

CADTH RAPID RESPONSE REPORT:  
PEER REVIEWED SUMMARY WITH CRITICAL APPRAISAL

# Rapid Tests for the Diagnosis of Group A Streptococcal Infection: A Review of Diagnostic Test Accuracy, Clinical Utility, Safety, and Cost- Effectiveness

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## Context and Policy Issues

Group A Streptococcus (GA Strep) also referred to as Group A beta-hemolytic Streptococcus, or Streptococcus pyogenes is a gram positive bacteria which causes a variety of disease conditions and complications.<sup>1-4</sup> These include conditions such as pharyngitis (throat infection) and skin infections, and more serious conditions such as glomerulonephritis, sepsis, rheumatic heart disease, toxic shock syndrome and necrotizing fasciitis.<sup>5,6</sup> Pharyngitis is one of the common conditions that present at the primary health care facilities or emergency departments.<sup>7</sup> Pharyngitis arises commonly from viral infection and less commonly from bacterial infection.<sup>4</sup> It is estimated that GA Strep accounts for 20% to 40% of cases of pharyngitis in children and 5% to 15% in adults.<sup>4</sup> It is associated with considerable cost to society; in the US the estimated annual cost incurred from GA Strep pharyngitis in children is between \$224 and \$539 million.<sup>7</sup>

Accurate and rapid diagnosis of GA Strep is important as there is a possibility that throat and skin infections could lead to severe life-threatening invasive conditions as well as post infection immune mediated complications if left untreated.<sup>5</sup> Diagnosis of GA strep is challenging which makes it difficult to decide on the appropriate care pathway. It is difficult to distinguish between GA strep infection and viral infection.<sup>7</sup> Antibiotics are useful to treat pharyngitis from bacterial infection but not viral infection. Considering the issue of antimicrobial resistance which is on the rise, unnecessary use of antibiotics could be detrimental, hence accurate diagnosis is important.

Diagnostic tests based on throat culture are generally considered as the gold standard for diagnosing GA Strep.<sup>3,8</sup> However, these culture based tests are associated with a time lag between sample collection and obtaining test results, and may take up to 48 hours.<sup>7,9</sup> It may not always be feasible for the patient to return to the clinic and get appropriate treatment based on test results or while waiting for test results there is a possibility that the patient's symptoms may worsen. Several non-culture-based, rapid tests for diagnosing GA Strep have been developed. These rapid tests are based on immunoassays and more recently on molecular assays. There are several types of immunoassays such as latex agglutination, enzyme immunoassay, immunochromatographic assays and optical immunoassays.<sup>4,7</sup> Molecular assays are based on methods such as DNA probes, polymerase chain reaction (PCR) and fluorescence in situ hybridization.<sup>7</sup> There is a perception that use of these rapid tests may enable faster diagnosis and hence prevent inappropriate use of antibiotics and use of more effective treatment strategies.

The purpose of this review is to evaluate the diagnostic accuracy of non-culture based tests to diagnose GA Strep infection; their clinical utility; their associated adverse effects, if any; and their cost-effectiveness.

## Research Questions

1. What is the diagnostic test accuracy of non-culture-based tests for the diagnosis of suspected group A strep infection?

2. What is the clinical utility of non-culture-based tests for the diagnosis of suspected group A strep infection?
3. What is the safety of non-culture-based tests for the diagnosis of suspected group A strep infection?
4. What is the cost-effectiveness of non-culture-based diagnostic tests for suspected group A strep infection?

## Key Findings

From systematic reviews and observational studies the sensitivity values ranged between 82% and 100% for molecular assays and between 55% and 94% for immunoassays. Specificities for the two test types were 91% to 99% for molecular assays and 81% to 100% for immunoassays.

One pragmatic adaptive RCT showed no clear advantage of rapid antigen test over clinical score for management of group A streptococcus infection. Evidence regarding change in treatment strategy with respect to use of antibiotics resulting from use of rapid antigen detection tests for diagnosis is conflicting.

No evidence was available regarding adverse effects associated with the non-culture-based tests.

One cost-effectiveness analysis suggested that compared to diagnosis using rapid antigen test, diagnosis using medical scores was more cost-effective. However, results of the corresponding cost-utility analysis were less clear.

## Methods

### Literature Search Methods

A limited literature search, with main concepts appearing in title, abstract, or major subject heading was conducted on key resources including Medline via Ovid, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to the main search to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and March 27, 2018.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	<p>Patients (of any age) suspected of group A strep infection</p> <p>Potential subgroups of interest: school-aged children; adults [parents of school-aged children]; elderly</p> <p>Potential settings of interest: community [including pharmacy], long-term and residential care</p>
<b>Intervention</b>	Non-culture-based rapid diagnostic tests (both point-of-care and lab based) for group A strep
<b>Comparator</b>	<p>Q1: Microbiological culture (throat culture or from another body site) reference standard; alternative non-culture-based rapid diagnostic tests as comparator index tests</p> <p>Q2 to 4: Microbiological culture (throat culture or from another body site); alternative non-culture-based rapid diagnostic test; no testing</p>
<b>Outcomes</b>	<p>Q1: Diagnostic test accuracy outcomes (e.g., sensitivity, specificity, NPV, PPV)</p> <p>Q2: Clinical utility outcomes (e.g., change in duration of symptoms, change in length of stay, change in patient management [e.g., antibiotic prescribing practices], failure rate)</p> <p>Q3: Safety outcomes (e.g., adverse events associated with the test)</p> <p>Q4: Cost-effectiveness outcomes (e.g., cost per quality adjusted life year or cost per quality adjusted life day)</p>
<b>Study Designs</b>	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-randomized studies, and economic evaluations

## Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013. Studies that were already included in the included systematic reviews were excluded. Studies assaying only a restrictive sample such as samples which had negative results from prior testing were excluded. In vitro studies on test accuracy were excluded.

## Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR 2,<sup>10</sup> randomized controlled trials were critically appraised using Downs and Black checklist,<sup>11</sup> diagnostic studies were assessed using QUADAS-2,<sup>12</sup> and economic studies were assessed using the Drummond checklist.<sup>13</sup> Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were narratively described.

## Summary of Evidence

### Quantity of Research Available

A total of 594 citations were identified in the literature search. Following screening of titles and abstracts, 554 citations were excluded and 40 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 13 publications were excluded for various reasons, while 27 publications met the inclusion criteria and were included in this report. These 27 publications comprised three systematic

reviews,<sup>4,7,14</sup> one RCT including an economic analysis,<sup>15</sup> and 23 observational studies.<sup>9,16-37</sup> Appendix 1 provides the PRISMA flowchart of the study selection.

## Summary of Study Characteristics

Study characteristics are summarized below and details are available in Appendix 2, Tables 10 to 12.

### *Study Design*

Three systematic reviews<sup>4,7,14</sup> were identified. One systematic review<sup>4</sup> was published by the Cochrane collaboration in 2016 and included 98 studies published between 1987 and 2015. A second systematic review<sup>7</sup> was published in 2014 from Australia, and included 48 studies published between 1996 and 2012. A third systematic review<sup>14</sup> was published from the USA and included 59 studies published between 2000 and 2012. There was considerable overlap in the included studies in these three systematic reviews.

One pragmatic adjusted RCT including an economic analysis was published in 2014 from the UK. This economic analysis included a cost-effectiveness analysis (cost per change in symptom severity) and a cost-utility analysis (cost per quality adjusted life-year [QALY]). The analysis was based on a healthcare perspective and time horizons of 14 and 28 days. Health related quality of life (HRQoL) was evaluated using EQ5D. QALYs were calculated using mean EQ5D scores obtained from the 14-day diary records. A cost-effectiveness acceptability curve (CEAC) was generated using bootstrapping with 5000 samples.

The 23 included observational studies,<sup>9,16-37</sup> comprised 20 prospective studies,<sup>16-31,33,35-37</sup> published between 2014 and 2018, and three retrospective analysis<sup>9,32,34</sup> published between 2014 and 2015.

### *Country of Origin*

The three systematic reviews<sup>4,7,14</sup> included studies conducted in both developed and developing countries. The included RCT with economic analysis was conducted in UK.<sup>15</sup> Of the 20 prospective observational studies, eleven studies were conducted in USA,<sup>16-21,23-25,27,29</sup> two studies were conducted in Turkey,<sup>22,30</sup> and one study each was conducted in Canada,<sup>33</sup> Finland,<sup>37</sup> India,<sup>36</sup> New Zealand,<sup>26</sup> Poland,<sup>35</sup> Switzerland,<sup>31</sup> and Yemen.<sup>28</sup> The three retrospective studies were conducted in Sweden,<sup>32</sup> Turkey,<sup>9</sup> and the USA.<sup>34</sup>

### *Patient Population*

One systematic review<sup>4</sup> included children with suspected pharyngitis. The other two systematic reviews<sup>7,14</sup> included both children and adults with suspected pharyngitis, with one systematic review<sup>7</sup> also reporting results for children separately.

The RCT with economic analysis included both adults and children with acute sore throat together with erythema and/or pus.<sup>15</sup>

Of the 20 prospective observational studies on patients with sore throat or pharyngitis, 10 studies<sup>16-18,21,24,25,27,29,35,37</sup> included both adults and children, nine studies<sup>20,22,23,26,28,30,31,33,36</sup> included children, and one study<sup>19</sup> did not report on age. Of the 10 studies<sup>16-18,21,24,25,27,29,35,37</sup> on both adults and children, the majority were children (< 18 years) in four studies<sup>17,18,21,25</sup> and the majority were < 19 years in one study.<sup>16</sup>

Of the three retrospective studies, one study<sup>9</sup> included children with acute sore throat, fever and inflamed throat or tonsils, one study<sup>34</sup> included both adults and children with sore

throat, with the majority being children, and one study<sup>32</sup> included both adults and children with necrotizing fasciitis.

### *Interventions and Comparators*

One systematic review<sup>4</sup> assessed various immunoassays with culture method as the reference standard. The second systematic review<sup>7</sup> assessed various immunoassays and molecular assays with culture method as the reference. The third systematic review<sup>14</sup> assessed various immunoassays with culture method as the reference.

The RCT with economic analysis compared decision making and the impact with use of immunoassay (rapid antigen detection test [RADT]), clinical score, and delayed antibiotic use.<sup>15</sup> In the control group (delayed antibiotic) the patients were instructed to collect the prescription after 3 to 5 days if symptoms persisted, or sooner if symptoms markedly worsened. In the clinical score group, for patients with scores 0 or 1, antibiotics were not offered; for patients with scores 2 or 3, delayed antibiotics were offered; and for patients with scores 4 or higher, immediate antibiotics were offered. In the RADT group, for patients with scores of 0 or 1, no RADT or antibiotics were offered; for patients with score 2, delayed antibiotics were offered; and for patients with scores 3 or higher, RADTs were offered and antibiotics were not offered if test results were negative.

Of the 20 prospective observational studies, six studies<sup>16,18,19,24-26</sup> assessed molecular assays with culture method as reference; eight studies<sup>28-31,33,35-37</sup> assessed immunoassays with culture method as reference; five studies<sup>17,20-22,27</sup> assessed both molecular assays and immunoassays with culture method as reference; and one study<sup>23</sup> assessed immunoassay and a lymphocyte esterase assay with culture method as reference.

The three retrospective studies<sup>32,34,38</sup> assessed immunoassays with culture method as reference.

### *Outcomes*

For diagnostic accuracy, outcomes assessed included sensitivity and specificity,<sup>4,7,9,14,16-37</sup> positive predictive value (PPV),<sup>9,16,18-20,22-24,26,28-31,33,35,37</sup> and negative predictive value (NPV).<sup>9,16,18-20,22-24,26,28-31,33,35,37</sup>

One study<sup>15</sup> reported on duration of symptoms, severity of condition and use of antibiotics . cost-effectiveness and cost-utility. One study<sup>30</sup> reported on use of antibiotics and change in cost of treatment with antibiotics . One study<sup>17</sup> reported on use of antibiotics .

### *Summary of Critical Appraisal*

Critical appraisal of the studies is summarized below and details are available in Appendix 3, Tables 13 to 16.

In all three systematic reviews,<sup>4,7,14</sup> the objectives and inclusion and exclusion criteria were stated, a comprehensive literature search was undertaken, the study selection was described, a list of included studies were provided, and meta-analyses were conducted and appeared to be appropriate. In one systematic review<sup>4</sup> the review methods were established prior to conducting the review and in the other two systematic reviews<sup>7,14</sup> it was unclear if methods had been established previously. In one systematic review<sup>4</sup> a list of excluded studies were provided but not in the other two systematic reviews.<sup>7,14</sup> Article selection was done in duplicate in two systematic reviews<sup>4,14</sup> and was unclear if done in duplicate in one systematic review.<sup>7</sup> Data extraction was done in duplicate in one



systematic review and was unclear in two systematic reviews.<sup>7,20</sup> Quality assessment of the included studies was conducted in all three systematic reviews and reported to be generally of low quality in two systematic reviews<sup>4,7</sup> and appeared to be of variable quality in one systematic review.<sup>14</sup> Publication bias was explored in one systematic review<sup>14</sup> and potential for bias was reported. It was unclear if publication bias had been explored in the other two systematic reviews.<sup>4,7</sup> In all three systematic reviews it was mentioned that the authors had no conflicts of interest.

In the included pragmatic adaptive RCT,<sup>15</sup> the objective, and inclusion and exclusion criteria were stated, and the patient characteristics, intervention and outcomes were described. Sample size calculation was conducted and appeared to be appropriate. Randomization method appeared to be appropriate. Due to the pragmatic nature of the trial complete blinding was not possible. Not all analyses included all patients and the reason for this was not apparent. Conflicts of interest were declared and potential for concern was not apparent. This RCT included an economic study.<sup>15</sup> In the economic study, the objective, strategies compared, time horizon, perspective, clinical and cost data sources were stated. The time horizon was short (28 days) hence long term effects would not be captured. It was assumed that the HRQoL changes linearly over time. However this may not always be true. Indirect costs did not appear to have been considered. Incremental analysis and sensitivity analysis were conducted.

Of the 23 observational studies, 20 studies,<sup>16-31,33,35-37</sup> were prospective and three studies<sup>9,18,34</sup> were retrospective. Twenty studies<sup>9,16-22,24-31,33,35-37</sup> provided descriptions of both index and reference test and three studies<sup>23,32,34</sup> did not. In all the 23 studies, the reference standard used appeared to be the gold standard; and all samples were assayed using both the index and reference tests. The reference test appeared to be the same for all the test samples in all the studies except in one study<sup>34</sup> in which partial reference testing was conducted with only samples that were negative with the index test. All positive RADT results were assumed to be positive with culture testing, which could affect the calculated sensitivity of the test. In 19 studies<sup>9,16-31,35,37</sup> all samples were included in the analysis, in one study<sup>33</sup> most samples were included in the analysis, in one study<sup>34</sup> not all samples were included in the analysis because of incomplete data or patients being discharged and in two studies<sup>32,36</sup> it was unclear. In two studies<sup>21,33</sup> consecutive patients were selected and in the other 21 studies<sup>9,16-20,22-32,34-37</sup> the method of patient selection was unclear, hence the potential of selection bias is unclear. In one study<sup>34</sup> the index test results were interpreted before the reference test was conducted and the reference test was conducted with knowledge of the index test results. In the other 22 studies<sup>9,16-33,35-37</sup> it was unclear if the index test results were interpreted without the knowledge of the reference test results and if the reference test results were interpreted without the knowledge of the index test results, hence potential for bias is unclear. In nine studies<sup>9,18,23,29,32-36</sup> the authors mentioned that there were no conflicts of interest and in the remaining 14 studies<sup>16,17,19-22,24-28,30,31,37</sup> there was either no mention of conflicts of interest or one or more authors had some association with the manufacturer. In two studies<sup>22,23</sup> it was mentioned that no funding was received from the manufacturer, in nine studies<sup>9,28-30,32,34-37</sup> there was no mention of funding, and 12 studies<sup>16-21,24-27,31,33</sup> received funding from the manufacturer.

## Summary of Findings

Findings are summarized below and details are available in Appendix 4, Table 17

*What is the diagnostic test accuracy of non-culture-based tests for the diagnosis of suspected group A strep infection?*

Twenty six studies<sup>4,7,9,14,16-37</sup> reported on specificity and sensitivity and are discussed in the text below. Of these 26 studies, 16 studies,<sup>9,16,18-20,22-24,26,28-31,33,35,37</sup> also presented data on PPV and NPV which are available in Appendix 4, Table 15

### Molecular assays

#### *Children*

One systematic review,<sup>7</sup> including four test evaluations on molecular assays conducted in children, reported pooled estimates of sensitivity of 93% (95% confidence interval [CI]: 89% to 96%), and specificity of 99% (95% CI: 98% to 100%). Also, four prospective observational diagnostic studies<sup>18,20,22,26</sup> on molecular assays conducted in children showed sensitivities in the range of 82% to 100% and specificities in the range 91% to 96% (Table 2).

**Table 2: Performance of molecular assays in children**

Obs. Study (first author, year, country)	Test	Sensitivity,% (95% CI)	Specificity,% (95% CI)
Kolukirik, <sup>22</sup> 2016, Turkey	qPCR (laboratory developed)	100 (95% CI not reported)	96.4 (95% CI not reported)
Upton, <sup>26</sup> 2016, New Zealand	Illumigene	81.5 (72.0 to 88.9)	92.6 (90.4 to 94.5)
Cohen, <sup>18</sup> 2015, USA	Alere i Strep A	96.1 (92.7 to 99.5)	93.4 (90.2 to 96.6)
Felsentein, <sup>20</sup> 2014, USA	Illumigene	93.1 (83.1 to 97.8)	91.4 (87.7 to 94.1)

CI = confidence interval; obs = observational

#### *Adults*

One prospective observational diagnostic study<sup>18</sup> on a molecular assay (Alere i Strep A) conducted in adults and children reported results separately for adults and showed sensitivity of 95% (95% CI: 84% to 105%) and specificity of 97%, (95% CI: 94% to 100%.

