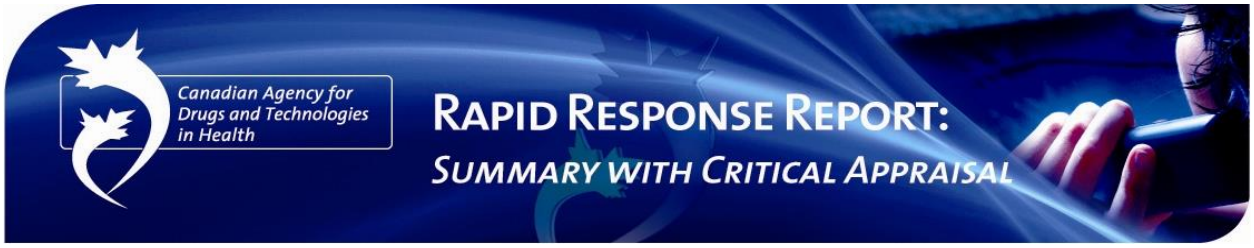

TITLE: Streptococcal Antigen Test for Pneumonia Detection: A Review of Clinical and Cost-Effectiveness and Guidelines

DATE: 13 November 2015

CONTEXT AND POLICY ISSUES

Pneumonia is a disease typified by an inflammation of the lungs which occurs in response to microbial infection. It is the leading cause of death due to infection globally and accounts for approximately 4 million mortalities yearly.[1,2] The microbes that most commonly cause this condition are bacteria and viruses but fungi and parasites also contribute and in some cases a combination of factors are responsible.[3,4] Over 100 different microorganisms have been found to cause pneumonia but the bacteria *Streptococcus pneumoniae* (SP) is the most common.[2,4-8] SP is a Gram-positive encapsulated microbe that is typically found in the nasopharynx of adults and children.[1,4,9] It was first isolated as one of the causative agents for pneumonia in the 19th century and since then it has been linked to other conditions such as meningitis, bacteremia and mucosal infections like otitis media.[9]

The World Health Organization estimated that in 2005 pneumococcal pathogens were responsible for 1.6 million deaths annually in all age groups.[10] In the northern hemisphere the incidence of pneumococcal pneumonia occurs at a rate of 12 cases per 1000 otherwise healthy people.[3] In 2000 it was the cause of 14.5 million cases of severe pneumonia globally which resulted in 830,000 deaths in children five years old or less .[9] In Canada there have been more than 90 different serotypes of this bacterium found, all of which cause varying severities of pneumonia.[9] In the years before 1950 the predominant serotypes causing disease were 1, 2, 3, and 5.[9] Between the 1950s and the late 1980s there was a shift where serotypes 4, 6, 9, 14, 18, 19 and 23 became responsible for up to 87% of pneumococcal pneumonia cases. This shift coincided with the widespread use of sulfa antibiotics and penicillin G.[9] This led to the development of the PCV7 vaccine which was released in Canada in 2002. Currently in Canada non-PCV7 serotypes such as 3, 7F, 19A and 22F have risen in prevalence by over 183% between 1998 and 2007. As a result of these types of changes it is believed that the use of antibiotics may be one of the key contributing factors in determining which strains are responsible for pneumonia outbreaks.[9]

The two most common sites of origin for pneumonia development are within the community (community acquired pneumonia [CAP], and within a hospital (hospital acquired pneumonia

[HAP].[8,11,12] CAP is diagnosed in 5-12% of adults who go to their doctor with lower respiratory tract infections and between 22-42% of these cases are admitted into the hospital.[12] On average 1.2% of these patients will be moved into the intensive care unit and will have mortality rates of approximately 30%. It has been estimated that approximately 1.5% of people under care in a hospital are suffering from some sort of hospital acquired illness.[12] Half of these afflictions will be a result of HAP, which will increase the duration of their stay by eight days on average and raise their mortality rate to a range between 30-70%.[12]

When a patient arrives at a hospital and presents with a condition suspected of being pneumonia the standard practice is to conduct a chest radiograph.[12] The gold standard for diagnosis occurs when progressive infiltrates are found in a patient who has symptoms such as cough, fever and issues with breathing.[3,12] Unfortunately these symptoms and the evidence on x-ray may be absent in many circumstances.[3,4] In addition the etiology of the infection cannot be determined from x-ray images. As a result of this, microbiologic investigations may be necessary to complete diagnosis and identify treatment options. Standard applications are to use blood and sputum cultures but may also include pleural fluid and respiratory aspirates or lavage sampling. These approaches have high specificity but only low to moderate sensitivity.[1,8,13] For example investigation has demonstrated that blood cultures may in some circumstances result in only 30% sensitivity.[1] Sputum cultures have improved sensitivity, though it has been found to be as low as 57% in some instances.[1] Even though sputum culturing is a well-established technique it is controversial, as in many circumstances patients are unable to produce adequate sample volumes to allow for culturing.[13] Another problem is that culturing of these specimens takes a minimum of 24 hours to achieve viable results.[6,8] These limitations are part of the reason that many therapeutic regimens are conducted empirically instead of using targeted antibiotic treatment.

Rapid treatment with an antibiotic has been shown to improve survival rates indicating that fast etiologic identification is important for management of pneumonia.[3,6] A growing concern in health care practice is that the use of general purpose antibiotics are contributing to the rise in the prevalence of antibiotic resistant microbes that cause pneumonia.[1,7,12,14] In order to resolve these problems more rapid identification techniques are under investigation. Over the past decade, the use of urinary antigen testing has demonstrated high specificity and sensitivity for the identification of pneumococcal antigens in patient's urine. This testing takes only 15 minutes to complete and indicates the presence of a protein found in all pneumococcal bacteria.[15,16] It is believed that a switch to more targeted treatment will allow for reductions in costs and time in hospital, and will reduce contributions to microbial antibiotic resistance.[1,6]

The purpose of this report is to examine both clinical and cost effectiveness, and to review evidence-based guidelines for the use of urinary antigen testing for the diagnosis of pneumonia.

RESEARCH QUESTIONS

1. What is the clinical effectiveness of the streptococcal antigen test for the detection of pneumonia in pediatric and adult patients?

2. What is the cost-effectiveness of the streptococcal antigen test for the detection of pneumonia in pediatric and adult patients?

3. What are the evidence-based guidelines associated with the use of the streptococcal antigen test for the detection of pneumonia in pediatric and adult patients?

KEY FINDINGS

Streptococcal antigen testing was found to be both sensitive and highly specific under most conditions, though evidence was found that demonstrated high variability depending on the serotype that was encountered. The cost savings as a result of its use are heterogeneous in nature and more powerful investigation is required to form reliable conclusions. Evidence-based guidelines indicate that it is not appropriate for use in children due to high false-positives, and they further stated that its use in adults should be limited to admitted patients with moderate to high disease severity.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI Institute, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was limited to English language documents published between Jan 1, 2008 and Oct 16, 2015.

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

Population	All patients (pediatric through geriatric) suspected of having pneumonia
Intervention	Streptococcal antigen test
Comparator	Standard of care (other molecular or serum tests); No comparator
Outcomes	Q1: Clinical effectiveness (including patient safety) Q2: Cost-effectiveness Q3: Guidelines
Study Designs	HTA/Systematic Reviews/Meta-Analyses, Randomized Controlled Trials, Non-Randomized Studies, Economic Evaluations, Evidence-based Guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, were published prior to 2008 or they were included in a selected systematic review.

Critical Appraisal of Individual Studies

The included health technology assessment and systematic review were critically appraised using the Assessment of Multiple Reviews (AMSTAR) tool.[17] Non-randomized studies were assessed using the Downs and Black checklist for the adequacy of allocation concealment, blinding of healthcare providers, clinicians, data collectors and outcome assessors, losses to follow-up, description of intention-to-treat, and early stopping of the trial.[18] In addition the QUADAS-2 tool was used to assess diagnostic accuracy studies.[19] Guidelines were assessed using the Appraisal of Guidelines for Research and Evaluation II.[20] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Details of study characteristics, critical appraisal, and study findings are located in Appendices 2, 3, and 4, respectively.

Quantity of Research Available

A total of 574 citations were identified in the literature search. Following screening of titles and abstracts, 541 citations were excluded and 33 potentially relevant reports from the electronic search were retrieved for full-text review. Seven potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 24 publications were excluded for various reasons, while 16 met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Clinical effectiveness of the streptococcal antigen test for the detection of pneumonia in pediatric and adult patients

Study Design

There was one health technology assessment (HTA) found for the clinical effectiveness of streptococcal antigen testing.[8] In addition, one systematic review[5] and seven non-randomized studies were found. The non-randomized studies are made up of five prospective[13,16,21-23] and two retrospective cohort investigations.[15,24] Details of each study are found in Appendix 2.

Clinical effectiveness of the streptococcal antigen test for the detection of pneumonia in pediatric and adult patients

The HTA was produced in 2012 by the University of McGill - University Health Centre.[8] This assessment included 27 publications that were produced between 2004 and 2011. Reviewers obtained literature from the Cochrane Collaboration, the Centre for reviews and Dissemination of the University of York, the International Network of Agencies for Health Technology Assessment, the Canadian Agency for Drugs and Technology in Health, and EMBASE.

Horita et al. published a systematic review in 2013.[5] This publication reviewed 10 studies that were produced up to December 2012 from MEDLINE and Cochrane databases. Their goal was

to assess the sensitivity and specificity of streptococcal pneumonia UAT from adult patients with pneumonia.

There were a total of five prospective cohort investigations identified to address this research this question. The first was authored by Molinos et al. published in 2015.[21] They enrolled 4374 patients age 18 years or more at 13 sites in Spain in order to analyze the sensitivity and specificity of UAT and develop a predictive model for positive identification of CAP in patients. All patients were given a chest x-ray and were analyzed for disease severity using the pneumonia severity index (PSI) and the CURB-65 scoring systems. In addition blood and sputum cultures were taken at admission or if the patient was intubated respiratory secretions and pleural fluid was sampled.

Chen et al.[13] conducted the second prospective investigation on adults aged 15 to 97 years old. Their goal was to determine the clinical effectiveness of UAT in patients that had been treated empirically with antibiotics. A total of 487 patients were enrolled between January 2008 and March 2010 from the Department of Respiratory Medicine at First Affiliated Hospital of Yangtzee in China. They were then divided into two groups: those where sampling was completed before antibiotic treatment and those where they were collected afterwards. All patients had urine and two blood samples collected. In addition sputum was collected in situations where patients could produce it and samples of nasopharyngeal swab, pleural fluid, protected specimen brush, and bronchoalveolar lavage or aspirates were used as required according to clinical investigation.

Zalacain et al.[22] completed the third study on 350 patients over 18 years old who were recruited between 2002 and 2010 from two hospitals. Their goal was to analyze the clinical effectiveness of UAT for the detection of *S. pneumoniae* and to determine if results from this testing have any relationship with disease outcomes. All patients received two blood cultures within 24 hours of admission and a urine sample was taken. In addition an analysis of the serotypes responsible for infection was examined.

Another study was completed by Huijts et al.[16] on 1095 patients aged 18 years or older who were treated at 23 different hospitals in The Netherlands between January 2008 and April 2009. Their goal was to evaluate the clinical effectiveness and utility of a serotype specific UAT for use on patients with CAP. This method utilized a urinary antigen process for the detection of the 13 serotypes targeted by the13-valent pneumococcal conjugate vaccine (PCV13) in a multiplex urinary antigen detection assay (UAD). All patient samples were taken immediately upon admission up to a maximum of 48 hours afterwards. Analyses included of blood, pleural fluid, and sputum microbiological analysis, chest x-ray, and urine testing. Severity was calculated using PSI scoring and sensitivity and specificity of testing was analyzed.

The final prospective cohort investigation was completed by Cheong et al.[23] and included 245 patients aged <18 years old and recruited between January and December of 2004 from the Kaohsiung Veterans General Hospital. The severity of disease was determined using chest x-rays and consultation with a pediatrician and a thoracic radiologist, with scores of 4 or 5 required for inclusion, indicating more severe illness. These individuals were then divided into four groups based on the treatment approach that was utilized. The four groups were defined as follows:

- Group 1 – UAT examination and treated with penicillin G if positive and ampicillin-sulbactam or cefuroxamine if negative following Infectious Diseases Society of Taiwan (IDST) guidelines
- Group 2 – UAT examination not following IDST guidelines for treatment
- Group 3 – No UAT and treat following IDST guidelines
- Group 4 – No UAT and treatment does not follow IDST guidelines

The goal was to evaluate the efficacy of pneumococcal UAT in severe pediatric pneumonia using an analysis of the length of hospital stay and the number of days to reach an afebrile state.

There were two retrospective cohort investigations identified. The first was produced by Choi et al.[15] and was conducted on medical records of patients aged 19 years or older. Case records were obtained from a hospital in South Korea. The goal was to evaluate the amount of pneumococcal pneumonia occurring after the introduction of the PCV13 vaccine and to determine how effective UAT testing is for *S. pneumoniae* detection in CAP patients. These were compared against standard techniques such as cultures of blood, sputum and pleural fluid as well as respiratory viral PCR.

