,026
8	NADAL Strep A plus - cassette (nal von minden GmbH)	£56,035	939.77347194	£5,850	0.0032728	£1,787,386
9	NADAL Strep A plus - test strip (nal von minden GmbH)	£55,980	939.77347194	£5,795	0.0032728	£1,770,666
10	NADAL Strep A scan test - cassette (nal von minden GmbH)	£56,160	939.77347194	£5,976	0.0032728	£1,825,846
11	OSOM Strep A test – test strip (Sekisui Diagnostics)					
12	QuikRead Go Strep A test kit (Orion Diagnostica)	£58,012	939.76701428	£7,827	-0.0031849	Dominated
13	Alere TestPack Plus Strep A - cassette (Abbott)	£56,389	939.76939575	£6,204	-0.0008034	Dominated
14	Bionexia Strep A plus - cassette (Biomerieux)					
15	Bionexia Strep A dipstick – test strip (Biomerieux)					
16	Biosynex Strep A - cassette (Biosynex)					
17	Sofia Strep A FIA (Quidel)					
18	ALERE i Strep A (Abbott)					
19	ALERE i Strep A 2 (Abbott)	£61,907	939.77326996	£11,722	0.0030708	£3,817,336
20	Cobas Strep A Assay on Liat system (Roche Diagnostics)	£74,425	939.77326996	£24,240	0.0030708	£7,893,857
21	Xpert Xpress Strep A (Cepheid)	£65,521	939.77368771	£15,336	0.0034885	£4,396,205

[1]Test accuracy data for Biopanda Reagents Strep A rapid test – test strip not available, assumed the strip has same test accuracy as the cassette version of the test

Note: Missing cost-effectiveness estimates are for the tests where either test accuracy or cost data were not available

Overall, 14 of the 21 tests were included in the child primary care model. Cost-effectiveness estimates for these tests compared with usual care are presented in Table 46. Simulated mean costs and QALYs were multiplied by 1,000 to aid clarity in presentation because of the small amount of QALYs accrued over a one-year time horizon. The base-case cost-effectiveness for children presenting in primary care largely mirrored those for the adult population. However, because of the slightly higher prevalence of GAS in children (30.2%) compared with adults (22.6%), simulated costs over the one-year time horizon were generally higher in the children model than those in the adult primary care model.

The mean costs simulated under base-case assumptions were £50,185 (£49,147 in the adult primary care model) per 1,000 children treated in primary care under usual care practice and ranged from £55,952 (£54,394 in the adult primary care model) per 1,000 children for NADAL Strep A - test strip (nal von minden GmbH) to £74,425 (£71,277 adult primary care model) per 1,000 children treated in primary care for Cobas Strep A Assay on Liat system supplied by Roche Diagnostics. Simulated QALYs were also higher for children treated in primary care than adults because of the higher baseline utility in children (0.94) compared with a utility norm of 0.863 for adults in the UK. Simulated mean QALYs were 939.7702 (859.8246 in the adult primary care model) for children treated in primary care under usual care practice and ranged from 939.7631 (859.8206 adult primary care model) for Abbott's Clearview Exact Strep A test cassette and strip to 939.7737 (859.8285 in the adult primary care model) for the other tests.

In terms of incremental cost-effectiveness, the base-case estimates suggest usual care was cheaper and generated marginally more QALYs than (and therefore dominated) the QuikRead Go Strep A test kit (Orion Diagnostica), the cassette and strip versions of the Clearview Exact Strep A test cassette supplied by Abbott and the Alere TestPack Plus Strep A - cassette also supplied by Abbott. Incremental cost-effectiveness ratios (ICERs) for the remaining ten tests suggest that testing for children in primary care under base-case assumptions produced ICERs ranging from £1,762,306 per QALY gained for NADAL Strep A - test strip (nal von minden GmbH) to £7,893,857 per QALY gained for the Xpert Xpress Strep A by Cepheid compared with usual care.

Table 47: Children primary care model: Probabilistic sensitivity analysis results

TestID	Test Name	Mean costs / 1000 individuals	Mean QALYs / 1000 individuals	Inc. Costs / 1000 individuals	Inc. QALYS / 1000 individuals	ICER versus usual care	Probability of cost-effectiveness at £20,000 per QALY
	Usual care (Clinical scoring based on Centor ≥3 plus clinical assessment)	£50,204	940.0932608	£0	0.0000000		1
1	Clearview Exact Strep A cassette (Abbott)	£57,887	940.0862286	£7,683	-0.0070321	Dominated	0
2	Clearview Exact Strep A dipstick – test strip (Abbott)	£57,668	940.0862027	£7,464	-0.0070580	Dominated	0
3	BD Veritor Plus system group A Strep Assay - cassette (Beckton Dickinson)						
4	Strep A rapid test - cassette (Biopanda Reagents)	£57,016	940.0954301	£6,812	0.0021694	£3,140,063	0
5	Strep A rapid test – test strip (Biopanda Reagents)*	£56,964	940.0955022	£6,760	0.0022415	£3,015,747	0
6	NADAL Strep A - test strip (nal von minden GmbH)	£56,046	940.0960689	£5,841	0.0028082	£2,080,115	0
7	NADAL Strep A - cassette (nal von minden GmbH)	£56,101	940.0960859	£5,897	0.0028251	£2,087,246	0
8	NADAL Strep A plus - cassette (nal von minden GmbH)	£56,128	940.0961173	£5,924	0.0028566	£2,073,823	0
9	NADAL Strep A plus - test strip (nal von minden GmbH)	£56,073	940.0961534	£5,869	0.0028927	£2,028,782	0
10	NADAL Strep A scan test - cassette (nal von minden GmbH)	£56,255	940.0961639	£6,051	0.0029031	£2,084,258	0
11	OSOM Strep A test – test strip (Sekisui Diagnostics)						
12	QuikRead Go Strep A test kit (Orion Diagnostica)	£58,149	940.0895996	£7,944	-0.0036612	Dominated	0
13	Alere TestPack Plus Strep A - cassette (Abbott)	£56,482	940.0924978	£6,278	-0.0007629	Dominated	0
14	Bionexia Strep A plus - cassette (Biomerieux)						
15	Bionexia Strep A dipstick – test strip (Biomerieux)						
16	Biosynex Strep A - cassette (Biosynex)						
17	Sofia Strep A FIA (Quidel)						
18	ALERE i Strep A (Abbott)						
19	ALERE i Strep A 2 (Abbott)	£62,058	940.0960474	£11,854	0.0027866	£4,253,800	0
20	Cobas Strep A Assay on Liat system (Roche Diagnostics)	£74,704	940.0960301	£24,500	0.0027693	£8,846,880	0
21	Xpert Xpress Strep A (Cepheid)	£65,741	940.096771	£15,536	0.0035102	£4,426,070	0

[1]Test accuracy data for Biopanda Reagents Strep A rapid test – test strip not available, assumed the strip has same test accuracy as the cassette version of the test

4.2.19 Children primary care model: exploratory sensitivity analyses

Exploratory analyses conducted to test the robustness of economic base-case estimates for children presenting in primary care with suspected GAS infection. The base-case ICERs are highly sensitive to various modelling assumptions and input values. In the sections that follow, sensitivity analysis results are presented only for those tests where the ICER is sensitive to the alternative modelling assumptions and parameter inputs (as indicated by changes in the direction of incremental costs or incremental QALYs compared with usual care).

