NICE National Institute for Health and Care Excellence

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

Diagnostics Assessment Report (DAR) - Comments

[1]

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
Abbott Diagnostics	1			No comments	No response required (NRR)
Orion Diagnostica Oy	2	30/293	1.3 Comparative technical overview of the point-of-care tests for Strep A	Table 1. Row: "QuikRead Go Strep A test kit (Orion Diagnostica)", Column: "Time to results (minutes)" The time to result of all lateral flow tests includes only the reading time and excludes the extraction steps and handling time. The time to result for QuikRead go Strep A test is presented as < 7 min, which includes the extraction and handling time. To be comparable to other tests, we suggest that the incorrect time < 7 min is replaced with the correct QuikRead go reading time < 4 minutes.	The timings reported in this column of Table 1 came from NICE Medtech innovation briefing 145 (https://www.nice.org.uk/advice/mib145). We have submitted an erratum to reflect this reference as a footnote (a) for Table 1 and Table 2.
Orion Diagnostica Oy	3	53/293	3.2.2 Study characteristics	Table 6. Row: Azrad 2019[31], Column: Study Population N The total N size of the Azrad 2019 study was 100 but the study included patients who did not use antibiotics (n=39) and patients already using antibiotics (n=61) before Strep A testing. Inclusion of patients with on-going antibiotic treatment should be additionally mentioned in this report or the results of antibiotic-treated patients should be completely excluded because antibiotic use affects the bacteria by lowering their number and reducing their viability. Therefore, the sensitivity and specificity compared to culture does not reflect the performance in the intended patient group presented in this report. We suggest using the N = 39 that includes only the non-antibiotic treated patients.	We acknowledge the possibility of a link between antibiotic treatment and the accuracy of a point-of-care test. However, there is currently insufficient evidence on this relationship to justify selecting only a subgroup of patients from the Azrad et al. 2019 study. In addition, the final scope did not describe specific patient level characteristics in the inclusion/exclusion criteria, and we were consistent with the scope when generating our final protocol and selecting studies/populations for inclusion in our review.

[1]

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				If the comment on patient population or removal of antibiotic-treated patients from the analysis is not possible, the publication should not be included in the DAR as the majority of patients were not relevant for Strep A testing and for making decisions on antibiotic prescribing and thus their results are not relevant for the report.	
Orion Diagnostica Oy	4	77/293	3.2.6.1. Accuracy of point-of-care tests with culture as reference standard	QuikRead go Strep A Kit (Orion) Azrad[31] 2019 study included patients already using antibiotics. As explained above in comment no 2, antibiotic treatment decrease the number of viability and number of the bacteria causing unreliable performance values. Also, when evaluating the test for aiding targeted antibiotic prescribing in cases of sore throat only the performance values of patients without on-going antibiotic treatment should be included. Therefore, we suggest that the incorrect sensitivity and specificity values that have included antibiotic treated patients are replaced with the correct sensitivity and specificity values. The correct values are presented in the Azrad[31] article on page 1181 in Table 3. According the table, the sensitivity and specificity values for the QuikRead go Strep A kit when compared to cultures is 94.1 (73.0-98.9) and 95.5 (78.2-99.2) (N=39). Also, the sensitivity and specificity values calculated using univariate model should be revised accordingly. If it is not possible to exclude the antibiotic treated patient's data, we suggest that the publication should not be included in the DAR as the majority of the included patients are not relevant for deciding on antibiotic prescription and thus their results are not relevant for the report.	Please see response to comment 3.
Orion Diagnostica Oy	5	83/293	3.2.6.1. Accuracy of point-of-care tests with culture	Table 11: Summary of available evidence by test, QuikRead Go Strep A Kit – Orion	Please see response to comment 3.

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
			as reference standard	As explained above, the study by Azrad[31] 2019 presented sensitivity, specificity, PPV, and NPV values where antibiotic treated patients were included in the analysis (Total N=100, antibiotic treated patients N=61, and not treated patients N=31). The antibiotic treatment lower the number of bacteria and reducing their viability leading to decreased performance values. Therefore, the sensitivity, specificity, PPV, and NPV values compared to culture do not reflect the performance in the intended patient group presented in this report. We suggest to use only those sensitivity, specificity, PPV, and NPV values where non-treated patients test results are used. Therefore, we suggest modifying the table 11 as highlighted in red below in the table. The performance values are calculated using only the non-antibiotic treated patients results (N=39) from the Azrad 2019, page 1182 and Table 3. The text in the brackets on columns “Strep A infections prevalence” and “TN” depicts the explanation how these values are calculated and can be removed from the final version. (see table below) If it is not possible to include only the results of the patients who are not already treated with antibiotics, the publication should not be included in the DAR as the majority of the included patients are not relevant for deciding on antibiotic prescription and thus their results are not relevant for the report.	