The final study was produced by Shen et al.[24] and was conducted on the medical records of 119 patients positive for pneumococcal UAT. These records were obtained from National Cheung Kung University Hospital from February 2002 to February 2007. All patients were screened with blood and sputum cultures, sputum smears, viral isolation and *Mycoplasma* analysis upon admission. Their goal was to determine if a UAT reactivity score based on the time for the test to become positive and the intensity of the reactive band might be directly associated with the severity of the disease.

Country of Origin

The health technology assessment[8] was produced in Canada and the systematic review was written in Japan.[5] Two of the seven non-randomized studies were composed in Spain[21,22] and two more were written in Taiwan.[23,24] The remaining three studies were completed in China,[13] The Netherlands,[16] and Korea.[15]

Intervention

The majority of the included investigations used the BinaxNOW-SP UAT as their intervention and this was compared to other testing methods. The systematic review applied no restrictions to the reference testing that was utilized. The health technology assessment compared UAT to blood and sputum culture as well as either pleural fluid or respiratory tract fluid culture. All of these assessments focused on methods using unconcentrated urine for analysis.

All but one of the non-randomized studies also examined the use of the BinaxNOW-SP urine antigen test (UAT) against other standard treatment options. In one report the primary intervention was a novel UAT produced by Luminex that focused on the 13 serotypes targeted by the PCV13 vaccine.[16] This investigation included the BinaxNOW-SP testing in their reference method grouping. All of these studies conducted urinary analysis on unconcentrated urine

samples except for the investigation completed by Zalacain et al.[22] In this study urine samples were obtained within 24 hours of admission and were then concentrated 25 fold before analysis.

Outcomes

Sensitivity and specificity of the UAT were the primary outcomes of interest in six of the ten publications assessing clinical effectiveness.[1,5,8,13,16,21] The health technology assessment[8] also sought to provide an estimation of the costs associated with UAT and the cost of antibiotic treatment used in response to positive or negative results. In addition to the outcomes described above, Molinos et al.[21] were interested in the development of a probabilistic model based on various symptoms for use in the diagnosis of CAP. The study by Chen et al.[13] examined patients after they had been treated with antibiotics to determine the sensitivity and specificity of UAT in this type of patient.

Zalacain et al.[22] additionally sought to determine whether there was a relationship between the type of testing and the outcomes of the disease. Cheong et al.[23] focused on the length of hospital stay and examined the pattern of fever between various groups using UAT and not using it. This was then compared to the duration of time to reach afebrile stages. In a retrospective analysis Choi et al.[15] analyzed the positive UAT rate and how it compared to demographics such as patient age, comorbidity, disease severity and serotype to determine if any changes occurred to UAT effectiveness. The final study completed by Shen et al.[24] was focused on determining if the length of time for UAT to produce a detectable result has any relationship to disease severity and to assess if this could be used for probability scoring.

Cost-effectiveness of the streptococcal antigen test for the detection of pneumonia in pediatric and adult patients

Study Designs

In addition to the clinical findings, the included HTA[8] provided an analysis of cost-effectiveness of UAT. The purpose of this analysis was to examine the sensitivity and specificity of the BinaxNOW-SP UAT and provide an estimation of its cost effectiveness. The cost analysis focused on incremental costs and incremental correction classifications from adding the BinaxNOW-SP test into the protocols. In addition the expense associated with antibiotic use was analyzed. Any expenditures incurred for nursing time, physician visits, duration of stay and cultures that were assumed to remain unchanged from the addition of BinaxNOW-SP and were excluded from the analysis. Effectiveness was defined as the number of patients that were classified (treated) correctly, therefore the incremental cost-effectiveness is the difference in cost of cultures plus the BinaxNOW-SP versus cultures alone divided by the increase in the number of patients correctly classified due to the addition of BinaxNOW-SP testing to the regimen.

In addition, one retrospective cohort analysis reporting on costs was found. This study was produced in The Netherlands in 2013[6] in two hospitals between the years of 2005 and 2011. In total, 217 medical records were analyzed from patients 18 years old or older and were included if they had a positive pneumococcal UAT. Costs were analyzed from a hospital perspective as opposed to a societal one and included the cost of the pneumococcal UAT and the antibiotic regimen that was prescribed. Authors also assessed whether a positive UAT result leads to the use of targeted treatment in patients hospitalized with CAP.

Intervention

Both studies reporting on cost utilized the BinaxNOW-SP UAT as their intervention. This was compared against standard techniques such as cultures using blood, sputum and pleural fluid.
Outcomes

The HTA[8] calculated the budgetary impact for an estimated 1700 patient population derived from a summary of respiratory admissions at the McGill University Health Centre in the 2008-2009 fiscal year. The retrospective cohort analysis by Engel et al.[6] examined costs of targeted treatment, cumulative testing, and per patient costs associated with UAT. In addition they also examined a secondary grouping that included all pneumococcal UATs including those in non-CAP patients, children and trial runs in order to give a more realistic analysis of how a functioning clinic would operate.

Evidence-based guidelines associated with the use of the streptococcal antigen test for the detection of pneumonia in pediatric and adult patients

Six evidence-based guidelines for the use of streptococcal antigen testing for the detection of pneumonia were identified. The first of these assessments was produced in Australia in 2015 and did not limit any study type in the selection process and was developed for use in pediatric treatment.[14] Another study, also without restrictions on study design, was written by the Swedish Society for Infectious Disease in Sweden in 2012 for use on adult patients.[4] Three of the remaining guidelines were produced in the United Kingdom, one in 2014[12] and the final two in 2011.[11,25] Two of these assessments were conducted for use in adult patients[12,25] and the other one[11] was for use on children from 1 month to 12 years of age. The final publication was produced in the United States of America in 2011.[26] Their goal was to provide guidance on the care of infants and children for the diagnosis and management of CAP.

All of these publications used a scoring system in order to determine the strengths of the included studies. Three of them[12,14,26] used the Grades of Recommendation Assessment, Development and Evaluation methodology. The guideline produced by Woodhead et al.[12] also included the QUADAS-2 system for assessment of diagnostic studies. Spindler et al.[4] and Harris et al.[11] both included a scoring system obtained from the British Thoracic Society whereby grades from A+ to D are given out based on the level of evidence. The final guideline by Woodhead et al.[25] also included a scoring system for the included literature. This involved both a letter and a number rating for each study. A description of the scoring systems is provided in Appendix 2.

Summary of Critical Appraisal

Details of the critical appraisal can be found in Appendix 3.

The HTA[8] found for this question was well written and contained a comprehensive literature search with clearly defined literature inclusion and exclusion criteria. In addition they provided a cost analysis for both individual patient and total budgetary expenditure for the use of UAT. The number of reviewers included in the literature selection process and whether a scoring system was used to assess the strength of the literature were not provided. No common reference standard was found for the comparison across all of the included studies. As a result of this the authors were dependent on the definition of SP from each individual study and where results for

definite and probable cases were encountered they were combined into only one grouping. This may impart bias as this group may have included false-positive patients, those who were treated as SP positive but actually were not. In addition due to the above limitation the authors treated all patients in a study as potentially having had all reference testing completed on them, though they state that this may not have been the true situation. The meta-analysis models that were used for sensitivity and specificity are estimates that rely on the assumption that the results of BinaxNOW-SP and reference testing are independent within the SP pneumonia and non-SP pneumonia subgroup of patients. This assumption will not be valid if a patient characteristic caused a correlation between the two tests so that severe cases are more likely to be positive on both tests, such as severity of pneumonia. This correlation would result in lower estimates of sensitivity and specificity than those that are reported. This problem was also encountered in the review by Horita et al.[5] where it resulted in difficulty producing a definition of specificity. The investigation by Huijts et al.[16] also encountered problems with this when they were establishing their "true positives" and "true negatives" groupings. Since no test is 100% reliable these results must be considered with caution.

Moderate heterogeneity and the potential for publication bias was detected in the analysis of specificity in the review by Horita et al.[5] This occurred for Groups C and D, called "other" and "unknown", which prevented the investigators from giving reliable specificity analyses for these two categories. This review also did not contain any discussion of investigation into grey literature for either the synthesis of their report or for the studies that they included for analysis.

Two of the included prospective studies suffered from a lack of any discussion of potential conflicts of interest.[13,21] The study by Molinos et al.[21] included a large sample population enrolled from a wide variety of hospitals but did not utilize any sort of guideline or training session in order to ensure that all of the clinicians involved completed analysis in an organized framework which would allow for comparisons to be made. In addition the group that did not utilize the UAT and the group that did were not equal in terms of disease severity and age which may have skewed results. A similar situation was found in the study by Cheong et al.[23] where pneumonia and chest x-ray severity as well as gender were not evenly distributed.

The study by Chen et al.[13] also suffered from a narrow spectrum of patients obtained from only a single hospital. This limitation was also found in one other prospective investigation[23] and both of the retrospective investigations[15,24] which indicates that caution must be utilized when applying the results of their studies to the general population. Choi et al.[15] were also limited in that only a small number of case with pneumococcal isolates were available for serotyping. In addition the authors stated that little information could be found regarding the vaccination history of the patients which may have had significant effect of the results.

The study by Zalacain et al.[22] mentioned that the most likely explanation of poor prognosis for a positive UAT patient is due to bacterial burden. However no assessment of this was included in the investigation which leaves this conclusion open to interpretation. The study by Shen et al.[24] stated that urine samples were stored at -20C until testing was conducted but no detail on the duration of storage was is provided. This may result in alterations to the bacterial content which can result in inaccurate outcomes. It is also possible that the true infection results are overlapped by patients who have colonization and not true infection which may result in an overestimation of positive numbers.

All but one of these prospective cohort investigations also suffered from a lack of discussion of blinding of clinicians and technical staff to the results of reference testing and UAT. This has the

potential to bias the results especially in situations with positive cultures and subsequent UAT. The study by Huijts et al.[16] was the only investigation of this type where blinding of the technical staff was ensured.

The retrospective analysis captured for economic information by Engel et al.[6] based the diagnosis of CAP on the actual clinical results not on criteria developed in a laboratory. They also obtained medical records from both a secondary and a tertiary hospital setting allowing their results to represent a large percentage of the population. The UAT examination was completed as an addition to routine analysis for diagnosis and as a result more influence in decision making may have been garnered from its results, as it may receive more attention compared to routine testing protocols without the additional analysis. Also, positive pneumococcal UAT could potentially lead to a decrease in the use of other microbial testing, a shorter duration in hospital or a reduction in mortality rates. All of these situations could substantially alter the economic expenditure included in the analysis. Finally, due to the retrospective nature of this investigation, the reason for switching to targeted treatment had to be theorized based upon available evidence as an actual answer from the supervising physicians could not be obtained.

The guidelines that were found were all organized in easy to follow manners and many posed typical questions that clinical professionals would ask and included guidelines formulated to answer these questions. The most detailed publication found in this review was completed by NICE[25] and utilized a PICO framework for inclusion/exclusion of literature. They included guidelines for all aspects of CAP management though the section detailing the use of UAT is brief and lacks detail. It contained an analysis of costs but unfortunately many of the results of the economic evaluation are based on estimates due to the low quality of supporting evidence. The results for the economic findings were based on a systematic search which identified one cohort investigation; randomized trials or additional evidence were lacking. The model used for this evaluation was based on the assumption that each patient suffering from CAP was afflicted with only one pathogen which may not be the real world situation and could have imparted bias in cost analysis. The cost associated with urinary antigen detection also may not fully capture the benefits that are imparted as SP is susceptible to empirical treatment which means that there is no decrease in mortality as is assumed when using targeted treatment.

The guideline produced by Woodhead et al.[12] is limited in that they did not include any discussion of potential conflicts of interest for their contributing members. In addition they did not discuss any cost implications for the implementation of any portion of their recommendations. They have also not mentioned how the use of UAT may be inhibited by any organizational barriers.

The guideline by the Government of New South Wales[14] is limited in that they did not include any conflict of interest statement and did not include the level of supporting evidence for each section of their analysis. In addition the search terms and databases used to capture publications have not been provided. This limitation was also found for three more of the guidelines.[4,11,26] In the document from Harris et al.[11] the total number of studies retrieved from the initial search is provided but no further detail is given. Finally the guideline from Harris et al.[11] used statements throughout the body of their document such as “severe pneumonia” but no qualifying description of it is provided leaving these statements open to interpretation.

Summary of Findings

Clinical effectiveness of the streptococcal antigen test for the detection of pneumonia in pediatric and adult patients

The HTA[8] included one systematic review which analyzed 24 studies found between 1950 and 2007. This study focused on patients with human immunodeficiency virus and resulted in a sensitivity of 74% and a specificity of 94%, 95% confidence intervals (CI) were 72-77%, and 93-95% respectively. They also determined that the use of BInaxNOW-SP increased the etiologic diagnosis by 23% with a range of 10-59%. They also examined two randomized controlled trials that contained a total of 480 patients. When comparing targeted treatment (as a result of BinaxNOW-SP) to empirical treatment one investigation found no statistically significant difference in the clinical outcomes or adverse events though more relapses were found in the targeted treatment group. The other study found that there was no significant difference in the length of hospital stay or the intention to treat between the groups though a non-significant increase in deaths was found in the empirically treated group. Six observational studies were included and two of them were unable to detect any modification in the treatment that was prescribed as a result of the BinaxNOW-SP UAT. The third study demonstrated mixed results where, of the 58 patients with positive UAT testing, 38% were changed to targeted therapy however none of these three studies included interventions with the purpose of modifying physician behavior. In another two of these studies when treatment was changed to a more targeted regimen no beneficial treatment response was found compared to patients who remained on their original regimens. In summary, from these six studies, a positive UAT resulted in the use of targeted treatment in only a minority of patients and this change did not appear to improve clinical outcomes.