4.2.19.1 Children primary care model - Centor threshold for starting antibiotics and testing

In the base-case children primary care model, Centor score ≥3 was used cut-off for starting antibiotic treatment in the usual care arm and to initiate testing in the intervention arm. Lowering the threshold to Centor score ≥1 favoured testing. The ICER for QuikRead Go Strep A test kit (Orion Diagnostica) and the Alere TestPack Plus Strep A - cassette (Abbott) changing from being dominated in the base-case to £2,163,678 and £7,367,395 per QALY gained respectively compared with usual care (see Table 48). Lowering the threshold to Centor score ≥2 favoured testing with the ICER for Alere TestPack Plus Strep A - cassette (Abbott) changing from being dominated in the base-case to £5,525,377 per QALY gained compared with usual care. ICERs for the other tests remain unchanged in comparison to base-case ICERs.

Table 48: Children primary care model: Deterministic sensitivity analyses - Centor threshold for starting antibiotic therapy

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#1 - Changed Centor threshold for starting antibiotics from ≥3 to ≥2						
Alere TestPack Plus Strep A - cassette (Abbott)	£6,204	-0.0008	Dominated	£12,460	0.00226	£5,525,377
SA#2 - Changed Centor threshold for starting antibiotics from ≥3 to ≥1						

QuikRead Go Strep A test kit (Orion Diagnostica)	£7,827	-0.00318	Dominated	£25,379	0.00344	£7,367,395
Alere TestPack Plus Strep A - cassette (Abbott)	£6,204	-0.0008	Dominated	£19,273	0.00891	£2,163,678

4.2.19.2 Children primary care model - Prevalence of GAS

Changing the prevalence of GAS infection among children presenting in primary care from 30.2% base-case value to 40.1% (upper value reported in studies included in the test accuracy systematic review) had minimal impact on base-case cost-effectiveness results. Changing the prevalence rate to 10% favoured testing but only the ICERs for Clearview Exact Strep A test - cassette (Abbott), the Clearview Exact Strep A dipstick - test strip (Abbott), QuikRead Go Strep A test kit (Orion Diagnostica) and Alere TestPack Plus Strep A - cassette (Abbott) changed from being dominated in the base-case to values between £1,319,975 per QALY gained for Alere TestPack Plus Strep A - cassette (Abbott) and £4,635,543 per QALY gained for Clearview Exact Strep A cassette (Abbott) compared with usual care (Table 49).

Table 49: Children primary care model: Deterministic sensitivity analyses - prevalence of GAS

	Base case Sensitivity analysis			**Sensitivity analysis**		
Test	**Inc. costs per 1000 individuals**	**Inc. QALYs per 1000 individuals**	**ICER**	**Inc. costs per 1000 individuals**	**Inc. QALYs per 1000 individuals**	**ICER**
SA#5 - Changed GAS prevalence from 30.2% to 10% (Neuner et al 2003[75])						
Clearview Exact Strep A cassette (Abbott)	£7,588	-0.00714	Dominated	£6,088	0.00131	£4,635,543
Clearview Exact Strep A dipstick - test strip (Abbott)	£7,369	-0.00714	Dominated	£5,919	0.00131	£4,507,015
QuikRead Go Strep A test kit (Orion Diagnostica)	£7,827	-0.00318	Dominated	£6,328	0.00247	£2,564,058
Alere TestPack Plus Strep A - cassette (Abbott)	£6,204	-0.0008	Dominated	£4,707	0.00357	£1,319,975

4.2.19.3 Children primary care model - Complication rates in treated and untreated GAS infection

In the base-case analysis, GAS related complications rates were set to 1.5% for untreated infection and 1.3% for treated GAS infection based on UK primary care data published by Little et al (2013b).[81] Doubling the complications rate in the treated group to 2.6% favoured

testing and changed the ICERs for Clearview Exact Strep A cassette (Abbott), Clearview Exact Strep A dipstick - test strip (Abbott), QuikRead Go Strep A test kit (Orion Diagnostica) and Alere TestPack Plus Strep A - cassette (Abbott) from being dominated to values between £2,412,772 per QALY gained for Alere TestPack Plus Strep A - cassette (Abbott) to £26,635,474 per QALY gained for Clearview Exact Strep A cassette (Abbott) compared with usual care (Table 50). Decreasing complications in the untreated group to 0.75% favoured testing and changed the ICER for Alere TestPack Plus Strep A - cassette (Abbott) from being dominated in the base-case analysis to £5,652,302 per QALY gained compared with usual care. The ICERs for all other tests were much lower in comparison to the base-case estimates but remained well above £100,000 per QALY gained in comparison to usual care.

Table 50: Children primary care model: Deterministic sensitivity analyses – complications following GAS infection

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	**Inc. QALYs per 1000 individuals**	**ICER**	**Inc. costs per 1000 individuals**	**Inc. QALYs per 1000 individuals**	**ICER**
SA#10 - Doubled complications in treated GAS infection to 2.6%						
Clearview Exact Strep A cassette (Abbott)	£7,588	-0.00714	Dominated	£6,822	0.00026	£26,635,474
Clearview Exact Strep A dipstick - test strip (Abbott)	£7,369	-0.00714	Dominated	£6,603	0.00026	£25,780,890
QuikRead Go Strep A test kit (Orion Diagnostica)	£7,827	-0.00318	Dominated	£7,348	0.00144	£5,111,532
Alere TestPack Plus Strep A - cassette (Abbott)	£6,204	-0.0008	Dominated	£5,869	0.00243	£2,412,772
SA#11 - Halved complications, untreated GAS infection to 0.075%						
Alere TestPack Plus Strep A - cassette (Abbott)	£6,204	-0.0008	Dominated	£6,010	0.00106	£5,652,302

4.2.19.4 Children primary care model - Side-effects of penicillin

Changing the rate of penicillin-induced rash from 0.01% to 0.64% as reported in Van Howe and Kusnier (2006)[76] favoured testing – the ICERs for Clearview Exact Strep A dipstick - test strip (Abbott), Clearview Exact Strep A cassette (Abbott), QuikRead Go Strep A test kit (Orion Diagnostica) and Alere TestPack Plus Strep A - cassette (Abbott) changed from being dominated by usual care in the base-case, ranging from £264,313 and £404,873 per QALY gained compared with usual care.

