Diagnostic accuracy of QuickVue® Dipstick Strep A test and its effect on antibiotic prescribing in children in the United Arab Emirates

Seyed Ali Safizadeh Shabestari
Mohammed Bin Rashid University of Medicine and Health Sciences College of Medicine
Zainab A. Malik
Mediclinic City Hospital
Fadil Y A Al-Najjar (fadil1952@hotmail.co.uk)
Mediclinic City Hospital https://orcid.org/0000-0003-0391-2155

Research article

Keywords: Diagnostic accuracy; pharyngotonsillitis; children; Group A Streptococcus; rapid bacterial antigen tests.

Posted Date: July 29th, 2019

DOI: https://doi.org/10.21203/rs.2.12084/v1

Version of Record: A version of this preprint was published on November 11th, 2019. See the published version at https://doi.org/10.1186/s12887-019-1761-7.

Abstract

Background: Unnecessary antibiotic prescription to children with upper respiratory tract infections (URTIs) has led to the increase in antibiotics resistant bacteria rates. In this study, we evaluated the diagnostic accuracy of QuickVue® Dipstick Strep A test (QV-SAT) in children presenting with acute pharyngotonsillitis and its effect on antibiotic prescribing. Methods: A single-gated diagnostic accuracy study of children with acute catarrh, fever, and inflamed tonsils presenting to a pediatric clinic between March 2016 and September 2018. Paired throat swabs for QV-SAT and culture were collected. None of the children received antibiotics prior to sample collection. Diagnostic accuracy of the QV-SAT was achieved by estimating the area under the ROC curve (AUC). Furthermore, the positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios of the test were calculated. Results: 204 children were included in this study. 111 (54.4%) were boys and 146 (71.6%) were under the age of five years. QV-SAT was positive in 44 (21.6%) and throat culture was positive for Group A β- haemolytic Streptococcus (GAS) in 42 (20.6%) of the children. The results of QV-SAT were highly consistent with culture results: only 2 (0.9%) children with negative results had a positive throat culture. The sensitivity of the QV-SAT in the identification of GAS infection was 100% (95% CI 91.6%, 100%) and the NPV was 100% (95% CI 70%, 95%). Only 42 children (21%) were given antibiotics, while 162 (79%) were not. Conclusion: The QV-SAT is a quick and reliable test which can help dramatically reduce antibiotic prescriptions to children presenting with fever and acute pharyngotonsillitis.

Introduction

The spread of antibiotic-resistant bacteria (ARB) has reached alarming proportions. It is estimated that ARB account for 700,000 annual deaths globally. This number could multiply to 10 million deaths a year by 2050 without a coordinated global response to this epidemic [1]. The primary driver for increasing resistance rates is the inappropriate use of antibiotics in healthcare settings. Measures taken to reduce unnecessary antibiotic use have led to a reduction in rates of antibiotic resistance [2]. In countries that lack guidelines on responsible antibiotic prescribing, however, rising rates of ARB threaten the dawn of a post-antibiotic era [3].

Children are frequently prescribed oral antibiotics for upper respiratory tract infections (URTIs), even though the majority of episodes are viral in origin [4]. This unnecessary antibiotic use not only drives increasing rates of antibiotic resistance but also leads to adverse drug reactions. In the United States, adverse drug reactions from antibiotic use are the most common reason for pediatric and adolescent visits to the emergency room [5].

In an earlier study in the United Arab Emirates (UAE) [6], bacterial pharyngotonsillitis secondary to *group A ß-hemolytic streptococcus* (GAS) infection accounted for only 14% of pediatric URTIs. Most children with

GAS pharyngotonsillitis will recover without antibiotics. However, treatment is recommended to prevent transmission to contacts and limit complications such as acute rheumatic fever and post-streptococcal glomerulonephritis, which can cause significant morbidity [7].

