NICE National Institute for Health and Care Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

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

Diagnostics Consultation Document – Comments

Diagnostics Advisory Committee date: 20th August 2019

THEME: PREVALENCE OF STREP A THROAT INFECTIONS

Comment number	Name and organisation	Section number	Comment	NICE response
1	Abbott	3.3	Prevalence affects the predictive values of diagnostic tools and can affect study outcome and cost efficiency modelling.	Thank you for your comment which the committee considered. It recalled that the EAG did sensitivity analyses to explore the impact of Strep A prevalence on model results. The sensitivity analyses assumed 10% and 35.9% prevalence rates in the adult models (compared to 22.6% in the base-case analysis), and 10% and 40.1% prevalence in the children's models (compared to 30.2% in the base-case analysis). Changing prevalence of strep A had minimal impact on the model results, and did not change the interpretation of cost-effectiveness of the rapid strep A tests.
2	British Infection Association	3.26	Model inputs - the % prevalence is highly seasonal especially in temperate regions. In the springtime the % could be higher than the % cited. How was this % decided upon?	Thank you for your comment which the committee considered. It recalled that the prevalence estimates (for adults and children) used in the model were based on published literature (Little et al. 2014 for adults; a median of 3 non-UK studies of children in primary care for children), and that the EAG did sensitivity analyses to explore the impact of strep A prevalence on model results. The sensitivity analyses assumed 10% and 35.9% prevalence

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				rates in the adult models (compared to 22.6% in the base-case analysis), and 10% and 40.1% prevalence in the children's models (compared to 30.2% in the base-case analysis). Changing prevalence of strep A had minimal impact on the model results, and did not change the interpretation of cost-effectiveness of the rapid strep A tests.
3	Public Health England	General	The prevalence estimates for the presence of GAS, even in the presence of symptoms, seems high based on our clinical experience.	Thank you for your comment which the committee considered. It recalled that the prevalence estimates of strep A (for adults and children) used in the model were based on published literature (Little et al. 2014 for adults; a median of 3 non-UK studies of children in primary care for children), and that the EAG did sensitivity analyses, and that the EAG did sensitivity analyses to explore the impact of strep A prevalence on model results. The sensitivity analyses assumed 10% and 35.9% prevalence rates in the adult models (compared to 22.6% in the base-case analysis), and 10% and 40.1% prevalence in the children's models (compared to 30.2% in the base-case analysis). Changing

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				prevalence of strep A had minimal impact on the model results, and did not change the interpretation of cost-effectiveness of the rapid strep A tests.

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4	Abbott	2.7	Strep A patients cause costs; and the severity level or complication can be a cost driver. In addition, diagnostic accuracy can prevent complications, by reducing the likelihood of silent antibody response and thus improve outcomes. The *de novo* model of NICE presented in the "*Rapid tests for group A streptococcal infections in people with a sore throat Committee Papers"* does not include all necessary risk and subgroups: pregnant women, for which underdiagnosis of Strep A can lead to severe complications, or Paediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAs) might be also added to the scope of future studies (to name just a few examples). We appreciate that the de-*novo* model assumes a 1-year time horizon to capture rare, serious events caused by Strep A, but low incidence of these rare cases might have led to a bias of the results. "Complications are considered as a rare effect" (Page 158, DAP44 Committee papers redacted document), using for example *Little et al. (Ref. 81,* DAP44 Committee papers redacted document*)* as a reference. The direct and indirect effect on ICERs, QALYs could change and thus potentially	Thank you for your comment which the committee considered. It recalled that high risk groups such as women who are pregnant or postnatal were not included in this assessment. This was because people who are at high risk of complications should be assessed and treated in agreement with NICE guidelines on antimicrobial prescribing in acute sore throat. A summary box was added at the beginning of the guidance document to specify which populations were considered in the assessment, and which were not. The committee heard from the EAG that they chose the 1-year time horizon to capture rare but significant (and thus having longer-terms impact on QALYs) complications of strep A, such as rheumatic fever. They advised that this time horizon is unlikely to have introduced bias as disutilities were only applied to the time the symptoms and complications were experienced. A shorter time horizon of 14 days was explored in sensitivity analyses, which only had a minor

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			render RADT and Rapid Molecular solutions not only cost efficient but also beneficial for patients in the UK. We see a need to provide tailored Strep A solutions to the individual segments in the UK and would like to explore the integration for a multi-technology Strep A solution.	impact on the model results, and did not change the conclusions of this assessment. The EAG did a number of sensitivity analyses varying the probability of complications (with and without antibiotics) and associated disutilities, but these did not change the conclusions.
5	British Infection Association	2.1	The statements implying rarity of bacterial causes of sore throat and rarity of Strep A complications perhaps should be amended in view of >30,000 cases of scarlet fever last year in England and rising rates of invasive Strep A /associated high mortality. This could be achieved without reducing the impact of the message regarding unnecessary use of antibiotics	Thank you for your comment which the committee considered. It discussed that the model did not consider scarlet fever as a complication of sore throat because of a lack of data to allow the external assessment group to quantify its impact on quality of life. The committee was aware that scarlet fever is more likely in children than adults and that people presenting with suspected scarlet fever were outside the scope of this assessment because this is a notifiable condition which requires different clinical decisions compared with managing an uncomplicated throat infection. The committee heard from clinical experts that rates of scarlet fever appear to be increasing in

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				the UK in recent years but are still low considering the total number of children presenting with a sore throat. It is uncertain whether this increase is linked to changes in antimicrobial prescribing in recent years. The committee also heard that the rates of invasive strep A appear to be increasing in the UK in recent years, but are still relatively low. Section 4.12 of the guidance document was updated to capture this discussion and a summary box was added at the beginning of the document to specify that people with scarlet fever were not considered in this guidance.
6	British Infection Association	2.7	The risk of mortality from invasive Strep A is higher in children aged under 1. Scarlet fever is mentioned just twice (once in section 2.5 -as a symptom-whereas it is in fact a statutorily notifiable disease- and once in 2.7 as a complication). Scarlet fever and strep A throat are overlapping conditions and there is currently an epidemic in England; was this considered in the assessment?	Thank you for your comment which the committee considered. It recalled children aged under 1 year were not considered in this assessment because they often present with a temperature and have difficulty communicating their symptoms; the assessment of under 5s is described in NICE's guideline on fever in under 5s: assessment and initial management.