Table 51: Children primary care model: Deterministic sensitivity analyses - complications of penicillin

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#16 - Doubled rates of mild penicillin reaction (rash) to 4%						
QuikRead Go Strep A test kit (Orion Diagnostica)	£7,827	-0.00318	Dominated	£7,724	0.00113	£6,823,310
Alere TestPack Plus Strep A - cassette (Abbott)	£6,204	-0.0008	Dominated	£6,100	0.00355	£1,718,859
SA#17 - Changed rates of anaphylaxis from 0.01% (Neuner 2003[75]) to 0.64% (Van Howe and Kusnier 2006[76])						
Clearview Exact Strep A cassette (Abbott)	£7,588	-0.00714	Dominated	£6,211	0.01554	£399,674
Clearview Exact Strep A dipstick - test strip (Abbott)	£7,369	-0.00714	Dominated	£5,992	0.01554	£385,589
QuikRead Go Strep A test kit (Orion Diagnostica)	£6,204	-0.00318	Dominated	£5,005	0.0164	£404,873
Alere TestPack Plus Strep A - cassette (Abbott)	£6,254	-0.0008	Dominated	£4,878	0.01894	£264,313

Note that of the tests with ICERs in the region of £30,000/QALY, only the Alere TestPack Plus used test accuracy data from published peer-reviewed studies. See Table 15 for more information.

4.2.19.5 Children primary care model - Utility decrement, Strep A sore throat and related complications

As in the adult primary and secondary care models, decreasing the utility decrement associated with untreated GAS by half, doubling the utility treatment for treated GAS and doubling the utility decrement for penicillin-induced rash all favoured testing; whilst doubling the decrement associated with untreated infection favoured usual care (Table 53).

Table 53: Children primary care model: Deterministic sensitivity analyses - utility decrements associated with GAS related complications

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#27 - Halved the utility decrement, untreated GAS						
Clearview Exact Strep A cassette (Abbott)	£7,588	-0.00714	Dominated	£7,588	0.00706	£1,074,366
Clearview Exact Strep A dipstick - test strip (Abbott)	£7,369	-0.00714	Dominated	£7,369	0.00706	£1,043,375
QuikRead Go Strep A test kit (Orion Diagnostica)	£7,827	-0.00318	Dominated	£7,827	0.00569	£1,375,142
Alere TestPack Plus Strep A - cassette (Abbott)	£6,204	-0.00080	Dominated	£6,204	0.00541	£1,146,652
SA#28 - Doubled utility decrement, untreated GAS						
Strep A rapid test - cassette (Biopanda Reagents)	£6,715	0.00224	£2,992,743	£6,715	-0.00219	Dominated
Strep A rapid test - test strip (Biopanda Reagents)	£6,665	0.00224	£2,970,792	£6,665	-0.00219	Dominated
SA#30 - Doubled utility decrement, treated GAS						
Clearview Exact Strep A cassette (Abbott)	£7,588	-0.00714	Dominated	£7,588	0.00990	£766,212
Clearview Exact Strep A dipstick - test strip (Abbott)	£7,369	-0.00714	Dominated	£7,369	0.00990	£744,109
QuikRead Go Strep A test kit (Orion Diagnostica)	£7,827	-0.00318	Dominated	£7,827	0.00747	£1,048,198
Alere TestPack Plus Strep A - cassette (Abbott)	£6,204	-0.00080	Dominated	£6,204	0.00665	£932,465
SA#36 - Doubled utility decrement, penicillin-induced rash						
QuikRead Go Strep A test kit (Orion Diagnostica)	£7,827	-0.00318	Dominated	£7,827	0.00113	£6,914,611
Alere TestPack Plus Strep A - cassette (Abbott)	£6,204	-0.0008	Dominated	£6,204	0.00355	£1,748,223

4.2.19.7 Children primary care model - Lower and upper estimates of the accuracy for the clinical score and test

Changing the test accuracy data from the central estimate of test sensitivity and specificity to the lower confidence limit for all test and the Centor score favoured testing but only the ICER for Alere TestPack Plus Strep A - cassette (Abbott) changed from being dominated by usual care under base-case assumption to £13,737,541 per QALY gained compared with usual care (Table 54). The upper limits of test sensitivity and specificity favoured testing (results not presented) but none of the ICERs changed substantially to suggest different interpretation of base-case cost-effectiveness results.

Table 54: Children primary care model: Deterministic sensitivity analyses - Lower and upper limits of confidence intervals for test accuracy data

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#39 - Lower confidence limits of test accuracy						
Alere TestPack Plus Strep A - cassette (Abbott)	£6,204	-0.0008	Dominated	£6,987	0.00051	£13,737,541

4.2.20 Children in secondary care: base-case analysis results

The models for adults in secondary care (section 4.2.14) and children in primary care (section 0) were adapted to model suspected GAS infection among children in secondary care settings (urgent care/walk-in centres and emergency departments). The modelled pathways remain the same as depicted Figure 12 to Figure 14. The prevalence rate was maintained at 30.2% as in the children primary care model. Test accuracy estimates obtained from our systematic review remained broadly the same as those used to inform the primary care models except for six tests (BD Veritor Plus system group A Strep Assay - cassette (Beckton Dickinson), OSOM Strep A test - test strip (Sekisui Diagnostics), QuikRead Go Strep A test kit (Orion Diagnostica), Alere TestPack Plus Strep A - cassette (Abbott), ALERE i Strep A (Abbott) and Xpert Xpress Strep A (Cepheid)). Table 55 presents test accuracy estimates used in children secondary care model for these tests.

Table 55: Children secondary care model: Test accuracy of point-of-care tests used in economic model*

Test Name Manufacturer	Sensitivity (95% CI)	Specificity (95% CI)	Assumed distribution	Data source
OSOM Strep A test - test strip (Sekisui Diagnostics)	0.94 (0.89, 0.98)	0.97 (0.95, 0.99)	Normal (logit)	2 studies (Rogo 2011; Weinzierl 2018)
QuikRead Go Strep A test kit (Orion Diagnostica)	0.87 (0.78, 0.95)	0.78 (0.71, 0.85)	Normal (logit)	2 studies (Azrad 2019; Stefaniuk 2017)
Alere TestPack Plus Strep A - cassette (Abbott)	0.77 (0.73, 0.8)	0.97 (0.93, 0.99)	Normal (logit)	4 studies (Kurtz 2000; Lacroix 2018; Penney 2016; Santos 2003)

*Only tests with secondary care accuracy estimates that are different from those used to inform the children primary care model are presented here

Table 56 presents cost-effectiveness estimates for children treated in secondary care. As with the adult primary care model, only 14 of the 21 tests that have test accuracy and costs data are included in this analysis. The base-case estimates suggest usual care was cheaper and generated marginally more QALYs than (and therefore dominated) four tests (Clearview Exact Strep A cassette (Abbott), Clearview Exact Strep A dipstick – test strip (Abbott), QuikRead Go Strep A test kit (Orion Diagnostica) and Alere TestPack Plus Strep A - cassette (Abbott)). Incremental cost-effectiveness ratios (ICERs) for the remaining tests suggest testing was more costly and more effective than usual care with ICERs ranging from £65,122 per QALY gained for the NADAL Strep A - test strip (nal von minden GmbH) to £5,723,279 per QALY gained for Cobas Strep A Assay on Liat system (Roche Diagnostics) compared with usual care.

