Centre universitaire de santé McGill
McGill University Health Centre

Technology Assessment Unit of the McGill University Health Centre (MUHC)

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

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by

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PRINCIPAL MESSAGES

BinaxNOW Streptococcus pneumoniae (BinaxNOW-SP) is an immunochromatographic test for *Streptococcus pneumoniae* (SP) coat antigen. Applied to an initial urine sample, it can suggest a diagnosis of SP infection within an hour, and potentially allow for earlier targeted treatment of SP.

There is currently no evidence that the introduction of BinaxNOW-SP influences physicians' prescribing habits. Observational studies examining this question were inconclusive.

Our meta-analysis estimated that the pooled sensitivity of BinaxNOW-SP is 74.0% (95% CrI 66.6%, 82.3%) and pooled specificity is 97.2% (95% CrI 92.5%, 99.8%). There was considerable heterogeneity between studies in these parameters across studies. Despite the higher sensitivity of BinaxNOW-SP, cultures will continue to be required to provide information about antibiotic resistance. Assuming that the prevalence of SP pneumonia is 30% among patients with suspected CAP, we estimated that addition of BinaxNOW-SP to the diagnostic work-up would result in an increase in the percentage of SP pneumonia cases diagnosed by 30% (95% CrI 17%, 41%). This would be, accompanied by a smaller increase in the percentage of false-positive cases 3% (95% CrI 0%, 7%).

Given the uncertainty in the impact of Binax-NOW on clinical practice we recommend that it should not be used in the routine testing of patients suspected of community acquired pneumonia. Any use that takes place should be carried out within a protocol, to be determined by the Departments of Microbiology and Infection Control, with the objective of defining the value of this test. This issue should be reviewed in one year at which time usage and value of this test should be reviewed.

LIST OF ABBREVIATIONS

BinaxNOW-SP	BinaxNOW test for *Streptococcus pneumonia*
CAP	Community acquired pneumonia
CADTH	Canadian Agency for Drugs and Technologies in Health
CDAD	Clostridium difficile associated diarrhea
CI	Confidence interval
CRD	Centre for Reviews and Dissemination
CrI	(Bayesian) credible interval
INAHTA	International Network of Agencies for Health Technology Assessment
ITT	Intention-to-treat
MUHC	McGill University Health Centre
ND	Not defined
PSI	Pneumonia severity index
SP	*Streptococcus pneumoniae*
TAU	Technology Assessment Unit, MUHC

EXECUTIVE SUMMARY

Background

BinaxNOW *Streptococcus pneumoniae* (BinaxNOW-SP) is an immunochromatographic test for the presence of *Streptococcus pneumoniae* (SP) coat antigen. Applied to an initial urine sample, it can suggest a diagnosis of SP infection within an hour or less, in contrast to cultures, which may take 24 hours or more. BinaxNOW-SP is believed to have higher sensitivity than blood culture and is expected to increase the percentage of patients who receive a precise bacteriological diagnosis. This has the potential to permit the use of narrower-spectrum antibiotic therapy, and in turn reduce risk of antibiotic resistance or *Clostridium difficile* associated diarrhea. The Technology Assessment Unit (TAU) was requested to evaluate clinical effectiveness and cost effectiveness of BinaxNOW-SP in the diagnosis of community acquired pneumonia (CAP) in patients admitted to the MUHC.

Methods

We conducted a systematic search and literature review of articles describing the application of BinaxNOW-SP in practice and of articles estimating its sensitivity and specificity in patients with CAP. Databases used were EMBASE(Ovid), PubMed, Cochrane, DARE, INAHTA, and CADTH.

There is no gold standard test for the diagnosis of SP pneumonia. Therefore we used a Bayesian meta-analysis model to estimate the pooled sensitivity and specificity of BinaxNOW-SP while adjusting for the lack of a single, perfect reference standard. The model incorporated three reference standards: blood culture only; sputum Gram stain or blood or sputum culture; and sputum Gram stain, blood or sputum culture, or culture of any other respiratory sample.