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				The committee discussed that the model did not consider scarlet fever as a complication of sore throat because of a lack of data to allow the external assessment group to quantify its impact on quality of life. The committee was aware that scarlet fever is more likely in children than adults and that people presenting with suspected scarlet fever were outside the scope of this assessment because this is a notifiable condition which requires different clinical decisions compared with managing an uncomplicated throat infection The rates of scarlet fever appear to be increasing in the UK in recent years but are still low considering the total number of children presenting with a sore throat. It is uncertain whether this increase is linked to changes in antimicrobial prescribing in recent years. Section 4.12 was expanded to capture the committee discussion; a summary box was added at the beginning of the diagnostic guidance to specify that under 5s and people with

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				scarlet fever were not considered in this guidance.
7	British Infection Association	3.33	Rates of quinsy are increasing.	Thank you for your comment which the committee considered. It recalled that the external assessment group did sensitivity analyses around the rates of complications. When the rate of complications was doubled from the value used in the base case (to 3% for untreated infections, or to 2.6% for treated infections), it did not have a major impact on the model results.

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THEME: DIAGNOSTIC ACCURACY OF RAPID STREP A TESTS

Comment number	Name and organisation	Section number	Comment	NICE response
8	Abbott	2.12 & 2.13	The rationale for culture confirmation testing lies in the performance of Rapid Antigen Detection tests. The sensitivity of rapid antigen tests in comparison with the gold standard Cell Culture is often not high enough to rule out Strep A disease. As Strep A can cause complications, confirmation is recommended. The same rationale would be applicable for any other diagnostic tool like the CENTOR or FeverPain Scores to increase the diagnostic confidence in our opinion. In contrast [to the accuracy of clinical scoring tools] the clinical accuracy of Rapid Antigen Detection Tests is higher. Page 17 of the *Committee Paper* describes the performance of diagnostic tests is a key driver in HEOR studies. One limitation that Abbott sees in agreement with the author´s is the variation in sensitivities listed in the results overview, which is not a true representation of the performance of Abbott´s Strep A tests (both rapid antigen detection tests and rapid molecular). In agreement with the authors of the *Committee Paper,* we see a need to independently test performance of Strep A tests in the various UK settings, in which Strep A diagnosis can be beneficial. We would like to discuss study proposals to overcome the current limitations of heterogenous-, and not NHS pathway matching, data sets.	Thank you for your comment which the committee considered. It recalled that the cost of confirmatory microbiological testing (for negative rapid strep A results) was only applied to rapid strep A tests which specified the need for such testing in their information for use document, or if the company confirmed to NICE that this is required. This assumption was also explored in sensitivity analyses. This is captured in Table 1 of the diagnostics guidance document. Clinical experts advised during scoping that throat swabs are not routinely take in practice. The committee reflected that the diagnostic accuracy data for all tests were taken either from the systematic literature review done by the EAG, or from unpublished information submitted by the manufacturers. As noted in section 3.28 of the diagnostics guidance document, the estimates of accuracy based on unpublished manufacturers' data or FDA reports were consistently higher than the estimates from the published peer-reviewed studies. The committee noted that that some tests only had accuracy data from studies done

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			Abbott provides a broad selection of Strep A tests. As described the *Committee Paper and in section 2.12*, the characteristics of cohorts and thus the overall performance of tests can vary. We agree with section 3.2.6.8 (DAP44 Committee papers redacted document) performance of RADTs including the TestpackTM, which is estimated higher than clinical scores and in general a combination of which might be of benefit and even cost effective (also documented with peer reviewed studies). Besides, we do not agree that the studies provided for the brands Clearview, TestpackTM or Alere i / ID NOW are biased. We would appreciate to have a deeper discussion not only about the landscape of commercially available tests but also have a closer look at the technologies used and in which setting the value of each of the products and their price ranges could be. New rapid molecular technologies like the ID NOW Strep A 2 test have the highest performance characteristics which are shown by studies listed in the instructions for use. With the performance increase in comparison with conventional rapid antigen tests, cell culture confirmation is not necessary anymore. While independent clinical studies are currently rare and not available for the primary care- as well as secondary	under ideal conditions such as in unpublished manufacturer studies, which is unlikely to be repeatable in routine clinical practice. Therefore, the economic models based solely on manufacturers' test accuracy data should be interpreted with caution. The committee also noted that the estimates across different studies were highly varied (even for the same test). concluding that the performance of the rapid tests in routine clinical practice is uncertain and difficult to predict. This consideration is captured in section 4.5 of the guidance document. Further advice on evidencing the value of products can be sought from NICE's office for market access or the NICE scientific advice programme The committee noted that the values quoted here for the ID Now Strep A 2 test (previously called Alere Strep A 2) are equivalent to those used in the economic model for this technology. These can be found in table 4 of the guidance document.