Table 56: Children secondary care model: Base-case cost-effectiveness results

TestID	Test Name	Mean costs / 1000 individuals	Mean QALYs / 1000 individuals	Inc. Costs / 1000 individuals	Inc. QALYS / 1000 individuals	ICER versus usual care
	Usual care (Clinical scoring based on Centor ≥3 plus clinical assessment)	£50,185	939.77019917	£0	0.0000000	
1	Clearview Exact Strep A cassette (Abbott)	£52,219	939.76305927	£2,034	-0.0071399	Dominated
2	Clearview Exact Strep A dipstick – test strip (Abbott)	£52,000	939.76305927	£1,815	-0.0071399	Dominated
3	BD Veritor Plus system group A Strep Assay - cassette (Beckton Dickinson)					
4	Strep A rapid test - cassette (Biopanda Reagents)	£51,345	939.77244279	£1,160	0.0022436	£517,066
5	Strep A rapid test – test strip (Biopanda Reagents)*	£51,296	939.77244279	£1,111	0.0022436	£495,115
6	NADAL Strep A - test strip (nal von minden GmbH)	£50,398	939.77347194	£213	0.0032728	£65,122
7	NADAL Strep A - cassette (nal von minden GmbH)	£50,453	939.77347194	£268	0.0032728	£81,845
8	NADAL Strep A plus - cassette (nal von minden GmbH)	£50,480	939.77347194	£295	0.0032728	£90,205
9	NADAL Strep A plus - test strip (nal von minden GmbH)	£50,425	939.77347194	£240	0.0032728	£73,482
10	NADAL Strep A scan test - cassette (nal von minden GmbH)	£50,606	939.77347194	£421	0.0032728	£128,662
11	OSOM Strep A test – test strip (Sekisui Diagnostics)					
12	QuikRead Go Strep A test kit (Orion Diagnostica)	£52,457	939.76701428	£2,273	-0.0031849	Dominated
13	Alere TestPack Plus Strep A - cassette (Abbott)	£50,834	939.76939575	£649	-0.0008034	Dominated
14	Bionexia Strep A plus - cassette (Biomerieux)					
15	Bionexia Strep A dipstick – test strip (Biomerieux)					
16	Biosynex Strep A - cassette (Biosynex)					
17	Sofia Strep A FIA (Quidel)					
18	ALERE i Strep A (Abbott)					
19	ALERE i Strep A 2 (Abbott)	£56,353	939.77326996	£6,168	0.0030708	£2,008,522
20	Cobas Strep A Assay on Liat system (Roche Diagnostics)	£67,760	939.77326996	£17,575	0.0030708	£5,723,279
21	Xpert Xpress Strep A (Cepheid)	£52,190	939.77368771	£2,006	0.0034885	£574,900
[1]Test accuracy data for Biopanda Reagents Strep A rapid test – test strip not available, assumed the strip has same test accuracy as the cassette version of the test						

*Note: Missing cost-effectiveness estimates are for the tests where either test accuracy or cost data were not available.

Table 57: Children secondary care model: Probabilistic sensitivity analysis results

TestID	Test Name	Mean costs / 1000 individuals	Mean QALYs / 1000 individuals	Inc. Costs / 1000 individuals	Inc. QALYS / 1000 individuals	ICER versus usual care	Probability of cost-effectiveness at £20,000 per QALY
	Usual care (Clinical scoring based on Centor ≥3 plus clinical assessment)	£50,000	940.2967868	£0	0.0000000		1
1	Clearview Exact Strep A cassette (Abbott)	£51,783	940.2897117	£1,783	-0.0070750	Dominated	0
2	Clearview Exact Strep A dipstick – test strip (Abbott)	£51,563	940.2897075	£1,563	-0.0070792	Dominated	0
3	BD Veritor Plus system group A Strep Assay - cassette (Beckton Dickinson)						
4	Strep A rapid test - cassette (Biopanda Reagents)	£51,138	940.2989313	£1,138	0.0021445	£530,655	0
5	Strep A rapid test – test strip (Biopanda Reagents)*	£51,088	940.2989679	£1,088	0.0021812	£498,896	0
6	NADAL Strep A - test strip (nal von minden GmbH)	£50,217	940.2996263	£217	0.0028395	£76,288	0
7	NADAL Strep A - cassette (nal von minden GmbH)	£50,272	940.299611	£272	0.0028243	£96,309	0
8	NADAL Strep A plus - cassette (nal von minden GmbH)	£50,299	940.2996798	£299	0.0028931	£103,485	0
9	NADAL Strep A plus - test strip (nal von minden GmbH)	£50,245	940.2995732	£245	0.0027865	£87,781	0
10	NADAL Strep A scan test - cassette (nal von minden GmbH)	£50,427	940.2995398	£427	0.0027531	£154,933	0
11	OSOM Strep A test – test strip (Sekisui Diagnostics)						
12	QuikRead Go Strep A test kit (Orion Diagnostica)	£52,132	940.2930891	£2,132	-0.0036976	Dominated	0
13	Alere TestPack Plus Strep A - cassette (Abbott)	£50,652	940.2959919	£652	-0.0007948	Dominated	0
14	Bionexia Strep A plus - cassette (Biomerieux)						
15	Bionexia Strep A dipstick – test strip (Biomerieux)						
16	Biosynex Strep A - cassette (Biosynex)						
17	Sofia Strep A FIA (Quidel)						
18	ALERE i Strep A (Abbott)						
19	ALERE i Strep A 2 (Abbott)	£56,210	940.2995831	£6,210	0.0027963	£2,220,667	0
20	Cobas Strep A Assay on Liat system (Roche Diagnostics)	£67,693	940.2994655	£17,693	0.0026787	£6,605,137	0
21	Xpert Xpress Strep A (Cepheid)	£52,023	940.3002769	£2,023	0.0034902	£579,711	0

[1]Test accuracy data for Biopanda Reagents Strep A rapid test – test strip not available, assumed the strip has same test accuracy as the cassette version of the test

4.2.22 Children secondary care model: exploratory sensitivity analyses

Exploratory analyses conducted to test the robustness of economic base-case estimates for children presenting in secondary care with suspected GAS infection. The base-case ICERs are highly sensitive to various modelling assumptions and input values. In the sections that follow, sensitivity analysis results are presented only for those tests where the ICER is sensitive to the alternative modelling assumptions and parameter inputs (as indicated by changes in the direction of incremental costs or incremental QALYs compared with usual care).