Based on the estimates of sensitivity and specificity from the meta-analysis, we calculated the incremental costs and incremental percentage of patients who receive an accurate bacteriological diagnosis due to using BinaxNOW-SP in addition to cultures. We did not consider replacing cultures with BinaxNOW-SP as culture results, when available, also provide information on antibiotic sensitivity. We considered costs for antibiotic treatment of pneumonia and cost of BinaxNOW-SP only. We ignored costs of clinical outcomes, such as decreased risk of nosocomial infection which, though relevant, are difficult to quantify. We assumed that the true prevalence of SP pneumonia in patients admitted to both regular wards and the ICU was 30%; given the lack of a definitive diagnostic method, however, we cannot confirm the assumption.

Results

Three studies assessed the effect of the availability of the results of BinaxNOW-SP testing on prescribing behaviour in patients with CAP. Two did not find a consistent effect on the number of patients receiving therapy targeted for SP, and one showed a movement towards more targeted therapy. Two RCTs studied the efficacy of empirical treatment versus treatment adjusted according to the results of BinaxNOW-SP testing in CAP. Neither found a significant difference in clinical outcomes or adverse events between groups, however, in both instances, the number of patients who were both randomized to targeted treatment and had a positive BinaxNOW-SP test were small.

A single study examined the potential cost savings of implementing early targeted therapy for SP in patients with severe pneumonia, and found that BinaxNOW-SP offered no cost savings for their cohort.

We found twenty-seven eligible studies with data suitable for a meta-analysis. We estimated a pooled sensitivity of BinaxNOW-SP of 74.0% (95% CrI 66.6%, 82.3%) and specificity of 97.2% (95% CrI 92.5%, 99.8%). There was considerable heterogeneity between studies in these parameters with the 95% credible interval ranging from 48.8% to 90.9% for the predicted sensitivity, and from 84.4% to 100.0% for the predicted specificity in an individual study.

Costs

Compared with culture alone, using BinaxNOW-SP plus cultures significantly improves the overall sensitivity by identifying an additional 30% (95% CrI 17%, 41%) of SP patients. It would also increase the number of false-positives by about 3% (95% CrI 0%, 7%). In a cohort of 1000 patients with suspected CAP and a true prevalence of 30%, this would translate into 90 additional SP pneumonia patients being diagnosed and 21 patients without SP pneumonia being false positive.

In non-ICU patients (empirical treatment ceftriaxone and azithromycin vs. targeted treatment penicillin G), this corresponds to an incremental cost per patient of $36.20 (95% CrI $35.70, $36.60), with an incremental cost per case correctly classified of $500 (95% CrI $283, $2180). In ICU patients (empirical treatment ceftriaxone and amoxicillin versus targeted treatment penicillin G), the increased accuracy corresponds to an incremental cost per patient of $3.70 (95% CrI -$10.60, $14.60), and an increase in incremental cost per case correctly classified of $50 (95% CrI 0, $418).

For an estimated 1700 patients with CAP (based on admissions to MGH and RVH during 2008-2009), assuming a 30% prevalence of SP pneumonia and that 170 patients (10%) required ICU admission, routine use of BinaxNOW-SP plus cultures would represent a budget impact of $56,022 (95% CrI $52,938, $58,342). Assuming test

results determine prescribing practices, this would result in the targeted treatment of 457 patients.