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

Diagnostics Assessment Report (DAR) - Comments

Study	Care Setting	Age group	Clinical Tool Score Restriction	Strep A infections Prevalence	Ref Type	N	TP	FN	FP	TN	Accuracy Data
QuikRead Go Strep A Kit - Orion											
Azrad 2019 [31]	Secondary	NR	None	44% (calculated from 39 patients and 17 culture positives)	Strep selective	39	16 (calculated from 94.1% out of 17)	1	1	21 (calculated from 95.5% out of 22)	Patients not using antibiotic Sens = 0.94 (95% CI 0.73, 0.99)* Spec = 0.96 (95% CI 0.78, 0.99)* PPV = 0.94 (95% CI 0.71, 1.00)* NPV = 0.96 (95% CI 0.77, 1.00)* *Patients already being treated with antibiotics are excluded

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Orion Diagnostica Oy	6	88	3.2.6.1 Accuracy of point-of-care tests with culture as reference standard	Figure 7: The sensitivity of QuikRead Go Strep A Kit (Orion) by Azrad 2019 is presented as 0.80 (0.59, 0,93). As explained above (Please see Comment no. 2-4) this calculation includes test results from antibiotic-treated patients, which is against the original scope of this DAR. We suggest revising the sensitivity value to include only the non-antibiotic treated patient's test results (N=39). As presented in the table 3 in Azrad 2019, the correct sensitivity is 0.94 (0.73, 0.99)	Please see response to comment 3.
Orion Diagnostica Oy	7	89	3.2.6.1 Accuracy of point-of-care tests with culture as reference standard,	Figure 8: The specificity of QuikRead Go Strep A Kit (Orion) by Azrad 2019 is presented as 0.73 (0.62, 0,83). As explained above (Please see Comment no. 2-4) this calculation includes test results from antibiotic-treated patients, which is against the original scope of this DAR.	Please see response to comment 3.

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				We suggest revising the specificity value to include only the non-antibiotic treated patient's test results (N=39). As presented in the table 3 in Azrad 2019, the correct specificity is 0.96 (0.78, 0.99).	
Orion Diagnostica Oy	8	90/293	3.2.6.2 Head-to-head (direct) comparison between tests	Due to the scope of the DAR, the evaluation should only include data from Azrad[31] 2019 where QuikRead go Strep A test is used in the patient group not using antibiotics. The data where the test is used for antibiotic treated patients should be excluded. We suggest to use only the data of non-antibiotic treated patiens (as explained also in the comments 2-6) and revise the second paragraph on the page 90 as follows: "Azrad et al. compared both the BD Veritor System (Beckton Dickinson) and QuikRead Go Strep A Kit (Orion) tests to culture for 39 patients.31 The BD Veritor System had a sensitivity of 0.94 (0.73, 0.99) and specificity of 0.86 (0.67, 0.95). The QuikRead Go test had an identical sensitivity of 0.94 (0.73, 0.99) and a slightly better point estimate for specificity of 0.96 with overlapping confidence intervals (0.78, 0.99). If it is not possible to include only the results of the patients who are not already treated with antibiotics, the publication should not be included in the DAR as the majority of the included patients are not relevant for deciding on antibiotic prescription and thus their results are not relevant for the report.	Please see response to comment 3.
Orion Diagnostica Oy	9	91	3.2.6.2 Head-to-head (direct) comparison between tests	Figure 9: Due to the scope of the DAR the evaluation should only include data from Azrad[31] 2019 where QuikRead go Strep A test is used in the patient group not using antibiotics. The data where test is used for antibiotic treated patients should be excluded. We suggest to revise the sensitivity and specificity values of QuikRead Go Strep A Kit (Orion) by Azrad 2019 to the correct values: Sensitivity 0.94 (0.73, 0.99) and Specificity 0.96 (0.78, 0.99).	Please see response to comment 3.