#### *Mixed population of adults and children*

One systematic review<sup>7</sup> including six test evaluations on molecular assays conducted in a mixed population of adults and children reported sensitivities in the range 89% to 96% and specificities in the range 96% to 100%. Also, seven prospective observational diagnostic studies,<sup>16-18,21,24,25,27</sup> on molecular assays conducted in a mixed population of adults and children with sore throat or pharyngitis, showed sensitivities in the range 96% to 100% and specificities in the range 91% to 97% (Table 3). Of note, in four studies<sup>17,18,21,25</sup> majority of patients were children (< 18 years) and in one study<sup>16</sup> majority of patients were < 19 years.

**Table 3: Performance of molecular assays in a mixed population of adults and children**

Obs. Study (first author, year, country)	Test	Sensitivity,% (95% CI)	Specificity,% (95% CI)
Berry, <sup>17</sup> 2018, USA	Alere i Strep A test	100.0 (91.6 to 100.0)	91.3 (86.1 to 95.1)
Wang, <sup>27</sup> 2017, USA	PCR-based point-of-care assay	97.7 (93.4 to 99.2)	93.3% (89.9% to 95.6%)
Tabb, <sup>24</sup> 2016, USA	Simplexa™ Group A Strep Direct assay	97.4 (93.6 to 99.0)	95.2 (93.9 to 96.3)
Uphoff, <sup>25</sup> 2016, USA	Solana GA strep assay	98.2 (95.5 to 99.3)	97.2 (95.9 to 98.1)
Cohen, <sup>18</sup> 2015, USA	Alere i Strep A	95.9 (92.7 to 99.1)	94.6 (92.2 to 97.0)

Obs. Study (first author, year, country)	Test	Sensitivity,% (95% CI)	Specificity,% (95% CI)
Anderson, <sup>16</sup> 2013, USA	illumigene group A Strep test	100 (95 to 100)	94.2 (92 to 94)
Henson, <sup>21</sup> 2013, USA	illumigene group A Strep test	100 (95% CI not reported)	95.9 (95% CI not reported)

CI = confidence interval; GA strep = group A strep; obs = observational; PCR = polymerase chain reaction; strep = streptococcus

### Unspecified population

One prospective observational diagnostic study,<sup>19</sup> on molecular assay (Ampli Vue) conducted in an unspecified population, showed sensitivity of 98%, (95% CI: 95% to 100%) and specificity of 93% (95% CI: 91% to 95%).

In summary, reports, on children or mixed populations of children and adults who were tested using molecular assay and with culture assay as the reference test, showed that for molecular assay based tests, generally the sensitivity varied between 93% and 99%, with the exception of one study presenting a sensitivity of 82%; and the specificity varied between 91% and 99%.

### Immunoassays

#### Children

Three systematic reviews<sup>4,7,14</sup> reported pooled estimates of sensitivities between 80% and 86%, and specificities between 92% and 97% for various immunoassays on children. Sensitivities and specificities of the different types of immunoassays are shown in Table 4.

**Table 4: Performance of immunoassays in children from systematic reviews**

Systematic review (first author, year, country)	Test	Number of evaluations	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Cohen (Cochrane Collaboration), <sup>4</sup> 2016, France	EIA	86	85.4 (82.7 to 87.8)	95.8 (94.8 to 96.2)
	OIA	19	86.2 (82.7 to 89.2)	93.7 (91.5 to 95.4)
	EIA and OIA	105	85.6 (83.3 to 87.6)	95.4 (94.5 to 96.2)
Lean, <sup>7</sup> 2014, USA	OIA	11	85 (80 to 89)	95 (93 to 97)
	Lateral flow/ immunochromatographic assay	14	84 (80 to 89)	97 (95 to 98)
Stewart, <sup>14</sup> 2014, Australia	EIA	3	86 (79 to 92)	92 (88 to 95)
	OIA	3	80 (77 to 82)	93 (92 to 94)
	Immunochromatographic assay	28	86 (85 to 87)	96 (95 to 96)

CI = confidence interval; EIA = enzyme immunoassay; ELISA = enzyme linked immunosorbent assay; OIA = optical immunoassay

Seven prospective observational diagnostic studies,<sup>20,23,28,30,31,33,36</sup> conducted immunoassays in children with sore throat or pharyngitis, and reported sensitivities in the range 55% to 92%, and specificities in the range 92% to 100% (Table 4). One retrospective study<sup>9</sup> on children with sore throat and immunoassay results reported a sensitivity of 60% and specificity of 97% (Table 5).

**Table 5: Performance of immunoassays in children from observational studies**

Obs. Study (first author, year, country)	Test	Sensitivity,% (95% CI)	Specificity,% (95% CI)
Lacroix, <sup>31</sup> 2018, Switzerland	Sofia StrepA FIA (optical immunoassay)	84.9 (82.6 to 86.7)	96.8 (95.4 to 97.9)
	Alere TestPack Strep A (immunochromatographic assay)	75.3 (73.1 to 76.7)	98.1 (96.8 to 98.9)
Kose, <sup>30</sup> 2016, Turkey	ACON Strep A Rapid Test Device (immunochromatographic assay)	92.1 (78.6 to 98.3)	97.3 (93.8 to 99.1)
Penney, <sup>33</sup> 2016, Canada	Alere TestPack Plus Strep A kit (immunochromatographic assay)	76.3 (63.4 to 86.4) (conducted by nurse)	96.6 (90.4 to 99.3) (conducted by nurse)
	Alere TestPack Plus Strep A kit (immunochromatographic assay)	81.4 (69.1 to 90.3) (conducted by technologist)	97.7 (92.0 to 99.7) (conducted by technologist)
Nibhanipudi, <sup>23</sup> 2015, USA	Rapid antigen strep test	56.3 (95% CI not reported)	92.3 (95% CI not reported)
Subashini, <sup>36</sup> 2015, India	SD Bioline rapid antigen test (immunochromatographic assay)	55.5 (95% CI not reported)	100 (95% CI not reported)
Ba-Saddik, <sup>28</sup> 2014, Yemen	Reveal Color Strep A Latex agglutination test	92.2 (95% CI not reported)	95.5 (95% CI not reported)
Felsentien, <sup>20</sup> 2014, USA	OSOM Ultra Strep A	55.2 (42.5 to 67.3)	99.1 (96.9 to 99.8)
Küçük, <sup>9</sup> 2014, Turkey	Quickvue Strep A cassette test	59.5 (52.6 to 66.2) <sup>a</sup>	97.2 (95.6 to 98.3) <sup>a</sup>

CI = confidence interval; obs = observational; strep = streptococcus

<sup>a</sup>range, not 95% CI

### Adults

One systematic review,<sup>14</sup> including nine test evaluations on immunoassays conducted in adults and from studies of generally high methodological quality, reported pooled estimates of sensitivities and specificities for various types of immunoassays. This systematic review<sup>14</sup> reported for immunochromatographic assays, enzyme immunoassays, and optical immunoassays, pooled estimates of sensitivities of 91% (95% CI: 87% to 94%); 86% (95% CI: 81% to 91%); and 94% (95% CI: 80% to 99%) respectively, and pooled estimates of specificities of 93% (95% CI: 92% to 95%); 97% (95% CI: 96% to 99%); and 69% (95% CI: 54% to 81%) respectively.

### Mixed population of adults and children

One systematic review<sup>7</sup> including 51 test evaluations on various immunoassays conducted in a mixed population of adults and children reported pooled estimates for sensitivities between 84% and 86%, and specificities between 94% and 96%. Sensitivities and specificities of the different types of immunoassays are shown in Table 6.

**Table 6: Performance of immunoassays in mixed population of adults and children from a systematic review**

Systematic review (first author, year, country)	Test	Number of evaluations	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Lean, <sup>7</sup> 2014, USA	ELISA	11	86 (81 to 91)	96 (93 to 98)
	OIA	19	86 (82 to 89)	94 (91 to 96)
	Lateral flow/ immunochromatographic assay	21	84 (80 to 88)	96 (94 to 97)

CI = confidence interval; EIA = enzyme immunoassay; ELISA = enzyme linked immunosorbent assay; OIA = optical immunoassay

Five prospective observational diagnostic studies,<sup>17,21,29,35,37</sup> conducted immunoassays on a mixed population of adults and children, and reported sensitivities in the range 73% to 94%, and specificities in the range 81% to 96% (Table 7). One retrospective study,<sup>34</sup> on a mixed population of adults and children with sore throat, reported a sensitivity of 84% (Table 7). Of note, in two studies<sup>21,34</sup> majority of the patients were children.

One retrospective analysis,<sup>32</sup> on immunoassays conducted in a mixed population of adults and children with necrotizing fasciitis, reported a sensitivity of 87% and specificity of 100%.

**Table 7: Performance of immunoassays in a mixed population of adults and children from observational studies**

Obs. Study (first author, year, country)	Test	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Berry, <sup>17</sup> 2018, USA	BD Veritor system (immunoassay)	76.2 (60.5 to 87.9)	93.6 (88.9 to 96.8)
Stefaniuk, <sup>35</sup> 2017, Poland.	QuickRead go® Strep A test (immunoassay)	85 (95% CI not reported)	91 (95% CI not reported)
Gonsu, <sup>29</sup> 2015, Cameroun	Strep A rapid test (lateral flow immunoassay)	75 (95% CI not reported)	96 (95% CI not reported)
Shapiro, <sup>34</sup> 2015, USA	Rapid antigen detection test	84 (77 to 91)	NR
Vakkila, <sup>37</sup> 2015, Finland	mariPOC (immunofluorescence assay)	93.8 (95% CI not reported)	81.3 (95% CI not reported)
Henson, <sup>21</sup> 2013, USA	GA Strep rapid antigen assay (immunoassay)	73.3 (95% CI not reported)	89.1 (95% CI not reported)

CI = confidence interval; obs = observational; strep = streptococcus

In summary, reports, on children or mixed populations of children and adults, with suspected pharyngitis, who were tested using immunoassays and with culture assays as the reference test, showed that for immunoassay based tests, generally the sensitivity varied between 55% and 94%; and specificity varied between 81% and 100%.

#### Other assays

One prospective observational diagnostic study<sup>23</sup> on children with pharyngitis conducted a leukocyte esterase test using a test strip which is currently used for urine dipstick, and reported a sensitivity of 45% and specificity of 80%.

Studies with more than one index test

Findings from studies with two index tests are presented in Tables 8 and 9 for the purpose of comparison. Of note, in two studies<sup>17,21</sup> majority of the patients were children. The individual tests have been discussed above in the appropriate sections.

**Table 8: Comparison of molecular assays and immunoassays in children with culture method as reference**

Obs. Study (first author, year, country)	Test	Sensitivity,% (95% CI)	Specificity,% (95% CI)
Kolukirik, <sup>22</sup> 2016, Turkey	qPCR (laboratory developed molecular assay)	100 (95% CI not reported)	96.4 (95% CI not reported)
	Clearview Strep A Exact II Cassette test (molecular assay)	69.4 (95% CI not reported)	100 (95% CI not reported)
Nibhanipudi, <sup>23</sup> 2015, USA	Rapid antigen strep test	56.3 (95% CI not reported)	92.3 (95% CI not reported)
	Leukocyte esterase (LE) test using test strip currently used for urine dipstick	45 (95% CI not reported)	80 (95% CI not reported)
Felsentein, <sup>20</sup> 2014, USA	illumigene group A Strep (molecular assay)	93.1 (83.1 to 97.8)	91.4 (87.7 to 94.1)
	OSOM Ultra Strep A (immunoassay)	55.2 (42.5 to 67.3)	99.1 (96.9 to 99.8)

CI = confidence interval; obs = observational

**Table 9: Comparison of molecular assays and immunoassays in mixed population of adults and children with culture method as reference**

Study (first author, year, country)	Test	Sensitivity,% (95% CI)	Specificity,% (95% CI)
Berry, <sup>17</sup> 2018, USA	Alere i Strep A test (molecular assay)	100.0 (91.6 to 100.0)	91.3 (86.1 to 95.1)
	BD Veritor system (immunoassay)	76.2 (60.5 to 87.9)	93.6 (88.9 to 96.8)
Wang, <sup>27</sup> 2017, USA	PCR-based point-of-care assay	97.7% (93.4% to 99.2%)	93.3% (89.9% to 95.6%)
	RADT various types (such as Consult Strep A, Quidel QuickVue Dipstick, and McKesson Strep A Dipstick)	84.5% (77.3% to 89.7%)	95.3% (92.3% to 97.2%)
Henson, <sup>21</sup> 2013, USA	illumigene group A Strep test (molecular assay)	100 (95% CI not reported)	95.9 (95% CI not reported)
	GA Strep rapid antigen assay (immunoassay)	73.3 (95% CI not reported)	89.1 (95% CI not reported)

CI = confidence interval; obs = observational; PCR = polymerase chain reaction; RADT = rapid antigen detection test; strep = streptococcus

*What is the clinical utility of non-culture-based tests for the diagnosis of suspected group A strep infection?*

One pragmatic adjusted RCT<sup>15</sup> of a mixed population of adults and children with sore throat investigated three management strategies. These strategies comprised management based on delayed antibiotic use according to the patient's perception of symptoms, management based on clinical score, and management based on a rapid antigen detection test (RADT). The mean severity scores after two to four days was 3.11, 2.88, and 2.83 in the delayed antibiotic, clinical score, and RADT groups respectively; higher scores indicate worse condition. The median duration of symptoms was 5 days, 4 days, and 4 days in the delayed antibiotic, clinical score, and RADT groups respectively. The proportion using antibiotics was 46%, 37%, and 35% in the delayed antibiotic, clinical score, and RADT groups respectively. In the delayed antibiotic, clinical score, and RADT groups, the proportion returning within one month with sore throat was 8%, 8%, and 6% respectively; and the proportion returning after one month with sore throat was 15%, 12%, and 16% respectively. In summary, the authors found no clear advantage of RADT over clinical score for the management of GA strep infection with respect to duration of symptoms, severity of condition, or antibiotic use. It should be noted that in this study, due to its pragmatic nature, clinicians were requested to use the intended strategy, but had the flexibility to use a different strategy if deemed necessary, hence potential for selection bias cannot be ruled out.

In one observational study<sup>30</sup> of children with suspected pharyngitis, patients were evaluated before the RADT and also after the RADT and the decisions to prescribe antibiotics were recorded. It was found that before RADT (i.e. based on clinical findings and signs, the decision to prescribe antibiotics was in 80% of the patients whereas after RADT the decision to prescribe antibiotics was reduced to 37% of the patients.

In one observational study,<sup>17</sup> on a mixed population of 215 adults and children, a molecular assay and an immunoassay were investigated. Charts of these 215 patients were later reviewed and it was found that 73 of the 215 patients were given antibiotics at the time of the clinic visit. Of these 73 patients, 26 (36%) patients were likely prescribed antibiotics inappropriately based on confirmation of negative GA strep results. The proportion of patients who would have benefited from antibiotics but did not receive them was not reported. However, chart review did not show any documentation of adverse outcomes associated treatment differences.

In summary, one pragmatic adaptive RCT showed no clear advantage of rapid antigen test over clinical score, for management of GA strep infection. Evidence regarding change in treatment strategy with respect to use of antibiotics, resulting from use of rapid antigen detection tests for diagnosis, consisted of a limited number of available relevant studies with conflicting results.

*What is the safety of non-culture-based tests for the diagnosis of suspected group A strep infection?*

No reports on safety of non-culture based tests for the diagnosis of suspected group A strep infection were identified.



*What is the cost-effectiveness of non-culture-based tests for the diagnosis of suspected group A strep infection?*

The pragmatic adjusted RCT by the PRISM investigators<sup>15</sup> also included a cost-effectiveness analysis and a cost-utility analysis. The cost-utility analysis was conducted on a smaller sample than that of the cost-effectiveness analysis, as EQ5D data were not available for all patients.

In the cost-effectiveness study the mean symptom scores were adjusted for baseline differences. The mean symptom scores were 3.15 (95% CI: 2.93 to 3.37) for the delayed antibiotic group, 2.84 (95% CI: 2.62 to 3.07) for the RADT group, and 2.83 (95% CI: 2.61 to 3.05) for the clinical score (FeverPAIN) group. The costs (in £) were 51 (95% CI: 43 to 59) for the delayed antibiotic group, 49 (95% CI: 46 to 53) in the RADT group, and 44 (95% CI: 41 to 47). The clinical score group dominated both the delayed antibiotic group and the RADT group, as it was more clinically effective (lower symptom score) and less costly. However, the point estimate of symptom score and the corresponding 95% CI for clinical score and RADT groups were quite close hence it was important to consider uncertainty around these results. To determine the impact of uncertainty CEACs were generated to show the probability that the intervention is cost-effective at different values of the outcome variable. For this, the value of a point change in the symptom score was varied between £0 and £500, and it was found that over the entire range the clinical score group was most likely to be cost-effective.

In the cost-utility analysis, the delayed group was dominated by the clinical score group for both the time frames. The ICER for RADT group compared to clinical score group was £74,286 for the 14 day time frame and £24,528 for the 28 day time frame. The authors reported that there was considerable uncertainty in the data. To show the impact of uncertainty, CEACs were generated. Considering a threshold of £30,000 per QALY, for the 14-day time frame, the probabilities of being cost-effective were 25%, 35%, and 40% for delayed antibiotic group, RADT group, and clinical score group respectively, and for the 24-day time frame the corresponding probabilities were 28%, 35%, and 38% respectively.

In one observational study,<sup>30</sup> on children with suspected pharyngitis, patients were evaluated before the RADT and also after the RADT. After RADT, there was a reduction in the decision to prescribe antibiotics which was estimated to result in a reduction of cost of antibiotic use by 76%.

## Limitations

There was considerable overlap among the studies included in the included systematic reviews, hence the findings are not mutually exclusive. Also there was considerable heterogeneity among the included studies in the systematic reviews. There was considerable variation in sensitivity of the tests assessed in the individual studies included in the systematic reviews.

In most of the studies the method of patient selection was unclear, and also the blinding of index test and reference test results was unclear, hence potential for bias cannot be ruled out.

Most of the studies were on patients with suspected pharyngitis. Information on GA strep testing in patients with necrotizing fasciitis was limited; a single retrospective analysis using medical records of 22 patients was identified.



Most of the studies were on children or mixed population of adults and children. One study on a mixed population of adults and children reported results separately for adults and children, however, no relevant studies specifically on adults or on the elderly population were identified.