4.2.22.1 Children secondary care model - Centor threshold for starting antibiotics and testing

In the base-case model for children treated in secondary care, a threshold of ≥3 on the Centor score plus clinical assessment was used as the basis for immediate antibiotic treatment in the usual care arm and to initiate testing in the intervention arm. Changing this threshold to Centor score ≥2 had minimal impact on the base-case cost-effectiveness of all tests included in the analysis (except the Alere TestPack Plus Strep A - cassette (Abbott)). Using a threshold of ≥1 on the Centor score, favoured testing and changed the ICERs for the Alere TestPack Plus Strep A - cassette (Abbott) and the QuikRead Go Strep A test kit (Orion Diagnostica) from being dominated in the base-case to £205,449 per QALY gained and £2,303,715 per QALY gained compared with usual care, respectively (Table 58).

Table 58: Children secondary care model: Deterministic sensitivity analyses - Centor threshold for starting antibiotics and testing

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#1 - Changed Centor threshold for starting antibiotics from ≥3 (base case) to ≥2						
NADAL Strep A - test strip (nal von minden GmbH)	£213	0.00327	£65,122	£371	0.00879	£42,226
NADAL Strep A - cassette (nal von minden GmbH)	£268	0.00327	£81,845	£482	0.00879	£54,800
NADAL Strep A plus - cassette (nal von minden GmbH)	£295	0.00327	£90,205	£537	0.00879	£61,086
NADAL Strep A plus - test strip (nal von minden GmbH)	£240	0.00327	£73,482	£426	0.00879	£48,513

NADAL Strep A scan test - cassette (nal von minden GmbH)	£421	0.00327	£128,662	£791	0.00879	£90,007
Alere TestPack Plus Strep A - cassette (Abbott)	£649	-0.0008	Dominated	£1,241	0.00226	£550,135
SA#2 - Changed Centor threshold for starting antibiotics from ≥3 (base case) to ≥1						
NADAL Strep A - test strip (nal von minden GmbH)	£213	0.00327	£65,122	£495	0.01670	£29,604
NADAL Strep A - cassette (nal von minden GmbH)	£268	0.00327	£81,845	£666	0.01670	£39,891
NADAL Strep A plus - cassette (nal von minden GmbH)	£295	0.00327	£90,205	£752	0.01670	£45,035
NADAL Strep A plus - test strip (nal von minden GmbH)	£240	0.00327	£73,482	£580	0.01670	£34,748
NADAL Strep A scan test - cassette (nal von minden GmbH)	£421	0.00327	£128,662	£1,148	0.01670	£68,697
QuikRead Go Strep A test kit (Orion Diagnostica)	£2,273	-0.00318	Dominated	£7,936	0.00344	£2,303,715
Alere TestPack Plus Strep A - cassette (Abbott)	£649	-0.0008	Dominated	£1,830	0.00891	£205,449

4.2.22.2 Children secondary care model - Prevalence of GAS

Changing the prevalence of GAS infection among children presenting in secondary care from 30.2% to 40.1% (upper value reported in studies included in the test accuracy systematic review) had minimal impact on the base-case ICERs in the children secondary care model. In contrast (see Table 59), a lower prevalence of disease at 10% was more favourable to testing with ICERs ranging from £20,575 per QALY gained for NADAL Strep A - test strip (nal von minden GmbH) to £1,374,151 per QALY gained for the Clearview Exact Strep A cassette (Abbott) compared with usual care. ICERs for all other tests did not change substantially to change the direction of the base-case cost-effectiveness estimates.

Table 59: Children secondary care model: Deterministic sensitivity analyses - prevalence of GAS infection among children presenting in secondary care

	Base case			Sensitivity analysis		
Test	**Inc. costs per 1000 individuals**	**Inc. QALYs per 1000 individuals**	**ICER**	**Inc. costs per 1000 individuals**	**Inc. QALYs per 1000 individuals**	**ICER**
SA#5 - Changed GAS prevalence from 22.6% to 10%						
Clearview exact Strep A cassette (Abbott)	£2,034	-0.00714	Dominated	£1,805	0.00131	£1,374,151
Clearview exact Strep A dipstick - test strip (Abbott)	£1,815	-0.00714	Dominated	£1,636	0.00131	£1,245,623

NADAL Strep A - test strip (nal von minden GmbH)	£213	0.00327	£65,122	£100	0.00488	£20,575
NADAL Strep A - cassette (nal von minden GmbH)	£268	0.00327	£81,845	£143	0.00488	£29,227
NADAL Strep A plus - cassette (nal von minden GmbH)	£295	0.00327	£90,205	£164	0.00488	£33,553
NADAL Strep A plus - test strip (nal von minden GmbH)	£240	0.00327	£73,482	£121	0.00488	£24,901
NADAL Strep A scan test - cassette (nal von minden GmbH)	£421	0.00327	£128,662	£261	0.00488	£53,453
QuikRead Go Strep A test kit (Orion Diagnostica)	£2,273	-0.00318	Dominated	£2,045	0.00247	£828,590
Alere TestPack Plus Strep A - cassette (Abbott)	£649	-0.0008	Dominated	£424	0.00357	£118,942

4.2.22.3 Children secondary care model - Complication rates

Halving complications in the untreated group to 0.75%, the ICER was favourable to testing for the Alere TestPack Plus Strep A - cassette (Abbott) in comparison to ICERs produced under base-case assumptions. Doubling the complications rate in the treated group to 2.6% favoured testing, the ICER for the Clearview Exact Strep A dipstick - test strip (Abbott), Clearview Exact Strep A cassette (Abbott) , Alere TestPack Plus Strep A - cassette (Abbott) and QuikRead Go Strep A test kit (Orion Diagnostica) changed from being dominated by usual care to between £129,172 (Alere TestPack Plus Strep A - cassette (Abbott)) and £4,949,827 (Clearview Exact Strep A cassette (Abbott)) per QALY gained compared with usual care respectively (Table 60).