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			care systems in the UK, Abbott would like to state that the ID NOW Strep A 2 test, and its high performance (Sensitivity: 98.5% (95%CI: 95.6%-99.5%), Specificity 93.4% (95%CI: 91.4%-94.9%)) accompanied by the CLIA waiver by the FDA, is a unique and accessible solution for all healthcare settings in the UK.	
9	Becton Dickinson and company	General	Secondly, the analysis uses a mixed approach to modeling diagnostic test accuracy. Where available, the analysis uses clinically derived estimates of sensitivity and specificity but, where not available, validation data from the manufacturer is used. This is often unhelpful to interpreting accurate results and can even lead to misleading conclusions. BD believes that the analysis should use either one approach or the other in assessing diagnostic test performance. If this is not feasible then the analysis should be split into two separate parts.	Thank you for your comment which the committee considered. The committee noted that some tests only had accuracy data from studies done under ideal conditions such as in unpublished manufacturer studies, which is unlikely to be repeatable in routine clinical practice. This is noted in section 4.5 of the guidance document. Tables 4 and 5 of the guidance document specify the sources of diagnostic accuracy data; this is also captured in footnotes to table 10 and 11.
10	Public Health England	General	There is no comment anywhere on what would be an appropriate sensitivity for use in clinical setting e.g. 90-95% or over. This would be useful.	Thank you for your comment which the committee considered. Because of the low rate of adverse events and longer term impacts of a sore throat, the cost effectiveness of these technologies is likely to be driven by their impact

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				on antibiotic prescribing, rather than by test accuracy alone. Also, it is not within the remit of the committee to advise on the appropriate sensitivity; technologies are assessed using published evidence and data submitted by companies.

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Comment number	Name and organisation	Section number	Comment	NICE response
11	Abbott	2.12 & 2.13	With high interest we have read about performance (sensitivity / specificity) values used for the "Centor SCORE" in the publication, which overall seems to be too unreliable from our perspective. Hence, considering role of Healthcare Professionals to care for individual patients, we would find it worthwhile to discuss cost-effectiveness of a Strep A health care intervention further.	Thank you for your comment which the committee considered. It noted that the rapid strep A tests would be used in addition to clinical scoring tools, not instead of them. The tools are recommended for use in NICE's antimicrobial prescribing guideline on sort throat. The committee noted that there is no evidence that the use of rapid strep A tests (used in addition to clinical scoring tools) translates into reduced antimicrobial prescribing in routine clinical practice. This discussion is captured in section 4.6 of the diagnostics guidance document.
12	Abbott	3.18	ICER and QALY values are highly sensitive to the inputs and assumptions, and we would like to highlight a few observations: a) "Most studies making direct comparisons between sore-throat clinical scoring tools and point-of-care tests indicated that sensitivity estimates were higher for the point-of-care tests, and that specificity was generally comparable between the two approaches." (Page 134, DAP44 Committee papers redacted document)	Thank you for your comment which the committee considered. It noted that the rapid strep A tests would be used in addition to clinical scoring tools, not instead of them. Sensitivity analyses explored the use of alternative cut-offs for the Centor tool, which had minimal impact on the model results. The accuracy data quoted for Centor are the values used in the economic model and so the analyses capture these elements. The

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			b) The accuracy of clinical scoring algorithms is low: CENTOR at the Cut-off >=3 has a sensitivity at 49% and a specificity of 82% and the authors of the *Committee Papers* have been unable to evaluate the FeverPain score due to lack of estimates. c) Section 4.3 (of the DAP44 Committee papers redacted document) "Summary of economic modelling describes additional costs of 4.- GBP per minute for GP time and 8.- GPB for throat culture when RADT tests display a negative result. Abbott sees the rationale for culture confirmation testing in the not perfect performance of RADT tests as also discussed regarding the Scoring systems in comment 4 [here: comment #8]. Note that rapid molecular tests such as ID NOW Strep A 2 have such high performance that no cell culture confirmation testing is needed. With the points a.) to c.) in mind we would like to raise two questions: 1. Would culture confirmation be necessary for patients with a negative CENTOR score as well, and hence be part of the model. 2. Would it not be of interest to compare the time and hence costs per minute to determine the score of CENTOR and	committee noted that there is a lack of comparative studies on the accuracy of clinical scoring tools and rapid strep A tests, and also on the comparative accuracy of different tests. Further the committee noted that there is no evidence that the use of rapid strep A tests (used in addition to clinical scoring tools) would translate into reduced antimicrobial prescribing in routine clinical practice. This discussion is captured in section 4.6 of the diagnostics guidance document. The committee recalled that the cost of confirmatory microbiological testing (for negative rapid strep A results) was only applied to rapid strep A tests which specified the need for such testing in their information for use document, or if the company confirmed to NICE that this is required. . This is captured in Table 1 of the guidance document. The committee understood that because rapid strep A tests were assessed in addition to the clinical scoring tools (not instead of them), the time needed to run the tests would be in