In clinical settings, viral and bacterial URTIs are indistinguishable [8,9] and results of throat culture, the current gold standard for diagnosis, can take up to 48 hours to become available. Efforts have been ongoing to develop increasingly sensitive rapid tests for diagnosis of GAS pharyngitis. An ideal test should be quick, simple and accurate. Most rapid tests suffer the major drawback of low sensitivity (ranging from 70%-90%), requiring a follow-up culture for those with a negative test result [7,9].

We previously reported an 85% reduction in antibiotic prescriptions for pediatric URTIs with the use of DiaQuick® rapid streptococcal antigen test (Dialab GmbH. Vienna, Austria) [6]. DiaQuick® is a one-step thin-layer chromatography sandwich-type immunoassay for the rapid, qualitative detection of GAS antigen from throat swabs, with a manufacturer-reported sensitivity of 90.5% and specificity of 97.5%.

In our current study, we evaluated the use of a newer generation rapid streptococcal antigen test in our pediatric patients presenting with symptoms of URTI. QuickVue® Dipstick Strep A test (QV-SAT), is a lateral flow immunoassay utilizing antibody labelled particles. The manufacturer (Quidel, San Diego, USA) reports a test sensitivity of 95%-99% and specificity of 86%-96%. We designed a diagnostic accuracy study to validate the use of QV-SAT in clinical practice and to determine its effect on antibiotic prescribing in children in the United Arab Emirates.

Methods

This was a single-gated diagnostic accuracy study conducted in the outpatient pediatric department of a multidisciplinary university-affiliated hospital in Dubai, UAE. Children with suspected pharyngotonsillitis presenting to the pediatric outpatient clinic at Mediclinic City Hospital between March 2016 and September 2018 were eligible for inclusion if they were younger than 16 years and presented with fever, acute catarrh and acutely inflamed throat/tonsils with or without exudates. We excluded children with clear viral infections like herpangina, herpetic stomatitis, influenza, rhinoconjunctivitis and who had received antibiotics during the preceding week. All subjects were evaluated and screened for study eligibility by a consultant pediatrician (Dr. Fadil Al-Najjar (FA)). Paired throat swabs for QV-SAT and culture were collected by FA and sent to the lab. No antibiotics were given before the results were known. In all cases, parents signed a consent form at the time of their child's hospital registration. The collection of paired swabs constitutes part of the child healthcare process, which covered by the above general consent, hence no separate consent was sought from parents at the time of sample collection. This study

was reviewed and approved by the Institutional Review Board (IRB) of Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU) Student Research Projects (SRP) Committee, (#MBRU-IRB-SRP2018-029).

Data were analyzed using the Statistical Package for Social Sciences (SPSS) 24 software. The overall diagnostic accuracy of the QV-SAT was achieved by estimating the area under the ROC curve (AUC). Furthermore, the PPV, NPV, and likelihood ratios of QV-SAT were calculated. There were no power and sample size calculations since it was a time-frame study.

Results

Two hundred and four patients were included in the study between 2016 and September 2018. Enrolled children had a mean age of 5.2 years. One hundred and forty-six (71.6%) children were under the age of five years and 111 (54.4%) were male. On throat examination, 137 (67%) children presented with tonsillar exudates.

Overall, the QV-SAT was positive in 44 (21.6%) and negative in 160 patients (78.4%), while throat culture was positive in 42 (20.6%) and negative in 162 (79.4%) (Figure 1). There was an inconsistency between QV-SAT and culture results in only two children. Sensitivity and specificity of the QV-SAT in the identification of GAS pharyngitis were 100% (95% CI 91.6%, 100%) and 98.8% (95% CI 95.6%, 99.8%), respectively. The QV-SAT had a positive predictive value (PPV) of 95.4% (95% CI 84.1%, 98.8%) and a negative predictive value (NPV) of 100% (95% CI 70%, 95%). The diagnostic accuracy of QV-SAT was 99% (95% CI 96.5% to 99.8%) with an AUC of 0.994 (asymptomatic 95% CI 98.4%,100%) (Figure 2).