Table 60: Children secondary care model: Deterministic sensitivity analyses - complications of GAS infection

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#10 - Doubled complications, treated infection to 2.6%						
Clearview Exact Strep A cassette (Abbott)	£2,034	-0.00714	Dominated	£1,268	0.00026	£4,949,827
Clearview Exact Strep A dipstick - test strip (Abbott)	£1,815	-0.00714	Dominated	£1,049	0.00026	£4,095,204
NADAL Strep A - test strip (nal von minden GmbH)	£213	0.00327	£65,122	£165	0.00374	£44,246

NADAL Strep A - cassette (nal von minden GmbH)	£268	0.00327	£81,845	£220	0.00374	£58,899
NADAL Strep A plus - cassette (nal von minden GmbH)	£295	0.00327	£90,205	£247	0.00374	£66,225
NADAL Strep A plus - test strip (nal von minden GmbH)	£240	0.00327	£73,482	£193	0.00374	£51,574
NADAL Strep A scan test - cassette (nal von minden GmbH)	£421	0.00327	£128,662	£373	0.00374	£99,924
QuikRead Go Strep A test kit (Orion Diagnostica)	£2,273	-0.00318	Dominated	£1,794	0.00144	£1,247,882
Alere TestPack Plus Strep A - cassette (Abbott)	£649	-0.0008	Dominated	£314	0.00243	£129,172
SA#11 - Halved complications, untreated infection 0.75%						
Alere TestPack Plus Strep A - cassette (Abbott)	£649	-0.0008	Dominated	£456	0.00106	£428,791

4.2.22.4 Children secondary care model - Adverse effects of penicillin

Cost-effectiveness estimates were most sensitive to adverse effects of penicillin. Halving the mild/uncomplicated side-effects of penicillin (rash) to 1.0% favoured usual care (results not shown here), whilst doubling it favoured testing (see Table 61). Changing the rate of penicillin-induced anaphylaxis from 0.01% to the 0.64% favoured testing and generated ICERs with the Alere TestPack Plus Strep A - cassette (Abbott) and the NADAL tests all dominating usual care. The Clearview Exact Strep A dipstick - test strip and cassette supplied by Abbott produced ICERs of £28,181 and £42,266 per QALY gained whilst the Strep A rapid test - test strip and cassette supplied by Biopanda Reagents produced £1,643 and £4,105 per QALY gained compared with usual care (Table 61). The Xpert Xpress Strep A (Cepheid) and QuikRead Go Strep A test kit (Orion Diagnostica) produced ICERs of £51,637 and £66,111 per QALY gained respectively. ICERs for the ALERE i Strep A 2 (Abbott) and Cobas Strep A Assay on Liat system (Roche Diagnostics) remained above £100,000 per QALY gained compared to usual care (not displayed in Table 61).

Table 61: Children secondary care model: Deterministic sensitivity analyses – Adverse effects of penicillin

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#16 - Doubled rates of mild penicillin reaction (rash) to 4%						
NADAL Strep A - test strip (nal von minden GmbH)	£213	0.00327	£65,122	£123	0.00705	£17,378
NADAL Strep A - cassette (nal von minden GmbH)	£268	0.00327	£81,845	£177	0.00705	£25,134
NADAL Strep A plus - cassette (nal von minden GmbH)	£295	0.00327	£90,205	£205	0.00705	£29,013
NADAL Strep A plus - test strip (nal von minden GmbH)	£240	0.00327	£73,482	£150	0.00705	£21,256
NADAL Strep A scan test - cassette (nal von minden GmbH)	£421	0.00327	£128,662	£331	0.00705	£46,855
QuikRead Go Strep A test kit (Orion Diagnostica)	£2,273	-0.00318	Dominated	£2,169	0.00113	£1,916,392
Alere TestPack Plus Strep A - cassette (Abbott)	£649	-0.0008	Dominated	£545	0.00355	£153,598
SA#17 – Changed penicillin-induced anaphylaxis from 0.01% (Neuner 2003[75]) to 0.64% (Van Howe and Kusnier 2006[76])						
Clearview Exact Strep A cassette (Abbott)	£2,034	-0.00714	Dominated	£657	0.01554	£42,266
Clearview Exact Strep A dipstick - test strip (Abbott)	£1,815	-0.00714	Dominated	£438	0.01554	£28,181
Strep A rapid test - cassette (Biopanda Reagents)	£1,160	0.00224	£517,066	£82	0.02000	£4,105
Strep A rapid test - test strip (Biopanda Reagents)	£1,111	0.00224	£495,115	£33	0.02000	£1,643
NADAL Strep A - test strip (nal von minden GmbH)	£213	0.00327	£65,122	-£828	0.02043	Dominant
NADAL Strep A - cassette (nal von minden GmbH)	£268	0.00327	£81,845	-£773	0.02043	Dominant
NADAL Strep A plus - cassette (nal von minden GmbH)	£295	0.00327	£90,205	-£746	0.02043	Dominant
NADAL Strep A plus - test strip (nal von minden GmbH)	£240	0.00327	£73,482	-£801	0.02043	Dominant

NADAL Strep A scan test - cassette (nal von minden GmbH)	£421	0.00327	£128,662	-£620	0.02043	Dominant
QuikRead Go Strep A test kit (Orion Diagnostica)	£2,273	-0.00318	Dominated	£1,084	0.0164	£66,111
Alere TestPack Plus Strep A - cassette (Abbott)	£649	-0.0008	Dominated	-£549	0.01894	Dominant
Xpert Xpress Strep A (Cepheid)	£2,006	0.00349	£574,900	£1,019	0.01974	£51,637

Note that of the tests with ICERs in the region of £30,000/QALY, only the Alere TestPack Plus used test accuracy data from published peer-reviewed studies. See Table 15 for more information.

4.2.22.5 Children secondary care model - Cost of testing in secondary care

Excluding confirmatory throat-culture costs following a negative test result favoured testing and generated ICERs ranging from £29,702 per QALY gained for Strep A rapid test - test strip (Biopanda Reagents) to £51,653 per QALY gained Strep A rapid test - cassette (Biopanda Reagents) compared with usual care (Table 62).

Table 62: Children secondary care model: Deterministic sensitivity analyses - exclude cost of confirmatory culture given negative test result

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#20 - Assume no Swab culture in those with a negative test result						
Strep A rapid test - cassette (Biopanda Reagents)	£1,160	0.00224	£517,066	£116	0.00224	£51,653
Strep A rapid test- test strip (Biopanda Reagents)	£1,111	0.00224	£495,115	£67	0.00224	£29,702

4.2.22.6 Children secondary care model - Utility decrement, GAS related complications

The base-case estimates were sensitive to changes in disutility associated with GAS related complications (Table 63). Scenarios that favoured testing include decreasing the utility decrement of untreated infection by half, doubling the decrement of treated infection and doubling the decrement associated with mild penicillin reaction. The ICER for the Clearview exact Strep A cassette and test strip supplied by Abbott were no longer dominated by usual care, whilst ICERs for NADAL's tests remained under £100,000 per QALY gained compared with usual care. On the otherhand, doubling utility decrement of untreated infection was less

favourable to testing and resulted in Strep A rapid test - cassette (Biopanda Reagents) Strep A rapid test - test strip (Biopanda Reagents) being dominated by usual care (Table 63).