Conclusions

- There is currently no evidence that the introduction of BinaxNOW-SP influences physicians' prescribing habits. Observational studies examining this question were inconclusive.
- Our meta-analysis shows that addition of BinaxNOW-SP to the diagnostic work-up of patients with suspected CAP may, in addition to providing an earlier bacteriological diagnosis, result in an increase in the percentage of SP pneumonia cases diagnosed by 30% (95% CrI 17%, 41%). This would be, accompanied by a smaller increase in the percentage of false-positive cases 3% (95% CrI 0%, 7%). Note that the credible intervals around these estimates are very wide due to the heterogeneity in sensitivity and specificity estimates across individual studies.
- Assuming that BinaxNOW-SP does influence prescribing practice, our cost-analysis showed that the addition of BinaxNOW-SP to the work-up will result in an incremental net cost of $36.2 (95% CrI $35.7, $36.6) per patient in a regular ward and $3.7 (95% CrI -$10.6, $14.6) per patient in the ICU, despite cost-savings from using targeted treatment. It should be noted that our estimates ignore the possible decrease in cost due to reduced risk of nosocomial infections. Cultures will continue to be required to provide information about antibiotic resistance.
- For 1700 patients with pneumonia (estimated admissions to MGH and RVH over one year), assuming that 170 (10%) required ICU admission, that represents a budget impact of $56,022 (95% CrI $52,938,$58,342). Assuming test results determine prescribing practices, this would result in the targeted treatment of 457 patients.
- The limited evidence available suggests that this change of therapy would produce no measurable benefit to the individual patient. We do not presently have the information to quantify the indirect benefits of improved antibiotic stewardship.

Recommendations

We recommend that Binax-NOW not be used in the routine testing of patients suspected of community acquired pneumonia. Any use that takes place should be carried out within a protocol, to be determined by the Departments of Microbiology and Infection Control, with the objective of defining the value of this test. This issue should be reviewed in one year at which time usage and value of this test should be reviewed.

SOMMAIRE

Contexte

Le BinaxNOW *Streptococcus pneumoniae* (BinaxNOW-SP) est un test immuno-chromatographique pour déceler la présence de l'antigène *Streptococcus pneumoniae* (SP). Lorsque appliqué à une première miction, ce test peut suggérer le diagnostic d'une infection au *Streptococcus pneumoniae* (SP) à l'intérieur d'une heure, par comparaison aux tests de culture dont le résultat peut prendre 24 heures ou plus. L'on soupçonne le test BinaxNOW-SP d'avoir une plus grande sensibilité qu'une culture de sang et de permettre une augmentation du pourcentage de patients recevant un diagnostic bactériologique précis. Un bénéfice potentiel de cette sensibilité est de permettre l'utilisation d'un antibiotique à spectre plus étroit, réduisant ainsi le risque de résistance à l'antibiotique pouvant entraîner la diarrhée au *Clostridium difficile*. L'Unité d'évaluation des technologies ("Technology Assessment Unit") fut sollicitée pour évaluer l'efficacité clinique et le coût-efficacité du BinaxNOW-SP dans le diagnostic d'une pneumonie acquise (PA) chez les patients hospitalisés au Centre universitaire de santé McGill (CUSM).

Méthodologie

Une recherche systématique et une revue de la littérature furent menées en regard des articles décrivant l'utilisation du BinaxNOW-SP en pratique et des articles évaluant sa sensibilité et sa spécificité chez les patients avec une PA. Les bases de données suivantes furent consultées: EMBASE (Ovid), PubMed, Cochrane, Dare, INAHTA et CADTH.

Puisqu'il n'existe pas de test de référence pour le diagnostic de la pneumonie SP, nous avons utilisé une méta-analyse bayésienne pour évaluer la sensibilité et la spécificité sommatives du test BinaxNOW-SP tout en tenant compte de l'absence d'une référence standard. Le modèle comportait trois références standards: la culture du sang, seulement; la coloration Gram d'une expectoration, ou la culture du sang ou d'une expectoration; la coloration Gram d'une expectoration, la culture du sang ou d'une expectoration, ou la culture de tout autre échantillon des voies respiratoires.