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			FeverPain in comparison with the Hands-on time to run a diagnostic test	addition to the time needed to apply the clinical scoring tools.
13	Becton Dickinson and company	General	Firstly, as has been pointed out by other commenters, the analysis uses clinical scoring tools as a comparator without accounting for the real-world appropriate use, accuracy of and compliance to these tools and. This limitation is significant as it does not account for the high degree of subjectivity in scoring tool implementation as well as the impact of subjective and empiric criteria on the physician/patient interaction with regards to antibiotic prescribing. While antibiotic prescribing continues to decline, even recent analyses illustrate the degree to which antibiotic prescribing remains unnecessary and unsupported, including prescriptions with inappropriate (38.8%) or unavailable (15.3%) medical codes. We believe the analysis should incorporate in its model a sensitivity analysis. This should include a defined range of specificity and sensitivity in the scoring tool accuracy, reflecting alignment to the diagnostic test analysis.	Thank you for your comment which the committee considered. The committee noted that there is no evidence that the use of rapid strep A tests (used in addition to clinical scoring tools) translates into reduced antimicrobial prescribing in routine clinical practice. This discussion is captured in section 4.6 of the diagnostics guidance document. As the rapid tests are unlikely improve clinical outcomes, the model's predicted reduction in antibiotic use might not be replicated in NHS practice and the recent publication of NICE's guideline on antimicrobial prescribing for acute sore throat is expected to further reduce antibiotic prescribing. The committee noted that once this is fully implemented the tests could have the potential to increase inappropriate antibiotic prescribing. These considerations are captured in sections 4.6 and 4.11 of the guidance document.
14	Becton Dickinson and company	General	Thirdly, the analysis does not appear to take into account poor compliance to NICE guidelines. Although studies evaluating compliance or adherence to NICE guidelines are limited, available	Thank you for your comment which the committee considered.

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			literature suggests considerable variation in adoption of these tools. While an imperfect surrogate, unnecessary antibiotic prescribing illustrates the need for objective criteria for patient diagnosis. A recent assessment of antibiotic prescribing in primary care demonstrates a significant over prescription of antibiotics for respiratory tract infections, presumably despite the availability of guidelines or expert advice. As the authors note, an "antibiotic was prescribed in 41% of all acute cough consultations when experts advocated 10%. For other conditions the proportions were: bronchitis (actual 82% versus ideal 13%); sore throat (actual 59% versus ideal 13%); rhinosinusitis (actual 88% versus ideal 11%); and acute otitis media in 2- to 18-year-olds (actual 92% versus ideal 17%)." This is supported by the high rate of unnecessary antibiotic prescribing in primary care where 30% or more of the antibiotics appear to be prescribed for conditions where antibiotics are not beneficial or recommended treatment.	The committee noted that there is no evidence that the use of rapid strep A tests (used in addition to clinical scoring tools) translates into reduced antimicrobial prescribing in routine clinical practice. This discussion is captured in section 4.6 of the diagnostics guidance document. The committee noted advice from experts that healthcare services are still in the process of adopting NICE's guideline on antimicrobial prescribing for acute sore throat. This is expected to reduce antibiotic prescribing and promote penicillin as the first lie treatment choice. This consideration is described in section 4.11 of the guidance document.
15	Becton Dickinson and company	General	With this level of variability in guideline adherence and prescribing practice there is a strong case for considering the external validity of the evidence base as part of the analysis. To address real world variability, which are often influenced by unfamiliarity with guidelines, BD believes that the work should be augmented by sensitivity analysis to model the impact of low compliance and adherence to guidelines on the effectiveness of these guidelines. While compliance with diagnostic testing is yet to be established in the UK, the presence of a quantified test result can be audited. This will optimise measurement of outcomes and may potentially	Thank you for your comment which the committee considered. The committee noted advice from experts that healthcare services are still in the process of adopting NICE's guideline on antimicrobial prescribing for acute sore throat. This is expected to reduce antibiotic prescribing and promote penicillin as the first lie treatment choice. This consideration is described in section 4.11 of the guidance document.

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			improve compliance. While compliance with diagnostic testing is yet to be established in the UK, the presence of a quantified test result can be audited. This will optimise measurement of outcomes and may potentially improve compliance.	
16	British Infection Association	2.14	You have stated the reference comparator is a clinical scoring system which is free. As a result any other test might struggle to compete due to cost.	Thank you for your comment which the committee considered.
17	British Infection Association	3.27	Accuracy estimates for the scoring tool were not evaluated in children so this is likely to be a limitation given the major patient group will be children.	Thank you for your comment which the committee considered. The committee was aware of this limitation but accepted the assumption in the absence of evidence.
18	Public Health England	General	It should also be noted that in secondary care settings tools such as FeverPain are very unlikely to be used – this may have an impact on model assumptions.	Thank you for your comment which the committee considered. The comparator used in this assessment was taken from NICE's antimicrobial prescribing guideline on acute sore throat, which is intended to provide information for all care settings.

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19	Abbott	3.21 – 3.32	The model uses Test Process time to define the extra labour costs / GP time. Hands-on time for Abbott tests is only seconds and thus overall cost assumptions should be decrease. An interesting question would be to compare the time to evaluate the patient following the FeverPain and Centor Scores in comparison with the Abbott test solutions. Please note tests with longer turnaround times would disrupt the usual workflow in the GP setting (and most likely in the hospitals (ward, paediatric ED / MAU) as well, increasing the costs.	Thank you for your comment which the committee considered. It recalled that the model accounted only for the time for the test read-out, and not for the time needed to prepare the test and take the throat swab. Therefore, the total time needed to run the test in routine practice is likely underestimated. Including a more realistic estimate of test processing time would further increase the costs and ICERs for the rapid tests. This discussion is captured in section 4.9 of the diagnostic guidance document.
20	Roche Diagnostics Ltd	3.2	We would like to reiterate our concern around the test costs used in the model and listed in Table 9 on page 22 of the DCD. In the technology appraisal process, the list price of pharmaceuticals can be found in the public domain, typically from a single source i.e. the British National Formulary, and negotiated discounts can be redacted from the final report. However, the Diagnostics Assessment Programme (DAP) does not have a single source of tests costs, relying heavily on information provided by the manufacturer, nor does it give the option of having discounted prices redacted to maintain commercial confidentiality. Therefore, in the spirit of being	Thank you for your comment which the committee considered. It discussed that the economic model used prices provided by the manufacturers as long as they were transparent (that is, were not provided as confidential) and widely available to the NHS. Prices that are available to the NHS need to be published in the diagnostics guidance so that users are able to understand the price at which the test can be considered cost-effective. Confidential discounts can be submitted if the