Table 63: Children secondary care model: Deterministic sensitivity analyses - Utility decrement, Strep A sore throat and related complications – children secondary care model

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#27 - Halved utility decrement, untreated infection						
Clearview exact Strep A cassette (Abbott)	£2,034	-0.00714	Dominated	£2,034	0.00706	£287,940
Clearview exact Strep A dipstick - test strip (Abbott)	£1,815	-0.00714	Dominated	£1,815	0.00706	£256,947
NADAL Strep A - test strip (nal von minden GmbH)	£213	0.00327	£65,122	£213	0.00416	£51,228
NADAL Strep A - cassette (nal von minden GmbH)	£268	0.00327	£81,845	£268	0.00416	£64,383
NADAL Strep A plus - cassette (nal von minden GmbH)	£295	0.00327	£90,205	£295	0.00416	£70,959
NADAL Strep A plus - test strip (nal von minden GmbH)	£240	0.00327	£73,482	£240	0.00416	£57,804
QuikRead Go Strep A test kit (Orion Diagnostica)	£2,273	-0.00318	Dominated	£2,273	0.00569	£399,281
Alere TestPack Plus Strep A - cassette (Abbott)	£649	-0.0008	Dominated	£649	0.00541	£120,004
SA#28 - Doubled utility decrement, untreated infection						
Strep A rapid test - cassette (Biopanda Reagents)	£1,160	0.00224	£517,066	£1,160	-0.00219	Dominated
Strep A rapid test - test strip (Biopanda Reagents)	£1,111	0.00224	£495,115	£1,111	-0.00219	Dominated
SA#30 - Doubled utility decrement, treated infection						
Clearview exact Strep A cassette (Abbott)	£2,034	-0.00714	Dominated	£2,034	0.00990	£205,352
Clearview exact Strep A dipstick - test strip (Abbott)	£1,815	-0.00714	Dominated	£1,815	0.00990	£183,248
NADAL Strep A - test strip (nal von minden GmbH)	£213	0.00327	£65,122	£213	0.00434	£49,131
NADAL Strep A - cassette (nal von minden GmbH)	£268	0.00327	£81,845	£268	0.00434	£61,748

NADAL Strep A plus - cassette (nal von minden GmbH)	£295	0.00327	£90,205	£295	0.00434	£68,055
NADAL Strep A plus - test strip (nal von minden GmbH)	£240	0.00327	£73,482	£240	0.00434	£55,438
NADAL Strep A scan test - cassette (nal von minden GmbH)	£421	0.00327	£128,662	£421	0.00434	£97,068
QuikRead Go Strep A test kit (Orion Diagnostica)	£2,273	-0.00318	Dominated	£2,273	0.00747	£304,351
Alere TestPack Plus Strep A - cassette (Abbott)	£649	-0.0008	Dominated	£649	0.00665	£97,588
SA#36 - Doubled utility decrement, penicillin-induced rash						
NADAL Strep A - test strip (nal von minden GmbH)	£213	0.00327	£65,122	£213	0.00705	£30,212
NADAL Strep A - cassette (nal von minden GmbH)	£268	0.00327	£81,845	£268	0.00705	£37,970
NADAL Strep A plus - cassette (nal von minden GmbH)	£295	0.00327	£90,205	£295	0.00705	£41,848
NADAL Strep A plus - test strip (nal von minden GmbH)	£240	0.00327	£73,482	£240	0.00705	£34,090
NADAL Strep A scan test - cassette (nal von minden GmbH)	£421	0.00327	£128,662	£421	0.00705	£59,689
QuikRead Go Strep A test kit (Orion Diagnostica)	£2,273	-0.00318	Dominated	£2,273	0.00113	£2,007,701
Alere TestPack Plus Strep A - cassette (Abbott)	£649	-0.0008	Dominated	£649	0.00355	£182,962

4.2.22.7 Children secondary care model - Lower and upper estimates of the accuracy for the clinical score and test

Changing the test accuracy data from the central estimate of test sensitivity and specificity to the lower confidence limit for all test and the Centor score favoured testing but only the ICER for Alere TestPack Plus Strep A - cassette (Abbott) changed from being dominated by usual care under base-case assumption to £1,356,265 per QALY gained compared with usual care, whilst ICERs for NADAL's tests remained under £100,000 per QALY gained compared with usual care (Table 64). The upper limits of test sensitivity and specificity favoured testing (results not presented) but none of the ICERs changed substantially to suggest different interpretation of base-case cost-effectiveness results.

Table 64: Children secondary care model: Deterministic sensitivity analyses - Lower and upper limits of confidence intervals for test accuracy data

Test	Base case			Sensitivity analysis		
	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER	Inc. costs per 1000 individuals	Inc. QALYs per 1000 individuals	ICER
SA#39 - Lower confidence limits of test accuracy						
NADAL Strep A - test strip (nal von minden GmbH)	£213	0.00327	£65,122	£208	0.00378	£54,933
NADAL Strep A - cassette (nal von minden GmbH)	£268	0.00327	£81,845	£270	0.00378	£71,352
NADAL Strep A plus - cassette (nal von minden GmbH)	£295	0.00327	£90,205	£301	0.00378	£79,562
NADAL Strep A plus - test strip (nal von minden GmbH)	£240	0.00327	£73,482	£239	0.00378	£63,143
Alere TestPack Plus Strep A - cassette (Abbott)	£649	-0.0008	Dominated	£690	0.00051	£1,356,265

4.2.23 Additional sensitivity analyses

Table 65 in Appendix 7 displays the list of the 39 deterministic sensitivity analyses conducted to explore the impact of alternative modelling assumptions and parameter inputs on base-case ICERs. In the majority of cases, the ICERs were robust to the implemented changes in the majority of the analyses implemented and the base-case cost-effectiveness conclusions remain unchanged. In particular, assuming a shorter 14-day time horizon (SA#3) which is consistent with typical duration and resolution of symptoms of GAS sore throat infection

favoured usual care but the ICERs did not changed substantially to suggest a different interpretation of the base-case cost-effectiveness. Assuming that the treating primary care healthcare professional in both the intervention and usual care arms is a nurse or a pharmacist (SA#19) rather than a GP doctor favoured testing, only if the test cannot be done with the allocated consultation time. In this instance, the costs associated with the additional clinician time taken to administer and process test results is much lower if seen by a nurse or pharmacist in comparison to if the treating clinician is a GP doctor. Similarly, excluding the cost of the additional clinician time required for process test results (SA#22) favoured testing only where testing cannot be done within allocated primary care consultation time.

4.3 Summary of economic modelling

We undertook a systematic search for economic evaluation studies of the use of point-of-care tests as listed in the NICE scope for patients with suspected GAS infection. We did not identify any relevant economic models that could be adapted. Hence, a *de novo* decision tree model was built to compare point-of-care testing in conjunction with clinical scoring tools with clinical scoring tools alone for children and adults presenting with GAS infection in primary and secondary care settings.

The model took account of the presenting prevalence of disease in the modelled population, accuracy of clinical scoring and testing, the prescribing behaviour of treating clinicians and complications of the infection and treatment. In the base-case analysis, costs were calculated from a UK NHS/PSS perspective over the one-year time horizon. The health impact of intervention was expressed in QALYs captured through application of disutilities associated with treated and untreated infection and related complications over the modelled time horizon.