Information on clinical utility of these rapid tests with respect to outcomes such as change in patient outcomes and change in management of patients was limited. It was unclear if there were any adverse events associated with these tests as there was no mention regarding absence or presence of such adverse events in the reports.

It should be noted that these rapid tests are able to detect GA strep but not able to distinguish between patients who are carriers of GA strep and those who are actually infected with GA strep.<sup>22</sup> Decisions based on positive test results would result in unnecessary antibiotic prescribing for patients who are carriers without active infection.<sup>15</sup>

There was limited information regarding the cost-effectiveness of these tests; a single economic study, nested in a pragmatic adaptive RCT, was identified. This study compared RADT with a clinical scoring tool. No additional culture tests appeared to have been undertaken in this study. No study comparing the cost-effectiveness of non-culture based rapid detection test with culture-based detection tests was identified.

## Conclusions and Implications for Decision or Policy Making

A total of 27 relevant reports were identified. These comprised three systematic reviews,<sup>4,7,14</sup> one RCT including an economic analysis,<sup>15</sup> and 23 observational studies.<sup>9,16-37</sup> Reports, on children or mixed populations of children and adults who were tested using molecular assays and with culture assays as the reference test, showed that for molecular assay based tests, generally the sensitivity varied between 93% and 100%, with the exception of one study presenting a sensitivity of 82%; and the specificity varied between 91% and 99%. Whereas, reports on children or mixed populations of children and adults, who were tested using immunoassays and with culture assay as the reference test, showed that for immunoassay based tests, the sensitivity varied between 55% and 94%; and specificity varied between 81% and 100%. Based on three studies<sup>17,21,27</sup> which investigated both molecular assay and immunoassay, it appears that the molecular assays based tests are likely to be more sensitive than immunoassays based tests.

One pragmatic adaptive RCT<sup>15</sup> showed no clear advantage of rapid antigen test over clinical score for management of GA strep infection with respect to duration of symptoms, severity of condition, or antibiotic use. However, one observational study comparing antibiotic use before and after the introduction of rapid antigen detection tests showed that there was a reduction in antibiotic use following introduction of rapid antigen detection tests.

No evidence regarding any adverse effects associated with the tests was identified.

One economic analysis which was nested in the RCT<sup>15</sup> showed that management strategies based on clinical score was more effective in reducing symptoms and less costly than management strategies based on rapid antigen detection tests. However, results of the cost-utility analysis were less clear.

It should be noted that the success of a test is dependent on several factors. Some factors that may affect RADT results include type of test kit used, expertise of the personnel performing the test, method of specimen collection, severity of disease of the patient, and

prevalence of GA strep.<sup>9,31,33</sup> Careful sampling, which is crucial for the tests to produce accurate results, is often overlooked in the clinical units.<sup>37</sup>

It appears that even if throat cultures assays are replaced with other assays for detection of GA Strep it may still be necessary to maintain cultures for antimicrobial susceptibility testing.<sup>21</sup> It should be noted that qPCR assay cannot differentiate between DNA obtained from viable or non-viable organism.<sup>22</sup> Also it appears there are no tests to distinguish between GA Strep carriers or actual GA Strep infection.<sup>22</sup>

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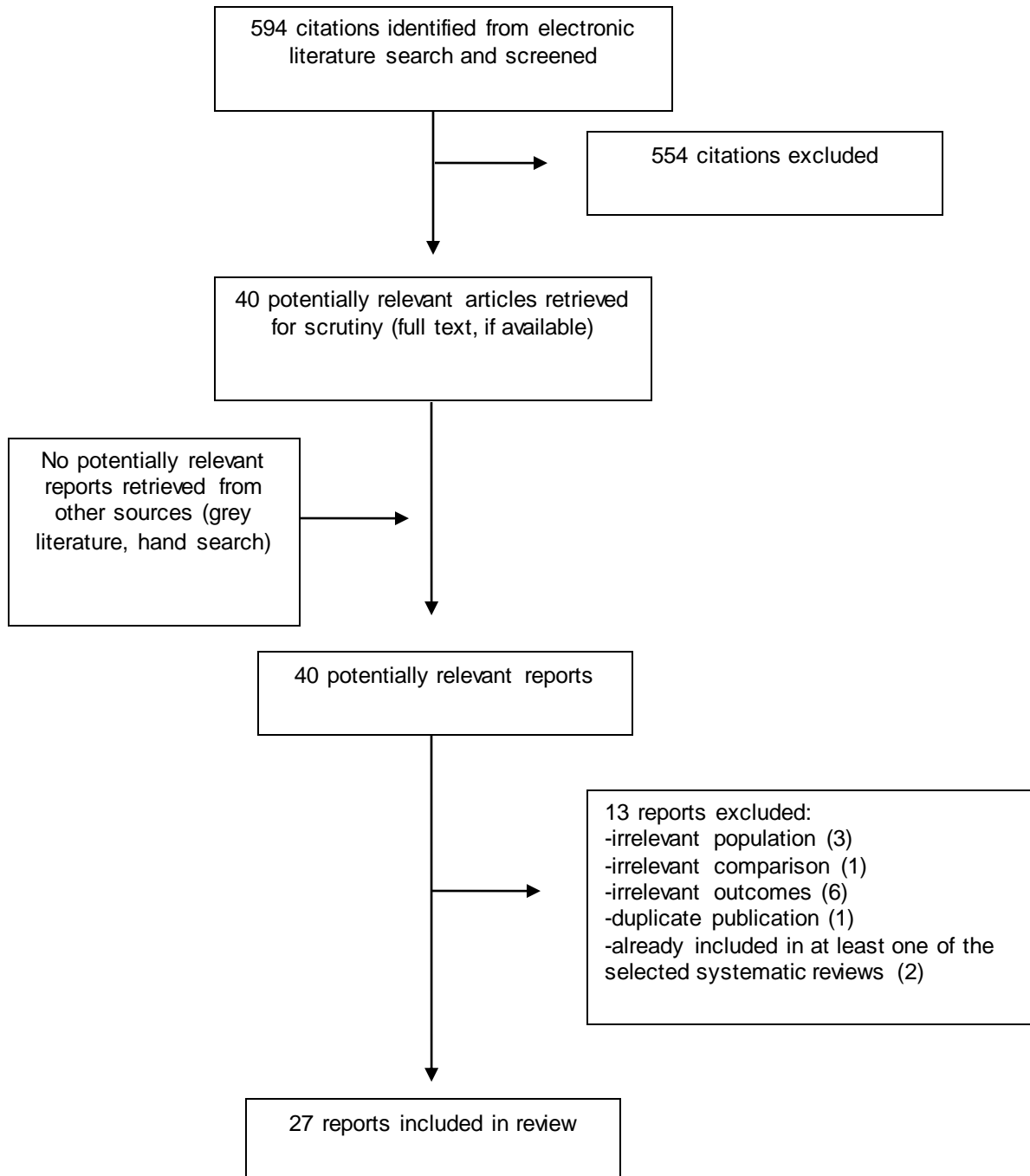
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## Abbreviations

AAFP	American Academy of Family Physicians
ACP	American College of Physicians
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
ED	emergency department
EIA	enzyme immunoassay
ELISA	enzyme-linked immunoassay
FISH	fluorescence in situ hybridization
FN	false negative
FP	false positive
GA Strep	group A Streptococcus
HRQoL	health related quality of life
ICER	incremental cost-effectiveness ratio
LE	leukocyte esterase
NA	not applicable
NLR	negative likelihood ratio
NPV	negative predictive value
NR	not reported
OIA	optical immunoassay
PCR	polymerase chain reaction
PLR	positive likelihood ratio
POC	point of care
POCT	point of care testing
PPV	positive predictive value
QALY	quality adjusted life year
RADT	rapid antigen detection test
QALY	quality adjusted life year
qPCR	quantitative PCR
RT-PCR	real time PCR
Sn	sensitivity
Sp	specificity
Strep	streptococcus
TN	true negative
TP	true positive

## Appendix 1: Selection of Included Studies



# Appendix 2: Characteristics of Included Publications

**Table 10: Characteristics of Included Systematic Reviews**

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcomes
Cohen (Cochrane Collaboration), <sup>4</sup> 2016, France	<p>Systematic review including 98 studies (cross-sectional studies) comprising a total of 116 cohorts (i.e. 116 test evaluations) and reporting a total of 101,121 test results.</p> <p>The studies were published between 1987 and 2015 from 25 different countries (Studies: USA - 43, France - 9, Spain - 6, Canada - 5, Turkey - 5, Switzerland - 4, Germany - 3, Italy - 3, Brazil, Croatia, Poland, and Scotland - 2 each, Argentina, China, Egypt, Greece, India, Korea, Latvia, the Netherlands, Taiwan, Tunisia, United Arab Emirates, and Vietnam - one each).</p> <p>Setting: Ambulatory care settings; mainly private offices, emergency departments, and walk-in clinics.</p> <p>Aim: To assess the diagnostic accuracy of RADTs for diagnosing G A Strep in children with pharyngitis.</p>	<p>Children with acute pharyngitis.</p> <p>N per study cohort (median [IQR])= 297 [196 to 539]</p> <p>Age (years) (median [IQR]): 6.6 [5.8 to 7.7] in 32 studies, not specifically reported in the remaining studies.</p> <p>% Female: varied between 39 to 59 as reported in 32 studies, not reported in the remaining studies</p> <p>Disease stage or prior therapy: Of the 98 studies, 18 studies mentioned disease stage in terms of a scores (such as McIsaac, Centor)</p>	<p>RADT (EIA or OIA tests for G A Strep) compared with throat culture on a blood agar plate.</p> <p>42 different commercially available RADTs kits were evaluated and in 3 studies no commercial name was mentioned. Six commercial kits that were assessed in at least 5 pediatric cohorts were: OSOM Strep A, QuickVue Inline Strep A, Strep A OIA, Strep A OIA max, TestPack Strep A, and TestPack Plus.</p>	Diagnostic accuracy (sensitivity, specificity)
Lean, <sup>7</sup> 2014, Australia	<p>Systematic review including 48 studies</p> <p>The studies were published between 1996 and 2012 from various countries (Brazil, Canada [4 studies], China, Croatia, Egypt, France, Greece, Iran, Israel, Korea, Latvia, Netherlands, Norway, Saudi Arabia, Scotland, Spain, Sweden, Switzerland, Turkey, UAE,</p>	<p>Children and adults or children only with GA strep pharyngitis.</p> <p>Number of patients: 23934</p> <p>Age (years): 17 studies included both adults and children and 31 studies included children (≤18 years)</p>	<p>Rapid antigen diagnostic test (authors included in this group latex agglutination, liposomal technology, lateral flow/ immunochromatographic assays, ELISA, OIA, DNA probe, PCR assay, and FISH) was compared with culture assays.</p> <p>Trade names of the test</p>	Diagnostic accuracy (sensitivity, specificity)



Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcomes
	<p>USA [majority of the studies], Vietnam). Of the 48 studies, 36 were conducted in a developed country and 12 in a developing country</p> <p>Settings: clinic or emergency department for majority of the studies, hospital for two studies and unknown for one study.</p> <p>Aim: To assess the diagnostic accuracy of RADTs for diagnosing GA Strep in children only and in children and adults combined.</p>	<p>% Female: NR</p> <p>Disease stage or prior therapy: NR</p>	<p>used: (Detect A Strep; Patho Dx, DPC for latex agglutination), Directigen 1,2,3 Strep A for liposomal technology), (Quickvue Flex StrepA, OSOM Ultra StrepA, SD Bioline Strep A Clearview Exact Strep A, Link 2 Strep A, and others for lateral flow/ immunoassays), (Abbott TestPack Plus, Abbott TestPack Plus Strep A and others for enzyme immunoassays), and (Biostar StrepA OIA, StrepA OIA Max and others for optical immunoassays)</p>	
Stewart, <sup>14</sup> 2014, USA	<p>Systematic review including 59 studies comprising a total of 55,766 patients. The studies were published between 2000 and 2012 from various countries (USA/Canada 37 studies, Europe 18 studies, and other countries 17 studies)</p> <p>Setting: outpatient clinic, or emergency room for the majority of studies; unknown for two studies.</p> <p>Aim: To assess the diagnostic accuracy of RADTs for diagnosing GA Strep in children and adults</p>	<p>Children and adults with GA strep pharyngitis.</p> <p>No. of patients: 55,766</p> <p>Age (years): 18 studies included both adults and children, 35 studies included children, 4 studies included adults and two studies did not provide specifics</p> <p>% Female: NR</p> <p>Disease stage or prior therapy: disease stage or prior antibiotic therapy as exclusion criteria was reported only for a few of the included studies</p>	<p>Index test (antigen detection test – immunoassays, EIA, OIA):</p> <p>Acceava Strep A, Clearview Strep A, Detector Strep A Direct kit, Diaquick Strep A test, IM-Strep A, INTEX Strep A test II, Mainline Confirms Strep A test, Quickvue Flex Strep A, Quickvue+ StrepA, Sacks RST, Signify Rapid Strep A, Strep A OIA Max test, StreptA test, and others)</p> <p>Reference test: culture</p>	Diagnostic accuracy (sensitivity, specificity)

EIA = enzyme immunoassay; ELISA = enzyme-linked immunoassay; FISH = fluorescence in situ hybridization; GA Strep = Group A Streptococcus; OIA = optical immunoassay; PCR = polymerase chain reaction; RADT = rapid antigen detection test; Strep = streptococcus

**Table 11: Characteristics of Included Clinical Studies**

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcome
Randomized controlled trial assessing RADTs				
Little, <sup>15</sup> 2014, UK	<p>RCT - pragmatic adaptive design. Randomization using a web-based computer randomization service. Clinicians were requested to use the intended strategy when this was agreed on by the patient but as this was a pragmatic trial, clinicians had the option to negotiate other strategies as is usual in practice</p> <p>Also economic modelling was conducted for assessing cost-effectiveness and cost-utility (described below in the Tables on economic studies)</p> <p>Setting: general practice in south and central England</p>	<p>Patients (adults and children <math>\geq 3</math> years) with acute sore throat (<math>\geq 2</math> weeks of sore throat together with erythema and/or pus)</p> <p>N = 631 (207 in group 1, Disease stage or prior therapy: patients with non-infective causes of sore throat or patients incapable of giving consent (e.g. with dementia) were excluded.</p>	<p>Group 1 (control): delayed antibiotic: A prescription was left at the reception and the patient was advised to collect it after 3 to 5 days, if symptoms were not improving or earlier if symptoms worsened.</p> <p>Group 2 (clinical score): antibiotic treatment offered depending on score. For low scores (0 to 1) no antibiotic, for intermediate scores (2 or 3 [39% streptococci]) delayed antibiotic, for high scores (<math>\geq 4</math> [63% streptococci]) immediate antibiotic.</p> <p>Group 3 (RADT [IMI test pack]): Economic modelling indicated that RADT was useful to use for those with intermediate and high scores for whom antibiotic treatment was most likely. For low scores (0 to 1 [<math>&lt; 20\%</math> streptococci]) no antibiotic or RADT offered, for intermediate scores (2 [33% streptococci]) delayed antibiotic offered, and for high scores (<math>\geq 3</math> [55% streptococci]) RADT offered at the GP surgery premises and if test results were negative no antibiotics were offered.</p>	Severity of condition, duration of symptoms, antibiotic use, and return of sore throat
Observational studies				
Anderson, <sup>16</sup> 2013, USA	<p>Cross-sectional, multicenter (3)</p> <p>Setting: three geographically distinct clinical centers</p>	<p>Patients with pharyngitis (796 dual pharyngeal swabs collected)</p> <p>Age (years): NR but inclusion criteria were <math>&lt; 1</math> to 87 years; majority were <math>&lt; 19</math> years.</p> <p>%Female: NR</p> <p>Disease stage or prior therapy: NR</p>	<p>Index test (molecular assay): Illumigene group A Strep test DNA amplification assay. Assay uses loop mediated amplification technology to target <i>speB</i> gene. An illumipro-10 incubator/reader was used. Results available within 40 minutes.</p> <p>Reference test (culture method): Routine culture assay. As well as extracted culture method to increase sensitivity of the culture approach.</p> <p>Dual swabs collected from each patient</p>	Sn, Sp, PPV, NPV

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcome
			Additional PCR assay conducted for samples with illumigene results discrepant with results from culture methods	
Ba-Saddik, <sup>28</sup> 2014, Yemen	Cross-sectional  Patients were enrolled between August 2006 and July 2007  Setting: School clinics, and private or public healthcare polyclinics in various districts in Yemen	Patients (children) with acute pharyngotonsillitis.  N = 730  Age (mean $\pm$ SD) (years): 11.8 $\pm$ 3.4  % Female: 56.3  Disease stage or prior therapy: Sore throat episodes reported per year varied between < 4 to > 12, with majority in the range 5 to 12 episodes per year. Patients treated with antibiotics in the previous two weeks of the study were excluded	Index test (immuno assay): Reveal Color Strep A agglutination test, Turnaround time 10 to 15 minutes  Reference test: routine culture  Two swabs collected, one for each test	Sn, Sp, PPV, NPV
Berry, <sup>17</sup> 2018, USA	Cross-sectional  Samples collected between May and June 2016.  Setting: Two outpatient clinics (mainly pediatric) within the University of Texas medical branch hospital system.	Patients with suspected strep throat (216 throat swab samples)  Age (years): <18 years for 119 (92.1%), $\geq$ 18 years for 17 (7.9%)  % Female: NR  Disease stage or prior therapy: Antibiotic use at the time of clinic visit was obtained from chart review of the patient	Index test (molecular assay): Alere i Strep A test performed using a Alere i testing platform. POCT platform. Assay uses isothermal nucleic acid amplification. Turnaround time 3 to 8 mins  Index test (rapid chromatographic immunoassay): BD Veritor system. Performed at clinic. 10 mins to set up and run.  Reference test: Routine culture assay  Dual swabs collected from each patient. One swab was used for the chromatographic assay and one swab was used for culture and molecular assay.  Additional tests using RT-PCR was performed in case of discordant test results.	Sn, Sp, Accuracy. Antibiotic use.
Cohen, <sup>18</sup> 2015, USA	Cross-sectional  Samples collected between 21 January	Patients with sore throat and signs of suspected pharyngitis	Index test (molecular assay): Alere i Strep A test. Alere i Strep A platform used. Testing done in a CLIA-waived setting. Target gene: <i>cepA</i>	Sn, Sp, PPV, NPV