There were 27 diagnostic studies included in the HTA and the average age of the patient population ranged from 43 to 79, with either class IV or V using the pneumonia severity index (PSI). Investigators found a large degree of heterogeneity in credible intervals (CrI) for predicted sensitivity which averaged at 74.3% with 95% CrI of 48.8-90.9%. The pooled sensitivity and specificity for reference standards was broken down into three groups:

- Group A: positive sputum Gram-stain or positive blood/sputum/other culture
- Group B: positive sputum Gram-stain or positive blood/sputum culture
- Group C: positive blood culture alone

The average sensitivity, specificity and 95% confidence intervals for the three reference groups were:

	Sensitivity	Specificity
Ref A	59.4% (43.9-76.3)	98.6% (95.1-99.8)
Ref B	56.2% (35.9-80.5)	97.4% (93.8-99.4)
Ref C	50.3% (24.6-78.8)	98.3% (91.2-99.8)

In order to further analyze this heterogeneity the authors conducted a meta-analysis that separated diagnostic from etiologic studies, prospective from retrospective, and studies conducted in North America from Europe, but no reduction in heterogeneity was found. They also examined the effect of prior antibiotic use prior to UAT on the average severity of pneumonia. This did not show any statistically significant result. As a result of these findings the

authors concluded that no evidence could be found indicating that the use of the BinaxNOW-SP influenced clinical decision making. They also state that it should not be used in routine procedures for CAP.

The systematic review completed by Horita et al.[5] included 10 publications and a total of 2315 patients. When sensitivity was examined using a fixed effects model meta-analysis the pooled results was 0.75 (95% CI 0.71 to 0.79). Authors here also analyzed for two different types of specificity. The specificity of "other" was used for patients with pneumonia from identified other etiologies. The second one was used for the specificity of patients with unknown etiology combined with those of other. This group was called "unknown and other". No heterogeneity was detected (I^2 = 9.0%, P for chi square =0.359). The specificity of the 'other' grouping using a fixed effects model gave a pooled result of 0.95 (95% CI 0.92 to 0.98) and no heterogeneity (I^2=20.5%, P for chi-square = 0.279). The specificity for the 'unknown and other' grouping using a fixed effects model meta-analysis gave pooled results of 0.80 (95% CI 0.78 to 0.82) and moderate to significant heterogeneity (I^2=59.7% P for chi-square=0.008).

Using a random effects model, the pooled sensitivity was 0.75 (95% CI 0.70 to 0.80) and no heterogeneity (I^2=1.7% P for chi-square=0.42). Using this same model for the 'other' grouping resulted in 0.95 (95% CI of 0.92 to 0.99) and no heterogeneity (I^2=4.6% P for chi-square=0.387). Finally, for the 'unknown and other' grouping the pooled result was 0.81 (95% CI of 0.77 to 0.84) with no heterogeneity (I^2=0% P for chi-square=0.450). The authors concluded that the UAT procedures utilized here will be very useful in ruling out *S. pneumoniae* as opposed to ruling it in.

All of the non-randomized studies found for this question support the conclusions made by the two systematic reviews to varying degrees. In the investigation by Molinos et al.[21] the overall sensitivity for UAT was 60% in patients with confirmed or probable CAP, was 68% in definitive CAP, and was 44% in probable CAP and the specificity was 99.7%. In total, 20.9% (916) of the investigated cases were caused by CAP, 653 of which were detected using UAT, 167 using blood culture, 66 by sputum culture, 5 by tracheal aspirate and 3 by bronchoalveolar lavage. This indicates that UAT was successful in identifying 71% of the CAP cases that were found while the combined percentage using the other methods was successful in 29%. Several variables were found to be highly associated with a positive UAT result. These were examined using models adjusted for logistic regression and resulted in female sex, heart rate ≥125 bpm, systolic blood pressure ≤90mmHg, saturated oxygen <90%, absence of antibiotic treatment before admission, pleuritic chest pain, chills, pleural effusion, and BUN ≥30mg/dl were all significant. The authors made three conclusions; firstly that SP was the predominant agent causing CAP, secondly that 71% of diagnoses in cases of pneumococcal pneumonia can be determined using UAT and if Gram stain and culture are used alone this number would be 29%, and finally that the main predictors of use for clinicians in CAP prognosis are systolic blood pressure ≤90mmHg, saturated oxygen level <90mg/dl and BUN ≥30mg/dl. When only one of these factors is present the probability of pneumococcal CAP is low but when 6 or more are present the probability increases to 52%.

The investigation by Chen et al.[13] examined how antibiotic use would affect the results from UAT. They gathered 487 consecutive patients admitted to hospital with CAP and divided them into two groups; those with samples collected before antibiotic treatment and those collected after. A total of 295 (60.6%) of the patients had antibiotics before sample collection. In group one, 99 of the 192 cases were able to determine the etiology of the infection and of these 50 were definite and 49 were probable. In group two, 70 definite results were obtained and 73

probable. These results indicated that there was no significant difference in the positive rates between groups that were collected prior or post antibiotic treatment (P>0.05). However, the positive rate of SP by culture decreased while the positive culture rate of Gram negative bacilli increased in culture methods. UAT detected 21 of 192 (10.9%) patients infected by SP in group 1 and 39 of 295 (13.2%) in group 2 and again positive rates were not statistically different (P>0.05). However, positive rates of culture methods for SP were different. For blood and pleural fluid there was a decline from 5.7% to 2.7% and sputum decreased from 16.2% to 9.2% after antibiotic treatment. It was also found that the positive rate of UAT detection has no relationship to time of antibiotic treatment as opposed to culturing. Authors concluded that UAT retains good sensitivity for the diagnosis of CAP in adults after empiric treatment and it may provide good guidance to narrow the spectrum of treatment options.

Zalacain et al.[22] found that the most common serotype found in patients who are negative for UAT is 1 while the most common in positive patients is 3 (P=0.006 and P=0.004, respectively). In the UAT positive group, serotypes 6A, 6B, 9N, 19E, 19A and 23F were more common than in the negative group (36.9% versus 18.5%, P=0.05). In the UAT negative group, serotypes 7E, 8, 4 and 5 were more prevalent (49.2% versus 29.4%, P=0.003). Patients who were antigen positive had higher rates of intensive care admission, invasive mechanical ventilation, treatment failure, adverse outcomes and 30 day mortality. The odds ratios for ICU admission (1), treatment failure (2) and adverse outcome (3) were:

1: OR=2.6, 95% CI 1.1-6.0, P=0.025
2: OR=3.2, 95% CI 1.2-9.2, P=0.023
3: OR=3.3, 95% CI 1.2-9.2, P=0.023

The use of Kaplan-Meier calculation demonstrated that 30 day mortality was more likely in the UAT positive group (P=0.036). The overall sensitivity of UAT was 74.6% in these bacteraemic cases. These outcomes indicate that patients with positive UAT results have a poorer prognosis which may be due to the serotypes responsible for the disease. UAT was not found to be influenced by any of the factors examined here and authors recommended that its use be adopted into routine practice.

Huijts et al.[16] included 1095 patients (9.9%, 22.1%, 23.0%, 34.6% and 10.4% in categories I-V respectively using PSI scoring). It was possible to identify the etiology of 403 cases (36.8%) when methods that included UAT were utilized. When the novel UAD test was included in these diagnoses, a total of 493 (45%) of cases could be determined. The proportions of episodes of pneumococcal CAP were 23.5% (257) and 32.6% (357) with and without UAD respectively. This indicates a relative increase in diagnostic yield of 39% and an absolute increase of 9.1% with UAD use. In total, 249 (22.7%) UAD tests and 211 (19.3%) UAT tests were positive in the population and of this 249 positive UAD tests, 122 were UAT negative. There were 49 bacteraemic isolates that belonged to one of the 13 serotypes that the UAD test focuses on, of which 48 were detected by the UAD. Therefore the sensitivity was 98%. Standard UAT detected 34 of these 49, therefore its sensitivity was 69.4%. These results led the authors to conclude that the addition of UAD testing into standard methods will increase the proportion of SP diagnosed from 23.3% to 32.6%.

Cheong et al.[23] found that the average duration of fever was 4 days for patients in group 1, 6 days for group 2 and 3, and 8 days for group 4. For group 1, 91% of patients were afebrile within seven days after admission and 95% had fever resolution within ten days. The percentage of fever resolution within seven or ten days in other groups was:

	7days	10days
Group 2	83%	88%
Group 3	68%	87%
Group 4	67%	79%

The average duration of hospital stay was 8.4, 11.4, 10 and 18 days for groups 1 to 4, respectively. Univariate testing using log rank analysis found a statistically significant difference in fever curves for age and bond formation (P=0.0281 and P=0.0234, respectively). Cox regression showed that the likelihood of reaching an afebrile stage was 1.673 and 1.663 times more likely in groups 1 and 2 versus 4, respectively. The positive blood culture rate was 4% and was 12.2% for sputum cultures. Higher C-reactive protein levels were found in groups 1 and 2. Even though the severity of disease was higher in groups 1 and 2, a much more rapid resolution of fever and shorter hospital stay were found indicating that pneumococcal UAT is of benefit to shorten fever duration.

The first retrospective investigation completed by Choi et al[15] determined that serotype 3 was the most common found in CAP cases (14.2%) followed by 19A (11.1%), 11A/11E (10.8%) and 19F (9.3%). Using conventional investigation, SP was diagnosed in 191 cases (8.6%) and an additional 85 cases (3.8%) when UAT was added. When the temporal shift in UAT was examined, it was determined that it significantly increased over a time between 2007 and 2013 with a spike between 2012 and 2013. The UAT positive rates according to time period were:

53.4% (94 of 176 cases) in 2007-2009
51.1% (70 of 137 cases) in 2010-2011
66.1% (84 of 127 cases) in 2012-2013

No significant difference was found between 2007-2009 or 2010-2011 (P=0.648) though between 2007-2009 and 2012-2013 a statistically significant difference was detected (P=0.026). The proportion of PCV13 serotypes decreased in 2012-2013 compared to 2007-2009 though it was not statistically significant (P=0.067). After PCV13 introduction, serotype 6A, 19F and 23F decreased while 6C increased and serotypes 3 and 19A were isolated across all time points. The positive rate of UAT varied depending on the serotype that was encountered:

Serotype	Rate of detection
3	50%
9V/9A	83.3%
11A/11E	59.1%
14	36.3%
19A	50%
19F	46%
20	75%
23F	37.5%
4	40%
Non-typeable	55.3%

The positive rate of UAT was 49.2% in PCV13 serotypes and 53.3% in others, which did not reach statistical significance (P=0.518). When the utility of UAT was analyzed among the 440 of 599 cases that underwent UAT pneumococcal antigen was detected in 248 of the 440 cases (56.4%). The patients that were UAT positive had higher C-reactive protein than those with

negative results (P=0.007) and no difference in procalcitonin. In addition cases of lobular pneumonia and diabetes had significantly higher UAT positive rates (P=0.006 and P=0.034, respectively). Multivariate analysis of lobular pneumonia had an odds ratio of 1.78 (95% CI 1.046 to 3.034), and C-reactive protein odds ratio of 1.002 (95% CI 1.000 to 1.005) and the authors concluded a statistically significant association with differences in UAT positive rate, though the confidence interval includes unity. The authors concluded that UAT will increase the diagnostic yield and that these results are dependent on the serotype that is encountered. They further stated that with the introduction of the PCV13 vaccine, the etiology of pneumococcal pneumonia may be changing and therefore the clinical effectiveness of UAT needs to be monitored.

The final study of clinical effectiveness was a retrospective analysis completed by Shen et al.[24] They found that there was no significant difference in the demographics of the three groups included in their study. These groups were formed based on the urinary antigen reactivity score which was calculated based on the time to reach a positive band during the UAT and the intensity of the band. Group 1 had a score of 8, group 2 had a score of 5 to 7 and group 3 had a score of 2 to 4. Patients in group one had significantly more respiratory distress (P=0.01), oxygen desaturation (P=0.04), febrile days (P=0.03), pulmonary conditions (P=0.01), bacteraemia (P=0.01), length of hospital stay (P<0.001), higher intensive care need (P=<0.001) and lower white blood cell count (P=0.01). Pleural effusion was found to be higher in groups one and two than in three (P=0.05). Children with the lowest white blood cell count scores had the highest scores on UAT and also had higher proportion of immature cells. Authors concluded that pneumococcal UAT is a useful tool for the evaluation of CAP and that predicting its severity may prove useful as an independent predictor of severity, hospitalization and prognosis

Cost-effectiveness of the streptococcal antigen test for the detection of pneumonia in pediatric and adult patients

The HTA found for this question found one study of 122 patients that fit the inclusion criteria of their review. The cost for treatment was divided into targeted treatment (using amoxicillin three times daily or penicillin G six times daily) and empirical treatment. When targeted therapy expenses were compared to the most expensive empirical regimen the savings per patient were €19.85 for amoxicillin and €8.11 for penicillin G. When targeted therapy was compared to an average cost empirical treatment there was an additional cost of €8.56 for amoxicillin and €20.30 for penicillin G. Therefore authors conclude that the use of BinaxNOW-SP did not offer any cost savings.