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				If it is not possible to include only the results of the patients who are not already treated with antibiotics, the publication should not be included in the DAR as the majority of the included patients are not relevant for deciding on antibiotic prescription and thus their results are not relevant for the report.	
Orion Diagnostica Oy	10	106/293	3.2.6.5 Accuracy of point-of-care tests split by primary/secondary care setting	Paragraph: QuikRead Go Strep A Kit (Orion) Due to the scope of the DAR the evaluation should only include data from Azrad[31] 2019 where QuikRead go Strep A test is used in the patient group not using antibiotics. The data where the test is used for antibiotic treated patients should be excluded. We suggest to revise the first sentence of the paragraph as follows: " Azrad et al. compared the performance of the QuikRead Go Strep A Kit to culture in a hospital setting, and reported a sensitivity of 0.94 (0.73, 0.99), and specificity of 0.96 (0.78, 0.99)". If it is not possible to include only the results of the patients who are not already treated with antibiotics, the publication should not be included in the DAR as the majority of the included patients are not relevant for deciding on antibiotic prescription and thus their results are not relevant for the report.	Please see response to comment 3.
Orion Diagnostica Oy	11	111/293	Table 14: Summary of test performance data by care setting	We suggest to revise the performance parameters of QuikRead Go Strep A Kit – Orion to include only patients not treated with antibiotics before Strep A testing. The recalculated performance parameters are highlighted in the table as red colour. The performance values are calculated using only the non-antibiotic treated patients results (N=39) from the Azrad 2019, page 1182 and Table 3. The text in the brackets on columns "Strep A infections prevalence" and "TN" depicts the explanation how these values are calculated and can be removed from the final version. (see table below)	Please see response to comment 3.

NICE National Institute for Health and Care Excellence

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				If it is not possible to include only the results of the patients who are not already treated with antibiotics, the publication should not be included in the DAR as the majority of the included patients are not relevant for deciding on antibiotic prescription and thus their results are not relevant for the report.	

Study	Care Setting	Age group	Clinical Tool Score Restriction	Strep A infections Prevalence	Ref Type	N	TP	FN	FP	TN	Accuracy Data
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Azrad 2019 [31]	Secondary	NR	None	44% (calculated from 39 patients 17 culture positives)	Strep selective	39	16 (calculated from 94.1% out of 17)	1	1	21 (calculated from 95.5% out of 22)	Patients not using antibiotic Sens = 0.94 (95% CI 0.73, 0.99)* Spec = 0.96 (95% CI 0.78, 0.99)* PPV = 0.94 (95% CI 0.71, 1.00)* NPV = 0.96 (95% CI 0.77, 1.00)* *Patients already being treated with antibiotics are excluded

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Orion Diagnostica Oy	12	116/293	3.2.6.6 Estimates of test accuracy for cost-effectiveness modelling Table 15:	Table 15: QuikRead Go Strep A test kit Due to the scope of the DAR the evaluation should only include data from Azrad[31] 2019 where QuikRead go Strep A test is used in the patient group not using antibiotics. The data where the test is used for antibiotic treated patients should be excluded.	Please see response to comment 3.

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				To remove antibiotic treated patients from the evaluation, we suggest to revise the n size for Azrad 2019 study to be n = 39, instead of n = 100: 2 studies (Azrad 2019, n = 39; Stefaniuk 2017, n = 95) – wrong setting, wrong age, wrong score restriction 2 studies (Azrad 2019, n = 39; Stefaniuk 2017, n = 95) – wrong setting, wrong age, wrong score restriction If it is not possible to include only the results of the patients who are not already treated with antibiotics, the publication should not be included in the DAR as the majority of the included patients are not relevant for deciding on antibiotic prescription and thus their results are not relevant for the report.	
Orion Diagnostica Oy	13	176	4.2.14 Adult secondary care model: base-case analysis results	Table 37. Row: QuikRead Go Strep A test Kit Due to the scope of the DAR the evaluation should only include data from Azrad[31] 2019 where QuikRead go Strep A test is used in the patient group not using antibiotics. The data where the test is used for antibiotic treated patients should be excluded. We suggest revision of the sensitivity and specificity values of QuikRead Go Strep A test kit to include only those patients from Azrad 2019 who have not been treated with antibiotics before testing. The revised sensitivity value should also be corrected to the text on page 175 that refers to the table 37. If it is not possible to include only the results of the patients who are not already treated with antibiotics, the publication should not be included in the DAR as the majority of the included patients are not relevant for deciding on antibiotic prescription and thus their results are not relevant for the report.	Please see response to comment 3.
Orion Diagnostica Oy	14	198	4.2.20 Children in secondary care:	Table 55. Row: QuikRead Go Strep A test Kit	Please see response to comment 3.