En se basant sur les évaluations de sensibilité et de spécificité tirées des méta-analyses, nous avons calculé les coûts additionnels et l'augmentation du pourcentage de patients recevant un diagnostic microbiologique exact suite à l'utilisation du BinaxNOW-SP en plus des tests de culture. Nous n'avons pas considéré de remplacer les résultats des tests de culture par ceux du BinaxNOW-SP, lorsque disponibles, et également de fournir des informations sur la sensibilité aux antibiotiques. Nous avons

considéré uniquement le coût des traitements antibiotiques pour pneumonie et ceux du BinaxNOW-SP. Nous avons aussi ignoré les coûts reliés aux impacts cliniques tels que la diminution des risques d'une infection nosocomiale qui, même si cela est pertinent, est difficile à quantifier. Nous avons supposé que la prévalence véritable de la pneumonie SP chez les patients admis sur les unités de soins régulières et aux soins intensifs était de 30%; étant donné l'absence d'une méthode diagnostique reconnue, nous ne pouvons cependant confirmer cette hypothèse.

Résultats

Trois études ont évalué l'impact de la disponibilité des résultats des tests BinaxNOW-SP sur les pratiques de prescription pour les patients avec une PA. Deux études n'ont pas trouvé d'effet sur le nombre de patients recevant une thérapie ciblée pour une PA et une étude montra une tendance vers une thérapie plus ciblée. De même, deux études randomisées ont comparé l'efficacité du traitement classique versus un traitement plus adapté selon les résultats du test BinaxNOW-SP lors de PA. Aucune n'a trouvé de différences significatives dans les résultats cliniques ou les effets indésirables entre ces groupes où le nombre de patients qui furent randomisés quant à un traitement ciblé et qui avaient un test BinaxNOW-SP positif, était faible.

Une seule étude analysa les économies potentielles découlant de l'implantation d'une thérapie précoce et ciblée pour une PA chez les patients avec une pneumonie sévère et conclua que le test BinaxNOW-SP n'offrait pas d'économies pour leur cohorte.

Nous avons identifié 27 études comportant des données se prêtant à une méta-analyse. Nous avons ainsi évalué une sensibilité sommative du BinaxNOW-SP de 74,0% (95% Icr 66,6% à 82,3%) et une spécificité sommative de 97,2% (95% Icr 92,5% à 99,8%). Il y avait une hétérogénéité considérable entre ces études pour ces paramètres avec un intervalle de crédibilité de 95% variant de 48,8% à 90,9% pour la sensibilité prédite et de 84,4% à 100,0% pour la spécificité prédite, pour une étude particulière.

Coûts

Si l'on compare aux tests de culture, seuls, les tests combinant le BinaxNOW-SP et les tests de culture améliorent de façon significative la sensibilité globale en identifiant 30% (95% Icr 17% à 41%) de plus de patients ayant une pneumonie de type SP mais avec un ajout de 3% (95% Icr 0% à 7%) de faux positifs. Dans une cohorte de 1 000 patients soupçonnés d'avoir une PA et en présumant une prévalence de 30% (pneumonie de type SP), ceci se traduirait par un ajout de 90 patients diagnostiqués avec pneumonie de type SP et un ajout de 21 patients faux positifs, sans pneumonie de type SP.

Pour les patients qui ne sont pas traités aux soins intensifs (i.e. avec un traitement empirique de ceftriaxone et d'azithromycine vs un traitement ciblé de pénicilline G), le coût additionnel par patient est de 36,20 $ (95% Icr 35,70 $ à 36,60 $), ce qui implique un coût additionnel de 500 $ (95% Icr 283 $ à 2 180 $) pour chaque cas correctement diagnostiqué. En ce qui concerne les patients traités aux soins intensifs (i.e. avec un traitement empirique de ceftriaxone et d'amoxicilline vs un traitement ciblé de pénicilline G), la précision accrue des tests entraîne un coût additionnel par patient de 3,70 $ (95% Icr -10,60 $ à 14,60 $) et un coût additionnel de 50$ (95% Icr 0 à 418$) pour chaque cas correctement diagnostiqué.