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcome
	and 14 March, 2014.  Setting: 10 sites in USA (in 6 provinces). The sites comprised general and pediatric emergency departments, private practices (with clinical research), and an urgent care center,	No. of patients: 501 enrolled (481 analyzed)  Age (years) (median [interquartile range]): 11 (7 to 19). (11 patients were <3 years)  % Female: 62  Disease stage or prior therapy: McIsaac scores of patients were recorded, however % of patients in each category were not presented. Patients using antibiotics in the past two weeks, or were part of a vulnerable population deemed inappropriate were excluded	Turnaround time approx. 8 minutes  Culture method (reference test): Routine culture assay  Additional tests using RT-PCR was performed in case of discordant test results	
Faron, <sup>19</sup> 2015, USA	Cross-sectional  Samples collected in February and March 2014.  Setting: Five clinical centers	Pharyngeal swab specimens were collected  No. of specimens 1192 (481 using ES swabs and 711 using wound fiber swabs)  Age of patients: NR  % Female: NR  Disease stage or prior therapy: NR	Index test (molecular test): AmpliVue GAS. Isothermal helicase-dependent amplification assay. Target sequence: <i>sdaB</i> region The assay takes < 1 hour.  Culture method (reference test): Routine culture assay  All testing was conducted using residual material within 72 hour of sample collection  At a central lab, additional tests using RT-PCR (Lyra direct Strep assay) was performed in case of discordant test results	Sn, Sp, PPV, NPV
Felsenstein, <sup>20</sup> 2014, USA	Cross-sectional  Samples collected between December 2012 and March 2013.  Setting: Emergency department at Children's hospital Los Angeles	Patients (children) who had McIsaac score $\geq 2$ or presented with fever of unknown origin, upper respiratory tract symptoms, or complaints of throat pain or discomfort.  No. of patients: 361  Age: (years) (mean $\pm$ SD): 7.4 $\pm$ 4.2 (range: 2 to 18)  % Female: NR	Index test (RADT): OSOM Ultra Strep A  Index test (molecular assay): Illumigene group A Strep test. Based on loop mediated isothermal amplification targeting <i>speB</i> gene. Illumipro-10 incubator/reader used. Turnaround time 40 minutes  Reference test: routine culture  Additional tests using RT-PCR was performed in case of discordant test results	Sn, Sp, PPV, NPV

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcome
		Disease stage or prior therapy: disease stage as described above		
Gonsu, <sup>29</sup> 2015, Cameroun	Cross-sectional  Samples collected between January and April 2011.  Setting: 2 hospitals in Cameroun	Patients consulting for pharyngitis or sore throat  Samples collected: 72  Age (years) (mean $\pm$ SD): 25.87 $\pm$ 16.45 (range: 3 to 72 years; of these patients 24 were 3 to 15 years)  % Female: 65  Disease stage or prior therapy: No antibiotic treatment in the previous 72 hours	Index test (RADT): StrepA rapid test (lateral flow immunoassay) Samples were immediately transported to the laboratory.  Reference test: Routine culture assay	Sn, Sp, PPV, NPV
Henson, <sup>21</sup> 2013, USA	Cross-sectional  Samples collected between 12 December 2012 and 30 January 2013.  Setting: Children's hospital in Chicago	Patients (mainly children) who were symptomatic  Consecutive samples: 440 (437 tested, 3 excluded because of incomplete data)  Age: 14 months to 37 years with 98% <18 years  % Female: NR  Disease stage or prior therapy: NR	Index test (molecular assay): Illumigene group A Strep test. Based on loop-mediated isothermal amplification targeting <i>speB</i> gene. Illumipro-10 device used Time taken approximately 1 hour  Index test (RADT): GA Strep rapid antigen assay (Only Sp Sn values were provided but no description of the test)  Reference tests: routine culture; RT-PCR	Sn, Sp
Kolukirk, <sup>22</sup> 2016, Turkey	Cross-sectional  Samples collected during winter/spring of 2012 and 2013.  Setting: IMU hospital and samples transported to University laboratory	Patients (children) presenting with acute sore throat  No. of patients: 687 (for each patient double swabs were collected)  Age (years): 5 to 12  % Female: 51.8  Disease stage or prior therapy: For inclusion there were no restrictions on medications or known pharmaceutical therapies	Index test (RADT): Clearview Strep A Exact II Cassette test (no additional details presented)  Index test (molecular assay): qPCR ()  Reference tests: routine culture  (One swab was used for RADT and culture assays and one swab was used for qPCR)  Samples were collected at IMU hospital and transported to the Istanbul Medipol university laboratory and tested the same day of sample collection.	Sn, Sp

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcome
Kose, <sup>30</sup> 2016, Turkey	Cross-sectional  Samples collected between February 2012 and May 2014.  Setting: A training and research hospital in Turkey	Children with suspected pharyngitis  No. of patients: 223  Age (months) (mean $\pm$ SD): 89.2 $\pm$ 36.6 (range: 36 to 168)  % Female: 42.2  Disease stage or prior therapy: No antibiotic treatment in the previous 7 days. Patients with diagnosis of rheumatic fever, or acute otitis media, sinusitis, or undergoing immunosuppressive therapy were excluded. Centor scores of patients were recorded	Index test (rapid chromatographic immunoassay): ACON Strep A Rapid Test Device. Performed at POC by trained physician  Reference tests: routine culture	Sn, Sp, PPV, NPV, PLR, NLR.  Antibiotic use.  Cost per patient
Küçük, <sup>9</sup> 2014, Turkey	Retrospective analysis  Patients came in between 1 January and 31 December 2011  Setting: Pediatric emergency or pediatric outpatient clinics	Children with acute sore throat, fever and acutely inflamed throat or tonsils with or without exudates.  No. of patients: 892  Age (years): 639 patients in age range 0 to 6 (Group 1), and 253 patients in age range 7 to 17 (Group 2)  % Female: 42  Disease stage or prior therapy: Patients who had received antibiotic treatment prior to the study and patients with obvious viral infection were excluded	Index test (rapid antigen test): Quickvue Strep A cassette test  Reference tests: routine culture	Sn, Sp, PPV, NPV
Lacroix, <sup>31</sup> 2018, Switzerland	Cross-sectional  Patients came in between June 2014 and October 2016  Setting: A tertiary care hospital	Patients (children) with a clinical diagnosis of pharyngitis (McIsaac score $\geq 2$ )  No. of patients: 1002 (1109 were enrolled but 107 were excluded for	Index test (rapid antigen test- optical immunoassay): Sofia StrepA FIA (a immunofluorescence based assay)  Index test (rapid antigen test): Alere TestPack Strep A (a immunochromatographic assay)	Sn, Sp, PPV, NPV

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcome
	and a regional hospital	<p>various reasons such as missing obligatory data)</p> <p>Age (years) (mean <math>\pm</math> SD): 6.1 <math>\pm</math> 3.3 (range: 3 to 16)</p> <p>% Female: 49.3%</p> <p>Disease stage or prior therapy: Patients who had received antibiotic treatment in the previous 2 weeks were excluded. Patients had McIsaac score <math>\geq</math> 2</p>	<p>Reference tests: routine culture</p> <p>Additional PCR assay was conducted for discrepant results between culture and the corresponding RADT (i.e. positive RADT but negative culture for GA Strep)</p>	
Nibhanipudi, <sup>23</sup> 2015, USA	<p>Cross-sectional</p> <p>Time period: NR</p> <p>Setting: NR. This was an institutional review board-approved prospective study</p>	<p>Children with acute pharyngitis (no child was given antibiotics until confirmation by culture test was obtained)</p> <p>No. of patients: 100</p> <p>Age: NR (mentioned as children)</p> <p>% Female: NR</p> <p>Disease stage or prior therapy: NR</p>	<p>Index test (rapid antigen strep test) (no details presented)</p> <p>Index test (Leukocyte esterase test using test strip currently used for urine dipstick)</p> <p>Reference tests: routine culture</p> <p>Three swabs collected, one for each test</p>	Sn, Sp, PPV, NPV
Nordqvist, <sup>32</sup> 2015, Sweden	<p>Retrospective analysis using medical records</p> <p>Time period: over 10 years (January 2003 to January 2013)</p> <p>Setting: Hospital</p>	<p>Patients (adults and children) with necrotizing fasciitis</p> <p>No. of patients: 22 (Of the 31 patients examined for management and outcomes of necrotizing fasciitis, 22 patients received RADT either during surgery, or if they had open wounds at the time of admission)</p> <p>Age: NR for the 22 patients separately (For the 31 patients, the median age was 57 years (range: 3 to 99 years))</p> <p>% Female: NR for the 22 patients separately (For</p>	<p>Index test (RADT): no further details presented</p> <p>RADT was conducted at the emergency department and also at the laboratory (by a technologist)</p> <p>Reference tests: routine culture (blood culture or wound culture)</p>	Sn, Sp

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcome
		<p>the 31 patients, % female = 35%)</p> <p>Disease stage or prior therapy: Necrotizing fasciitis (stages I, 2, or 3). Prior therapy: NR</p>		
Penney, <sup>33</sup> 2016, Canada	<p>Cross-sectional</p> <p>Patients recruited between November 2015 to January 2016</p> <p>Setting: pediatric emergency department of hospital</p>	<p>Patients (children) with suspected pharyngitis</p> <p>No. of patients = 147 (160 approached for consent, Of the 152 who consented, 5 were excluded for various reasons and 147 were analyzed)</p> <p>Age (years) (mean <math>\pm</math> SD): 8.8 <math>\pm</math> 4.3</p> <p>% Female: 53.1</p> <p>Disease stage or prior therapy: NR</p>	<p>Index test (rapid antigen detection test – immunochromatographic method): Alere TestPack Plus Strep A kit. RADT conducted at emergency department and also by technologist at microbiology lab.</p> <p>Reference tests: routine culture</p>	Sn, Sp, PPV, NPV
Shapiro, <sup>34</sup> 2018, USA	<p>Retrospective analysis of a previously conducted study</p> <p>Time period: patients who came in between 1 October 2013 and 31 January 2015</p> <p>Setting: Urban tertiary care emergency department</p>	<p>Patients (adults and children) with sore throat (a selective population in whom RADT had been performed; does not include all patients that were included in the study)</p> <p>No. of patients: 320 (Of the 542 eligible patients 222 patients were excluded for various reasons)</p> <p>Age (years): range: 3 to 21, with majority &lt; 18 years (87.5% between 3 and 17)</p> <p>% Female: 60</p> <p>Disease stage or prior therapy: Modified Centor score was between 0 and 5, with majority of patients having scores 2 or 3.</p>	<p>Index test (rapid antigen detection test): No further details presented. RADTs were conducted at POC</p> <p>Reference tests: routine culture</p> <p>Testing with both RADT and culture methods were done only for samples that were negative by RADT.</p>	Sn



Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcome
Stefaniuk, <sup>35</sup> 2017, Poland	Cross-sectional  Study carried out between March and May 2014  Setting: "Orlik" GP Practice in Warsaw	Patients (adults and children) suspected of having bacterial pharyngitis  No. of patients: 96  Age (years): NR (however 46% were between 3 and 14, 25% were between 31 and 35)  Disease stage or prior therapy: NR	Index test (rapid diagnostic test-immuno assay based on turbidimetric method): QuickRead go® Strep A test. Test was conducted by a nurse and immediately communicated to the physician  Reference test: routine culture  Two swabs taken, one for each test	Sn, Sp, PPV, NPV
Subashini, <sup>36</sup> 2015, India	Cross-sectional  Time period: NR  Setting: NR	Children with acute pharyngitis  No. of samples: 111  Age (years): NR  % Female: NR  Disease stage or prior therapy: NR	Index test (rapid antigen detection test based on immunochromatography): SD Bioline rapid antigen test  Reference test: routine culture	Sn, Sp
Tabb, <sup>24</sup> 2016, USA	Cross-sectional  Samples collected between 6 May 2014 and 28 October 2014  Setting: 4 sites in USA (California, Texas, Indiana, and Florida)	Patients with signs and symptoms of GA strep pharyngitis  No of samples: 1352  Age (years): <1 month to >21 years as reported  % Female: NR  Disease stage or prior therapy: NR	Index test (molecular assay): Simplexa™ Group A Strep Direct assay Uses a combination of Simplexa Direct chemistry, Direct amplification Disc, and Integrated Cyclor system. Simplex Direct chemistry uses fluorescent RT-PCR with specialized buffers which eliminates the need for prior nucleic acid extraction. Target gene: <i>speB</i> Assay intended for hospital reference laboratory or state laboratory settings.  Reference test: Routine culture assay  Discrepant results were further tested using bidirectional sequencing assay	Sn, Sp, PPV, NPV
Uphoff, <sup>25</sup> 2016, USA,	Cross-sectional  Time period of sample collection: NR  Setting: 4 sites in USA	Patients with symptoms of GA strep  No. of samples: 1082 (1081 analyzed)  Age (years) (mean): 15 (range: <2 to 94)	Index test (molecular assay): Solana GA strep assay (rapid helicase dependent amplification [HAD] method) Samples were sent to testing laboratory and tested within 48h  Reference test: Routine culture assay  Discrepant results were further tested	Sn, Sp

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcome
		% Female: 56  Disease stage or prior therapy: NR	using Lyra GA strep PCR assay (which has a genetic target different from that of Solana GA strep assay)	
Upton, <sup>26</sup> 2016, New Zealand	Cross-sectional  Time period of study: NR  Setting: single South Auckland primary school which had school based public health intervention program. The program was initiated for tackling an unique environment that had pockets of high incidences of ARF	Patients (school children participating in a school based public health intervention program) were asked to self-identify as having a sore throat.  No. of samples: 757  Age (years): 5 to 11  % Female: NR  Disease stage or prior therapy: NR	Index test (molecular assay): illumigene A illumipro-10 incubator/reader was used. Samples were transported to the testing laboratory within 8 hours of sample collection  Reference test: Routine culture assay  Discrepant results were retested using RT-PCR. Also for some samples repeat illumigene assays or repeat culture assays were conducted	Sn, Sp, PPV, NPV
Vakkila, <sup>37</sup> 2015, Finland	Cross-sectional (main focus determination of prevalence of GA strept)  Samples collected between March and June 2012 at outpatient unit in Helsinki and between February and May 2013 at outpatient unit in Turku. The study samples were collected during an internal laboratory validation study. Tests were ordered by clinicians who were unaware of the study  Setting: 2 units as described above	Patients with clinical suspicion of streptococcal throat infection visiting the Mehiläinen Laboratories in Helsinki and Turku  No of samples: 219 (121 in Helsinki and 98 in Turku)  Age (years) (mean [median]): 24.9 [9.3] for 121 patients in Helsinki, and 9.9 [7.0] for 98 patients in Turku.  % Female: NR  Disease stage or prior therapy: NR	Index test (rapid antigen detection test, immunoassay): marIPOC (immunofluorescence method)  Reference test: routine culture  Swabs were collected from patients visiting the Mehiläinen Laboratories in Helsinki and Turku. The samples were collected during an internal laboratory method validation study. Clinicians who had ordered the tests were not aware of the study Two swabs collected, one for each test.  In addition of the 219 samples, 42 of the throat swab patient samples stored in marPOC buffers were also analyzed by qPCR	Sp, Sn
Wang, <sup>27</sup> 2017, USA	Cross-sectional  Samples were collected between December 2013 and April 2014  Setting: 5 primary	Patients with symptoms of pharyngitis such as sore throat and at least one other symptom (such as tonsillar swelling, tender cervical lymphadenopathy, redness of the posterior	Index test (molecular assay): cobas Liat Strep A assay. It is PCR-based point-of-care assay Turnaround time: 15 minutes  Index test (immunoassay): RADT various types (such as Consult Strep A, Quidel QuickVue Dipstick, and	Sn, Sp

Author, Year, Country	Study Design	Population Characteristics	Comparison	Outcome
	care clinics (4 pediatric physician office and 1 family physician office) in USA (Connecticut, Georgia, New York, Texas and Virginia)	pharyngeal wall pharyngeal or tonsillar exudate, or fever >38°C)  No. of samples: 427  Age (years): ≥3 (24.4% between 3 and 5, 72.1% between 6 and 21, 3.5% ≥ 22)  % Female: 52.9  Disease stage or prior therapy: Patients treated with antibiotics at the time of enrollment or in the previous week were excluded	McKesson Strep A Dipstick)  Reference test: routine culture  Two to three swabs were collected from each patient. One swab was used for both cobas Liat Strep A assay and culture assay. The remaining one or two swabs were used for the site's standard diagnostic method (RADT and/or culture)  Discordant results between cobas Liat Strep A and culture assays were further analyzed by PCR and bidirectional sequencing	

ARF = acute rheumatic fever; CLIA = Clinical Laboratory Improvement Amendments; group A Strep = group A streptococcus; GP = general practitioner; LAMP = loop mediated isothermal amplification; NLR = negative likelihood ratio; NPV = negative predictive value; PCR = polymerase chain reaction; PLR = positive likelihood ratio; POC = point of care; POCT = point-of-care testing; PPV = positive predictive value; qPCR = quantitative PCR; RT-PCR = real time PCR; Sn = sensitivity; Sp = specificity; strep = streptococcus;

**Table 12: Characteristics of Included Cost Studies**

Author, Year, Country	Study Design	Perspective, Time Horizon, Currency, Discounting	Population	Intervention	Outcomes
Little, <sup>15</sup> 2014, UK	Cost-effectiveness and cost-utility study based on results from a RCT (described in Table 8 above)  Aim: to examine resource use and HRQoL associated with use of clinical scores and RADTs	Healthcare (NHS) perspective  Time horizon: 1 month  Currency: £  Discounting: NA	Patients with acute sore throat	Clinical scoring algorithm (Fever/PAIN), delayed prescribing, and RADT compared	Cost-effectiveness (i.e. cost per change in symptom severity), and cost-utility (i.e. cost per QALY)

HRQoL = health related quality of life; NHS = National Health Service, UK; QALY = quality adjusted life year; RADT = rapid antigen detection test; RCT = randomized controlled trial