Out of a potential 204 antibiotic prescriptions, only 42 children (21%) were given antibiotics, while a staggering 162 (79%) were not. In two children with positive QV-SAT, antibiotics were prescribed but subsequently discontinued when throat cultures grew no GAS.

Discussion

This is the first study evaluating the accuracy of QV-SAT in the Middle East. The majority of children with fever and pharyngitis presenting to our clinic were under the age of 5 years. As expected, most of them had viral infections contributing to their symptoms as confirmed by a negative throat culture. This diagnostic test demonstrated high diagnostic accuracy and an enviable NPV of 100%. Among our patients, the prevalence of GAS pharyngitis was 21%. However, a previous study from UAE by FA [6],

reported a positive GAS infection in 14% of 505 children with acute Pharyngotonsilitis. These figures are consistent with the reported prevalence of 15-36% in pediatric studies from other countries [10,11].

In our study, the QV-SAT demonstrated an AUC of 0.99, which is above the benchmark for diagnostic tests [12]. In contrast to single measures of sensitivity and specificity, the AUC is not affected by diagnostic criteria and is independent of disease prevalence, making it a robust measure for diagnostic tests [13]. Ehrlich and colleagues have previously reported that using throat cultures as a confirmatory test on patients with a negative rapid test detects 21 additional cases of rheumatic heart disease at a societal cost of an additional $8 million per case prevented [14]. The extremely high NPV of 100% of QV-SAT in our study suggests that children with a negative test may not require routine throat cultures to definitively rule out GAS pharyngitis, leading to a substantial reduction in healthcare costs and laboratory utilization. However, larger studies in several other clinical settings are needed before this strategy can be adopted into routine clinical practice.

Our findings of a 100% sensitivity alongside a 100% NPV are in stark contrast to other studies that have acknowledged excellent specificity but poor sensitivity of rapid streptococcal antigen tests [15]. The high test sensitivity in our study can be explained by high-quality sampling and a high pre-test probability for GAS pharyngitis since we excluded children with clear viral infections like herpangina, rhinosinusitis, influenza, etc. Since collecting a throat swab from children is fraught with difficulty, it should be emphasized that the reliability of QV-SAT is dependent on the quality of the throat swab samples. Therefore, it is just as important to collect a good sample as it is to follow the QV-SAT instructions provided with each kit. The high quality of throat samples collected by FA could likely have resulted in an overestimation of QV-SAT sensitivity in our study. This hypothesis can be tested by replicating our study in other clinical settings including pediatric emergency departments and primary healthcare settings to determine whether the experience of the person collecting the sample has any bearing on the sensitivity and specificity of the QV-SAT.

In children, viral and bacterial pharyngotonsillitis are clinically indistinguishable [9], making children with URTIs the main consumers of antibiotics [16]. To date, various strategies have been employed to clinically identify patients with GAS pharyngitis to limit antibiotic prescribing. These include the World Health Organization (WHO) acute respiratory infections guidelines [17], WHO clinical decision rule for streptococcal pharyngitis, sore throat score [18], Centor’s criteria [19] and McIsaac score [19]. Unfortunately, all these measures have displayed uniformly disappointing results. There is evidence, however, to support nationwide educational campaigns directed towards physicians and the public, which have dramatically reduced antibiotic use in Europe [20]. Also, the restriction of unnecessary

antibiotic prescriptions and providing decision-assisted physician orders through integrated computerized programs have proven to help control the use of antibiotics in advanced healthcare systems [3].

Utilizing QV-SAT in children presenting with fever and pharyngitis led to a marked reduction in antibiotic prescriptions in our study. Only 42 children (21%) were prescribed antibiotics whilst a staggering 162 (79%) required no antibiotics! Fewer antibiotic prescriptions result in direct monetary savings and have a far-reaching effect on reducing antibiotic overuse in the community, the emergence of drug-resistant bacteria and potential antibiotic-related adverse effects. In addition to reliable diagnostic tests, increased awareness among physicians and parents plays a key role to further reduce antibiotic overuse in all settings [4].