Si l'on évalue à 1 700 le nombre de patients avec une PA (en se basant sur les admissions à l'HGM et l'HRV au cours de l'année 2008-2009), que l'on estime à 30% la prévalence de la pneumonie de type SP et que 170 patients (10%) nécessitent une admission aux soins intensifs, l'utilisation courante du BinaxNOW-SP avec les tests de culture représenterait un impact budgétaire annuel de 56 022 $ (95% Icr 52 938 $ à 58 342 $). Si l'on assume que les résultats des tests influencent les pratiques de prescription, ceci résulterait en un traitement ciblé de 457 patients.

Conclusions

- Actuellement, il n'y aucune preuve à l'effet que l'introduction du BinaxNOW-SP influence les habitudes de prescription des médecins. Les études observationnelles étudiant cette question furent non-concluantes.
- Notre méta-analyse montre que l'ajout du BinaxNOW-SP au bilan diagnostique des patients soupçonnés d'une PA peut, en plus de permettre un diagnostic bactériologique anticipé, se traduire par une augmentation de 30% (95% Icr 17% à 41%) du nombre de cas de pneumonie de type SP diagnostiqués. Par contre, l'on note une augmentation de 3% (95% Icr 0% à 7%) du nombre de cas faux-positifs. Il faut souligner que l'intervalle de crédibilité de ces estimés est très large dû à l'hétérogénéité des estimés de sensibilité et de spécificité parmi les études.
- Si l'on assume que le BinaxNOW-SP influence effectivement la pratique de prescription, notre analyse des coûts montra que l'ajout du BinaxNOW-SP au bilan diagnostique entraînait une augmentation nette des coûts de 36,20 $ (95% Icr 35,70 $ à 36,60 $) par patient admis sur une unité de soins régulière, et 3,70 $ (95% Icr -10,60 $ à 14,60 $) par patient admis aux soins intensifs, malgré les économies découlant d'une thérapie ciblée. À noter que nos estimés ne tiennent pas compte d'une diminution potentielle des coûts rattachés à une diminution des risques d'infections nosocomiales. Les tests de culture seront toujours requis pour nous renseigner sur la résistance aux antibiotiques.

- Si l'on assume que 170 patients (10%) parmi 1 700 patients qui ont une pneumonie (ce dernier chiffre découlant des admissions à l'HGM et à l'HRV au cours d'une année) nécessitent une admission aux soins intensifs, l'impact budgétaire annuel serait de 56 022 $ (95% Icr 52 938 $ à 58 342 $). Si l'on accepte que les résultats des tests influencent les pratiques de prescription, ceci résulterait en un traitement ciblé de 457 patients.
- Actuellement, les preuves limitées suggèrent que ce changement de thérapie n'apporterait pas de bénéfices tangibles au niveau du patient. Présentement, nous ne possédons pas d'information pour quantifier les bénéfices indirects découlant d'un guide antibiotique bonifié.

Recommendations

Nous recommandons que le BinaxNOW ne soit pas utilisé dans le bilan diagnostique de routine pour identifier les patients soupçonnés d'avoir contracté une pneumonie. Toute utilisation de ce test devrait être encadrée par un protocole reconnu par les départements de microbiologie et du contrôle des infections, avec l'objectif de définir la valeur de ce test. Cette question devrait être réévaluée dans un an à la lumière des résultats obtenus.

The clinical effectiveness and cost of pneumococcal urine antigen immunochromatographic test (BinaxNOW) in the diagnosis of community acquired *Streptococcus pneumoniae* pneumonia in patients admitted to hospital

1. BACKGROUND

Community-acquired pneumonia (CAP; pneumonia contracted outside an acute or long-term care facility) is the leading cause of death from infection in developed countries[1]. *Streptococcus pneumoniae* (SP) is the most commonly-identified causative organism. However, due to the lack of sensitivity of current diagnostic methods, the aetiology of a significant number of pneumonias cannot be identified[1, 2]. In the McGill University Health Centre (MUHC) records for the fiscal year 2008-2009, two thirds of cases of pneumonia were listed as being due to an unspecified organism. In addition, methods of diagnosis that rely on cultures of organisms take 24 hours or longer to produce results.