# Appendix 3: Critical Appraisal of Included Publications

**Table 13: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2<sup>10</sup>**

Strengths	Limitations
Cohen (Cochrane Collaboration), 2016, France	
<ul style="list-style-type: none"> <li>The objective was clearly stated (specified population, intervention and outcome).</li> <li>Review methods were established prior to conducting the systematic review</li> <li>The inclusion and exclusion criteria were stated.</li> <li>Databases searched included: Medline, Embase, Cochrane database) of Systematic Reviews, DARE, MEDION, and TRIP. Literature was searched up to May 2013, and then updated in July 2015. Also, reference lists of relevant retrieved articles were searched and manufacturers were contacted for additional information.</li> <li>Study selection was described</li> <li>Flow chart of study selection was provided</li> <li>List of included studies was provided</li> <li>List of excluded studies was provided</li> <li>Article selection was done in duplicate</li> <li>Data extraction was done in duplicate</li> <li>Characteristics of the individual studies were provided</li> <li>Funding sources for the individual studies were presented</li> <li>Quality of the included studies was assessed based on QUADAS-2 and judged to be generally of low quality, however quality appraisal was hampered by suboptimal reporting. Risk of bias concerns were mostly related to patient selection and reference standard methods.</li> <li>Meta-analysis was conducted and appeared to be appropriate</li> <li>Conflicts of interest were declared and did not appear to be of concern. Of note though that of the 4 authors, 3 had been involved with the included studies.</li> </ul>	<ul style="list-style-type: none"> <li>Assessment of publication bias was not mentioned</li> </ul>
Lean, <sup>7</sup> 2014, USA	
<ul style="list-style-type: none"> <li>The objective was clearly stated (specified population, intervention and outcome).</li> <li>Not specifically mentioned if review methods were established prior to conducting the systematic review</li> <li>The inclusion and exclusion criteria were stated.</li> <li>Databases searched included: Medline, and Embase. Literature was searched between 1996 and 2013. Also, reference lists of relevant retrieved articles were searched. Only English language articles were included</li> <li>Study selection was described</li> <li>Flow chart of study selection was provided</li> <li>List of included studies was provided</li> <li>Quality of the included studies was assessed by two reviewers based on QUADAS (modified) checklist and checklist results for each individual study were tabulated. It</li> </ul>	<ul style="list-style-type: none"> <li>List of excluded studies was not provided</li> <li>Assessment of publication bias was not mentioned</li> <li>Funding sources for the individual studies were not presented</li> <li>Unclear if article selection was done in duplicate</li> <li>Unclear if data extraction was done in duplicate</li> </ul>

Strengths	Limitations
<p>was stated that blinding of reference standard test results and information on uninterpretable results were poorly reported but no summary statement for quality of the studies was presented.</p> <ul style="list-style-type: none"> <li>• Meta-analysis was conducted and appeared to be appropriate</li> <li>• Authors stated that there were no potential conflicts of interest</li> </ul>	
Stewart, <sup>14</sup> 2014, Australia	
<ul style="list-style-type: none"> <li>• The objective was clearly stated (specified population, intervention and outcome).</li> <li>• Not specifically mentioned if review methods were established prior to conducting the systematic review</li> <li>• The inclusion and exclusion criteria were stated.</li> <li>• Databases searched included: Medline, and Pubmed. Literature was searched between 2000 and 2012. Also Cochrane Reviews, Center for Reviews and Dissemination, Scopus, SciELO, CINAHL, and guidelines were searched. Also, reference lists of relevant articles were searched. Only English language articles were included</li> <li>• Study selection was described</li> <li>• Flow chart of study selection was provided</li> <li>• List of included studies was provided</li> <li>• Article selection was done in duplicate</li> <li>• Quality assessment of the studies was conducted based on QUADAS and quality was variable.</li> <li>• Publication bias was assessed using Funnel plot and the authors stated that there was suggestion of bias</li> <li>• Meta-analysis was conducted and appeared to be appropriate</li> <li>• Of the six authors one author had received funding from Justin Rogers Foundation however the funders had no role in the study. Nothing was stated for the other authors</li> <li>• Authors stated that there were no potential conflicts of interest</li> </ul>	<ul style="list-style-type: none"> <li>• List of excluded studies was not provided</li> <li>• Unclear if data extraction was done in duplicate</li> <li>• Funding sources for the individual studies were not presented</li> </ul>

**Table 14: Strengths and Limitations of Randomized Controlled Study based on Downs and Black checklist<sup>11</sup>**

Strengths	Limitations
PRISM investigators, <sup>15</sup> 2014, UK	
<ul style="list-style-type: none"> <li>• The objective was clearly stated</li> <li>• The inclusion and exclusion criteria were stated</li> <li>• Patient characteristics, intervention and outcomes were described.</li> <li>• Randomized trial – pragmatic adaptive design. Randomization using a web-based computer randomization</li> </ul>	<ul style="list-style-type: none"> <li>• Due to the pragmatic nature of the trial complete blinding was not possible</li> <li>• Not all analyses included all patients.</li> </ul>

Strengths	Limitations
<p>service</p> <ul style="list-style-type: none"> <li>Patients were blinded but as this was a pragmatic trial, total blinding was not possible. Research team, collecting data, was blinded, however patient management notes were available.</li> <li>Sample size calculation was conducted and appeared to be appropriate</li> <li>Follow-up for symptoms using diary information was 80%</li> <li>P values were reported</li> <li>Conflicts of interest were declared and potential for concern was not apparent</li> </ul>	

**Table 15: Strengths and Limitations of Diagnostic Studies using QUADAS II<sup>12</sup>**

Strengths	Limitations
<b>Observational studies</b>	
Anderson, <sup>16</sup> 2013, USA	
<ul style="list-style-type: none"> <li>Cross-sectional study</li> <li>Descriptions of both index and reference tests were provided</li> <li>Reference standard generally considered as the gold standard</li> <li>All samples assayed with the index test and reference test</li> <li>Reference test appeared to be the same for all samples</li> <li>All samples included in the analysis</li> </ul>	<ul style="list-style-type: none"> <li>Unclear if consecutive or random samples</li> <li>Unclear if there was any inappropriate exclusion</li> <li>Limited information on patient characteristics</li> <li>Unclear if index test results were interpreted without knowledge of reference test results</li> <li>Unclear if reference test results were interpreted without knowledge of index test results</li> <li>This study was funded by the manufacturer of the index test. One of the authors received honoraria from the manufacturer.</li> </ul>
Ba-Saddik, <sup>28</sup> 2014, Yemen	
<ul style="list-style-type: none"> <li>Cross-sectional study</li> <li>Descriptions of both index and reference tests were provided</li> <li>Reference standard generally considered as the gold standard</li> <li>Reference test appeared to be the same for all samples</li> <li>All samples included in the analysis.</li> <li></li> </ul>	<ul style="list-style-type: none"> <li>Unclear if consecutive or random samples</li> <li>Unclear if index test results were interpreted without knowledge of reference test results</li> <li>Unclear if reference test results were interpreted without knowledge of index test results</li> <li>Nothing was mentioned with respect to conflicts of interest of the authors</li> <li>There was nothing mentioned regarding funding</li> </ul>
Berry, <sup>17</sup> 2018, USA	
<ul style="list-style-type: none"> <li>Cross-sectional study</li> <li>Descriptions of both index and reference tests were provided</li> <li>Reference standard generally considered as the gold standard</li> <li>All samples assayed with the index test and reference test</li> <li>Reference test appeared to be the same for all samples</li> <li>All samples included in the analysis</li> </ul>	<ul style="list-style-type: none"> <li>Unclear if consecutive or random samples</li> <li>Unclear if there was any inappropriate exclusion</li> <li>Limited information on patient characteristics</li> <li>Unclear if one index test (immunoassay: BD Veritor) results were interpreted without knowledge of reference test results. However personnel performing the index test (molecular assay: Alere i strep test) was blinded to the culture (reference standard test) and BD Veritor test results</li> </ul>

Strengths	Limitations
	<ul style="list-style-type: none"> <li>Unclear if reference test results were interpreted without knowledge of index test results</li> <li>The study material was provided by the manufacturer. Of the seven authors, two authors were associated with the manufacturer; nothing was mentioned with respect to the other authors.</li> </ul>
Cohen, <sup>18</sup> 2015, USA	
<ul style="list-style-type: none"> <li>Cross-sectional study</li> <li>Descriptions of both index and reference tests were provided</li> <li>Reference standard generally considered as the gold standard (however there was adjudication of discrepant results by PCR)</li> <li>All samples assayed with the index test and reference test</li> <li>Reference test appeared to be the same for all samples</li> </ul>	<ul style="list-style-type: none"> <li>Unclear if consecutive or random samples</li> <li>Some patients (22 of 501) were excluded for various reasons (such as after enrollment due to delayed sample delivery, mishandling, and invalid Alere I strep results)</li> <li>Unclear if index test results were interpreted without knowledge of reference test results</li> <li>Unclear if reference test results were interpreted without knowledge of index test results</li> <li>The study was supported by a grant from the manufacturer. The authors stated that there were no potential conflicts of interest.</li> </ul>
Faron, <sup>19</sup> 2015, USA	
<ul style="list-style-type: none"> <li>Cross-sectional study</li> <li>Descriptions of both index and reference tests were provided</li> <li>Reference standard generally considered as the gold standard (however there was adjudication of discrepant results by molecular assay [RT-PCR])</li> <li>All samples assayed with the index test and reference test</li> <li>Reference test appeared to be the same for all samples</li> <li>All samples included in the analysis</li> </ul>	<ul style="list-style-type: none"> <li>Unclear if consecutive or random samples</li> <li>Unclear if index test results were interpreted without knowledge of reference test results</li> <li>Unclear if reference test results were interpreted without knowledge of index test results</li> <li>The manufacturer of the index test provided the materials and financial support for the study. There was nothing mentioned regarding conflicts of interest of the authors</li> </ul>
Felsentein, <sup>20</sup> 2014, USA	
<ul style="list-style-type: none"> <li>Cross-sectional study</li> <li>Descriptions of both index and reference tests were provided</li> <li>Reference standard generally considered as the gold standard (however there was adjudication of discrepant results by molecular assay [RT-PCR])</li> <li>All samples assayed with the index test(s) and reference test</li> <li>Reference test appeared to be the same for all samples</li> <li>All samples included in the analysis</li> </ul>	<ul style="list-style-type: none"> <li>All samples collected during the study period were analyzed, but it was unclear if the two index tests were assigned to the patients consecutively or randomly</li> <li>Unclear if index test results were interpreted without knowledge of reference test results</li> <li>Unclear if reference test results were interpreted without knowledge of index test results</li> <li>The manufacturer of the index test (molecular) provided the materials for the study. There was nothing mentioned regarding conflicts of interest of the authors</li> </ul>
Gonsu, <sup>29</sup> 2015, Cameroun	
<ul style="list-style-type: none"> <li>Cross-sectional study</li> <li>Descriptions of both index and reference tests were provided</li> <li>Reference standard generally considered as the gold standard</li> <li>Reference test appeared to be the same for all samples</li> <li>All samples included in the analysis.</li> <li>The authors stated that there were no potential conflicts of interest</li> </ul>	<ul style="list-style-type: none"> <li>Unclear if consecutive or random samples</li> <li>Unclear if index test results were interpreted without knowledge of reference test results</li> <li>Unclear if reference test results were interpreted without knowledge of index test results</li> <li>There was nothing mentioned regarding funding</li> </ul>



Strengths	Limitations
Henson, <sup>21</sup> 2013, USA	
<ul style="list-style-type: none"> <li>• Cross-sectional study</li> <li>• Consecutive samples were collected for the study</li> <li>• Descriptions of one index test (Illumigene) and reference tests were provided.</li> <li>• Reference standard generally considered as the gold standard</li> <li>• Reference test appeared to be the same for all samples</li> <li>• Most of the samples (437 of 440 samples) were included in the analysis. Three samples were excluded from the analysis due to incomplete data</li> </ul>	<ul style="list-style-type: none"> <li>• Description was not presented for one index test (RADT) of the two index tests assessed</li> <li>• Unclear if index test results were interpreted without knowledge of reference test results</li> <li>• Unclear if reference test results were interpreted without knowledge of index test results</li> <li>• The manufacturer of the index test (molecular) provided the materials for the study. One of the five authors received an unrestricted travel grant from the manufacturer and for the remaining five authors nothing mentioned regarding conflicts of interest.</li> </ul>
Kolukirik, <sup>22</sup> 2016, Turkey	
<ul style="list-style-type: none"> <li>• Cross-sectional study</li> <li>• Descriptions of both index and reference tests were provided</li> <li>• Reference standard generally considered as the gold standard (All samples assayed with the index test(s) and reference test</li> <li>• Reference test appeared to be the same for all samples</li> <li>• All samples included in the analysis</li> </ul>	<ul style="list-style-type: none"> <li>• Unclear if consecutive or random samples</li> <li>• Unclear if index test results were interpreted without knowledge of reference test results</li> <li>• Unclear if reference test results were interpreted without knowledge of index test results</li> <li>• The study was funded by one university and an environmental, energy, biotechnology company. The molecular assay tested was developed by the authors. There was nothing mentioned with respect to conflicts of interest of the authors.</li> </ul>
Kose, <sup>30</sup> 2016, Turkey	
<ul style="list-style-type: none"> <li>• Cross-sectional study</li> <li>• Descriptions of both index and reference tests were provided</li> <li>• Reference standard generally considered as the gold standard</li> <li>• Reference test appeared to be the same for all samples</li> <li>• All samples included in the analysis</li> </ul>	<ul style="list-style-type: none"> <li>• Unclear if consecutive or random samples</li> <li>• Unclear if index test results were interpreted without knowledge of reference test results</li> <li>• Unclear if reference test results were interpreted without knowledge of index test results</li> <li>• Nothing was mentioned with respect to conflicts of interest of the authors</li> <li>• There was nothing mentioned regarding funding</li> </ul>
Küçük, <sup>9</sup> 2014, Turkey	
<ul style="list-style-type: none"> <li>• Descriptions of both index and reference tests were provided</li> <li>• Reference standard generally considered as the gold standard</li> <li>• Reference test appeared to be the same for all samples</li> <li>• All samples included in the analysis</li> <li>• The authors stated that there were no potential conflicts of interest.</li> </ul>	<ul style="list-style-type: none"> <li>• Retrospective analysis</li> <li>• Unclear if consecutive or random samples</li> <li>• Unclear if index test results were interpreted without knowledge of reference test results</li> <li>• Unclear if reference test results were interpreted without knowledge of index test results</li> <li>• There was nothing mentioned regarding funding</li> </ul>
Lacroix, <sup>31</sup> 2018, Switzerland	
<ul style="list-style-type: none"> <li>• Cross-sectional study</li> <li>• Descriptions of both index tests and reference test were provided</li> <li>• Reference standard generally considered as the gold standard</li> </ul>	<ul style="list-style-type: none"> <li>• Unclear if consecutive or random samples</li> <li>• Unclear if index test results were interpreted without knowledge of reference test results</li> <li>• Unclear if reference test results were interpreted without knowledge of index test results</li> </ul>



Strengths	Limitations
<ul style="list-style-type: none"> <li>Reference test (culture method) appeared to be the same for all samples at initial step, but in case of discrepant results the reference was culture method+ PCR</li> <li>All samples included in the analysis.</li> </ul>	<ul style="list-style-type: none"> <li>The study was funded by the manufacturer of the index test (main focus of study). Of the eight authors, one author received travel grant from the manufacturer and the remaining authors were stated to have no potential conflicts of interest.</li> </ul>
Nibhanipudi, <sup>23</sup> 2015, USA	
<ul style="list-style-type: none"> <li>Cross-sectional study</li> <li>Reference standard generally considered as the gold standard</li> <li>Reference test appeared to be the same for all samples</li> <li>All samples included in the analysis</li> <li>The authors stated that there were no potential conflicts of interest</li> <li>No funding was received from the manufacturer</li> </ul>	<ul style="list-style-type: none"> <li>Details of both index and reference tests were lacking</li> <li>Unclear if consecutive or random samples</li> <li>Unclear if index test results were interpreted without knowledge of reference test results</li> <li>Unclear if reference test results were interpreted without knowledge of index test results</li> </ul>
Nordqvist, <sup>32</sup> 2015, Sweden	
<ul style="list-style-type: none"> <li>Retrospective analysis using medical records</li> <li>Reference standard generally considered as the gold standard</li> <li>Reference test appeared to be the culture method for all samples (blood culture or wound culture)</li> <li>The authors stated that there were no potential conflicts of interest.</li> </ul>	<ul style="list-style-type: none"> <li>Description of the index and culture tests were not provided</li> <li>Unclear if consecutive or random samples</li> <li>Unclear if index test results were interpreted without knowledge of reference test results</li> <li>Unclear if reference test results were interpreted without knowledge of index test results</li> <li>Unclear if all samples were included in the analysis</li> <li>There was nothing mentioned regarding funding</li> </ul>
Penney, <sup>33</sup> 2016, Canada	
<ul style="list-style-type: none"> <li>Cross-sectional study</li> <li>Consecutive patients were recruited</li> <li>Descriptions of both index and reference tests were provided</li> <li>Reference standard generally considered as the gold standard</li> <li>Reference test (culture method) appeared to be the same for all samples</li> <li>Most patients were included in the analysis. (Of the 160 patients approached, 152 patients consented. Of these 152 patients, 5 were excluded for various reasons and 147 were included in the analysis)</li> </ul>	<ul style="list-style-type: none"> <li>Unclear if index test results were interpreted without knowledge of reference test results</li> <li>Unclear if reference test results were interpreted without knowledge of index test results</li> <li>Test kits were donated by the manufacturer of the kits. It was mentioned that the manufacturer had no influence on data collection, analysis, or interpretation and that the authors had no potential conflicts of interest regarding the publication of the study report</li> </ul>
Shapiro, <sup>34</sup> 2018, USA	
<ul style="list-style-type: none"> <li>Reference standard generally considered as the gold standard</li> <li>The authors stated that there were no potential conflicts of interest.</li> <li>Index test results were not interpreted before culture test was conducted</li> </ul>	<ul style="list-style-type: none"> <li>Retrospective analysis</li> <li>Details of the index and reference tests were not provided</li> <li>Partial dual testing: Only those samples that gave negative RADT results were further tested by culture method</li> <li>Not all patients were included in the analysis. Of the 542 eligible patients, 222 were excluded from the analysis</li> <li>Unclear if consecutive or random samples</li> <li>Reference test results were interpreted with knowledge of index test results</li> <li>There was nothing mentioned regarding funding</li> </ul>