The main strength of our study is that it was conducted in the pediatric department of a multidisciplinary hospital, thus studying the single most important sector which is the cause for a rising number of ARB in the hospital setting [21]. All patients underwent both the QV-SAT and culture test, with no inconclusive results, hence there was no chance for a differential verification bias. Since throat samples were collected using paired throat swabs, there could be no verification bias or delay in the timing of testing leading to over or under-estimation of results. The major limitation of our study is that it represents a convenience sample of patients from a single clinic in a multidisciplinary hospital, thus limiting its generalizability to other clinical settings within the United Arab Emirates.

In conclusion, this study is the first of its type to assess the accuracy of QuickVue® Dipstick Strep A test in the Middle East. The QV-SAT is a simple, rapid and highly reliable test that can help reduce unnecessary antibiotic prescriptions in children presenting with symptoms of URTI.

Abbreviations

QV-SAT: QuickVue® Rapid Strep A test

URTI: Upper respiratory tract infections

GAS: *Group A β- haemolytic Streptococcus*

ARB: antibiotic-resistant bacteria

PPV: Positive predictive value

NPV: Negative predictive value

UAE: United Arab Emirates

WHO: World Health Organization

Declarations

Acknowledgements

We gratefully acknowledge Dr. Tom Loney, Dr. Aida Azar, and Dr. Ammar Hassan, faculty at the College of Medicine of Mohammed Bin Rashid University of Medicine and Health-Sciences, for their advice and guidance throughout the study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials

The data that support the findings of this study are available from Mediclinic City Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Mediclinic City Hospital, Dubai, UAE.

Authors' contributions

FA designed the study. FA collected samples and clinical information. SS analyzed the data and performed statistical analysis. SS drafted the initial manuscript. ZM commented and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was reviewed and approved by the Mohammed Bin Rashid University of Medicine and Health Sciences (MBRU)-IRB Student Research Projects (SRP) Committee, (#MBRU-IRB-SRP2018-029).

Consent for publication

Not applicable.

Competing interests

Not applicable.

References

1. de Kraker MEA, Stewardson AJ, Harbarth S. Will 10 Million People Die a Year due to Antimicrobial Resistance by 2050? PLOS Med [Internet]. 2016 Nov 29 [cited 2019 Jan 15];13(11):e1002184. Available from: https://dx.plos.org/10.1371/journal.pmed.1002184
2. Wiskirchen DE, Wu U, Summa M, Perrin A. Inpatient antibiotic resistance: Everyone's problem. J Fam Pract [Internet]. 2018 Feb 1 [cited 2019 Jan 15];67(2):E1–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29400898
3. Aly M, Balkhy HH. The prevalence of antimicrobial resistance in clinical isolates from Gulf Corporation Council countries. Antimicrob Resist Infect Control [Internet]. 2012 Jul 19 [cited 2019 Jan 15];1(1):26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22958584
4. Wong GWK. Reducing antibiotic prescriptions for childhood upper respiratory tract infections. Lancet Glob Heal [Internet]. 2017 Dec [cited 2019 Jan 15];5(12):e1170–1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29102352
5. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US Emergency Department Visits for Outpatient Adverse Drug Events, 2013-2014. JAMA [Internet]. 2016 Nov 22 [cited 2019 Apr 2];316(20):2115. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2016.16201
6. Al-Najjar FYA, Uduman SA. Clinical utility of a new rapid test for the detection of group A Streptococcus and discriminate use of antibiotics for bacterial pharyngitis in an outpatient setting. Int J Infect Dis [Internet]. 2008 May [cited 2019 Jan 15];12(3):308–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18024107
7. Undeland DK, Kowalski TJ, Berth WL, Gundrum JD. Appropriately prescribing antibiotics for patients with pharyngitis: a physician-based approach vs a nurse-only triage and treatment algorithm. Mayo Clin Proc [Internet]. 2010 Nov [cited 2019 Jan 15];85(11):1011–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21037044
8. Rondini G, Cocuzza CE, Cianflone M, Lanzafame A, Santini L, Mattina R. Bacteriological and clinical efficacy of various antibiotics used in the treatment of streptococcal pharyngitis in Italy. An epidemiological study. Int J Antimicrob Agents [Internet]. 2001 Jul [cited 2019 Jan 15];18(1):9–17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11463521
9. Lin M-H, Fong W-K, Chang P-F, Yen C-W, Hung K-L, Lin S-J. Predictive value of clinical features in differentiating group A beta-hemolytic streptococcal pharyngitis in children. J Microbiol Immunol