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			transparent, we have always provided our list prices and asked for a caveat to be included to affirm that costs may vary in different settings because of negotiated procurement discounts. Despite asking at the DAR stage, this caveat is missing. The price has also changed since the start of the DAP process (average selling price is currently £35 - subject to volume-based discounts). Moreover, we have serious concerns that the cost associated with some tests is incorrect and advise that NICE check specifically with the manufacturers to confirm the accuracy of the costs provided and how the costs were derived, to ensure consistency. For example, the GENEXpert system is a cartridge based-solution and while we have no price points for this test in the UK market we do have price points for other assays using the same cartridge-based technology. The costs provided do not reflect a realistic market price for assays based around this technological approach, may misrepresent the market for such technologies and therefore affect the validity of the report.	technology meets the criteria outlined in the interim addendum on access proposals https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-diagnostics-guidance/Diagnostics-interim-addendum-access-proposals.pdf The committee accepted revised economic analyses for Roche's Cobas Strep A assay (submitted by the external assessment group in Addendum 3 and shown in tables 9 to 11 of the guidance document). It understood the cost submitted by the company to be an average selling price, based on volume-based discounts, which may not be available to all NHS trusts; the range associated with the average selling price was not provided to NICE. The updated test cost did not change the conclusions of the analyses and the committee noted that the updated cost did not include analyser costs, therefore the incremental costs associated with this test are likely to have been underestimated. This consideration is captured in section 4.9 of the guidance document.

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				The committee recalled its previous discussion the of Xpert Xpress Strep A test cost, and noted that it is likely to be underestimated because the external assessment group had assumed a higher number of tests per day would be run for this technology. This has resulted in more favourable ICERs and overestimates of the cost effectiveness estimates. This committee consideration is captured in section 4.9.

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THEME: OTHER MODEL INPUTS AND ASSUMPTIONS

Comment number	Name and organisation	Section number	Comment	NICE response
21	Abbott	3.15	Failure rates are critical, not only from a direct cost per test perspective but also indirectly as costs for labour must be added. Thus, failure rate costs should be weighted with precise modelling and assumptions to compare commercially available tests. Please note that the ID NOW Strep A2 has a reduced failure rate in comparison to the Alere i Strep A test listed in the respective section in the *Committee Papers (Page 135,* DAP44 Committee papers redacted document*)*. In addition to the differences that the authors have listed, a technology itself can be a driver for invalid results as described for other parameters than Strep A (for example Influenza or RSV) in the literature.	Thank you for your comment which the committee considered. The committee noted that failure rates may vary between technology, and that they are an important element of test performance. However, it heard from the external assessment group that the model did not consider test failure rates because of the lack of data.
22	Abbott	3.21 – 3.32	The sections discuss the model parameters and thus static costs for diagnostic tests and treatment next to extra Health Care professional labor costs as well as costs due to complications. As described above, the probability rates for disease and complications as well as test accuracy and costs impact the result of the cost efficiency analysis. Therefore, Abbott would like to discuss in detail on how a collaboration of the NHS and Abbott as a partner could improve Strep A diagnosis in the future in relation to ICER & QALY gains, and transmission rate reduction.	Thank you for your comment which the committee considered. It noted that although very small, there is a risk of penicillin-induced anaphylaxis and so it should be considered in the economic model. It also noted that the external assessment group had done sensitivity analyses around this parameter because the true rate is uncertain, this is described in section 4.10 of the guidance document.

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			For example, adverse effects of penicillin and costs for treatment, favouring the Scoring systems are listed: Penicillin is broadly prescribed and the treatment with Penicillin would be stopped if allergic reactions, or other adverse events, are observed. As Penicillin caused events would be documented in the patient history file, cost savings by not using Penicillin for the patients at a later event would occur. Hence, we would consider Penicillin caused effects as one timer events that would happen at least once during a patient lifetime and thus balance the effect. Accordingly, these costs should not be evaluated and accounted in the Strep A model. Another example: earlier, we described the rationale for Culture Confirmation Testing for negative results which is accounted in the de *novo model* of the *Committee Papers*. Accordingly, the model should fairly compare the diagnostic tools and confirmation testing needs based on the performance. Rapid molecular tests without the need for Culture Confirmation should be calculated respectively	The committee recalled that the cost of confirmatory microbiological testing (for negative rapid strep A results) was only applied to rapid strep A tests which specified the need for such testing in their information for use document or the company confirmed to NICE that this was required. This is captured in Table 1 in the guidance document.