Strengths	Limitations
Stefaniuk, <sup>35</sup> 2017, Poland	
<ul style="list-style-type: none"> <li>• Cross-sectional study</li> <li>• Descriptions of both index and reference tests were provided</li> <li>• Reference standard generally considered as the gold standard</li> <li>• Reference test (culture method) appeared to be the same for all samples</li> <li>• All samples included in the analysis.</li> <li>• The authors stated that there were no potential conflicts of interest.</li> </ul>	<ul style="list-style-type: none"> <li>• Unclear if consecutive or random samples</li> <li>• Unclear if index test results were interpreted without knowledge of reference test results</li> <li>• Unclear if reference test results were interpreted without knowledge of index test results</li> <li>• There was nothing mentioned regarding funding</li> </ul>
Subashini, <sup>36</sup> 2015, India	
<ul style="list-style-type: none"> <li>• Cross-sectional study</li> <li>• Descriptions of both index and reference tests were provided</li> <li>• Reference standard generally considered as the gold standard</li> <li>• Reference test (culture method) appeared to be the same for all samples</li> </ul>	<ul style="list-style-type: none"> <li>• Unclear if consecutive or random samples</li> <li>• Unclear if index test results were interpreted without knowledge of reference test results</li> <li>• Unclear if reference test results were interpreted without knowledge of index test results</li> <li>• Unclear if all samples were included in the analysis</li> <li>• Nothing was mentioned with respect to conflicts of interest of the authors</li> <li>• There was nothing mentioned regarding funding</li> </ul>
Tabb, <sup>24</sup> 2016, USA	
<ul style="list-style-type: none"> <li>• Cross-sectional study</li> <li>• Descriptions of index test presented but details of reference tests were lacking</li> <li>• Reference standard generally considered as the gold standard</li> <li>• Reference test appeared to be the same for all samples</li> <li>• All samples included in the analysis.</li> </ul>	<ul style="list-style-type: none"> <li>• Unclear if consecutive or random samples</li> <li>• Unclear if index test results were interpreted without knowledge of reference test results</li> <li>• Unclear if reference test results were interpreted without knowledge of index test results</li> <li>• The authors were employees of the company (subsidiary) manufacturing the index test being studied and also owned stocks of the parent company.</li> </ul>
Uphoff, <sup>25</sup> 2016, USA	
<ul style="list-style-type: none"> <li>• Cross-sectional study</li> <li>• Descriptions of both index and reference tests were provided</li> <li>• Reference standard generally considered as the gold standard</li> <li>• Reference test appeared to be the same for all samples</li> <li>• Nearly all samples (1081 of 1082 samples) included in the analysis. The excluded sample had invalid results.</li> </ul>	<ul style="list-style-type: none"> <li>• Unclear if consecutive or random samples</li> <li>• Unclear if index test results were interpreted without knowledge of reference test results</li> <li>• Unclear if reference test results were interpreted without knowledge of index test results</li> <li>• Nothing mentioned regarding the conflicts of interest of the authors</li> <li>• The study was funded by the manufacturer of the index test</li> </ul>
Upton, <sup>26</sup> 2016, New Zealand	
<ul style="list-style-type: none"> <li>• Cross-sectional study</li> <li>• Descriptions of both index and reference tests were provided</li> <li>• Reference standard generally considered as the gold standard</li> </ul>	<ul style="list-style-type: none"> <li>• Unclear if consecutive or random samples</li> <li>• Unclear if index test results were interpreted without knowledge of reference test results</li> <li>• Unclear if reference test results were interpreted without knowledge of index test results</li> </ul>

Strengths	Limitations
<ul style="list-style-type: none"> <li>Reference test appeared to be the same for all samples</li> <li>All samples included in the analysis.</li> </ul>	<ul style="list-style-type: none"> <li>Of the six authors, one author had received funding from the manufacturer of the index test, however it was mentioned that the funder had no role in study design, data collection, and interpretation. Nothing was mentioned with respect to conflicts of interest of the remaining five authors.</li> </ul>
Vakkila, <sup>37</sup> 2015, Finland	
<ul style="list-style-type: none"> <li>Cross-sectional study</li> <li>Descriptions of both index and reference tests were provided</li> <li>Reference standard generally considered as the gold standard</li> <li>Reference test (culture method) appeared to be the same for all samples</li> <li>All samples included in the analysis.</li> </ul>	<ul style="list-style-type: none"> <li>Unclear if consecutive or random samples</li> <li>Unclear if index test results were interpreted without knowledge of reference test results</li> <li>Unclear if reference test results were interpreted without knowledge of index test results</li> <li>Of the 10 authors one author was an employee of the manufacturer of the test and the remaining authors had no financial association with the manufacturer</li> </ul>
Wang, <sup>27</sup> 2017, USA	
<ul style="list-style-type: none"> <li>Cross-sectional study</li> <li>Description of one index was provided. Details of the second index test and the reference test were lacking</li> <li>Reference standard generally considered as the gold standard</li> <li>Reference test appeared to be the same for all samples</li> <li>All samples included in the analysis.</li> </ul>	<ul style="list-style-type: none"> <li>Unclear if consecutive or random samples. The order of specimen collection was at the discretion of the clinical staff.</li> <li>Unclear if index test results were interpreted without knowledge of reference test results</li> <li>Unclear if reference test results were interpreted without knowledge of index test results</li> <li>All authors were employees of the company manufacturing the primary index test being assessed. Funding for the study was provided by the manufacturer.</li> </ul>

**Table 16: Strengths and Limitations of Economic Studies using Drummond checklist<sup>13</sup>**

Strengths	Limitations
PRISM investigators, <sup>15</sup> 2014, UK	
<ul style="list-style-type: none"> <li>Objectives were stated.</li> <li>The strategies compared were stated.</li> <li>Time horizon and perspective were stated.</li> <li>The economic analysis was conducted as part of a pragmatic randomized controlled trial</li> <li>Clinical data source were stated.</li> <li>Cost data source were stated</li> <li>Discounting was not applicable as time frame was 1 month</li> <li>Incremental analysis was reported.</li> <li>Sensitivity analyses were conducted</li> <li>Conclusions were consistent with the results reported.</li> <li>Conflicts of interest were declared and there appeared to be none</li> </ul>	<ul style="list-style-type: none"> <li>Indirect costs do not appear to have been considered.</li> <li>Time frame was short hence long term implications are unclear</li> </ul>

# Appendix 4: Main Study Findings and Author's Conclusions

Table 17: Summary of Findings of Included Studies

Main Study Findings					Author's Conclusion
Systematic reviews					
Cohen (Cochrane Collaboration), <sup>4</sup> 2016, France					
Diagnostic accuracy of immunoassays in children					The authors stated that “In a population of 1000 children with a GAS prevalence of 30%, 43 patients with GAS will be missed. Whether or not RADT can be used as a stand-alone test to rule out GAS will depend mainly on the epidemiological context. The sensitivity of EIA and OIA tests seems comparable. RADT specificity is sufficiently high to ensure against unnecessary use of antibiotics. Based on these results, we would expect that amongst 100 children with strep throat, 86 would be correctly detected with the rapid test while 14 would be missed and not receive antibiotic treatment.” <sup>4</sup> Page 2.
Test	No. of test evaluations	No. of test participants	RADT Sensitivity, % (95% CI)	RADT Specificity, % (95% CI)	
All	116	101,121	Range:38.6% to 100%	Range: 54.1% to 100%	
All	105 <sup>a</sup>	58,244	85.6 (83.3 to 87.6)	95.4 (94.5 to 96.2)	
EIA	86	48,808	85.4 (82.7 to 87.8)	95.8 (94.8 to 96.6)	
OIA	19	9436	86.2 (82.7 to 89.2)	93.7 (91.5 to 95.4)	
<sup>a</sup> studies w hich undertook only partial verification were excluded. Note: EIA and OIA tests appeared to have comparable accuracy (Pvalue = 0.23)					
Interpretation considering a cohort of 1000 participants and the RADT to have sensitivity 85.6% and specificity 95.8%, assuming various prevalence rates of G A Strep cases.					
Prevalence	Consequence in a cohort of 1000 participants				
20%	Of the 200 participants with positive culture test for G A Strep, 171 will be identified (true positive [TP]) and 29 will be missed (false negative [TN]). Of the 800 participants without G A Strep, 763 will be not be treated (true negative [TN]) and 37 may receive unnecessary treatment with antibiotic (false positive [FP]).				
30%	Of the 300 participants with positive culture test for G A Strep, 257 will be identified (TP) and 43 will be missed (TN). Of the 700 participants without G A Strep, 668 will be not be treated (TN) and 32 may receive unnecessary treatment with antibiotic (FP).				
40%	Of the 400 participants with positive culture test for G A Strep, 342 will be identified (TP) and 58 will be missed (TN). Of the 600 participants without G A Strep, 572 will be not be treated (TN) and 28 may receive unnecessary treatment with antibiotic (FP).				
Lean, <sup>7</sup> 2014, USA					
Performance of various tests: Sensitivity and Specificity with corresponding 95% or range, where available for a mixed population of adults and children					The authors stated that “RADTs can be used for accurate diagnosis of GAS pharyngitis to streamline management of sore throat in primary care. RADTs may not require culture backup for negative tests in most low-incidence rheumatic fever settings. Newer molecular tests have the highest sensitivity, but are not true point-of-care tests.” <sup>7</sup> Page 771
Latex agglutination (2 results): Specificity 0.53 to 0.91, and specificity 0.85 to 0.89;					
Liposomal technology (1 result): Specificity 0.85, and specificity 0.96;					
Lateral flow/ immunochromatographic assay(21 results): Sensitivity 0.84 (0.80 to 0.88) , specificity 0.96 (0.94 to 0.97) ;					
ELISA (11 results): Sensitivity 0.86 (0.81 to 0.91) , specificity 0.96 (0.93 to 0.98);					
OIA (19 results): Sensitivity 0.86 (0.82 to 0.89) , specificity 0.94 (0.91 to 0.96) ;					
DNA probe (3 results): Sensitivity 0.91 to 0.95 , specificity 0.96 to 1.0 ;					
PCR assay(1 results): Sensitivity 0.96 , specificity 0.99 ;					
FISH (2 results): Sensitivity 0.89 , specificity 0.98 ;					

Main Study Findings				Author's Conclusion			
Performance of various tests in the pediatric population							
Test	No. of test evaluations	Test performance % (95% CI)					
		Sensitivity	Specificity				
Immunochromatographic/ lateral flow	14	0.85 (0.80 to 0.89)	0.97 (0.95 to 0.98)				
Optical immunoassay	11	0.85 (0.80 to 0.89)	0.95 (0.93 to 0.97)				
Molecular assay	4	0.93 (0.89 to 0.96)	0.99 (0.98 to 1.00)				
Stewart, <sup>14</sup> 2014, Australia							
Performance of various tests in the pediatric population using studies of high methodological quality				The authors stated that “ <i>In conclusion, RAST immunochromatographic methods appear to be very sensitive and highly specific to diagnose group A streptococcal pharyngitis among adults but not in children. Using the best evidence, we could not identify important sources of variability of sensitivity and specificity.</i> ” <sup>14</sup> Page 8 of 10			
Test	No. of strata, (No. of patients)	Sensitivity				Specificity	
		% (95% CI)	Heterogeneity (I <sup>2</sup> ) (%)			% (95% CI)	Heterogeneity (I <sup>2</sup> )
Immuno-chromatographic assay	28 (10,325)	86 (85 to 87)	88			96 (95 to 96)	86
Enzyme immunoassay (EIA)	3 (342)	86 (79 to 92)	0			92 (88 to 95)	55
Optical immunoassay	3 (3,294)	80 (77 to 82)	67	93 (92 to 94)	90		
Performance of various tests in the adult population using studies of high methodological quality							
Test	No. of strata, (No. of patients)	Sensitivity				Specificity	
		% (95% CI)	Heterogeneity (I <sup>2</sup> ) (%)			% (95% CI)	Heterogeneity (I <sup>2</sup> )
Immuno-chromatographic assay	6 (1,216)	91 (87 to 94)	61			93 (92 to 95)	72
Enzyme immunoassay (EIA)	2 (333)	86 (81 to 91)	88			97 (96 to 99)	88
Optical immunoassay	1 (81)	94 (80 to 99)	NA	69 (54 to 81)	NA		
Performance of various tests in the adult and pediatric population based on studies of high methodological quality							
Test	Sensitivity		Specificity				
	% (95% CI)	Heterogeneity (I <sup>2</sup> ) (%)	% (95% CI)			Heterogeneity (I <sup>2</sup> )	
All types	84 (83 to 85)	87	95 (94 to 95)	90			

Main Study Findings			Author's Conclusion																																															
Randomized Controlled Trial on RADT and Economic Evaluation																																																		
PRISM investigators, <sup>15</sup> 2014, UK																																																		
<p><b>RCT findings</b></p> <p><b>Clinical utility of RADT, clinical score and delayed antibiotic use for the Streptococcal management of adults and children with sore throat</b></p> <table><tr><th rowspan="2">Outcome</th><th colspan="3">Management strategy</th></tr><tr><th>Delayed use of antibiotic (control)</th><th>Clinical score (FeverPAIN)</th><th>RADT</th></tr><tr><td>Severity score of condition<sup>a</sup> on days 2 to 4, mean (SD)</td><td>3.11 (1.49)</td><td>2.88 (1.52)</td><td>2.83 (1.62)</td></tr><tr><td>Duration of symptoms (rated moderately bad or worse), (median [interquartile range], days)</td><td>5 (3 to 7)</td><td>4 (2 to 6)</td><td>4 (2 to 7)</td></tr><tr><td>Antibiotic use, % (N)<sup>b</sup></td><td>46, (N = 164)</td><td>37, (N = 161)</td><td>35 (N = 164)</td></tr><tr><td>Return within one month with sore throat, % (N)<sup>b</sup></td><td>8, (N = 207)</td><td>8, (N = 210)</td><td>6 (N = 212)</td></tr><tr><td>Return after one month with sore throat, % (N)<sup>b</sup></td><td>15 (N = 207)</td><td>12 (N = 210)</td><td>16 (N = 211)</td></tr></table> <p><sup>a</sup>Severity of condition (sore throat and difficulty swallowing) assessed using a 7-point scale. (0 = no problem, i.e. higher scores indicate worse condition).</p> <p><sup>b</sup>N indicates total number of patients assessed.</p> <p><b>Mean difference (MD), hazard ratio (HR) or risk ratio (RR) for clinical score and RADT compared to control, based on analysis model adjusting for confounding variables</b></p> <table><tr><th rowspan="2">Outcome</th><th colspan="2">Management strategy</th></tr><tr><th>Clinical score (FeverPAIN)</th><th>RADT</th></tr><tr><td>Severity score of condition<sup>a</sup> on days 2 to 4, adj. MD (95% CI), P value</td><td>-0.33 (-0.64 to -0.02), P = 0.039</td><td>-0.30 (-0.61 to 0.004), P = 0.053</td></tr><tr><td>Duration of symptoms (rated moderately bad or worse), HR (95% CI), P value</td><td>1.30 (1.03 to 1.63), P = 0.028</td><td>1.11 (0.88 to 1.40), P = 0.372</td></tr><tr><td>Antibiotic use, RR (95% CI), P value</td><td>0.71 (0.50 to 0.95), P = 0.018</td><td>0.73 (0.52 to 0.98), P = 0.033</td></tr><tr><td>Return within one month with sore throat, RR (95% CI), P value</td><td>0.91 (0.47 to 1.72), P = 0.777</td><td>0.74 (0.36 to 1.47), P = 0.397</td></tr><tr><td>Return after one month with sore throat, RR (95% CI), P value</td><td>0.79 (0.47 to 1.29), P = 0.353</td><td>1.06 (0.66 to 1.63), P = 0.813</td></tr></table> <p><sup>a</sup>Severity of condition (sore throat and difficulty swallowing) assessed using a 7-point scale. (0 = no problem, i.e. higher scores indicate worse condition)</p> <p><b>Economic evaluation</b></p> <p><i>The cost-effectiveness findings were based on 498 individuals for whom symptom score and cost were available (Time frame = 1 month)</i></p>			Outcome	Management strategy			Delayed use of antibiotic (control)	Clinical score (FeverPAIN)	RADT	Severity score of condition <sup>a</sup> on days 2 to 4, mean (SD)	3.11 (1.49)	2.88 (1.52)	2.83 (1.62)	Duration of symptoms (rated moderately bad or worse), (median [interquartile range], days)	5 (3 to 7)	4 (2 to 6)	4 (2 to 7)	Antibiotic use, % (N) <sup>b</sup>	46, (N = 164)	37, (N = 161)	35 (N = 164)	Return within one month with sore throat, % (N) <sup>b</sup>	8, (N = 207)	8, (N = 210)	6 (N = 212)	Return after one month with sore throat, % (N) <sup>b</sup>	15 (N = 207)	12 (N = 210)	16 (N = 211)	Outcome	Management strategy		Clinical score (FeverPAIN)	RADT	Severity score of condition <sup>a</sup> on days 2 to 4, adj. MD (95% CI), P value	-0.33 (-0.64 to -0.02), P = 0.039	-0.30 (-0.61 to 0.004), P = 0.053	Duration of symptoms (rated moderately bad or worse), HR (95% CI), P value	1.30 (1.03 to 1.63), P = 0.028	1.11 (0.88 to 1.40), P = 0.372	Antibiotic use, RR (95% CI), P value	0.71 (0.50 to 0.95), P = 0.018	0.73 (0.52 to 0.98), P = 0.033	Return within one month with sore throat, RR (95% CI), P value	0.91 (0.47 to 1.72), P = 0.777	0.74 (0.36 to 1.47), P = 0.397	Return after one month with sore throat, RR (95% CI), P value	0.79 (0.47 to 1.29), P = 0.353	1.06 (0.66 to 1.63), P = 0.813	<p>Based on the RCT the authors concluded: "Targeting antibiotics for acute sore throat using a clinical score improves symptoms and reduces antibiotic use. RADTs used according to a clinical score provide similar benefits, but no clear advantages over a clinical score alone."<sup>15</sup> Page 29</p> <p>Based on the economic evaluation the authors concluded: "The FeverPAIN algorithm enabled an efficient use of health-care resources compared with the other two groups based on changes in symptoms, the primary outcome. As it appears to be more clinically effective and less costly than delayed prescribing and less costly than RADT, it would appear reasonable to prefer it to both alternatives on economic grounds. The cost per QALY analysis gave a less clear message, but did not contradict the cost-effectiveness analysis."<sup>15</sup> Page 63</p>
Outcome	Management strategy																																																	
	Delayed use of antibiotic (control)	Clinical score (FeverPAIN)	RADT																																															
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Main Study Findings	Author's Conclusion
<p><b>Symptom score, mean (95% CI) in the three groups:</b>  3.15 (2.93 to 3.37) for the delayed antibiotics group,  2.83 (2.61 to 3.05) for the FeverPAIN group,  2.84 (2.62 to 3.07) for the RADT group.</p> <p><b>Cost (UK £), mean (95% CI) in the three groups:</b>  51.30 (43.30 to 59.20) for delayed antibiotics group,  44.20 (41.30 to 47.00) for the FeverPAIN group,  49.30 (46.00 to 52.50) for the RADT group.</p> <p>The FeverPAIN group dominated both the delayed antibiotic group and the RADT group, as it was more clinically effective (lower symptom score) and less costly. However the point estimate of symptom score and the corresponding 95% CI for FeverPAIN and RADT groups were quite close. Further analyses were conducted by varying the cost of a point change in symptom score between UK£0 and UK£500 and it was found that over the entire range the FeverPAIN group was the most likely to be cost-effective.</p> <p><b><i>The cost-utility findings were based on 257 individuals for whom complete HRQoL data (based on EQ5D) were available for the calculation of QALY (Time frame was 14 days and 28 days)</i></b></p> <p><b>For Timeframe = 14 days</b>  <b>QALY, mean (95% CI) in the three groups:</b>  0.0057 (0.0044 to 0.007) for the delayed antibiotics group,  0.0058 (0.0045 to 0.0071) for the FeverPAIN group,  0.00584 (0.0046 to 0.0071) for the RADT group.</p> <p><b>Cost (£), mean (95% CI) in the three groups:</b>  49.70 (43.30 to 56.00) for the delayed antibiotics group,  45.90 (41.50 to 50.20) for the FeverPAIN group,  48.50 (45.00 to 52.00) for the RADT group.</p> <p><b>For Timeframe = 28 days</b>  <b>QALY, mean (95% CI) in the three groups:</b>  0.0171 (0.0131 to 0.0211) for the delayed antibiotics group,  0.01741 (0.0135 to 0.0213) for the FeverPAIN group,  0.01752 (0.0138 to 0.0212) for the RADT group.</p> <p><b>Cost (£), mean (95% CI) in the three groups:</b>  49.70 (43.30 to 56.00) for the delayed antibiotics group,  45.90 (41.50 to 50.20) for the FeverPAIN group,  48.50 (45.00 to 52.00) for the RADT group.</p> <p>The delayed group was dominated by the FeverPAIN group for both the time frames. The ICER for RADT group compared to FeverPAIN group was £74,286 for the 14 day time frame and £24,528 for the 28 day time frame. There were, however, no clear differences in QALY and cost in the three groups for both timeframes. Also the cost-effectiveness acceptability curves for the three groups showed considerable uncertainty for both time frames. Hence definitive conclusions on cost-utility were not possible.</p>	