Initial treatment of pneumonia, therefore, is usually empirical, based upon severity at presentation and comorbidities. In principle, early identification of a case of SP pneumonia could result in antibiotic therapy being better targeted, with reduced reliance on regimens that are associated with development of resistance or increased risk of Clostridium difficile associated diarrhea (CDAD)[2-4].

The BinaxNOW test for *Streptococcus pneumonia* (BinaxNOW-SP; marketed by Inverness Medical) is an immunochromatographic test that detects the presence of an SP coat protein (pneumococcal C-polysaccharide) in urine, and can provide results to support a diagnosis of infection within 15 minutes of specimen collection. It does not provide antibiotic sensitivities.

The Technology Assessment Unit has been asked by Dr Vivian Loo (Chief of the Department of Microbiology of the MUHC) and Marty Teltscher (Microbiologist and Infectious Disease Consultant, Lachine Campus of the MUHC) to evaluate the use of BinaxNOW-SP in the rapid diagnosis of *S pneumoniae* community acquired pneumonia (CAP). Its anticipated use would be as part of the diagnostic workup (culture of sputum, blood, urine) of adult patients who were to be admitted to hospital. The results would be used to direct antibiotic therapy. Its use on ambulatory patients is not anticipated, due to cost, and the lack of expectation that it would usefully lead to modification of therapy.

2. OBJECTIVES

- To determine whether use of BinaxNOW-SP at the time of admission to hospital would provide a diagnosis of adequate sensitivity and specificity compared to currently used culture procedures
- To estimate the budget impact and cost effectiveness of using the BinaxNOW-SP test in addition to currently used culture procedures for diagnosing CAP

3. METHODS

3.1. Literature search and quality assessment

3.1.1. Databases

We searched the following databases for systematic reviews, health technology assessments, and studies which addressed (1) clinical practice incorporating BinaxNOW-SP and (2) sensitivity and specificity for BinaxNOW-SP against any standard.

- The Cochrane Collaboration
- The Centre for Reviews and Dissemination (CRD), University of York
- International Network of Agencies for Health Technology Assessment (INAHTA)
- Canadian Agency for Drugs and Technologies in Health (CADTH and CADTH confederated search)
- EMBASE/Ovid (includes Medline)
- PubMed

3.1.2. Key terms/words

Two separate search strategies were used in EMBASE/Ovid and in PubMed, details of which are given in Appendix 1. Searches were manually reviewed to retrieve two groups of papers: RCTs and observational studies that explored clinical practice around BinaxNOW-SP, and studies that provided data on diagnostic performance of BinaxNOW-SP in patients with CAP.

3.1.3. Inclusion and exclusion criteria for studies in the diagnostic meta-analysis

We included studies that:

- Used a clinical definition of CAP as an inclusion criterion, or defined and analysed a subgroup with clinically defined CAP
- Used hospitalization as an inclusion criterion, or defined and analysed a subgroup of hospitalized patients
- Were studies of predominantly adult patients (age≥14 years). (Urinary antigen testing for SP is not recommended in children due to a high rate of SP colonization causing false positive results[5].)
- Collected urine specimens within 48 hours of hospital admission or described the collection of urine specimens as a part of the initial septic workup (ie, at the same time as cultures were collected).
- Reported results for unconcentrated urine. Urine could be frozen prior to assay, provided storage was not prolonged.
- Reported results for BinaxNOW-SP against diagnosis derived from blood culture (required) with or without one or more of pleural fluid culture, stain and culture of sputum, or other sample from the respiratory tract, in such a form that a diagnostic 2x2 table of SP vs. BinaxNOW-SP could be constructed for a single patient group representing CAP patients.
- Appeared in a peer-reviewed publication in English or French.
- Did not include the results of BinaxNOW-SP in the definition of SP, or reported the number of SP cases diagnosed by BinaxNOW-SP alone so as to allow isolation of data for patients diagnosed solely by conventional means.