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Comment number	Name and organisation	Section number	Comment	NICE response
23	Abbott	1.1	Antimicrobial resistance is a public health concern and Abbott has been a key driver to reduce unnecessary antibiotic prescriptions and targeted diagnosis and, hence, treatment of disease. Antimicrobial stewardship can have two main effects: a) the direct outcome of the individual as well as indirect on the population and b.) costs. Regarding costs, the authors of the "*Rapid tests for group A streptococcal infections in people with a sore throat Committee Papers"* do not consider antimicrobial resistance, as a factor for their model; rightly so in this study, as cost-effectiveness or outcome of the individual patient would not be affected. However, Antimicrobial resistance is a major threat to the patient society and the individual patient and can lead to high indirect costs as also described on page 25 of the above-mentioned *Committee Papers*. The authors touch the topic of Antimicrobial Resistance and indicate overuse of Antibiotics, but not fully explore it: "only 5-17% of sore throats are due to bacterial infection" (Page 21, DAP44 Committee papers redacted document) - could be prevented using an optimized pathway. Later rapid testing is reported as a potential solution to reduce antibiotics (Section 3.15 or Page 126, DAP44 Committee papers redacted document), "all three trials found higher antibiotic prescription rates or use in control arms with no point-of-care test compared to those given a point-of-care test" is listed." Please note	Thank you for your comment which the committee considered. The committee noted that the wider public health benefits of the tests, such as contribution to antimicrobial stewardship or effect on onward transmission rate were not captured in the model because of a lack of evidence to quantify these. The committee therefore recommended further research to measure the wider public health impact and the costs of antimicrobial stewardship associated with different classes of antibiotics used in different healthcare settings. Further, the committee noted that the rapid tests are unlikely to improve clinical outcomes and the model's predicted reduction in antibiotic use might not be replicated in NHS practice and the recent publication of NICE's guideline on antimicrobial prescribing for acute sore throat is expected to reduce antibiotic prescribing. The committee noted that once this is fully implemented the tests could have the potential to increase antibiotic prescribing. These

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			that overall prescription rates might be misleading, as only targeted treatment of bacteria caused Strep A would be beneficial and further insights would be of value.	considerations are captured in sections 4.6 and 4.11 of the guidance document. The committee noted that NICE's guideline on antimicrobial prescribing for sore throat recommends the use of penicillin which should reduce the use of broader spectrum antibiotics for sort throat. Although bacterial resistance to penicillin is not thought to be as great a problem as resistance to other classes of antibiotics such as macrolides (for example, erythromycin) or cephalosporins, there is very limited evidence to quantify this. This consideration is captured in section 4.13 of the guidance document.
24	Abbott	3.18	As mentioned in Comment No 2 [here: #23], Antimicrobial stewardship has also not been considered as a factor as high indirect costs are a risk as also described on page 25 of the <f.	Thank you for your comment which the committee considered. The committee noted that the wider public health benefits of the tests, such as contribution to antimicrobial stewardship or effect on onward transmission rate were not captured in the model because of a lack of evidence to quantify these. The committee therefore recommended further research to measure the wider public health impact and the costs of antimicrobial stewardship associated

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				with different classes of antibiotics used in different healthcare settings.
25	Becton Dickinson and company	General	Finally, as other commenters have noted, the analysis does not appear to take the public health perspective into account. This includes an absence of reference to the UK's strategy for tackling antimicrobial resistance. This is a significant omission as the data must be used in earnest to support the overarching UK strategy thus impacting antibiotic prescribing behaviors. By not considering inappropriate antibiotic use on public health, this analysis takes a short-term perspective without accounting for down-stream effects of antibiotic overprescribing. Ultimately a large part of the cost of antimicrobial resistance will fall upon the NHS. Some of this is already visible, but further costs to the system and to patients should be taken into account. These costs and burden will have impact across the breadth of Health and Social Care. Therefore, taking a public health perspective on this subject is fully aligned to the purpose of NICE to improve the quality, sustainability, and productivity of health and social care in England and will support NICE's position as a national and global leader in appraising technologies needed to help combat resistance.	Thank you for your comment which the committee considered. The committee noted that the wider public health benefits of the tests, such as contribution to antimicrobial stewardship or effect on onward transmission rate were not captured in the model because of a lack of evidence to quantify these. The committee therefore recommended further research to measure the wider public health impact and the costs of antimicrobial stewardship associated with different classes of antibiotics used in different healthcare settings.

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26	Abbott	3.18	Health Economic and Outcomes research (HEOR) as defined by the project group is a great way to assess a current status quo in comparison with future operating system. The calculations are normally limited, which is also the case in this study, by potential error risks regarding the key drivers, such as test performance as outlined in several sections of the study. With Strep A, we are looking at macro-economic changes that do not only affect the NHS system, but rather the UK economy: parents must stay at home to care for the children leading to sickness absence. Adult patients display unproductivity when sick at home. Associated costs are mentioned in the publication, but not considered in the base case model, which focuses on medical related costs only.	Thank you for your comment which the committee considered. The NICE reference case states that analyses should take the perspective of the NHS and personal social services. Further information on this can be found in the NICE diagnostics assessment programme manual: https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-diagnostics-guidance/Diagnostics-assessment-programme-manual.pdf
27	British Infection Association	4.2	A rapid test for Strep A could enable antimicrobial treatment to be targeted early and not delayed. It would also prevent unnecessary treatment of those without Strep A. Delay has potentially serious repercussions for the community (outbreaks, scarlet fever, cases of invasive Strep A) even if such events are rare. The risk of invasive Strep A is increased 12 fold in a household with a single case of scarlet fever. As there is no particular reason to think that scarlet fever and	Thank you for your comment which the committee considered. It recalled its discussion about the risk of onward transmission of untreated strep A infection to other household members, in particular, the risk of onward transmission leading to invasive strep A infection. It noted that although this risk exists, it is very small. It noted that the risk of onward transmission could be higher during an