Main Study Findings			Author's Conclusion		
Observational studies					
Anderson, <sup>16</sup> 2013, USA					
<b>Performance of Illumigene G A strep assay compared to two culture methods using data from three sites</b>			The authors stated that “ <i>The illumigene group A Streptococcus assay is a rapid accurate test with high sensitivity and specificity for the detection of GAS. It is easy to perform and provides reproducible results among different users in different settings, making it applicable to a variety of clinical environments.</i> ” <sup>16</sup> Page 1477		
Comparator culture method	Performance of group A strep assay, % (95% CI)				
	Sensitivity	Specificity		PPV	NPV
Standard culture	100 (95 to 100)	94.2 (92 to 94)		63.8 (54 to 72)	100 (99 to 100)
Extracted culture	98.0 (93 to 99)	97.7 (96 to 98)	86.2 (78 to 91)	99.7 (98 to 99)	
Routine culture using Lancefield antigen agglutination typing was considered as the gold standard for G A strep identification. Extracted culture was used to increase the sensitivity of the culture method.					
It was stated that majority of samples were from individuals < 19 years of age. Also the test performance was stated to be similar in the adult and pediatric groups, however no quantitative data were provided.					
Additional analysis using a laboratory developed PCR assay was performed with 16 samples that were positive by illumigene assay but negative by both standard and extracted culture methods. Of these 16 samples, 13 were positive by the PCR assay. It was reported that a possible explanation was that the PCR assay detected G A strep nucleic acids in the absence of viable organisms and may have come from patients whose infections were already resolving or who were receiving antimicrobial treatment.					
Ba-Saddik, <sup>28</sup> 2014, Yemen					
<b>Performance of RADTs compared to reference culture method in children</b>			The authors stated “ <i>We conclude that GAS pharyngotonsillitis is a major public health issue for Yemeni children [...] Clinical scoring systems in combination with RADT could be used for the identification of children who need treatment or further investigation.</i> ” <sup>28</sup> Page 432		
Sensitivity, %: 92.2 Specificity, %: 95.5 PPV, %: 92.6 NPV, %: 95.3					
The clinical scoring system with McIsaac score ≥ 4, had a sensitivity of 93% and a specificity of 82% compared to culture method					
Berry, <sup>17</sup> 2018, USA					
<b>Performance of two test methods compared to culture method using data from two clinics (in adults and children with majority children)</b>			The authors stated that “ <i>In this study, we showed that Alere i had a performance superior to that of BD Veritor when they were used to diagnose GAS infections, which could assist in the better utilization of antibiotics in real time. This new molecular platform should be considered a viable alternative POCT device for the diagnosis of GAS pharyngitis.</i> ” <sup>17</sup> Page 6 of 6		
Method	Performance of group A strep assay, % (95% CI)				
	Sensitivity	Specificity		Accuracy	
Alere i Strep A (molecular assay)	100.0 (91.6 to 100.0)	91.3 (86.1 to 95.1)		93.0 (88.8 to 96.0)	
BD Veritor (chromatographic immunoassay)	76.2 (60.5 to 87.9)	93.6 (88.9 to 96.8)	90.2 (85.5 to 93.9)		
There were 30 discordant test results. These were further analyzed by RT-PCR assay.					



Main Study Findings				Author's Conclusion
<p><b>Antibiotic use:</b> 73 of the 215 patients were given antibiotics at the time of the clinic visit. Of these 73 patients, 26 (36%) patients were likely prescribed antibiotics inappropriately based on confirmation of negative G A strep results. Of these 26 patients, 20 (77%) patients had negative G A strep results with all the tests, 5 (19%) patients had positive results with BD Veritor but had negative results with the other tests including RT-PCR. 13 (6%) of the 215 patients had negative results with BD Veritor and were not prescribed antibiotics at the initial clinic visit. However, these cases were shown to be positive with both Alere I Strep and RT-PCR. Of these 13 patients, 6 (46%) patients were started on antibiotics 2 to 6 days after the initial clinic visit after obtaining positive culture results. This time period (2 to 6 days) includes the time to get the culture results and follow up by the clinician.</p> <p>One patient was started on antibiotics even though the BD Veritor and culture results were negative as had history of GA strep pharyngitis.</p> <p><b>Adverse outcomes:</b> Chart review did not show any documentation of cases of adverse outcomes associated with treatment differences.</p>				
Cohen, <sup>18</sup> 2015, USA				
<b>Performance of molecular assay (Alere i strep test) in various age groups</b>				<p>The authors stated that “Overall, the Alere i strep A test could provide a one-step, rapid, point-of-care testing method for GAS pharyngitis and obviate backup testing on negative results.”<sup>18</sup> Page 2258</p> <p>The authors stated that “Overall, the test performs equally well in children and adults and is easily performed by nonlaboratory personnel in a variety of clinical settings.”<sup>18</sup> Page 2260</p>
Test evaluation	Outcome % (% 95 CI)	Age group		
		< 18 years	≥ 18 years	All
Molecular assay compared to culture method	Sensitivity	96.1 (92.7 to 99.5)	94.7 (84.7 to 104.8)	95.9 (92.7 to 99.1)
	Specificity	93.4 (90.2 to 96.6)	97.2 (94.1 to 100.3)	94.6 (92.2 to 97.0)
	PPV	89.1 (83.9 to 94.3)	85.7 (70.8 to 100.7)	88.7 (83.8 to 93.6)
	NPV	97.7 (95.7 to 99.7)	99.1 (97.2 to 100.9)	98.1 (96.7 to 99.6)
Molecular assay compared to culture but with discrepant results adjudicated by PCR	Sensitivity	98.5 (96.5 to 100.6)	100 (100.0 to 100.0)	98.7 (97.0 to 100.5)
	Specificity	98.2 (96.4 to 100.0)	99.1 (97.2 to 100.9)	98.5 (97.1 to 99.8)
	PPV	97.1 (94.3 to 99.9)	95.2 (86.1 to 104.4)	96.9 (94.1 to 99.6)
	NPV	99.1 (97.8 to 100.4)	100 (100.0 to 100.0)	99.4 (98.5 to 100.2)
Faron, <sup>19</sup> 2015, USA				
<b>Performance of molecular assay (Ampli Vue GAS assay)</b>				<p>The authors stated that “The results of this study demonstrate that the AmpliVue GAS assay is both sensitive and specific for detection of GAS in pharyngeal specimens. [...] This may be beneficial for use in near- point-of-care laboratories certified to perform tests of moderate complexity.”<sup>19</sup> Page 2366 - 2367</p>
Test evaluation	Performance of group A strep assay, % (95% CI)			
	Sensitivity	Specificity	PPV	NPV
Molecular assay compared to culture method (N = 1192)	98.3 (95 to 100)	93.2 (91 to 95)	71.2 (65 to 77)	99.7 (99 to 100)
Molecular assay compared to culture but with discrepant results adjudicated by RT-PCR (Lyra Direct Strep assay)	99.5 (97 to 100)	97.6 (96 to 98)	90.4	99.9

Main Study Findings					Author's Conclusion
Subgroup analysis by the type of swab used for sample collection					
<sup>a</sup> Molecular assay compared to culture method (in subgroup: ESwab used for sample collection, N = 481)	98.7 (92 to 100)	95.2 (93 to 97)	80.0 (70 to 87)	99.7 (98 to 100)	
<sup>a</sup> Molecular assay compared to culture method (in subgroup: wound fiber swab used for sample collection, N = 711)	97.9 (92 to 100)	91.8 (89 to 94)	65.5 (57 to 73)	100 (98 to 100)	
<sup>a</sup> Molecular assay: Lyra Direct Strep assay					
Of the 1,192 samples tested there were 72 discrepant results which were further analyzed by a molecular assay (Lyra). Forty six samples, which gave positive results with AmpliVue assay and negative results with culture assay, had positive results with Lyra assay. Twenty three samples, which gave positive results with AmpliVue assay and negative results with culture assay, had negative results with Lyra assay. One sample, which gave negative result with AmpliVue assay and positive result with culture assay, had positive result with Lyra assay. Two samples, which gave negative result with AmpliVue assay and positive results with culture assay, had negative result with Lyra assay.					
Felsentein, <sup>20</sup> 2014, USA					
<b>Performance of molecular assay (illumigeneG A strep assay) compared to culture</b> Sensitivity (% [95% CI]): 93.1 (83.1 to 97.8) Specificity (% [95% CI]): 91.4 (87.7 to 94.1) PPV (% [95% CI]): 67.5 (56.6 to 76.8) NPV(% [95% CI]): 98.5 (95.1 to 99.9)					The authors stated that “Overall, the illumigene assay was much more sensitive and was similarly specific for GAS detection, compared to culture alone, RADT alone, or the ACP/AAFP RADT/ culture algorithm. Combining high sensitivity with rapidly available results, the illumigene GAS assay is an appropriate alternative to culture for the laboratory diagnosis of GAS pharyngitis in patients for whom testing is clinically indicated.” <sup>20</sup> Page 3884
<b>Performance of molecular assay (illumigeneG A strep assay) compared to culture after adjusting for the discrepant results adjudicated using RT-PCR assay</b> Sensitivity (% [95% CI]): 98.6 (91.7 to 99.9) Specificity (% [95% CI]): 96.5 (93.6 to 98.2) PPV (% [95% CI]): 87.5 (78.3 to 93.3) NPV (% [95% CI]): 99.6 (97.8 to 99.9)					
<b>Performance of RADT (OSOM Ultra strep A assay) compared to culture</b> Sensitivity (% [95% CI]): 55.2 (42.5 to 67.3) Specificity (% [95% CI]): 99.1 (96.9 to 99.8) PPV(% [95% CI]): 91.4 (76.9 to 97.8) NPV (% [95% CI]): 92.0 (87.2 to 95.2)					
<b>Agreement between illumigene, RADT and culture assay results</b>					
Tests compared	Test results compared		Level of agreement between test results, % (95% CI)		
	illumigene vs culture				
	Positive		93.1 (83.1 to 97.8)		
	Negative		91.4 (87.7 to 94.1)		
	Overall (negative and positive)		91.7 (88.4 to 94.2)		

Main Study Findings					Author's Conclusion	
illumigene vs RADT	Positive	97.1 (84.2 to 99.9)			The authors stated that “A rapid test may have an additional value in the management of patients with high risk of having GAS infection. However, tests with a higher sensitivity are needed for accurate and reliable results for early diagnosis of patients with sore throat caused by GAS.” <sup>29</sup> Page 4	
	Negative	85.9 (81.7 to 89.3)				
	Overall (negative and positive)	86.9 (83.1 to 90.1)				
RADT vs culture	Positive	55.2 (42.5 to 67.3)				
	Negative	99.1 (96.9 to 99.8)				
	Overall (negative and positive)	91.9 (88.7 to 94.4)				
Gonsu, <sup>29</sup> 2015, Cameroun						
Performance of RADTs compared to reference culture method in adults and children						
Test	No of patients	Performance of group A strep assay, %				
		Sensitivity	Specifi city	PPV		NPV
	71 (all ages)	75	96	85.7	93	
	24 (3 to 15 years)	83.3	94.4	83.3	NR	
47 (> 15 years)	70	97.3	87.5	NR		
Henson, <sup>21</sup> 2013, USA						
Performance of two test methods compared to culture method						
Method	Performance of group A strep assay, %					
	Sensitivity	Specificity				
illumigene GA strep assay	100	95.9				
RADT	73.3	89.1				
Kolukirik, <sup>22</sup> 2016, Turkey						
Performance of two test methods compared to culture method						
Test	Performance of group A strep assay, %					
	Sensitivity	Specificity	PPV	NPV		
qPCR (developed by the authors)	100	96.4	92.9	100		
RADT	69.4	100	100	84.3		
Cost						
The authors reported that on the basis of the results of this study, the <i>S.pyogenes</i> fast PCR test was added to the reimbursement list in Turkey. Reimbursement for this test is estimated as \$1.95; calculation was based on a testing potential of two million tests annually.						
Kose, <sup>30</sup> 2016, Turkey						
Performance of RADTs compared to culture method (in children)						
Sensitivity, % (95% C): 92.1 (78.6 to 98.3)						
Specificity , % (95% C): 97.3 (93.8 to 99.1)						
PPV , % (95% C): 87.5 (73.2 to 95.8)						
NPV, % (95% C): 98.4 (95.3 to 99.7)						
The authors stated that “As a result, we can conclude that, in developing countries where unnecessary antibiotic usage is common, performing the RADT for all patients with pharyngitis						

Main Study Findings					Author's Conclusion
<b>Comparison of antibiotic prescription decisions in various patient (children) groups (N = 223)</b>					<i>has an important effect on reducing unnecessary antibiotic prescription, antibiotic costs and possible antibiotic resistance.”<sup>30</sup> Page 313</i>
Patient category	Number (%) of patients for whom the decision to prescribe antibiotic was “Yes”		Number (%) of patients for whom the decision to prescribe antibiotic was “No”		
	Before RADT <sup>a</sup>	After RADT	Before RADT <sup>a</sup>	After RADT	
All patients (N = 223)	178 (79.8)	83 (37.2)	38 (20.5)	140 (62.8)	
Non-GA strep pharyngitis patients (N = 185)	147 (79.5)	49 (26.5)	45 (20.2)	136 (73.5)	
GA strep pharyngitis patients (N = 38)	31 (81.6)	34 (89.5)	7 (18.4)	4 (10.5)	
<sup>a</sup> Before RADT the decision to prescribe was based on clinical findings and signs					
<b>Antibiotic costs based on decisions to prescribe before and after RADT was conducted in various patient (children) groups</b>					
Patient category	Antibiotic cost(\$) per patient		After RADT antibiotic cost (\$) per patient	After RADT reduction in antibiotic cost (%)	
	Before RADT <sup>a</sup>	After RADT			
All patients (N = 223)	1608.7/7.2	380.5/1.7	1228/5.5	76.4	
Non-GA strep pharyngitis patients (N = 185)	1372.7/7.4	262.6/1.4	1110.1/6.0	80.8	
GA strep pharyngitis patients (N = 38)	226.5/5.9	117.9/3.1	108.6/2.8	48	
<sup>a</sup> Before RADT the decision to prescribe was based on clinical findings and signs . Patients were evaluated twice (before and after RADT was conducted)					
Küçük, <sup>9</sup> 2014, Turkey					
<b>Performance of RADT (Quickvue Strep A) compared to culture method (in children)</b>					<i>The authors stated that “The low sensitivity of the RADT may be related to streptococcal carriage in some patients. The throat culture should be repeated after treatment to detect streptococcal carriage.”<sup>9</sup> Page 138</i>
Patient category	Performance of RADT, % (range)				
	Sensitivity	Specificity	PPV	NPV	
All groups (N=893)	59.5 (52.6 to 66.2)	97.2 (95.6 to 98.3)	87.0 (80.5 to 92.0)	88.3 (85.8(to 90.5)	
Age group 0 to 6 years (N = 639)	58.0	97.2	83.7	90.6	
Age group 7 to 17 years (N = 253)	61.5	96.9	91.8	81.8	