3.2. Meta-analysis

We used a Bayesian bivariate diagnostic meta-analysis to summarize sensitivity and specificity across all studies. The model incorporated adjustment for the lack of a "gold standard" comparator, as the chosen reference test varied across studies[6]. Comparators used in the selected studies fell into three different classes (see Section 4.3 for details):

A. Positive sputum Gram stain or positive blood, sputum, or other culture
B. Positive sputum Gram stain or positive blood or sputum culture
C. Positive blood culture alone

Further, we allowed for heterogeneity in the accuracy of the reference standards across studies. We estimated the model using non-informative prior distributions that would allow the observed data to dominate the final estimates of sensitivity and specificity of BinaxNOW-SP. We also estimated the model using informative prior distributions for the pooled sensitivity and specificity of the reference standards. Based on the input of our

expert consultant, Dr. Marty Teltscher, and a non-systematic review of the literature[2, 7-11], we proposed plausible ranges (spanning cited values) for the sensitivity and specificity of the three reference standard classes as shown in Table 1. These formed the basis of the informative prior distributions and were converted into Beta probability distributions.

Table 1 Informative priors for reference standard classes

Reference class	Plausible range of sensitivity	Plausible range of specificity
A	40-70%	80-100%
B	30-60%	80-100%
C	10-40%	90-100%

From each meta-analysis model we obtained estimates of the median and 95% credible interval of the pooled sensitivity and specificity of BinaxNOW-SP across studies as well as predicted sensitivity and specificity in an individual study. Analyses were carried out using WinBUGS 1.4.3[12].

In addition to our primary meta-analysis model described above, we also carried out separate meta-analyses within the three sub-groups of studies defined by the reference standard class in order to estimate sensitivity and specificity of BinaxNOW-SP with respect to each reference class[13]. We carried out a meta-regression analyses to investigate whether the heterogeneity in sensitivity and specificity of BinaxNOW-SP across individual studies could be explained by study design (retrospective vs. prospective), the purpose of the study (diagnostic vs. etiologic) or type of hospital (tertiary university-affiliated centre vs. other). Each of these study-level covariates was considered separately. The final selected model was one that fit the data the best in terms of the Deviance Information Criterion (DIC) statistic[51] among the models we considered.