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
			base-case analysis results	Due to the scope of the DAR the evaluation should only include data from Azrad[31] 2019 where QuikRead go Strep A test is used in the patient group not using antibiotics. The data where the test is used for antibiotic treated patients should be excluded. We suggest that the sensitivity and specificity values are revised accordingly as mentioned in the previous comments. If it is not possible to include only the results of the patients who are not already treated with antibiotics, the publication should not be included in the DAR as the majority of the included patients are not relevant for deciding on antibiotic prescription and thus their results are not relevant for the report.	
Institute of Biomedical Science	15	20		"Ideally, a throat swab culture should be undertaken to identify the organism causing the infection in cases where diagnosis is uncertain. However, this takes time, causing potential delays in administering the correct treatment." Would this impact on empirical treatment if required? Would it be possible that incorrect treatment be given based on a POCT test if a swab isn't sent to the lab for culture and sensitivity where a definitive antibiogram would be returned to primary care confirming susceptibility and resistance results?	It is possible that an incorrect treatment could be given, if an antibiogram is not performed, however there was insufficient data to consider individual strains of Strep A infection and anti-microbial resistance within this DAR.
Institute of Biomedical Science	16	23	1.1	"Overuse or inappropriate use of antibiotics can lead to bacteria developing resistance, leading to an emergence of multi-drug resistant pathogens, which are increasingly difficult to treat." Would POCT without antibiogram potentially increase the likelihood of inappropriate treatment?	Please see above response to comment 15.
Institute of Biomedical Science	17			General comment: would be concerned about introduction of POCT for GAS without lab confirmation as: 1. Lack of confirmatory antibiogram. 2. Potential for inappropriate antibiotic usage. 3. May reduce antibiotic overuse. 4. Lack of completeness in pathology records – especially current antibiogram if patient admitted with secondary GAS infection.	Thank you for your comments. Please see response to comment 15 and the erratum.

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				5. Lack of antibiogram may lead to failure to detect emerging resistance	
Institute of Biomedical Science	18			The model implies that acute pharyngitis in young persons with a negative test would not have a throat culture sample submitted – the incidence of Fusobacterium necrophorum infection may rise – and consequently the incidence of Lemierre's Disease	It is possible that failing to culture both negative and positive results may result in a failure to identify infections of Fusobacterium necrophorum, however infections other than GAS were considered outside the scope of this report. Note also that the majority of tests included in this DAR do have confirmation of negative tests, with only the NADAL tests, Alere TestPack Plus, Alere i Strep A 2 and Cobas Liat tests not requiring this confirmation.
Roche Diagnostics Ltd	19	74	Table 10	We believe that the conclusions on the use of clinical scores in Strep A sore throat in the report are not supported by their clinical utility and the value of this assessment is misaligned with the UK and Global strategy of reducing antimicrobial resistance. The use of clinical scoring systems is shown to increase the number of antibiotics administered via a prescription. Based on a Centor score of ≥ 3, the results from Llor 2009 showed that ~68% of patients would receive antibiotics and of these, only ~31% of these patients had a positive result when tested using the laboratory culture method. Of those patients that did not receive antibiotics, ~11% had a positive result for Strep A when tested using the laboratory culture method. A similar trend was seen with the use of the McIsaac score highlighting that these clinical scores have a poor positive and negative predictive	Thank you for your comment. In sections 3.2.5.1 – 3.2.5.3 and Table 10 of our report we indicated that the test accuracy of clinical scoring tools is variable, and at times low: specificity of point estimates are between 17.2% and 64.8%, and sensitivity point estimates were reported between 73.5% and 97.2%. We draw no conclusions on the use of clinical scores for Strep A, other than to indicate that rapid tests are generally more specific. The scope of this DAR did not focus on the value of molecular tests on appropriate antibiotic prescription, however we have provided results relevant to the impact on prescribing rates in an addendum.