Main Study Findings				Author's Conclusion	
Lacroix, <sup>31</sup> 2018, Switzerland					
<b>Performance (sensitivity and specificity) of two types of RADTs(SOFIA and Alere) with respect to reference methods: culture method or culture method + PCR in case of discrepant results (in children)</b>				<p>The authors stated that “The immunofluorescence-based assay demonstrated improved diagnostic performances over the standard immunochromatographic RADT. Similarly specific for GAS detection, it demonstrates significantly higher sensitivity in children with McIsaac scores 2 or more. A negative result rules out a risk of GAS pharyngitis in 91.6% of children, making it an appropriate tool in pediatric emergency settings. Combined to the low incidence of rheumatic strains, critical appraisal of current practice to routinely perform a backup throat culture from children with pharyngitis and with negative GAS RADT could be reconsidered.”<sup>31</sup> Page 206</p>	
Patient group	Specificity, % (95% CI)		Sensitivity, % (95% CI)		
	SOFIA	Alere	SOFIA		Alere
All (McIsaac score ≥ 2) (N = 1002)	84.9 (82.6 to 86.7)	75.3 (73.1 to 76.7)	96.8 (95.4 to 97.9)		98.1 (96.8 to 98.9)
McIsaac score = 2 (N = 153)	73.5 (64.1 to 77.9)	51.0 (42.5 to 53.0)	97.1 (92.7 to 99.2)		99.0 (95.0 to 99.9)
McIsaac score ≥ 3 (N = 849)	86.7 (84.2 to 88.6)	78.9 (76.5 to 80.5)	96.8 (95.2 to 97.9)		97.9 (96.4 to 98.9)
McIsaac score ≥ 4 (N = 486)	90.0 (87.0 to 91.7)	82.8 (79.9 to 84.3)	97.5 (95.3 to 98.8)		98.2 (96.0 to 99.3)
McIsaac score = 5 (N = 143)	94.1 (87.9 to 97.5)	83.8 (77.4 to 86.2)	94.7 (89.0 to 97.7)		97.3 (91.5 to 99.5)
<b>Performance (PPV and NVP)of two types of RADTs (SOFIA and Alere) with respect to reference method: culture method or culture method + PCR in case of discrepant results (in children)</b>					
Patient group	PPV, % (95% CI)		NPV, % (95% CI)		
	SOFIA	Alere	SOFIA	Alere	
All (McIsaac score ≥ 2) (N = 1002)	94.0 (91.4 to 96.0)	95.9 (93.1 to 97.7)	91.6 (90.3 to 92.6)	87.0 (85.9 to 87.8)	
McIsaac score = 2 (N = 153)	92.3 (80.6 to 97.9)	96.2 (80.2 to 99.8)	88.6 (84.6 to 90.5)	81.1 (77.8 to 81.8)	
McIsaac score ≥ 3 (N = 849)	94.3 (91.5 to 96.3)	95.9 (92.9 to 97.7)	92.2 (90.7 to 93.3)	88.3 (87.0 to 89.2)	
McIsaac score ≥ 4 (N = 486)	96.4 (93.3 to 98.3)	97.2(93.8 to 98.9)	92.8 (90.7 to 94.1)	88.3 (86.3 to 89.3)	
McIsaac score = 5 (N = 143)	94.1 (87.9 to 97.5)	96.6 (89.2 to 99.4)	94.7 (89.0 to 97.7)	86.9 (81.7 to 88.9)	
For the entire patient group as well as for the each of the subgroups (grouped according to McIsaac scores ), the sensitivity of SOFIA was higher than that of Alere and the specificity for both tests were comparable.					
Nibhanipudi, <sup>23</sup> 2015, USA					
<b>Performance of two test methods compared to culture method</b>				<p>The authors stated that “The throat swab testing for LE on the test strip currently used for urine dipstick may be as useful as the reagent strep test in screening for group A β-hemolytic streptococcal infections causing acute pharyngitis in children.”<sup>23</sup> Page 4</p>	
Test	Performance of group A strep assay, %				
	Sensitivity	Specificity	PPV		NPV
LE test strip	45	80	45		80
RADT	56.3	92.3	56.3		92.3
<b>Performance of LE test compared to RADT</b>					
Test	Performance of group A strep assay, %				
	Sensitivity	Specificity	PPV		NPV
LE test strip	81.3	90.5	61.9		96.2

Main Study Findings		Author's Conclusion																			
<b>Cost</b> It was stated by the authors (in the Discussion section) that throat swab testing for LE on the test strip currently used for urine dipstick may result in more cost saving as a multistick strip costs 10 cents compared with \$4 or \$5 for a single rapid test strep test for diagnosis of strep pharyngitis.																					
Nordqvist, <sup>32</sup> 2015, Sweden																					
<b>Performance of RADT compared to culture method (blood culture or wound culture) (in adults and children with necrotizing fasciitis)</b> Sensitivity, %: 87 Specificity, %: 100  <b>Clinical utility</b> For the 16 patients who had GA strep infection diagnosed using RADT and had surgery, the median time from admission to surgery was 8 hours and range 0 to 31 hours. For 11 patients who had other microbial infections and had surgery, the median time from admission to surgery was 14 hours and range 2 to 123 hours.		The authors stated that “Our results indicate that low mortality rates can be achieved by surgery, appropriate antibiotics and good supportive care. Furthermore, we show that the use of the rapid antigen detection test for group A streptococci, in this setting, helps to shorten the time to surgical intervention in patients suffering from necrotizing fasciitis. This also helps to guide the antibiotic treatment into a narrower spectrum.” <sup>32</sup> Page 319																			
Penney, <sup>33</sup> 2016, Canada																					
<b>Performance of RADT (Alere TestPack Plus Strep A kit) with respect to reference culture method (in children)</b> <table><tr><th rowspan="2">Test operator</th><th colspan="4">Performance of group A strep assay, % (95% CI)</th></tr><tr><th>Sensitivity</th><th>Specificity</th><th>PPV</th><th>NPV</th></tr><tr><td>ED Nurse</td><td>76.3 (63.4 to 86.4)</td><td>96.6 (90.4 to 99.3)</td><td>93.8 (82.8 to 98.7)</td><td>85.9 (77.4 to 92.1)</td></tr><tr><td>Technician</td><td>81.4 (69.1 to 90.3)</td><td>97.7 (92.0 to 99.7)</td><td>96.0 (86.3 to 99.5)</td><td>88.7 (80.6 to 94.2)</td></tr></table> There was little difference in performance result between the two categories of test operators. Possible explanations may be that the nurses had received extensive training or the Hawthorne effect due to participation in a study. However, it seems likely that POC RADT may approach laboratory RADT performance under ideal conditions.		Test operator	Performance of group A strep assay, % (95% CI)				Sensitivity	Specificity	PPV	NPV	ED Nurse	76.3 (63.4 to 86.4)	96.6 (90.4 to 99.3)	93.8 (82.8 to 98.7)	85.9 (77.4 to 92.1)	Technician	81.4 (69.1 to 90.3)	97.7 (92.0 to 99.7)	96.0 (86.3 to 99.5)	88.7 (80.6 to 94.2)	The authors stated that “The performance of the RADT was similar between technologists and ED nurses, although adequate power was not achieved. RADT may be employed in the ED without clinically significant loss of sensitivity.” <sup>33</sup> Page 1 of 4
Test operator	Performance of group A strep assay, % (95% CI)																				
	Sensitivity	Specificity	PPV	NPV																	
ED Nurse	76.3 (63.4 to 86.4)	96.6 (90.4 to 99.3)	93.8 (82.8 to 98.7)	85.9 (77.4 to 92.1)																	
Technician	81.4 (69.1 to 90.3)	97.7 (92.0 to 99.7)	96.0 (86.3 to 99.5)	88.7 (80.6 to 94.2)																	
Shapiro, <sup>34</sup> 2018, USA																					
<b>Performance of RADT with respect to reference culture method</b> Sensitivity, % (95% CI): 84 (77 to 91) No statistically significant differences in sensitivity of RADT were observed with varying numbers of viral features (presented graphically).  GA Strep was found to be less prevalent in patients with viral features than in patients without viral features		The authors stated that “Even with highly accurate RADTs, distinguishing viral pharyngitis from GAS pharyngitis remains a challenging and important component of antimicrobial stewardship. Our study suggests that a large proportion of patients tested for GAS pharyngitis have symptoms that are more consistent with viral illness than with true GAS infection. Until we have laboratory tests that can accurately distinguish between GAS infection and GAS carriage, judicious use of RADTs will remain the most important method to avoid unnecessary treatment of GAS carriers.” <sup>34</sup> Page 7 of 8																			



Main Study Findings	Author's Conclusion
Stefaniuk, <sup>35</sup> 2017, Poland	
<p><b>Performance of rapid diagnostic test (QuikRead go Strep A test) in adults and children and in various subgroups (by score [Centor/ McIsaac] or age)</b></p> <p><u>Sensitivity, %</u>            91 for All patients (adults and children)            100 for Ages &gt; 14 years            80 for Ages 3 to 14 years            100 for Score = 2            91 for Score = 3            89 for Score = 4            86 for Score = 5</p> <p><u>Specificity, %</u>            83 for All patients (adults and children)            77 for Ages &gt; 14 years            91 for Ages 3 to 14 years            67 for Score = 2            93 for Score = 3            83 for Score = 4            100 for Score = 5</p> <p><u>PPV, %</u>            83 for All patients (adults and children)            79 for Ages &gt; 14 years            89 for Ages 3 to 14 years            60 for Score = 2            91 for Score = 3            85 for Score = 4            100 for Score = 5</p> <p><u>NPV, %</u>            92 for all patients (adults and children)            100 for Ages &gt; 14 years            84 for Ages 3 to 14 years            100 for Score = 2            93 for Score = 3            88 for Score = 4            86 for Score = 5</p>	<p>The authors stated that “Quick diagnostic tests, such as QuikRead go® Strep A, can aid decision making on using antibiotics in acute pharyngitis and tonsillitis. However, it should be noted that test parameters differ in different age groups and values of Centor/ McIsaac score, which may affect clinical decisions.”<sup>35</sup> Page 1737</p>
Subashini, <sup>36</sup> 2015, India	
<p><b>Performance of rapid antigen test (SD Bioline rapid antigen test) (in children) with respect to reference culture method</b></p> <p>Sensitivity, %: 55.5            Specificity, %: 100</p>	<p>The authors stated that “With the sensitivity just over 50%, the validity of the test is questionable, as a clinical decision to treat or not treat pharyngitis becomes difficult, unless there is a culture report”<sup>36</sup> Page 1 of 2</p>
Tabb, <sup>24</sup> 2016, USA	
<p><b>Performance of molecular assay (Simplexa Group A Strep Direct assay) compared to culture assay</b></p>	<p>The authors stated that “The use of advanced molecular diagnostic kits and</p>

Main Study Findings					Author's Conclusion														
<table><tr><td rowspan="2">Test</td><td colspan="4">Performance of group A strep assay, % (95% CI)</td></tr><tr><td>Sensitivity</td><td>Specificity</td><td>PPV</td><td>NPV</td></tr><tr><td>Simplexa Group A Strep Direct assay</td><td>97.4 (93.6 to 99.0)</td><td>95.2 (93.9 to 96.3)</td><td>72.7 (66.3 to 78.3)</td><td>99.7 (99.1 to 99.9)</td></tr></table>					Test	Performance of group A strep assay, % (95% CI)				Sensitivity	Specificity	PPV	NPV	Simplexa Group A Strep Direct assay	97.4 (93.6 to 99.0)	95.2 (93.9 to 96.3)	72.7 (66.3 to 78.3)	99.7 (99.1 to 99.9)	technologies such as Simplexa Group A Strep Direct can provide rapid results with sensitivity equal to or better than culture, ultimately reducing time to patient diagnosis." <sup>24</sup> Page 274
Test	Performance of group A strep assay, % (95% CI)																		
	Sensitivity	Specificity	PPV	NPV															
Simplexa Group A Strep Direct assay	97.4 (93.6 to 99.0)	95.2 (93.9 to 96.3)	72.7 (66.3 to 78.3)	99.7 (99.1 to 99.9)															
Uphoff, <sup>25</sup> 2016, USA																			
<b>Performance of a molecular method (Solana GAS assay, a helicase-dependent amplification [HAD] method) compared to culture method</b>					The authors stated that “In 35 min, the HDA method provided rapid, sensitive GAS detection, making culture confirmation unnecessary.” <sup>25</sup> Page 2388														
<table><tr><td rowspan="2">Method</td><td colspan="2">Performance of group A strep assay, % (95% CI)</td></tr><tr><td>Sensitivity</td><td>Specificity</td></tr><tr><td>Solana GAS assay</td><td>98.2 (95.5 to 99.3)</td><td>97.2 (95.9 to 98.1)</td></tr></table>						Method	Performance of group A strep assay, % (95% CI)		Sensitivity	Specificity	Solana GAS assay	98.2 (95.5 to 99.3)	97.2 (95.9 to 98.1)						
Method	Performance of group A strep assay, % (95% CI)																		
	Sensitivity	Specificity																	
Solana GAS assay	98.2 (95.5 to 99.3)	97.2 (95.9 to 98.1)																	
Upton, <sup>26</sup> 2016, New Zealand																			
<b>Performance of a molecular method (illumigene assay) using culture method results as gold standard</b> Sensitivity (% [95% CI]): 81.5 (72.0 to 88.9) Specificity (% [95% CI]): 92.6 (90.4 to 94.5) PPV (% [95% CI]): 60.5 (51.3 to 69.1) NPV(% [95% CI]): 97.3 (95.7 to 98.4)					The authors stated that “In our unique setting of a school-based throat swabbing program, the illumigene assay did not perform quite as well as described in previous reports. Despite this, its improved sensitivity and rapid turnaround time compared with those of culture are appealing.” <sup>26</sup> Page 153														
<b>Performance of a molecular method (illumigene assay) and culture method using composite gold standard as gold standard for positive specimens and culture results as gold standard for culture negative specimens.</b> (The composite gold standard was either a positive culture result or positive results by two molecular assays.) Sensitivity (% [95% CI]): 86.5 (80.0 to 91.7) for illumigene, 73.2 (64.5 to 80.5) for culture Specificity (% [95% CI]): 97.6 (96.0 to 98.6) for illumigene, 100 (99.2 to 100) for culture PPV (% [95% CI]): 87.9 (80.5 to 92.8) for illumigene, 100 (98.1 to 100) for culture NPV(% [95% CI]): 97.3 (95.6 to 98.4) for illumigene, 94.8 (92.9 to 96.4) for culture																			
Vakkila, <sup>37</sup> 2015, Finland																			
<b>Performance<sup>a</sup> of rapid antigen test (mariPOC, immunoassay) (in adults and children, N = 219) with respect to reference culture method</b> Sensitivity, %: 81.3 Specificity, %: 93.8 PPV,%: 46.2 NPV,%: 98.7 <sup>a</sup> Values calculated by CADTH author.					The authors stated that “This study in which we compared the fully automated mariPOC GAS test with bacterial culture provided data suggesting that the new rapid POC test is more sensitive than bacterial culture. The high analytical sensitivity of the mariPOC GAS test enabled the detection of symptomatic patients that harbor only a low amount of group A streptococcal bacteria in their throat swab samples. This may also result in better understanding of symptomatic GAS pharyngitis and other GAS related disorders.” <sup>37</sup> Page 2082														
Actual data (for N = 219): Number of positive results with both mariPOC and culture methods = 30 Number of negative results with both mariPOC and culture methods = 152 Number of positive results with mariPOC and negative results with culture methods = 35 Number of negative results with mariPOC and positive results with culture methods = 2																			
<b>qPCR results with 42 samples stored in mariPOC, that were available for further analysis by qPCR</b>																			



Main Study Findings				Author's Conclusion	
No. of samples assessed by all three assays (N = 42)	Results with				
	Culture assay	mariPOC assay	qPCR assay		
	10	10 positive	10 positive		10 positive
	18	18 negative	18 negative		18 negative
	14	14 negative	14 positive		6 positive
GA strep concentrations and results obtained with mariPOC and culture methods					
Test results		GA strep concentration in CFU/ml, mean (range)			
Positive with both mariPOC and culture method		7,490 (637 to 14,700)			
Positive with mariPOC and negative with culture method		745 (302 to 3,623)			
Negative with both mariPOC and culture method		(0 to 287)			
Wang, <sup>27</sup> 2017, USA					
Performance of assay methods compared to reference culture method				The authors stated that “ <i>This prospective study found the sensitivity of the cobas Liat Strep A assay to be greater than that of RADTs, and equivalent to culture, coupled with a 15-minute turnaround time, demonstrating that POC testing does not always present a trade-off between time and accuracy. This improvement in diagnostic sensitivity has the potential to improve the diagnosis and management of pediatric patients with acute pharyngitis in primary care settings.</i> ” <sup>27</sup> Page 1133	
Method	No. of samples	Performance of group A strep assay, % (95% CI)			
		Sensitivity	Specificity		
cobas Liat Strep A assay	427	97.7% (93.4% to 99.2%)	93.3% (89.9% to 95.6%)		
RADT	427	84.5% (77.3% to 89.7%)	95.3% (92.3% to 97.2%)		

AAFP = American Academy of Family Physicians; ACP = American College of Physicians; CI = confidence interval; ED = emergency department; ELISA = enzyme-linked immunosorbent assay; FISH = fluorescence in situ hybridization; GA strep (or GAS) = group A streptococcus; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio; LE = leukocyte esterase; NA = not applicable; NPV = negative predictive value; OIA = optical immunoassay; PCR = polymerase chain reaction; POCT = point of care testing; PPV = positive predictive; strep = streptococcus; QALY = quality adjusted life year