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			Strep A sore throat differ in infectivity (they are caused by the same agent) then one must assume the same is true for each and every Strep A sore throat that is not treated promptly. The drawback is that they will not provide antimicrobial resistance information although thankfully this is of lesser concern for Strep A than other bacteria at present.	outbreak, for example in a care home, but use of the tests during an outbreak was outside the scope of this assessment. This committee consideration is captured in section 4.13 of the guidance document.
28	Public Health England	General	Many thanks for considering our responses to the review, which we think generally reads very well and clearly has involved a substantial amount of work. Our main comments relate to what is identified in the discussing as a limitation, namely the impact on transmission and public health benefit, and its omission from the model. If this is not able to be included then it would be good for this to be highlighted as an issue higher in the text/summary, as it may lead people to dismiss using these for cost implications when there are specific settings, including outbreaks, where more work is needed to determine their utility and overall cost effectiveness to the healthcare and wider economy.	Thank you for your comment which the committee considered. A summary box has been added at the beginning of the diagnostic guidance document to clarify which populations and settings are considered in the guidance, and which are not. It specified that the guidance has not considered the use of the tests as a tool to help manage outbreaks of group A streptococcal infections.
29	Public Health England	General	For the outcomes section of the 'Evidence Overview' section, there is not assessment of impact on transmission and therefore limiting spread of scarlet fever or GAS in general. This would be a key benefit if the intervention is proven to be cost effective and sensitive, though we appreciate there may	Thank you for your comment which the committee considered. A summary box has been added at the beginning of the diagnostic guidance document to clarify which populations and settings are considered in the guidance, and which are

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			not be data on this. Not including the under 5s in this review does limit its interpretability for scarlet fever and this could be commented on in more detail. The extrapolation to an elderly population is also of potential benefit as a rapid tool in interrupting care home iGAS outbreaks.	not. It specified that the guidance has not considered children under the age of 5 years, people with scarlet fever, or the use of the tests as a tool to help manage outbreaks of group A streptococcal infections.
30	Public Health England	General	The model assumptions do not include transmission and subsequent costs of infection in other individuals – this would seem to be one of the most beneficial aspects of rapid detection for public health benefit and ideally should be included in the model assumptions. It would also be useful for the models to also include an outbreak setting rather than simply a GP practice or secondary care settings, for example in a nursery school or elderly care home, as this is where it may be of significant benefit in curtailing spread.	Thank you for your comment which the committee considered. The potential use of the tests as a tool to help manage outbreaks of group A streptococcal infections was not considered in the assessment, and thus is not considered in the guidance. This has been noted in the summary box added at the beginning of the diagnostic guidance document.
31	Public Health England	General	We note lack of transmission is listed as a limitation however to give a full picture of utility we think it is important to capture. Asymptomatic carriage is also a consideration here, which we appreciate would not be captured by this review, and this could be further commented on.	Thank you for your comment which the committee considered. Asymptomatic carriage was not considered in this assessment, which focused on people with symptoms of a sore throat who were considered to be more and most likely to benefit from antibiotics (as assessed by clinical scoring tools).

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32	Abbott	1.1	Abbott is a global leader in Strep A diagnostic solutions, including molecular and antigen tests, and advocate for new and disrupting healthcare solutions that aim to improve both patient care while reducing costs, not only limited to diagnostic tools. We appreciate the explorative vision and the *de novo* model presented in the *Rapid tests for group A streptococcal infections in people with a sore throat Committee Papers*. Here, we understand the identified modelling uncertainties and Abbott would like to explore future collaborations and projects in partnerships with the objective to optimize Strep A diagnosis in alignment with the NHS Pathway and UK healthcare system. We would like to identify “key parameter inputs and confirm modelling assumptions” (Page 18, DAP44 Committee papers redacted document) hand in hand to provide the best healthcare to the UK citizens. We see high potential in the revision of the recommendations in section 1.1 to find a cost-effective solution with improved outcomes for Strep A patients and suspects in the UK. The below points aim to outline Abbott´s perspective and start a discussion. Abbott Team would be delighted to be invited to an	Thank you for your comment which the committee considered. Advice in evidencing the value proposition of a technology can be sought from NICE’s office for market access, or from NICE scientific advice.

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			in-depth discussion. Please use [redacted] and [redacted] as primary contacts to discuss next steps.	
33	Abbott	1.1	Section 1.1 also discussed the diagnostic accuracy of the commercially available tests. Again, accuracy of tests affects both costs and outcome and will be discussed below to reference the individual sections of the *Consultation Document.* Accordingly, Abbott would see an opportunity to optimize the *de novo* model build by NICE and take Antimicrobial Resistance costs into account and further would appreciate to discuss studies to assess the effect on Antibiotic prescription rates as well as the additional value of diagnostics results further.	Thank you for your comment which the committee consider. The committee noted that the wider public health benefits of the tests, such as contribution to antimicrobial stewardship or effect on onward transmission rate were not captured in the model because of a lack of evidence to quantify these. The committee therefore recommended further research to measure the wider public health impact and the costs of antimicrobial stewardship associated with different classes of antibiotics used in different healthcare settings.
34	Abbott	3.18	Further, kindergarten children (age 3-6) should be in scope of future studies and modelling. This cohort would have a specific set of features that would affect the results of the modelling	Thank you for your comment which the committee considered. It discussed that the guidance focused on the use of rapid tests for group A streptococcal infections in people aged 5 and over with a sore throat. The committee heard that children under 5 frequently present with a temperature and are unable to communicate their symptoms, they are therefore usually assessed