Infect [Internet]. 2003 Mar [cited 2019 Jan 15];36(1):21–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12741728

10. Linder JA, Bates DW, Lee GM, Finkelstein JA. Antibiotic Treatment of Children With Sore Throat. JAMA [Internet]. 2005 Nov 9 [cited 2019 Apr 27];294(18):2315. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16278359
11. Shaikh N, Leonard E, Martin JM. Prevalence of Streptococcal Pharyngitis and Streptococcal Carriage in Children: A Meta-analysis. Pediatrics [Internet]. 2010 Sep 1 [cited 2019 Apr 28];126(3):e557–64. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20696723
12. Hosmer DW, Lemeshow S. Applied Logistic Regression [Internet]. 2nd ed. New York: John Wiley and Sons; 2000 [cited 2019 Jan 15]. 160–164 p. Available from: http://resource.heartonline.cn/20150528/1_3kOQSTg.pdf
13. Hajian-Tilaki K. Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. Casp J Intern Med [Internet]. 2013 [cited 2019 Jan 15];4(2):627–35. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24009950
14. Ehrlich JE, Demopoulos BP, Daniel KR, Ricarte MC, Glied S. Cost-effectiveness of treatment options for prevention of rheumatic heart disease from Group A streptococcal pharyngitis in a pediatric population. Prev Med (Baltim) [Internet]. 2002 Sep [cited 2019 Jan 15];35(3):250–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12202067
15. Gerber MA, Shulman ST. Rapid Diagnosis of Pharyngitis Caused by Group A Streptococci. Clin Microbiol Rev [Internet]. 2004 Jul 1 [cited 2019 Jan 15];17(3):571–80. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15258094
16. Froom J, Culpepper L, Jacobs M, DeMelker RA, Green LA, van Buchem L, et al. Antimicrobials for acute otitis media? A review from the International Primary Care Network. BMJ [Internet]. 1997 Jul 12 [cited 2019 Jan 15];315(7100):98–102. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9240050
17. Rimoin A, Hamza H, Vince A, Kumar R, Walker C, Chitale R et al. Evaluation of the WHO clinical decision rule for streptococcal pharyngitis. Archives of Disease in Childhood. 2005;90(10):1066-1070.
18. McIsaac WJ, White D, Tannenbaum D, Low DE. A clinical score to reduce unnecessary antibiotic use in patients with sore throat. CMAJ [Internet]. 1998 Jan 13 [cited 2019 Jan 15];158(1):75–83. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9475915
19. Linder JA, Chan JC, Bates DW. Evaluation and Treatment of Pharyngitis in Primary Care Practice. Arch Intern Med [Internet]. 2006 Jul 10 [cited 2019 Jan 15];166(13):1374. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16832002
20. Goossens H, Ferech M, Vander Stichele R, Elseviers M, ESAC Project Group. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet [Internet]. 2005 Feb [cited 2019 Jan 15];365(9459):579–87. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15708101

21. Lean WL, Arnup S, Danchin M, Steer AC. Rapid Diagnostic Tests for Group A Streptococcal Pharyngitis: A Meta-analysis. Pediatrics [Internet]. 2014 Oct 1 [cited 2019 Jan 15];134(4):771–81. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25201792