In the retrospective analysis conducted by Engel et al.[6] the treatment decision to switch to targeted treatment resulted in a total of 293 fewer days of treatment. The cumulative cost for pneumococcal UAT in CAP was €43,613 (€22.87 per test for 1907 tests). The cumulative savings due to cheaper targeted treatment were €5090. The cost of one targeted treatment day gained was €131 (calculated from €43,613-€5090/293 days) though this amount varied between the hospitals that were examined (€257 University Medical Centre Utrecht and €72 Diakonessen Hospital). When handling costs for preparation and drug administration were included, it resulted in a modest decrease (from €131 to €126 per targeted treatment day). The direct pneumococcal UAT cost was €20 per CAP case and €514 per case receiving targeted treatment. Secondary analysis examined all pneumococcal UATs including those in non-CAP patients, children, and trial runs in order to give a more realistic analysis of what a real world clinic would exhibit. The cumulative testing cost of this secondary analysis resulted in a cost of €79,565 for pneumococcal UAT in CAP and €254 per targeted treatment dat. This number

again showed variation between the hospitals that were included (€522 at UMCH and €128 at DH). The direct cost was €39 per pneumococcal UAT and €993 per case receiving targeted treatment. Authors concluded that improving the selective use of pneumococcal UAT in hospitalized CAP patients may lead to increased cost efficiency.

Evidence-based guidelines associated with the use of the streptococcal antigen test for the detection of pneumonia in pediatric and adult patients

For the purposed of this review only the sections pertaining to urinary antigen testing are included

The six guidelines included in this review provided recommendations for either children or adult patients. Three of them focused on children.[11,14,26] The first of these was produced by the Government of New South Wales[14] were focused children <16 years old and were intended for use by medical professionals. The recommendations for UAT are provided for moderate to severe CAP only. They are state that urine should not be taken for pneumococcal antigen testing as specificity is less than optimal. This is a result of high false positive rates as a result of nasopharyngeal pneumococcal colonization. The remaining two guidelines both make similar recommendations. The publication by Bradley et al.[26] expands on this by stating that microbiologic investigations should only be conducted in children with severe pneumonia that is sufficient enough to require admission into pediatric care wards or those that have severe complications of CAP. They recommend that these approaches should not be completed in routine diagnosis of children with milder cases or those not admitted. The guidelines state that these testing methods should include blood culture, nasopharyngeal secretions and/or nasal swabs with PCR and/or immunofluorescence, acute and convalescent serology for respiratory viruses *Mycoplasma* and *Chlamydia*. They state that pleural fluid should be analyzed by microscopy/culture/pneumococcal antigen and/or PCR, and that urinary pneumococcal antigen detection should not be done in young children.

The remaining three guidelines focused on adult patients. In the publication by Woodhead et al.[12] the recommendations for CAP for patients with medium to high disease severity include the use of blood/sputum cultures and consideration of pneumococcal and legionella urinary antigen testing. Processes for the diagnoses of these tests, including x-rays, were recommended and treatment of CAP was recommended within four hours of presentation into hospital. They stated that the routine use of these analyses should not be completed in the routine management of patients with low severity CAP. The recommendations by Spindler et al.[4] stated that microbiological investigations are important for the introduction of targeted therapy and state that in patients with severe cases, extensive investigations should be used while less severe conditions are based on clinical presentation, epidemiological risk factors and previous antibiotic treatment. Blood, sputum and nasopharyngeal cultures were recommended. The guideline recommended that pneumococcal urinary antigen testing should include the rapid use of a test such as the BinaxNOW-SP which will increase the diagnostic yield of these infections. Previous evidence has shown that this testing has a 79% sensitivity compared with blood culture and 54% compared to blood and respiratory cultures. This indicates that a negative result will not rule out the possibility of SP infection. This investigation was recommended for all levels of pneumonia severity. Authors also cautioned that a positive result has the potential to remain positive for several weeks and may therefore be misleading in following pneumonia cases that are a result of a different microbe. Finally the guidelines produced by the National Institute for Health and Care Excellence[25] included a section of urinary antigen testing. Antigen testing such as immunochromatographic urinary antigen tests for SP was recommended for admitted

patients for determination of illness severity. This testing was recommended to be considered when a pleural fluid sample is obtained in the setting of parapneumonic effusion.

Limitations

This review was limited in than a low level of information could be found for the investigation of an economic evaluation. Two studies were identified to inform this question. The first was an HTA that was well developed but was limited by a lack of evidence as a single economic study could be identified. The second study was a retrospective investigation which may have led to underestimates in the costs of standard reference testing.

For the examination of the clinical effectiveness of UAT conflicting results were found depending on the source for the information. The HTA that was included contained an extensive analysis of existing literature and determined that the use of the BinaxNOW-SP UAT was not recommended as no defined benefit could be proven for patients. They therefore recommend that this testing method should not be included in routine testing procedures. The non-randomized studies were unanimous in their support of the benefits to diagnosis and increased sensitivity and specificity when using pneumococcal UAT unfortunately they are all either prospective or retrospective cohort examinations and therefore are of a lower methodological design. No true randomized controlled trials could be found to answer this question.

The guidelines included were generally well written and contained extensively researched investigations to produce the best possible recommendations. Unfortunately in one publication no discussion of the strength of the supporting evidence is provided therefore the reliability of the recommendations is unclear. In addition this guideline did not provide the literature search terms or the databases that were used for the study extraction. This problem was also found for three of the other guidelines where either search terms or number is included publications is not provided. The assessment produced by Harris et al.[11] also included terms such as “severe pneumonia” but no classification scheme is provided in order to provide a clear definition. Finally, the majority of these guidelines only included brief mention of the use of UAT and lacked specific detail.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

The evidence found regarding the clinical effectiveness of streptococcal antigen testing indicates that it is a sensitive and highly specific method of diagnosis. This conclusion must be approached with caution as a wide degree of heterogeneity in the results was encountered. In addition evidence has demonstrated that the sensitivity will vary depending upon the serotype of the pneumococcus that is encountered. A limited amount of evidence was found regarding costs, and the two studies that were included had differing conclusions. The HTA found that there was not enough evidence to support any cost savings incurred by UAT while the retrospective analysis indicated that with appropriate selection and use procedures the possibility of cost savings was evident.

The guidelines found for inclusion in this review recommended that UAT not be completed in children as the risk of false-positives in this population is high. In addition the use in adults was only recommended for patients that are admitted into hospital and have moderate or severe pneumonia. The use of UAT in patients with mild cases of pneumonia and those who are not admitted was not recommended.

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REFERENCES

1. Sinclair A, Xie X, Teltscher M, Dendukuri N. Systematic review and meta-analysis of a urine-based pneumococcal antigen test for diagnosis of community-acquired pneumonia caused by Streptococcus pneumoniae. J Clin Microbiol [Internet]. 2013 Jul [cited 2015 Oct 22];51(7):2303-10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3697702

2. Marrie TJ, Tuomanen EI. Pneumococcal pneumonia in adults. 2014 Sep 22 [cited 2015 Nov 2]. In: UpToDate [Internet]. Waltham (MA): UpToDate; c2005 - . Available from: www.uptodate.com Subscription required.

3. Loeb M. Community-acquired pneumonia. BMJ Clin Evid [Internet]. 2010 [cited 2015 Nov 2];1503. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3275325

4. Spindler C, Stralin K, Eriksson L, Hjerdt-Goscinski G, Holmberg H, Lidman C, et al. Swedish guidelines on the management of community-acquired pneumonia in immunocompetent adults--Swedish Society of Infectious Diseases 2012. Scand J Infect Dis. 2012 Dec;44(12):885-902.

5. Horita N, Miyazawa N, Kojima R, Kimura N, Inoue M, Ishigatsubo Y, et al. Sensitivity and specificity of the Streptococcus pneumoniae urinary antigen test for unconcentrated urine from adult patients with pneumonia: a meta-analysis. Respirology. 2013 Nov;18(8):1177-83.

6. Engel MF, van Velzen M, Hoepelman AI, Thijsen S, Oosterheert JJ. Positive urinary antigen tests for Streptococcus pneumoniae in community-acquired pneumonia: a 7-year retrospective evaluation of health care cost and treatment consequences. Eur J Clin Microbiol Infect Dis. 2013 Apr;32(4):485-92.

7. Postma DF, van Werkhoven CH, Huijts SM, Bolkenbaas M, Oosterheert JJ, Bonten MJ. New trends in the prevention and management of community-acquired pneumonia. Neth J Med [Internet]. 2012 Oct [cited 2015 Oct 22];70(8):337-48. Available from: http://www.njmonline.nl/getpdf.php?id=1218

8. Sinclair A, Xie X, Dendukuri N. The clinical effectiveness and cost of a pneumococcal urine antigen immunochromatographic test (BinaxNOW Streptococcus pneumoniae) in the diagnosis of community acquired Streptococcus pneumoniae pneumonia in patients admitted to hospital [Internet]. Montreal: McGill University Health Centre; 2012 Jan 31. [cited 2015 Nov 2]. (Report no. 57). Available from: https://www.mcgill.ca/tau/files/tau/muhc_tau_2011_57_binaxnow.pdf

9. Deng X, Church D, Vanderkooi OG, Low DE, Pillai DR. Streptococcus pneumoniae infection: a Canadian perspective. Expert Rev Anti Infect Ther. 2013 Aug;11(8):781-91.

10. Said MA, Johnson HL, Nonyane BA, oria-Knoll M, O'Brien KL, AGEDD Adult Pneumococcal Burden Study Team, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. PLoS ONE [Internet]. 2013 [cited 2015 Nov 2];8(4):e60273. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3615022

11. Harris M, Clark J, Coote N, Fletcher P, Harnden A, McKean M, et al. British Thoracic Society guidelines for the management of community acquired pneumonia in children: update 2011. Thorax. 2011 Oct;66 Suppl 2:ii1-23.

12. Pneumonia in adults: diagnosis and management [Internet]. London: National Institute for Health and Care Excellence; 2014 Dec. [cited 2015 Nov 2]. (NICE guidelines [CG191]). Available from: http://www.nice.org.uk/guidance/cg191/

13. Chen M, Zhou M, Xiao W, Ai B, Liu X, Li Y. The urinary antigen tests have high sensitivity in diagnosis of Pneumococcus caused community-acquired pneumonia posterior to antimicrobial therapy. Cell Biochem Biophys. 2014 Nov;70(2):1029-34.

14. Infants and children: acute management of community acquired pneumonia. Clinical Practice Guideline [Internet]. North Sydney (AU): Government of New South Wales; 2015 Mar 19. [cited 2015 Nov 2]. Available from: http://www0.health.nsw.gov.au/policies/gl/2015/pdf/GL2015_005.pdf

15. Choi MJ, Song JY, Cheong HJ, Jeon JH, Kang SH, Jung EJ, et al. Clinical usefulness of pneumococcal urinary antigen test, stratified by disease severity and serotypes. J Infect Chemother. 2015 Sep;21(9):672-9.

16. Huijts SM, Pride MW, Vos JM, Jansen KU, Webber C, Gruber W, et al. Diagnostic accuracy of a serotype-specific antigen test in community-acquired pneumonia. Eur Respir J. 2013 Nov;42(5):1283-90.

17. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol [Internet]. 2007 [cited 2015 Nov 4];7:10. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1810543/pdf/1471-2288-7-10.pdf

18. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health [Internet]. 1998 Jun [cited 2015 Nov 4];52(6):377-84. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1756728/pdf/v052p00377.pdf

19. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011 Oct 18;155(8):529-36.

20. Appraisal of guidelines for research & evaluation. AGREE II instrument [Internet].AGREE Trust; 2009 May [cited 2015 Nov 4]. Available from: http://www.agreetrust.org/wp-content/uploads/2013/06/AGREE_II_Users_Manual_and_23-item_Instrument_ENGLISH.pdf

21. Molinos L, Zalacain R, Menéndez R, Reyes S, Capelastegui A, Cillóniz C, et al. Sensitivity, specificity, and positivity predictors of the pneumococcal urinary antigen test in community-acquired pneumonia. Ann Am Thorac Soc. 2015 Oct;12(10):1482-9.

22. Zalacain R, Capelastegui A, Ruiz LA, Bilbao A, Gomez A, Uranga A, et al. Streptococcus pneumoniae antigen in urine: diagnostic usefulness and impact on outcome of bacteraemic pneumococcal pneumonia in a large series of adult patients. Respirology. 2014 Aug;19(6):936-43.