The scope of the appraisal had called for 21 tests to be evaluated in comparison to usual care practice, however, difficulties in obtaining reliable test accuracy and cost data for all tests, meant that we were only able to include 14 of the 21 tests for which relevant data were available in final economic modelling. Under the base-case model assumptions for adults presenting with suspected GAS in primary care, the incremental cost-effectiveness ratio (ICER) suggest usual care dominated two tests (Clearview Exact Strep A cassette and

Clearview Exact Strep A dipstick - test strip both supplied by Abbott). For the remaining 12 tests, testing was marginally more effective and more costly than usual care with ICER ranging from from £1,353,677 per QALY gained for NADAL Strep A test strip (nal von minden GmbH) to £6,059,081 per QALY for Roche Diagnostics's Cobas Strep A Assay on Liat system compared with usual care.

Probabilistic analyses based on 1,000 Monte-Carlo simulations of the ICER assessed parameter uncertainty and generated probability statements about the cost-effectiveness of point-of-care testing across a range of willingness-to-pay thresholds. Probabilistic ICERs produced results similar to the deterministic base-case ICERs, and suggested that testing was associated with zero probability of cost-effectiveness at willingness to pay thresholds of £0 to £100,000 per QALY gained under base-case assumptions. Similar cost-effectiveness results were obtained in the base-case models for adults presenting in secondary care, and primary and secondary care models for children.

Extensive exploratory deterministic sensitivity analyses of the base-case inputs and assumptions were conducted to understand key model drivers. The findings suggest that the ICER is highly sensitive to parameter inputs and assumptions that (i) increase the cost of testing (acquisition cost of test, additional clinician time for administering and processing test results, and cost of confirmatory throat culture for those testing negative) and ii) the penalty for antibiotic over-prescription/unnecessary antibiotic use (acquisition cost of antibiotic and probabilities for penicillin-induced anaphylaxis and rash). Factoring in costs associated with additional clinician time (at £4 per minute of GP time) for administering tests and £8 for a confirmatory throat culture given a negative test in the base-case both favour usual care as these costs can be substantially higher than the actual cost of the test and are applied only to the intervention arm. On the other-hand, the model predicts lower antibiotic use with testing compared with usual care; however, the cost of antibiotic treatment at £0.91 per course of penicillin, the treatment of choice for GAS infection, is considerably cheaper (than the acquisition costs for majority of the test kits) such that the penalty for supplying antibiotics to those who don't need it.

The base-case incorporates serious adverse-effects of penicillin such as penicillin-induced anaphylaxis with associated high treatment costs and disutility but the modelled rate of

0.01%[75] used in the base-case suggests anaphylaxis is very rare and its impact is therefore minimal on the cost-effectiveness of testing. Sensitivity analyses increasing the rate of anaphylaxis to 0.64% based on another economic evaluation of GAS pharyngitis[76] favoured testing – the ICER for Clearview Exact Strep A dipstick - test strip (Abbott) and Clearview Exact Strep A cassette (Abbott) changed from being dominated by usual care in the base-case to £288,702 and £299,305 per QALY gained compared with usual care.

Cost-effectiveness estimates were also sensitive to the prevalence of GAS infection (higher prevalence favouring usual care and lower prevalence favouring testing), the disutility for untreated infection (lower values favour testing whilst doubling the decrement associated with untreated infection favoured usual care), and disutility for treated GAS infection (doubling the disutility favours testing).

4.3.1 Points for discussion regarding the economic modelling

A number of limitations apply to the economic model:

- Although the economic model represented the clinical care pathway in the NHS, practice and management will vary from site to site (within and across both primary care and secondary care settings).
- We could only compare point-of-care testing for 14 of the 21 tests listed in the NICE scope as we did not have test accuracy and/or cost data for the other 7 point-of-care tests.
- There was not enough information on test accuracy data to model Strep A infection in the pharmacy setting or for the elderly population.
- Inputs (except for the sensitivity and specificity data from our effectiveness review) were generally available as point estimates without associated measures of uncertainty such as confidence intervals and standard errors required for probabilistic modelling. Thus, we have had to follow the common practice of assuming a ±10% around the central estimate to incorporate uncertainty in our modelling. This approach to probabilistic analysis is itself associated with degree of uncertainty as it may underestimate or overestimate the true uncertainty in the evidence.

Our protocol had specified a time horizon of 14-days as the evidence suggest GAS infection is a self-limiting illness with majority of patients making a complete recovery within two-weeks of the infection.[81] However, we extended the time horizon to one-year in the

base-case model to accommodate the impact of rare complications of GAS such as acute rheumatic fever where we found evidence to suggest that these complications could be associated with as much as 75 quality-adjusted-life days lost.[75-77] This longer time horizon however required further assumptions to keep the modelling feasible and supported by appropriate evidence.

There is some RCT evidence to suggest the use of rapid antigen detection tests may help reduce antibiotic prescribing rates, but there was no evidence on the effect of using molecular technologies. If a test was proven to be extremely accurate, then it is plausible that clinical staff would trust the outcomes. There was no evidence found on time to antimicrobial prescribing decision, number of appointments required per episode, and onward transmission of infection.

5.2.2 Cost-effectiveness

The systematic review of cost-effectiveness studies identified three studies that used the rapid antigen detection tests as identified in the NICE scope and were classed as economic evaluations. Two studies had some notable limitations and could not be fully data extracted. The one study that allowed a full data extraction, was classed as a high quality economic evaluation when checked against the CHEERS reporting tool.

Fourteen of the twenty-one tests listed in the NICE scope had relevant data on test accuracy and costs, to be included in the final economic modelling. In the base-case analysis, which included adult patients seen in primary care with suspected GAS infection, the economic model found considerable uncertainty about the cost-effectiveness of the different point-of-care tests for suspected GAS infection. This finding was also seen in the other economic models which were adapted for the different patient groups and settings (adult patients seen in the hospital, children seen in primary care and children seen in the hospital). Important uncertainties in the model include parameter inputs and assumptions that increase (i) the cost of testing (acquisition cost of test, additional clinician time for administering and processing test results, and cost of confirmatory throat culture for those testing negative) and ii) the penalty for antibiotic over-prescription/unnecessary antibiotic use (acquisition cost of antibiotic and probabilities for penicillin-induced anaphylaxis and rash).

5.3 Strengths and Limitations

We used a rigorous and exhaustive search to conduct a comprehensive systematic review (literature search, data extraction and analysis) and locate primary studies. All relevant

Although the economic model represented the clinical care pathway in the NHS, practice and management will vary from site to site (within and across both primary care and secondary care settings). There was not enough information on test accuracy data to model GAS for the pharmacy setting or for the elderly population. Furthermore, we could only compare 14 of the 21 point-of-care tests as listed in the NICE scope as we did not have test accuracy and/or cost data for the other 7 point-of-care tests. The modelling may have underestimated the costs as we did not take into account the different strains of GAS which may have influenced test performance and alter the profile of complications, seasonality of GAS infection, resistance to antimicrobial therapy, the onward transmission of the infection and the broader societal costs.