Figures

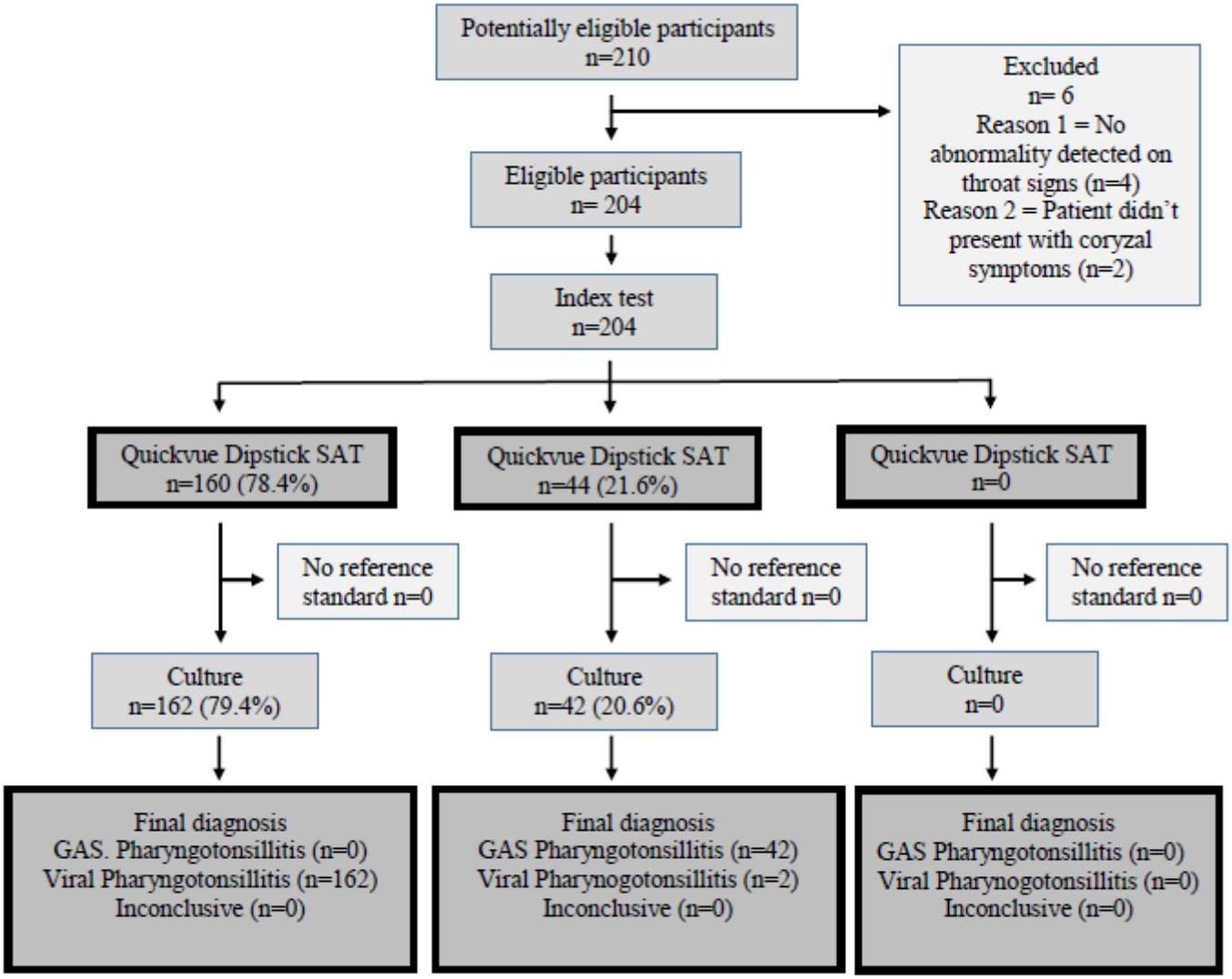

Figure 1- Flow of participants through study in a STARD prototype

Figure 1

Flow of participants through study in a STARD prototype

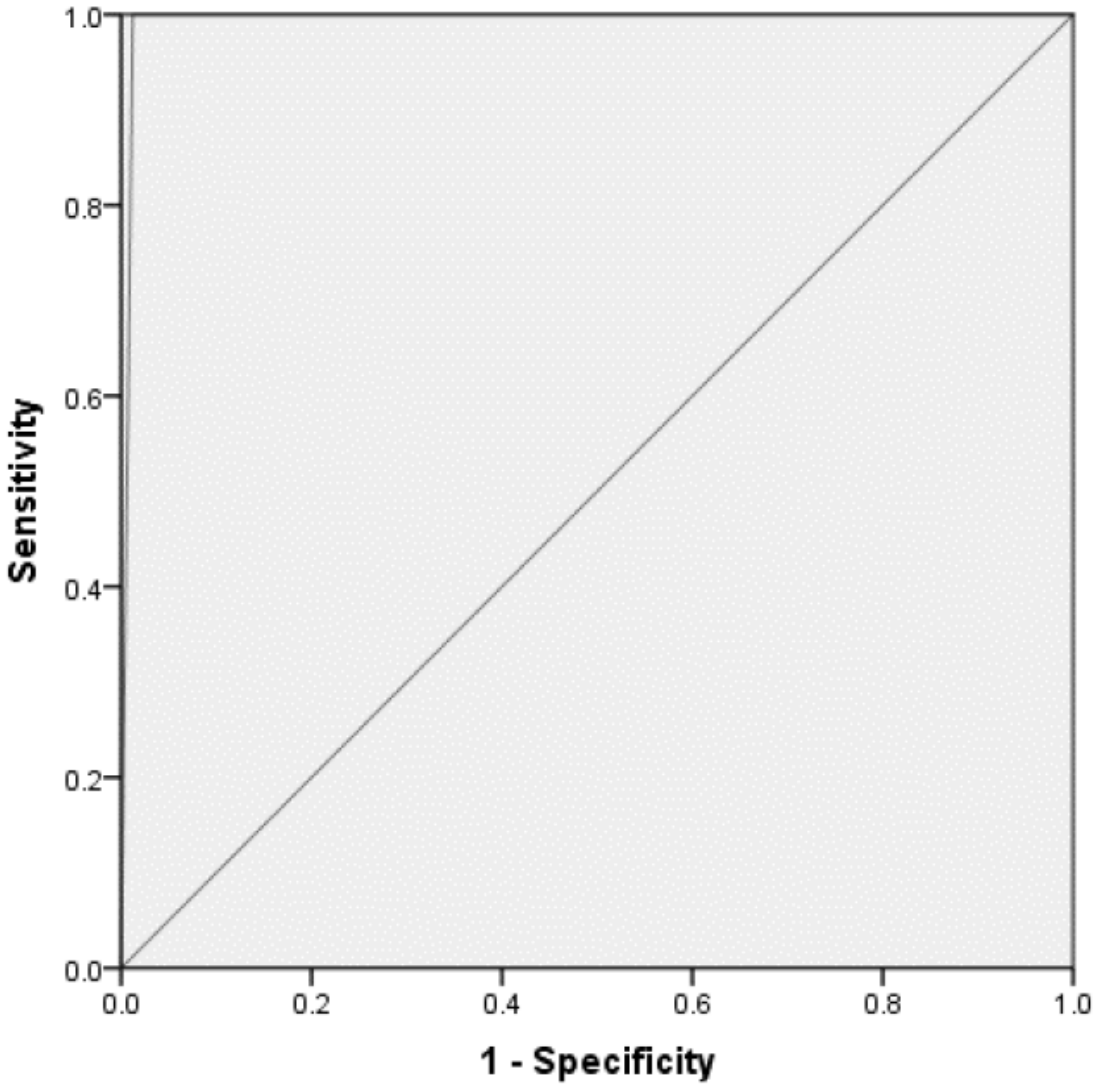

Figure 2 -Receiver Operating Characteristic (ROC) curve and Area Under Curve (AUC) for QuickVue® Dipstick Strep A test

Figure 2

Reciever Operating Chracteristic (ROC) curve and Area Under Curve (AUC) for QuickVue Dipstick Strep A test