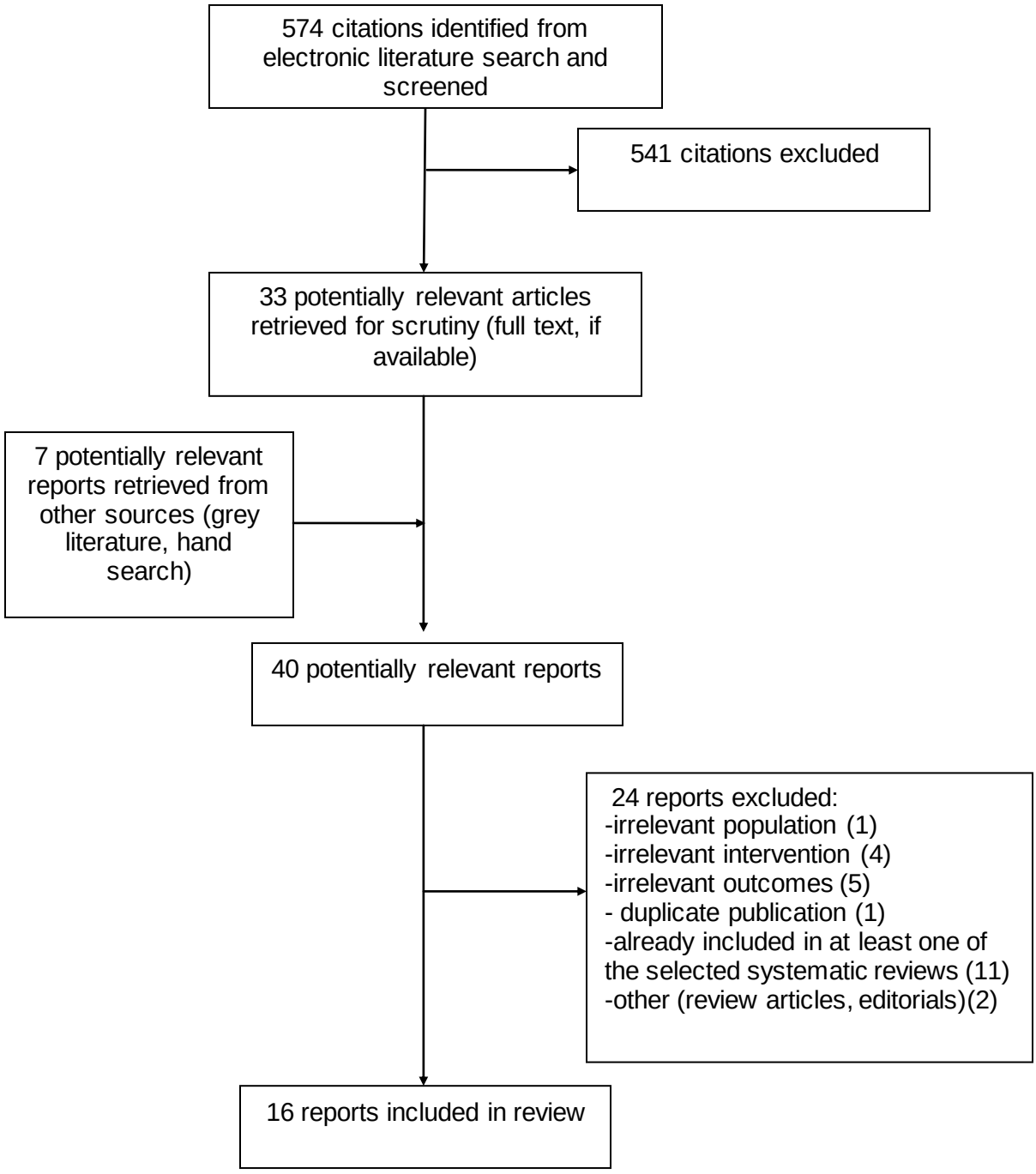
23. Cheong HF, Ger LP, Wu MT, Sun CP, Hsieh KS, Liu YC, et al. Clinical application of the rapid pneumococcal urinary antigen test in the treatment of severe pneumonia in children. J Microbiol Immunol Infect. 2008 Feb;41(1):41-7.

24. Shen CF, Wang SM, Liu CC. A new urinary antigen test score correlates with severity of pneumococcal pneumonia in children. J Formos Med Assoc. 2011 Oct;110(10):613-8.

25. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al. Guidelines for the management of adult lower respiratory tract infections--summary. Clin Microbiol Infect [Internet]. 2011 Nov [cited 2015 Nov 2];17 Suppl 6:1-24. Available from: http://ac.els-cdn.com/S1198743X14614038/1-s2.0-S1198743X14614038-main.pdf?_tid=24580c52-8199-11e5-be84-00000aacb361&acdnat=1446493224_833b8ec6a45beedd27830b6e2ad81f81

26. National Guideline Clearinghouse [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 1997 -. Guideline summary: The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America.; 2011 [cited 2015 Nov 2]. Available from: http://www.guideline.gov/content.aspx?f=rss&id=34433

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Health Technology Assessments and Systematic Reviews

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator	Clinical Outcomes, Goal
Health Technology Assessments					
Sinclair et al.,[8] 2012, Canada	- Published in French or English - Searched the Cochrane Collaboration, the Centre for reviews and Dissemination of the University of York, the International Network of Agencies for Health Technology Assessment, the Canadian Agency for Drugs and Technology in Health and EMBASE - Search for literature conducted on: clinical practice	- Patients included must be ≥14 years old	- Use BinaxNOW-SP - Samples must be taken within 48 hours of admission - Urinary analysis completed on unconcentrated urine	- Must analyze a blood culture along with one or more of the following: pleural fluid culture, stain and culture of sputum, sampling from respiratory tract	- Used Bayesian bivariate diagnostic meta-analysis to describe sensitivity across studies - Conduct a meta-analysis of the three groups of studies as defined by three classes depending on standards used: • Ref A – positive sputum Gram stain or positive blood/sputum/or other culture • Ref B – positive Gram Stain or positive blood/sputum culture • Ref C – positive blood culture alone - To investigate the sensitivity and specificity for providing diagnosis with the use of urinary antigen test BinaxNOW-SP at admission to hospital - To provide an estimation of the cost effectiveness and the impact of BinaxNOW-SP and other currently used techniques for analysis of CAP

Table A1: Characteristics of Included Health Technology Assessments and Systematic Reviews

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator	Clinical Outcomes, Goal
	using BinaxNOW-SP, specificity/sensitivity for BinaxNOW-SP versus standard techniques				
Systematic Reviews					
Horita et al.,[5] 2013, Japan	- 195 articles retrieved from literature search and 10 met inclusion criteria (7 prospective and 3 retrospective investigations) - 2 investigators independently search publications from MEDLINE and Cochrane databases up to December 2012 - Search terms: Binax, urine antigen, pneumonia, pneumococcus, sensitivity and specificity	- Adults >15 years **old** that have pneumonia	- Use BinaxNOW-SP on unconcentrated urine	- No restrictions applied	- Analyze for sensitivity and specificity - Sensitivity analyzed using pooled results from all studies and fixed or random meta-analysis models - Pooled specificity was examined in 2 ways; first by grouping patients with etiology identified as other, and secondly with a grouping that includes the other group outlined above combined with patients of unknown etiology - To assess the sensitivity and specificity of SpUAT for unconcentrated urine from adult patients with pneumonia

Table A1: Characteristics of Included Health Technology Assessments and Systematic Reviews

First Author, Publication Year, Country	Types and numbers of primary studies included	Population Characteristics	Intervention	Comparator	Clinical Outcomes, Goal
	- Must be published in English - Include both prospective and retrospective analysis - Exclude if use only history, physical examination or x-ray as a reference, if used nasopharyngeal culture for diagnosis or if the study was conducted on both adults and children but the data could not be separated				

Table A2: Characteristics of Non-Randomized Studies

First Author, Publication Year, Country	Study Design, Inclusion/Exclusion Criteria, Goal	Patient Characteristics (n)	Intervention	Comparator	Clinical Outcomes
Prospective Cohort Investigations					
Molinos et al.,[21] 2015, Spain	- Patients recruited from 13 Spanish hospitals between November 2005 and November 2007 - All patients had chest x-ray and grade severity using PSI and CURB-65 - On admission blood culture and serum are analyzed and urine sample taken (if possible obtain sputum sample) - Convalescent serum sample takes 4-6 weeks after admission - If patient is intubated obtain respiratory secretions and pleural fluid - CAP present if: 1) isolates found in blood or pleural fluid (2) was a ≥4 fold increase in antibody titers between acute and convalescent serum	- Included 4374 patients, 2859 men average age 66 (±18) years - Exclude patient if immunosuppressed, had tuberculosis, or had a previous diagnosis of pneumonia within last three months	- BinaxNOW-SP conducted on unconcentrated urine sample obtained at admission to hospital	- Blood culture, serum analysis, sputum culture, respiratory aspirate and pleural fluid	- Sensitivity and specificity of UAT - Used t-test to compare means and Mann-Whitney U-test where variables showed non-normal distribution - Pearson chi-square test used to compare qualitative variables and Fisher's exact test when necessary - Odds ratios used throughout with two-tailed analysis

Table A2: Characteristics of Non-Randomized Studies

First Author, Publication Year, Country	Study Design, Inclusion/Exclusion Criteria, Goal	Patient Characteristics (n)	Intervention	Comparator	Clinical Outcomes
	phases (3) UAT positive (4) likely pathogen found in bronchial aspirate or lavage - To analyze the sensitivity and specificity of UAT in the largest series of cases conducted to date and use regression calculations to analyze predictors of positive CAP patients in hospital on more than 4000 patients. In addition to develop a probabilistic model for use of UAT testing				
Chen et al.,[13] 2014, China	- Include consecutive patients from the Department of Respiratory Medicine at First Affiliated Hospital of Yangtze University - Divide patients into 2 groups: 1) specimen collected before	- Adult patients between 15-97 years old - Population included 309 males and 178 females - Pneumonia defined by the progression of	- Use BinaxNOW-SP on unconcentrated urine samples	- Collect 2 blood samples and 1 sputum sample (if patient able to produce) - Samples such as pleural fluid, nasopharynge	- Sensitivity and specificity , positive predictive values of UAT were calculated using standard formulae - Analyze for means or proportions as deemed appropriate

Table A2: Characteristics of Non-Randomized Studies

First Author, Publication Year, Country	Study Design, Inclusion/Exclusion Criteria, Goal	Patient Characteristics (n)	Intervention	Comparator	Clinical Outcomes
	antibiotic treatment (2) specimen collected after antibiotic treatment - To analyze the clinical effectiveness of ICT urinary antigen assay for the diagnosis of *S. pneumoniae* caused by CAP in adults after they have been treated empirically with antibiotics	infiltrates on chest x-ray and at least 2 symptoms of: fever, cough, dyspnea, leukocytosis or leukopenia, pleuritic chest pain - Exclude if have immunodeficiency virus, tuberculosis or fungal infection or have had a previous pneumonia diagnosis in the past year		al swab, protected specimen brush and bronchoalveolar aspirate and lavage were collected as needed	
Zalacain et al.,[22] 2014, Spain	- Patients recruited from 2 hospitals in Basque county Spain, Cruces Hospital and Galdakao-Usunsolo Hospital between 2002 and 2010 - Divide patients into two groups: UAT positive and UAT negative - Assess severity using	- All patients>18 years old and admitted for bacteraemic pneumococcal pneumonia - Exclude if immunodeficient or if had pneumonia within previous three months or if have	- BinaxNOW-SP conducted on all patients within 24 hours of admission on concentrated urine (25 fold)	- All patients receive 2 blood cultures within 24 hours of admission	- Frequencies, percentages, means, standard deviation, medians and interquartile ranges - Qualitative variables examined using chi-square or Fisher's exact test - Quantitative variables examined using student's t-test or non-parametric Wilcoxon test - Univariate logistic regression

Table A2: Characteristics of Non-Randomized Studies

First Author, Publication Year, Country	Study Design, Inclusion/Exclusion Criteria, Goal	Patient Characteristics (n)	Intervention	Comparator	Clinical Outcomes
	PSI - Examine serotypes: higher mortality 3,6A,6B,9N,19F,19A,23F lower mortality 1,7F,8,4,5 - Cause of illness and outcome analyzed using variables: admission to ICU, use of invasive mechanical ventilization, septic shock, in hospital mortality, treatment failure, adverse outcome, 30 day mortality, length of hospital stay - To determine the effectiveness of urinary immunochromatography in the detection of urinary pneumococcal pneumonia and additionally to examine if the results from this type of testing have any relationship with outcomes	HAP			models compared variables of course and outcome in groups - Multivariate logistic regression adjusted for severity multilobar involvement, previous antibiotic use and current antibiotic treatment usage - Kaplan-Meier survival curves used for in hospital and 30 day mortality of groups and compared using log-rank test