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
		257	Appendix 3	value (PPV and NPV) which results in the inappropriate prescribing of antibiotics. This contradicts the UK strategy for tackling antimicrobial resistance (AMR) and the evidence available in this area. UK strategy for tackling antimicrobial resistance (AMR)[1] In line with tackling antimicrobial resistance, the UK launched a five-year national action plan. The plan has ultimately been designed to ensure progress towards the 20-year vision on AMR, in which resistance is effectively contained and controlled. It focuses on three key ways of tackling AMR: ● reducing need for, and unintentional exposure to antimicrobials; ● optimising use of antimicrobials; and ● investing in innovation, supply and access The value of molecular testing on appropriate prescribing of antibiotics Luo et al. (2019)[2] and Rao et al. (2019)[3] were excluded from this report however these studies strongly support the value of diagnostic testing to inform appropriate antibiotic prescribing. This is not reflective of the findings in the report which favour clinical scoring and views diagnostic testing unfairly due to the high incremental cost-effectiveness ratios (ICERs). We would ask that the wealth of evidence supporting the use of diagnostic testing and the poor clinical value of clinical scores are considered when any recommendations are made from this report. 1. HM Government. Tackling antimicrobial resistance 2019–2024. The UK's five-year national action plan. January 2019. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf. Last accessed 05/06/19. 2. Luo R, Sickler J, Vahidnia F, Lee YC, Frogner B, Thompson M. Diagnosis and Management of Group a Streptococcal Pharyngitis in the United States, 2011-2015. BMC Infectious Diseases 2019;19(1):193. http://dx.doi.org/https://dx.doi.org/10.1186s12879-019-3835-4	

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				Rao A, Berg B, Quezada T, Fader R, Walker K, Tang S, et al. Diagnosis and antibiotic treatment of group a streptococcal pharyngitis in children in a primary care setting: impact of point-of-care polymerase chain reaction. BMC Pediatrics 2019;19(1):24. https://dx.doi.org/10.1186/s12887-019-1393-y	
Roche Diagnostics	20	General	General	We would ask the committee to seek clarification from healthcare professionals on the clinical utility of scoring methods for diagnostic purposes and the clinical confidence with uptake of these methods in routine practice in the UK. We believe that these clinical scoring tools may be used to support healthcare professionals in assessing which patients may or may not require subsequent diagnostic testing, but that treatment decisions should be made from a confirmatory diagnostic test and not based on empirical scoring methods due to the poor positive and negative predictive values (PPV and NPV) leading to likelihood of inappropriate antibiotic prescribing. This perspective is supported by the Infectious Disease Society of America guidelines and is in alignment with the UK strategy for antimicrobial resistance.[4,5] A cost-effectiveness analysis of any diagnostic test against a clinical scoring tool, which essentially has zero adoption costs, is anticipated to generate high incremental cost-effectiveness ratios (ICERs). We do not believe clinical scoring is the appropriate comparator if the research interest is to understand how best to diagnose Strep A and improve treatment decisions, especially antibiotic prescribing decisions. With any diagnostic comparator, the primary parameter of interest should be test performance (sensitivity and specificity) and how test performance impacts treatment management decisions. Effectively, a cost-effectiveness analysis of diagnostic interventions should capture down-stream consequences of diagnostic error / patient misclassification (e.g. false positive and false negatives) and subsequent resource utilization and clinical impact attributed to the incorrect treatment decisions. These aspects did not appear to be captured in the committee's cost-effectiveness analysis.	The agreed comparator was the use of clinical judgement and clinical scoring tools, which was established early on in the DAR process, and was agreed on at the Assessment Subgroup meeting (November 2018). The model captured diagnostic error for all POCT and for the clinical scoring tools, including the implications of misclassification.

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

Diagnostics Assessment Report (DAR) - Comments

Stakeholder	Comment no.	Page no.	Section no.	Comment	EAG Response
				4. Shulman ST, Bisno AL, Clegg HW, et al. Clinical Practice Guideline for the Diagnosis and Management of Group A Streptococcal Pharyngitis: 2012 Update by the Infectious Diseases Society of America. CID. 2012:55. 5. HM Government. Tackling antimicrobial resistance 2019–2024. The UK's five-year national action plan. January 2019. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/784894/UK_AMR_5_year_national_action_plan.pdf. Last accessed 05/06/19.	
Roche Diagnostics	21	162	Table 28	In the request for information, we submitted list prices to inform the cost-effectiveness analysis as these prices will be publicly available. However, we would like to clarify that these are not reflective of routine practice as volume based discounts will apply to sites who wish to implement the test. We would therefore ask for a comment to be included next to the price of the cobas® Strep A Assay on Liat® system here and in the final guideline document to highlight that this is the case e.g. this is the publicly available list price and volume based discounts are available. We would also ask for clarification on whether other manufacturers have submitted list prices because if consistency in prices has not been maintained then this will lead to an unfair comparison between the tests.	We considered the costs that were provided at the appropriate stage in the DAR process. We are not aware of any restriction that prevented Roche Diagnostics from submitting prices that were not publicly available at the time they provided NICE with the list price. The sources of the costs for the other tests are shown in Table 28, we believe that these are all list prices. NICE will be able to confirm whether they are or not.