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				according to NICE's guideline on fever in under 5s: assessment and initial management. A summary box has been added at the beginning of the guidance document to clarify this.
35	Abbott	5	Abbott would like to collaborate in future studies and HEOR research.	Thank you for your comment which the committee considered. The further research proposed by the committee will be considered by the NICE medical technologies evaluation programme research facilitation team for developing specific research study protocols as appropriate.
36	Becton Dickinson and company	General	Thank you to the NICE Diagnostics Assessment Programme for the opportunity to review and comment on the assessment for Rapid Tests for Group A Streptococcal Infections (GID-DG10025). BD believes that the approach taken by the NICE committee for the value assessment of the diagnostic test for Group A Strep has four key omissions in the methodology that limit the utility of the analysis for appraising the of the technology. We additionally hope the committee take into consideration the broader public health benefits of using accurate and objective diagnostics to both improve patient care and help incentivise appropriate antibiotic use.	Thank you for your comment which the committee considered. The committee noted that the wider public health benefits of the tests, such as contribution to antimicrobial stewardship or effect on onward transmission rate were not captured in the model because of a lack of evidence to quantify these. The committee therefore recommended further research to measure the wider public health impact and the costs of antimicrobial stewardship associated with different classes of antibiotics used in different healthcare settings

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37	Becton Dickinson and company	General	We would like to note that BD's company name is misspelled throughout the document. The correct spelling is "Becton Dickinson and Company" or "BD". Although it is not possible for us to verify all literature which were potentially missed as a result of the misspelling, we have identified two studies which appear to have been incorrectly excluded. References 145 and 146 (both by Papastergiou et al) reference the "BD Veritor" system but reference 145 is noted as being excluded from the analysis because "no specific RADT mentioned" despite the reference to "BD Veritor". These studies discuss pharmacist acceptance of these tests and their impact on time to antibiotic therapy. Upon request, BD would be happy to help confirm whether relevant omissions have occurred.	Thank you for your comment which the committee considered. This has now been amended throughout the guidance document. The EAG advised that the search strategy was not affected by the misspelling because it included multiple search terms such as "Veritor" as well as generic terms to capture studies on rapid strep A tests. The EAG also advised that both studies were correctly excluded during screening, but the reason for exclusion was incorrectly recorded. The studies were excluded due to the lack of comparison with the microbiological culture of throat swabs or with clinical scoring tools.
38	Becton Dickinson and company	General	Point of care diagnostic tests will improve in sensitivity, specificity and cost in time. The impact of the adoption of currently available technologies being disincentivised over inferior, albeit free, empirical analyses significantly reduces incentives to invest in new innovation and technology. In the long term, such an approach will impact resources and motivations for research and develop towards more clinically- and cost-effective rapid diagnostics for AMR in deference to	Thank you for your comment which the committee considered. All committee members agreed that development of rapid diagnostic tests that can help target antimicrobial prescribing and reduce antimicrobial resistance is very important. However, they noted that there is no evidence that the use of rapid strep A tests reduces antibiotic prescribing in

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			more commercially viable opportunities. It should be noted that this market behavior is already present in novel antibiotic research and development.	routine clinical practice, compared with the use of clinical scoring tools only.
39	British Infection Association	General	We agree with the specific findings in relation to what NICE planned however the scope appears to have been limited and children not considered sufficiently, as the key group affected by this condition.	Thank you for your comment which the committee considered. It recalled that children under the age of 5 years were not considered in this guidance as clinical advice during scoping suggested that they often present with a temperature and are unable to communicate their symptoms so they are typically assessed following NICE's guideline on fever in under 5s: assessment and initial management. A summary box has been added at the beginning of the diagnostic guidance document to clarify this.
40	British Infection Association	2.3	Is it true that the only intentions of the 2008 NICE guidance was to reduce antimicrobial prescribing /reduce AMR? ie rather than treat Strep A or prevent complications of Strep A? The earlier NICE guidance found that diagnostic testing was not worthwhile because there is no imperative to treat Strep A.	Thank you for your comment which the committee considered. One of the key purposes of the NICE's guidance on sore throat: antimicrobial prescribing is to ensure the appropriate use of antibiotics in treating sore throat. Using antibiotics only as recommended in the guideline will help to reduce antimicrobial resistance. The guidance states that acute sore throat is often caused by a virus, lasts for about a

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				week, and most people get better without antibiotics. Withholding antibiotics rarely leads to complications.
41	British Infection Association	2.4	Large numbers of patients with Strep A sore throat are aged 4-7. Scoring systems were not validated on younger children. It would be therefore helpful to have a guideline aimed at those aged under 7 based on results from children rather than including those aged 5-7 in the adult guideline.	Thank you for your comment which the committee considered. We have passed your comment onto the guidelines surveillance team.
42	British Infection Association	General	PHE and RCPCH do not appear to be listed as stakeholders and we would expect these large and relevant organisations to be stakeholders in this consultation.	Thank you for your comment which the committee considered. Organisations are able to register as stakeholders for the assessment via the NICE website. PHE has commented on the diagnostic consultation document.
43	British Infection Association	2.15	Regarding culture-based testing- there is a discrepancy between this guidance which assumes use of clinical scoring systems and guidance on scarlet fever which alludes to consideration of taking a throat swab; to reduce confusion in clinical practice please clarify or explain this in the text.	Thank you for your comment which the committee considered. The use of rapid strep A tests to guide antibiotic prescribing in scarlet fever was not considered in this guidance. This has been clarified in the summary box added at the beginning of the diagnostic guidance document.
44	Public Health England	General	To the reader unfamiliar with the cost effectiveness analysis, the descriptions on page 17 and 18 are hard to follow. This is also	Thank you for your comment. A Glossary of terms is available on the NICE website.

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			true when talking about utilities and disutilities on page 23. A brief description of unfamiliar terms would be useful.	