Table A2: Characteristics of Non-Randomized Studies

First Author, Publication Year, Country	Study Design, Inclusion/Exclusion Criteria, Goal	Patient Characteristics (n)	Intervention	Comparator	Clinical Outcomes
Huijts et al.,[16] 2013, The Netherlands	- Patients obtained from 23 Dutch hospitals between January 2008 and April 2009 - Severity analyzed using PSI - Patient demographics obtained along with blood analysis and chest x-ray - Compare results for detection methods with and without addition of UAD Luminex test - True positive for UAD are CAP with bacteraemia caused by one of 13 serotypes - True negatives are CAP with bacteraemia caused by a pathogen not included in the 13 serotypes of the UAD test - To evaluate the clinical effectiveness and utility of a serotype specific UAT for identification of 13 serotypes (CSV!#	- Patients are adults ≥18 years old - 1095 patients included and mean age was 69 years old - Include if present with a clinical suspicion of CAP or LRTI	- UAD for SP serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F (Luminex multiplex urinary antigen test) - All samples taken immediately upon admission up to a maximum of 48 hours afterwards. - Completed on unconcentrated urine	- Standard microbiological investigation included: blood culture, sputum culture, pleural fluid culture (if present) - BinaxNOW-SP UAT - All samples collected immediately after admission up to a maximum of 48 hours afterwards	- Sensitivity and specificity of the UAD Luminex test - Calculate frequency, mean or median and compare between groups using Pearson's chi-square test for dichotomous data and t-test or Mann-Whitney U-test for continuous data

Table A2: Characteristics of Non-Randomized Studies

First Author, Publication Year, Country	Study Design, Inclusion/Exclusion Criteria, Goal	Patient Characteristics (n)	Intervention	Comparator	Clinical Outcomes
	targets) in adult patients with CAP				
Cheong et al.,[23] 2008, Taiwan	- Patients included from Kaohsiung Veterans General Hospital between January 1 to December 31 2004 - Patients graded for severity upon entry based on results from chest x-ray, and consultation with pediatrician and thoracic radiologist - UAT conducted before treatment with antibiotic and those without UAT used as controls - Divided into 4 groups for treatment by separate teams: 1) exam with UAT treated with penicillin G if + and ampicillin-sulbactam or cefuroxamine if – follow guidelines of IDST (2) examine using UAT but did not	- Patients <18 years old admitted with severe pneumonia - Severe pneumonia defined as having symptoms of fever, cough, and the telltale signs on a chest x-ray - Patients must score 4 or 5 on severity scale - Exclude if patient examination did not include x-ray, had no fever and if they were given a macrolide alone - 245 cases met the criteria	- BinaxNOW-SP conducted on unconcentrated urine samples	- Chest x-ray and laboratory tests (these tests are not defined)	- Duration of fever (shorter duration indicates better treatment outcome) - Fever curves calculated using Kaplan-Meier product limit - Univariate analysis of statistical significance between fever subsistence curves of a single variable were analyzed using log-rank testing - Multivariate analysis examined the prognostic significance of UAT use on fever duration with adjustment for age, gender, severity of chest x-ray and band form using Cox regression

Table A2: Characteristics of Non-Randomized Studies

First Author, Publication Year, Country	Study Design, Inclusion/Exclusion Criteria, Goal	Patient Characteristics (n)	Intervention	Comparator	Clinical Outcomes
	follow guidelines for treatment (3) no UAT treat following IDST guidelines for treatment (4) no UAT did not follow IDST guidelines for treatment - To evaluate the efficacy of pneumococcal UAT in severe pediatric pneumonia				
Retrospective Cohort Investigations					
Choi et al.,[15] 2015, Korea	- Examined medical records from a single hospital in Seoul Korea between January 1 2007 to Dec 31 2013 - Reevaluate records to see if they fit criteria for CAP - Completed a retrospective analysis of microbiology using standard methods and pneumococcal UAT - All pneumococcal isolates were tested	- Patients ≥19 years old who had a discharge diagnosis of pneumonia - Include if CAP found to be from pneumococcal infection and include outpatients - Exclude if HAP is cause of infection	- Use BinaxNOW-SP on unconcentrated urine	- Microbiological examination included cultures of sputum and blood, pleural fluid and respiratory virus PCR	- Analyze positive UAT rate in relation to patient age, comorbidities, disease severity and *S. pneumoniae* serotype - Analyze patient demographics such as age, sex, admission date, previous antibiotic usage, smoking, CURB-65 score, 30 day mortality and comorbidities - Use Chi-square and Fisher's exact test for comparison of categorical variables and Student's t-test for

Table A2: Characteristics of Non-Randomized Studies

First Author, Publication Year, Country	Study Design, Inclusion/Exclusion Criteria, Goal	Patient Characteristics (n)	Intervention	Comparator	Clinical Outcomes
	for serotype following standard protocols - To evaluate the amount of pneumococcal pneumonia occurring after the introduction of the PCV13 vaccine in hospital admitted CAP patients and to determine how effective *S. pneumoniae* UAT is for diagnosis. Additionally the ability of UAT to differentiate between age, comorbidities, the severity of disease and the various *S. pneumoniae* serotypes was examined.				continuous variables
Shen et al.,[24] 2011, Taiwan	- Patients obtained from the National Cheng Kung University Hospital from February 2002 to February 2007 - Patients divided into three groups based on time to develop a positive test for UAT 1)	- 119 children with positive pneumococcal UAT - Exclude if nasopharyngeal or sputum culture contained *S. pneumoniae*, if	- Utilized BinaxNOW-SP, unconcentrated urine collected at admission and stored at -20C until testing completed	- All patients screened with blood culture, sputum smear, sputum culture, viral isolation and *Mycoplasma* antibody	- Continuous variables examined using t-test - Categorical variables examined using Pearson's chi-square test - Time to reactive band formation on UAT test determined up to maximum of 15 minutes

Table A2: Characteristics of Non-Randomized Studies

First Author, Publication Year, Country	Study Design, Inclusion/Exclusion Criteria, Goal	Patient Characteristics (n)	Intervention	Comparator	Clinical Outcomes
	total score 8 (2) score 5-7 (3) score 2-4, the score is the sum of the scores at the time of appearance and the intensity of the reactive band - To examine if a urinary antigen reactivity score that is based on the time for the test to become positive and the intensity of the reactive band might be directly associated with the severity of pneumococcal pneumonia	another pathogen than *S. pneumoniae* was isolated from blood or pleural effusion or if patient had a mixed infection		analysis upon admission	- Length of hospital stay and days of fever recorded
Engel et al.,[6] 2013, The Netherlands	- Investigate medical records from 2 Dutch Hospitals where pneumococcal UAT was conducted between May 2005 and September 2011 - Include costs of methods and antibiotics in calculations - Determination of	- Patients must be ≥18 years old and have CAP infection where UAT was used in the diagnosis - Exclude if analysis completed on children, were not completed on CAP or suspected	- Used UAT BinaxNOW-SP	- Empirical antibiotic treatment	- Secondary analysis of all UATs including non-CAP patients, children and trial runs - Primary analysis is on percentage of patients with positive UAT result receiving targeted treatment due to UAT - Analyze cost per day where broad-spectrum antibiotics were saved from use due to

Table A2: Characteristics of Non-Randomized Studies

First Author, Publication Year, Country	Study Design, Inclusion/Exclusion Criteria, Goal	Patient Characteristics (n)	Intervention	Comparator	Clinical Outcomes
	targeted treatment due to UAT: if switch to targeted treatment occurs after positive UAT but before positive culture or positive UAT is obtained before a negative culture result - Costs calculated using 2012 tariffs	CAP, were trial runs, had intermediate results and had negative results on UAT			targeted treatment - To estimate the cost of UAT from a hospital perspective and determine if a positive result leads to targeted treatment of patients hospitalized with CAP

Table A3: Study Characteristics of Guidelines

First Author, Publication Year, Country	Target Audience and Scope	Included Study Designs	Number of Studies Included and Databases Examined
Government of New South Wales.,[14] 2015, Australia	- Applicable to all institutions where paediatric patients are taken care of - For use by chief executive medical care professionals - To give medical professionals direction to provide the best possible guidelines for the paediatric care of patients afflicted with CAP	- No limits places on study design - Population if children <16 years old who have CAP	- Included 31 publications - Databases examined are not provided nor are search terms used for investigation - Exclude if is on sepsis, immunocompromised patients, HAP, herpes simplex virus, patients have congenital heart or lung conditions, tuberculosis, patients are premature babies not yet reached term, or have non-cystic fibrosis or have aspirated foreign body and/or gastric contents.
Woodhead et al.,[12] 2014, United Kingdom	- Applicable to ~80% of patients with CAP or HAP who are adults ≥18 years old with suspected or confirmed CAP or HAP - To focus on areas of uncertainty and variable practice - To provide the best clinical practice guidelines on both diagnosis and management of CAP and HAP which are formulated from investigations on scientific data and economic evaluation to reduce both the mortality and morbidity of pneumonia	- Used PICO framework to analyze studies - Limited to English - Include RCT, non-randomized studies, observational studies - Economic evaluations rejected if only reported cost per hospital instead of per patient, if only included average cost effectiveness without disaggregated cost effects, - Exclude literature reviews, abstracts, posters, reviews, letters, editorials, comment articles and unpublished studies	- Searched MEDLINE, EMBASE, The Cochrane Library, the NHS Economic Evaluation Database, the Health Economic Evaluations Database, and Health Technology Assessment databases with no date restrictions

Table A3: Study Characteristics of Guidelines

First Author, Publication Year, Country	Target Audience and Scope	Included Study Designs	Number of Studies Included and Databases Examined
Spindler et al.,[4] 2012, Sweden	- Healthcare providers managing patients with CAP in a hospital setting - Guidelines intended for the in-hospital treatment of adult non-immunocompromised patients with CAP	- Published in English and conducted on humans - Must have an available abstract - No limits placed on specific study type	-Total of 5386 articles found during literature search, 500 deemed relevant for inclusion -Searched MEDLINE using keywords: explode pneumonia or empyema or lung abscess or pulmonary infection or chest infection or respiratory tract infection NOT child or children or childhood or infant or paediatric or tuberculosis or in vitro or acquired immunodeficiency system or review -Limited to publication between September 2003 and July 2010
National Institute for Health and Care Excellence.,[25] 2011, United Kingdom	- This is an update to a guideline published in 2005, includes new evidence from recent publications - To provide evidence-based recommendations for the most common management questions occurring in routine clinical practice in the management of adult patients with lower respiratory infections	- Included the same search filters as the 2005 guideline	- Used same search filter at the 2005 guideline - Retrieved 15,261 articles published between July 2002 and May 2010, after analysis 1677 were included
Harris et al.,[11] 2011, United Kingdom	- To provide evidence-based recommendations for the management of CAP in children - Target population is infants (1-23 months old) and children (2-12 years old)	- Publication In English - No limits placed on study type	- Searched EMBASE, The Cochrane Library and MEDLINE - Retrieved 2587 publications published between 2000 to July 2010
Bradley et al.,[26] 2011, United States of America	- Clinical healthcare providers dealing with in and outpatient CAP patients - To provide guidance on the care of otherwise healthy infants and children and to address practical questions of diagnosis and management of CAP evaluated in outpatient or inpatient settings in the	- No limits placed on study type - Included professional meetings and existing guidelines on paediatric CAP	- Examined PubMed up to May 2010 - Completed hand-search of retrieved literature

Table A3: Study Characteristics of Guidelines			
First Author, Publication Year, Country	**Target Audience and Scope**	**Included Study Designs**	**Number of Studies Included and Databases Examined**
	USA - To decrease morbidity and mortality rates for CAP in children older than 3 months by presenting recommendations for clinical management that can be applied in individual cases if deemed appropriate by treating physicians		

Table A4: British Thoracic Society scoring system[4,11]		
Grade	Evidence Level	Definition
A+	Ia	a good recent systematic review of studies designed to answer the question of interest
A-	Ib	One or more rigorous studies designed to answer the question, but not formally combined
B+	II	One or more prospective clinical studies which illuminate, but not rigorously answer, the question
B-	III	One or more retrospective clinical studies which illuminate, but not rigorously answer, the question
C	IVa	Formal combination of expert views
D	IVb	Other information

Table A5: Grading system used in Woodhead et al.[25]		
Grade	Definition	Use
A	Consistent Evidence=clear outcome	All studies
B	Inconsistent evidence=unclear outcome	
C	Insufficient evidence=consensus	
1	Systematic review (SR), meta-analysis (MA) of randomized controlled trial (RCT)	Prevention and therapeutic intervention studies
2	1 RCT or >1 RCT but no SR or MA	
3	1 cohort study or >1 cohort study but no SR or MA	
4	Other	
1	SR or MA of cohort studies	Diagnostic, prognostic, aetiological and other types of studies
2	1 cohort study or > 1 cohort study but no SR or MA	
3	Other	

APPENDIX 3: Critical Appraisal of Included Publications

Table A6: Strengths and Limitations of Health Technology Assessments and Systematic Reviews based on AMSTAR[17]

Strengths	Limitations
Sinclair et al.[8]	
• The limits for the literature search and all inclusion and exclusion criteria are clearly described • Statistical evaluations are appropriate for the investigations being conducted • Provided cost analysis for individual patient and total budget impact which was divided into costs for differing treatment options	• No common reference standard was found for comparison across studies therefore the authors relied on the definition of SP from each individual study which may impart bias • Authors found no apparent relationship with the in-study reference standard and the sensitivity and specificity of the study therefore it is possible that variability due to other causes will obscure the differences due to the reference standard. As a result of this problem the authors treated all patients in a study as having potentially utilized all testing included in the methodology though they admit that this may not have been the case • The models used to analyze for sensitivity and specificity are estimates that are sensitive to the author's model and cannot be proven to be correct. All models are based on the assumption that the results of BinaxNOW-SP and reference testing are independent within the SP pneumonia patient sub-group and the sub-group of non-SP pneumonia patients. • No discussion of grey literature search is provided for review production of details from included studies
Horita et al.[5]	
• Bias was analyzed for each included study using a funnel plot to give quantitative results • Included a flow chart for study inclusion and exclusion • All search terms and the databases examined are provided in detail and a clear statement of the goals of the investigation is given • The literature search was conducted separately by two different individuals and results were confirmed by a group discussion	• All of the included studies contain a low sensitivity for their reference tests (culture or smear) for SP which makes it difficult for the development of a defined definition of specificity • Moderate heterogeneity was found in the specificity analysis and publication bias was identified for two of the groups analyzed for sensitivity analysis (group C and D – called "other" and "unknown") which prevented the investigators from giving reliable specificity analysis for these groups. • No mention of examination of grey literature is provided

Table A7: Strengths and Limitations of Non-Randomized Studies using the Downs and Black Checklist and QUADAS[18,19]

Strengths	Limitations
Prospective Cohort Investigations	
Molinos et al.[21]	
• Included a large sampling of patients from a large variety of hospitals therefore the results will be applicable for a wide range of patients • Patient demographics are well described and the experimental procedures are detailed extensively	• No discussion of bias is provided • Blinding of clinicians and technical staff for results of reference testing and UAT are not given • The variability in practice between each hospital and each clinician is not controlled for (would have been beneficial to include a training session to ensure that all analyses were completed according to guidelines) • The patients with no UAT were not equal to those with UAT in terms of disease severity and age which may impart bias
Chen et al.[13]	
• The patient characteristics and study outcomes are clearly defined in the introduction and methods sections • The patients included were gained from consecutive admission into the hospital under investigation and are a valid representation of the population • The study findings are clearly defined and the discussion section contained extensive comparison with other existing publications • The conclusions, while brief, logically portray the findings of the study	• No risk of bias is discussed in any section of the investigation • The results are analyzing the population from a single hospital and therefore caution must be used when generalizing them to larger populations • No discussion of the blinding of technical staff or clinicians to the results of reference testing and UAT is provided
Zalacain et al.[22]	
• Statistical calculations used controls for variables that had previously been found to influence these types of investigations • The inclusion and exclusion criteria are clearly provided and the patient population included all patients that met the criteria • All patient demographics were assessed and are detailed	• At multiple times within the discussion the authors point out that the most likely explanation for poor prognosis in the positive pneumococcal UAT group is likely due to bacterial burden but no assessment to confirm this was undertaken • No discussion of the blinding of technical staff or clinicians to the results of reference testing and UAT is provided
Huijts et al.[16]	
• Included a large sample population from an extensive number of hospitals all across The Netherlands which is representative of the population and will make the results applicable to all patients • Patient demographics are analyzed and provided in the results section • All groups are clearly described in the methods section and all patient samples were collected rapidly upon admission • Laboratory technicians were blinded to any clinical data from all reference tests and UAT and analysis was completed by two individuals	• No true gold standard exists for reference testing of SP this may therefore influence “true positives” and “true negatives” • Antigens for SP may persist in the urine for between 7 days to 3 months in cases where a previous episode has occurred which may impart bias as no medical history was taken • Clinicians could not obtain urine from 101 patients who were PSI class V which may impart bias as the BinaxNOW-SP test is known to be efficient in more severe cases • 17 hospitals discontinued enrollment in October of 2008 due to competition of another pneumonia study

Table A7: Strengths and Limitations of Non-Randomized Studies using the Downs and Black Checklist and QUADAS[18,19]

Strengths	Limitations
Cheong et al.[23]	
• During the time of the testing the cost of the pneumococcal UAT had been incorporated into the national healthcare coverage therefore the clinicians were under no financial restrictions for utilizing the test indicating that no influence from budgetary restrictions was encountered • The conclusions accurately reflect the experimentation that was conducted • The patient population is clearly defined as are all experimental procedures	• The distribution of the ages in each group under investigation is not evenly distributed which may impart bias • The pneumonia severity and other variables such as gender and chest x-ray severity were not evenly distributed between all groups and while the authors state that this was accounted for in Cox regressions bias may be imparted • No discussion of the blinding of technical staff or clinicians to the results of reference testing and UAT is provided
Retrospective Cohort Investigations	
Choi et al.[15]	
• All criteria for medical record inclusion or exclusion are clearly described • Statistical calculations utilized are appropriate for the population under examination and the variables being examined • The results are detailed and include appropriate confidence intervals where suitable	• The retrospective design of this investigation resulted in a low number of pneumococcal isolates being available for serotyping which means that the statistical significance of these results is limited • Authors state that they had little information on the vaccination status of the included cases which may impart bias to the results • No analysis of bias is included
Shen et al.[24]	
• Patient demographics are clearly defined • The inclusion and exclusion criteria are provided • Urine samples were collected at admission	• Urine was stored at -20C until tested but no information is provided on the storage duration which may result in changes to microbial content • Study was conducted on a small sample size and was recruited from only one hospital which indicated that it may not accurately represent a wide scale population • It is possible that there is overlap between true infection of SP and simple colonization which may impart bias to the results
Engel et al.[6]	
• Analyzed a group for both pneumococcal UAT for CAP (as per guidelines) and for its use in real world situations • CAP diagnosis was based on actual clinical results not on criteria developed in a laboratory setting • Data analysis included all positive results from a secondary and tertiary hospital setting giving support to the results as they are not narrowed down to a specific population in a certain setting	• The pneumococcal UAT examination included here has been completed in addition to the typical analysis that is routinely completed which indicates that it may influence decision making more than if it was used on its own • Positive pneumococcal UAT could potentially lead to a decrease in the use of other microbial testing, a shorter duration in hospital or a drop in mortality rates which could substantially alter the economic costs that have been calculated • Due to the retrospective nature of this study the reason for switching to targeted treatment had to be theorized

Table A8: Strengths and Limitations of Included Guidelines

Strengths	Limitations
Government of New South Wales[14], 2015, Australia	
• Clear focus, target population, and target audience • Clear inclusion and exclusion criteria • Broad spectrum of experts involved in guideline development	• Lack of conflict of interest statement • Lack of reporting of search terms used or databases searched • Level of supporting evidence for each recommendation not provided • Costs and barriers to implementation not discussed. • No procedure for updating provided • Unclear whether external peer review was conducted • Unclear whether the views and preferences of the target population were sought during the development process.
Woodhead et al.[12], 2014, United Kingdom	
• Systematic search performed • Explicit links between recommendations and evidence • Clear clinical questions, target audience, and target population • Guideline reviewed by external experts	• Costs and barriers to implementation not discussed • Lack of conflict of interest statement • Unclear whether the views and preferences of the target population were sought
Spindler et al.[4], 2012, Sweden	
• Systematic search performed • Explicit links between recommendations and guidelines • Guideline reviewed by external experts • Conflict of interest statement provided • Clear clinical questions, target audience, and target population	• Unclear whether the views and preferences of the target population were sought • Costs and barriers to implementation not discussed.
National Institute for Health and Care Excellence[25], 2011, United Kingdom	
• Broad spectrum of experts involved in guideline development • Patient perspective considered in guideline development • Clear focus, target population, and target audience • Potential conflicts of interest stated • Systematic search conducted • Clear inclusion and exclusion criteria • Procedure for updating the guideline provided • Costs considered in guideline development • Implementation considerations provided • Explicit links between recommendations and evidence	• Costs may not capture all costs or benefits associated with the interventions of interest • Organization barriers to implementation not explicitly discussed
Harris et al.[11], 2011, United Kingdom	
• Clear focus, target population, and target audience • Broad spectrum of experts involved in guideline development	• Unclear whether the views and preferences of the target population were sought during the development process. • Costs and barriers to implementation not

Table A8: Strengths and Limitations of Included Guidelines

Strengths	Limitations
• Systematic search conducted • Updating plan provided • Guideline externally reviewed • Explicit links between recommendations and evidence • Conflict of interest statement provided	discussed. • Unclear whether guideline was externally reviewed
Bradley et al.[26], 2011, United States of America	
• Clear focus, target population, and target audience • Based on a literature search • Broad spectrum of experts involved in guideline development • Guideline reviewed by external experts • Strength of recommendation and underlying evidence provided, however explicit links to supporting evidence were unclear • Conflict of interest statement provided	• Search terms and databases searched not provided • Unclear whether the views and preferences of the target population were sought • No implementation strategy provided

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A9: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Health Technology Assessments	
Sinclair et al.[8]	
• Found 1 systematic review which included 24 studies and focused on patients positive for HIV and demonstrated 74% sensitivity (95% CI 72%-77%) and 94% specificity (95% CI 93%-95%) • 2 RCT's found that examined CAP and the total patient population was 480. Both examined targeted treatment group where UAT was utilized versus empirical treatment where it was not. Significant differences were not found for length of hospital stay or clinical outcomes. One study found more relapses in the targeted group and the other found more deaths in the empirical group, though this was not statistically significant (OR 1.99, 95% CI 0.95-4.18) • 6 observational studies were found. 2 of them found no change in treatment due to UAT and one found mixed results. 2 of these studies found that when treatment was changed to more targeted therapy no beneficial response was detected • 1 economic evaluation was found and was conducted on 122 patients using either targeted treatment or empirical. Targeted treatment compared to most expensive empirical resulted in a savings of €19.85 for amoxicillin and €8.11 for penicillin G. When compared to an average empirical treatment there was an additional cost of €8.56 for amoxicillin and €20.30 for penicillin G • 27 diagnostic studies found a large degree of heterogeneity in credible intervals for predicted sensitivity (74.3% 95% CrI 48.8-90.9%) Sensitivity Specificity -Ref A 59.4% (43.9-76.3%) 98.6% (95.1-98.8%) -Ref B 56.2% (35.9-80.5%) 97.4$ (93.8-99.4%) -Ref C 50.3% (24.6-78.8%) 98.3% (91.2-99.8) • Meta-regression analysis conducted that separated diagnostic from etiologic studies, progressive from retrospective, and studies in North America from Europe; no reduction in heterogeneity found • Examined prior antibiotic use pre-BinaxNOW-SP on the average severity of pneumonia but no significant effect found • Compared to cultures alone the addition of	• No evidence has been found that the use of BinaxNOW-SP has any influence on clinical decision making • Use of Binax-NOW-SP in diagnosis of suspected CAP may provide earlier result and increase the percentage of cases diagnosed by 30%, this would entail a 3% increase in false-positives • Addition of BinaxNOW-SP to testing procedures in a regular ward results in incremental cost of $36.2 per patient and $3.7 per patient in an ICU • With the limited beneficial evidence found in this investigation no direct benefit to individual patients was found and there is presently not enough literature to indicate any indirect benefits of improved antibiotic treatment. • Authors recommend that BinaxNOW-SP not be used in routine testing of patients with suspected CAP

Table A9: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
BinaxNOW-SP improves sensitivity 30%, positive results are considered to be SP in all methods here therefore the addition of Binax-NOW-SP reduces the specificity which increases the number of false-positives (increased by 3%) • Overall accuracy increased by 7.2% (95% CrL 0.4-11.7%) • Cost associated with first line empirical treatment equals out to $36 per patient and incremental cost per case correctly classified of $501 • In ICU patients receiving more expensive alternate empirical treatment this increases accuracy and results in an incremental cost per patient of $3.7 and an incremental cost per case correctly classified of $51	
Systematic Reviews	
Horita et al.[5]	
• Included 10 publications, 7 prospective and 3 retrospective cohort investigations with a total of 2315 patients • Pooled sensitivity using a fixed model meta-analysis resulted in 0.75 (95% CI 0.71-0.79) with no heterogeneity (I^2=9.0%, P for chi square=0.359) • Specificity of Other group using a fixed model meta-analysis gave pooled specificity of 0.95 (95% CI 0.92-0.98) with no heterogeneity (I^2=20.5%, P for chi square=0.279) • Specificity of Unknown group using a fixed meta-analysis model gave a pooled specificity of 0.80 (95% CI 0.78-0.82) and significant heterogeneity (I^2=59.7%, P for chi square=0.008) • Sensitivity from a random model meta-analysis gave a pooled sensitivity of 0.75 (95% CI 0.70-0.80) and no heterogeneity (I^2=1.7%, P for chi square=0.42) • Sensitivity of Other group from a random model meta-analysis gave pooled result of 0.95 (95% CI 0.92-0.99) and no heterogeneity (I^2=4.6%, P for chi square=0.387) • Sensitivity of Unknown group from a random model meta-analysis gave pooled result of 0.81 (95% CI 0.77-0.84) and no heterogeneity (I^2=0%%, P for chi square=0.450)	• Pooled sensitivity and specificity were 0.75 and 0.95 respectively for SP UAT on patients with pneumonia • SP UAT is highly specific and moderately sensitive indicating that it will be very useful for ruling out SP infection as opposed to ruling it in • Authors warn that these characteristics may vary in certain situations, for example SP may persist in patients for 1-2 months therefore positive results may be found in successive episodes.
Non-Randomized Studies	
Prospective Cohort Investigations	
Molinos et al.[21]	
• Patients without UAT conducted were significantly older and had more comorbidities, also had higher PSI and CURB-65 scores but admission to	• Three key findings were identified: -SP was the predominant agent causing CAP and that only 21% of cases of CAP were caused by it

Table A9: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
ICU was less than the UAT group • Blood culture obtained from 2781 (62%) of population and had 305 positive for SP (11%), pleural fluid done in 270 (6%) with 51 positives (19%) • Able to establish etiology in 1608 cases (37%) using all methods • SP was most common cause of CAP and occurred in 917 cases (20.9%) • Of the SP cases diagnosis was made by UAT in 653 cases, blood culture in 167, sputum in 66 and tracheal aspirate in 5 and bronchoalveolar lavage in 3 • Area under curve for predicting positive pneumococcal UAT was 0.64 (95% CI 0.58-0.70) • Patients with PSI class of V overall sensitivity in probable and defined groups was 65% and specificity was 98% • In patients with CURB-65 score of 3 overall sensitivity was 71% and specificity was 99% • Significant variables for positive UAT: female sex, heart rate ≥125bpm, systolic blood pressure <90mmHg, saturated oxygen <90%, absence of antibiotic treatment before admission, pleuritic chest pain, chills, pleural diffusion and BUN≥30mg/dl were all significant	indicating that the prevalence is dropping -In 71% of cases of pneumococcal pneumonia diagnosis is made by UAT alone and that if Gram staining and culture are relied upon only 29% of these cases will be discovered -Predictors of use to clinicians to increase suspicion of pneumococcal pneumonia severity are: systolic blood pressure ≤90mmHg, SaO_2 ≤90%, BUN ≥30mg/dl. Additionally when only one of the variables listed is present the probability of pneumococcal CAP is low but when 6 or more are present probability increases to 52%
Chen et al.[13]	
• 296 (60.6%) had antibiotics before examination • Sputum obtained from 411 (only 270 good quality), pleural fluid from 42, 89 had other samples taken such as protected specimen brush, 107 naospharyngeal swab • Definite or probably CAP found for 242 (49.7%) • 228 had bacterial infection 14 had *Mycoplasma pneumoniae* • Group 1 had etiology for 99 of 192 cases (51.5%), of these 50 definite and 49 probable • Group 2 had 70 definite and 73 probable • No statistically significant difference in the number of positives between groups (P.0.05) that were collected pre- or post-antibiotic treatment however positive rate of SP by culture method decreased while positive rate of Gram negative bacilli increased in culture • UAT detected 21 of 192 (10.9%) of patients infected by SP in Group 1 and 39 of 295 (13.2% in Group 2, again the positive rates are not statistically different (P>0.05). Positive rates for culture methods were different: blood and pleural fluid declined from 5.7% to 2.7%, sputum declined from 16.2% to 9.2% after antibiotic	• UAT testing retains good overall sensitivity for diagnosis of CAP in adults after empiric antibiotic treatment • UAT may provide good guidance for the switch from empiric to narrow spectrum β-lactam for treatment

Table A9: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
treatment • Positive rate for UAT testing has no relationship to time of antibiotic treatment	
Zalacain et al.[22]	•
• 261 patients positive for UAT (74.6%) • No significant difference found for patients in the 2 groups for characteristics of number of days since illness onset • UAT positive group had higher respiratory rates, lower arterial oxygen pressure and pH levels and higher multi-lobar involvement • PSI scores were similar between groups (P=0.193) • Serotypes were identified in 288 cases: 1 most common in UAT negative group (P=0.006), 3 most common in UAT positive group (P=0.005) • UAT positive group serotypes were: 3, 6A, 6B, 9N, 19E, 19A and 23F (36.9% in UAT positive versus 18.5% in UAT negative P=0.005) • UAT negative group serotypes were: 1, 4, 5, 7E and 8 (49.2% in UAT negative versus 29.4% in UAT positive P=0.003) • UAT positive group had higher ICU admission (OR 2.6 95% CI 1.1-6 P=0.025), higher use of treatment failure (OR 3.2 95% CI 1.2-9.2 P=0.023), and higher adverse outcome (OR 3.3 95% CI 1.2-9.2 P=0.023) • Kaplan-Meier indicated differences in 30 day mortality, P=0.036 but the in-hospital mortality not statistically different P=0.062 • Sensitivity of UAT was 74.6%	• SP UAT technique has a sensitivity close to 75% in bacteraemic pneumococcal pneumonia cases and is not definitively affected by any of the factors examined here though authors do state that serotype etiology should be examined further • Positive pneumococcal UAT results resulted in poorer outcomes • Authors recommend routine use of UAT testing to initiate guided treatment by physicians
Huijts et al.[16]	
• 325 patients received antibiotics before admission • Patient population for PSI categories was 9.9%, 22.1%, 34.6%, 10.4% in categories I-V respectively • Etiology determined in 403 cases (36.8%) when culture methods were combined with pneumococcal UAT • When add in UAD could determine 493 cases (45%) • The proportion of pneumococcal CAP using cultures with UAT was 23.5% (257 cases) and when add in UAD was 32.6% (357) • In total 249 UAD tests and 211 UAT tests were positive in the population • Of the 244 UAD positives 122 were UAT negative • Sensitivity of UAD was 98% for bacteraemic CAP (detected 48 of 49 cases), UAT was 69.4% sensitive in the same group (detected 34 of 49)	• The addition of UAD testing to the standard methods increased the proportion of SP detection from 23.3% to 32.6% • The overall sensitivity was 63% using UAT , the sensitivity for the 13 serotypes focused on in this study was 69% • The addition of the novel UAD test increased the diagnostic yield of *S.pneumoniae* by 39%, for the 13 serotypes of focus a sensitivity of 98% and a specificity of 100% were found

Table A9: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
Cheong et al.[23]	
• 172 cases examined using pneumococcal UAT, Group 1 had 130 patients (76.2%) positive for UAT and 31 negative (23.8%) • The mean duration of stay was 3.9 and 5.5 days for positive and negative groups respectively • Group 2 had 37 positive UAT patients (88.1%) and 5 negative patients (11.9%) • Average length of hospital stay was 4 days for Group 1, 6 days for Group 2 and 3, and 8 days for Group 4 • 91% of Group 1 were afebrine within 7 days of admission and 95% had fever resolution within 10 days • The proportion of the remaining groups that had fever resolution within 7 or 10 days were: Group 2: 7 days 83%, 10 days 88% Group 3: 7 days 68%, 10 days 87% Group 4: 7 days 67%, 10 days 79% • Log rank testing found statistically relevant difference in fever curves for age and bond formation p=0.0281 and 0.0234 respectively • Cox regression found statistically significant difference for the likelihood to reach afebrile stage were 1.673 and 1.663 times more likely for Group 1 and 2 versus Group 4 respectively • Higher C-reactive protein levels and higher severity of chest x-ray found in Groups 1 and 2	• It is possible that pneumococcal UAT is a suitable non-invasive method to guide selection of antibiotic agents in hospital therapy in pediatric patients • While pneumococcal UAT does not aid in specific etiology it can aid in more rapid and less expensive therapy and shorter hospital stay.
Retrospective Cohort Investigations	
Choi et al.[15]	
• Pneumococcal pneumonia more common in males (67.1%) and the elderly • Serotype 3 was the most common (14.7%) followed by 19A (11.1%), 11A/11E (10.8%) and 19F (9.3%) • Using conventional culture methods SP diagnosed in 191 cases (8.6%) and an additional 85 cases with UAT (3.8% • UAT positive rates according to time period were: -53.4% (94 of 176 cases) in 2007-2009 -51.1% (70 of 137 cases) in 2010-2011 -66.1% (84 of 127 cases) in 2012-2013 • No significant difference between 2007-2009 and 2010-2011 P-0.684 • Significant difference between 2007-2009 and 2012-2013 P=0.026 • After introduction of PCV13 serotype 6A, 19F and 23F decreased while 6C increased • Positive rate of UAT varied diversely depending	• Pneumococcal UAT is a beneficial study for the detection of SP in urine samples and will increase the diagnostic yield regardless of antibiotic usage • Results of pneumococcal UAT are subject to differences in positivity depending on the serotype of the infection • With the introduction of PCV13 the etiology of pneumococcal pneumonia may be changing and therefore the clinical effectiveness of pneumococcal UAT needs to be monitored

Table A9: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
on serotype: 3 50%, 9V/9A 83.3%, 11A/11E 59.1%, 14 36.3%, 19A 50%, 19F 46%, 20 75%, 23F 37.5%, 4 40%, non-typable 55.3% • Cases with a positive UAT result had a significantly higher C-reactive protein level than those with negative results (P-0.007) • No significant difference was found for procalcitonin levels was found in UAT positive or negative • Positive rate of UAT not affected by age, sex, comorbidities, previous antibiotic use. Only diabetes showed any effect • Multivariate analysis of lobar pneumonia (OR 1.78 95% CI 1.046-3.034) and C-reactive protein (OR 1.002 95% CI 1.000-1.005) were significantly associated with differences in UAT positive rate	
Shen et al.[24]	
• No significant difference in demographics in any group though patients in Group 1 had significantly more respiratory distress (p=0.01), oxygen desaturation (p=0.04), febrile days (p=0.03), pulmonary conditions (p=0.01) and bacteremia (p=0.01), longer hospital stay (p=0.01), higher intensive care need (p<0.001) and lower white blood cell count (p=0.01) • Pleural effusion higher in Groups 1 and 2 than 3 (p<0.05) • Children with lowest white blood cell count had the highest scores on UAT and also had higher proportion of cells	• Pneumococcal UAT is a useful diagnostic tool for evaluation of CAP • The predicting of severity may prove useful as an independent predictor of severity, hospitalization requirement and prognosis
Engel et al.[6]	
• a total of 3479 pneumococcal UATs were performed during the testing interval, 1572 were not useable therefore 1907 were examined • 1638 (86%) were negative and 264 (14%) were positive • Median PSI was 97 (72-125) and median CURB-65 was 2 (1-2) • 52 of the positives were excluded as were duplicates or insufficient data was included • Therefore 217 were included in the trial • In 113 cases patient received targeted treatment upon admission and 35% of these were a result of UAT • Median length of stay was 8 days • Treatment decisions to switch to targeted treatment resulted in 293 less days of treatment, equals 7 less tests per day for CAP and 12 less for all testing procedures • Cumulative cost for UAT in CAP was €43613	• Testing cost for CAP only was €131 per targeted treatment days • Cost was €257 if local protocol dictated UAT use for all CAP cases as opposed to €72 if testing was reserved for severe cases only • Improving the selective use of pneumococcal UAT in hospitalized CAP patients may lead to increased cost efficiency

Table A9: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusions
(€23.87 per test x 1907 tests) • Cumulative savings due to use of cheaper targeted treatment expenses was €5090 • Cost of one targeted treatment day gained was €131 ((43613-5090)/293 days) though this amount varied between hospitals - €257 UMCU and €72 DH • Direct cost of UAT is €20 per CAP case and €514 per case receiving targeted treatment • Secondary analysis resulted in cumulative cost of €79565 (€22.87x3479) and €254 per targeted treatment day which varied between hospitals - €522 UMCH €128 DH • If handling costs for preparation and drug administration were included results indicate a modest decrease from €131 down to €126 per targeted treatment day • Direct cost in secondary analysis for UAT was €39 per test and €993 per case receiving targeted treatment.	

Table A10: Summary of Included Guideline Recommendations

Government of New South Wales[14], 2015, Australia
"Urine should not be taken for pneumococcal antigenuria as the specificity is too poor to be a useful test in diagnosis of CAP. False positivity occurs due to nasopharyngeal pneumococcal colonisation." (p. 14 of 32)
Woodhead et al.[12], 2014, United Kingdom
"The immunochromatographic urinary antigen test for *S. pneumoniae* should be performed in patients admitted to the hospital for reasons of illness severity. This test should also be considered whenever a pleural fluid sample is obtained in the setting of a parapneumonic effusion" [A3] (p. 6)
Spindler et al.[4], 2012, Sweden
"Rapid tests for the detection of pneumococcal antigen in urine, such as Binax NOW ® S. pneumoniae, increase the diagnostic yield of pneumococcal infections" (Ib, p. 888) "The test is also useful during ongoing antibiotic therapy" (B+, p. 889)
National Institute for Health and Care Excellence.[25], 2011, United Kingdom
"Do not routinely offer microbiological tests to patients with low-severity community-acquired pneumonia. For patients with moderate- or high-severity community-acquired pneumonia: • take blood and sputum cultures and • consider pneumococcal and legionella urinary antigen tests." (p. 153)
Harris et al.[11], 2011, United Kingdom
"Microbiological diagnosis should be attempted in children with severe pneumonia sufficient to require paediatric intensive care admission, or those with complications of CAP." [C] "Microbiological investigations should not be considered routinely in those with milder disease or those

Table A10: Summary of Included Guideline Recommendations
treated in the community." [C] "Urinary pneumococcal antigen detection should not be done in young children." [C] (p. ii1)
Bradley et al.[26], 2011, United States of America
Urinary antigen detection tests are not recommended for the diagnosis of pneumococcal pneumonia in children; false-positive tests are common. (strong recommendation; high-quality evidence)