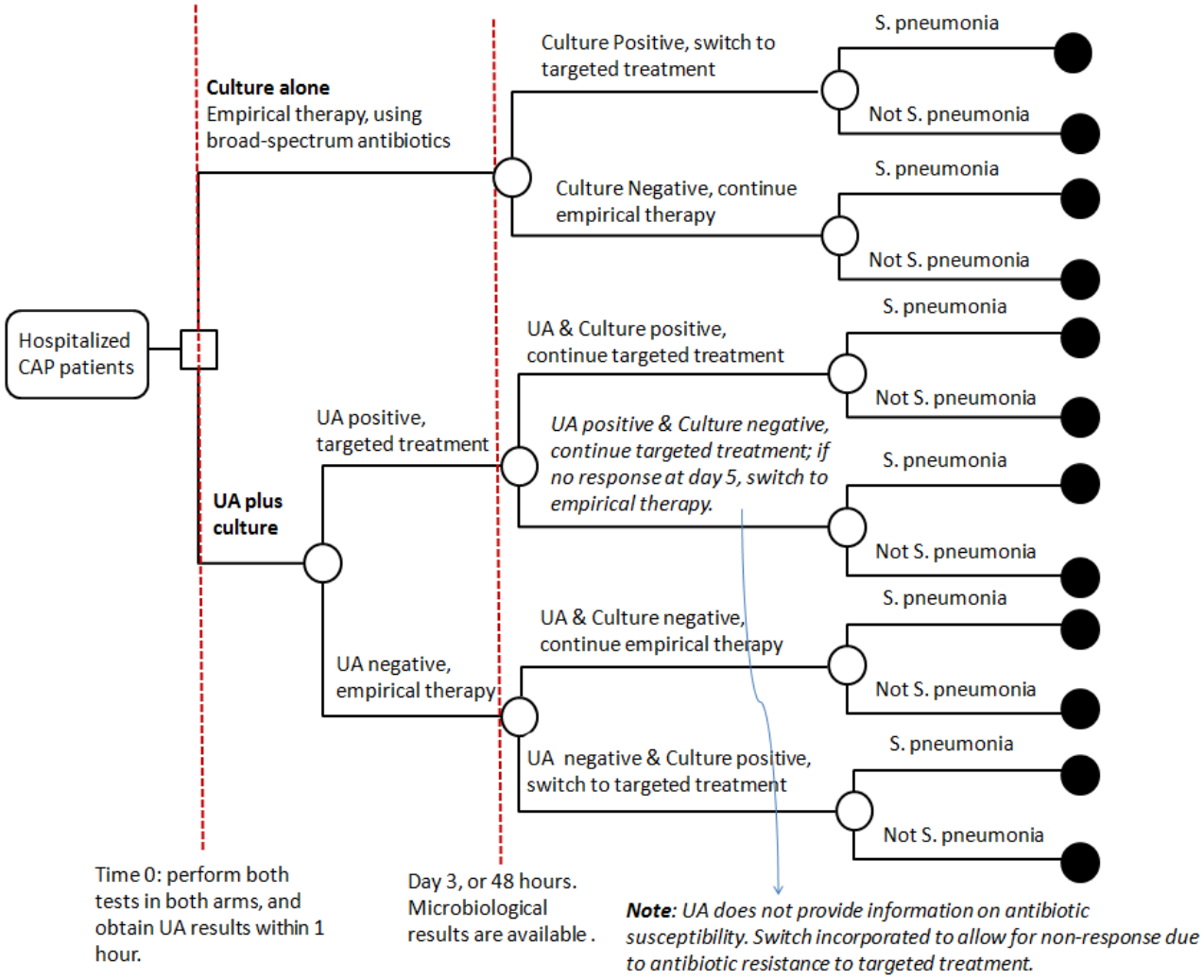
3.3. Cost-effectiveness analysis

The literature on the influence of BinaxNOW-SP on clinical outcomes was sparse (Section 4.2), therefore our analysis focused on the incremental costs and incremental correct classification from adding BinaxNOW-SP to cultures, as determined from our meta-analysis (see Section 4.3). Our cost components included the costs for antibiotics for treatment of SP and the cost of BinaxNOW-SP, and disregarded the resource consumption of nursing time, physician visits, length of stay, cultures, etc that were assumed to remain unchanged by adding BinaxNOW-SP.

Figure 1 shows the economic decision model. CAP patients are tested by BinaxNOW-SP and have cultures drawn as soon as they present. We assume culture results would be available 48 hours later, while urine antigen results would be available 1 hour after

sampling. In the culture alone arm, all patients are treated by empirical therapy for the first 2 days. From day 3, culture positive patients switch to targeted treatment, and culture negative patients continue on empirical treatment. In the BinaxNOW-SP and culture arm, patients who test positive for SP by either BinaxNOW-SP or culture are treated with targeted therapy. According to guidelines for the use of antibiotics for pneumonia at MUHC[14], the first line antibiotics for empirical treatment are ceftriaxone plus azithromycin . Among ICU patients, the second line treatment is ceftriaxone plus moxifloxacin in the event of recent treatment with, or contraindication to, a macrolide. According to the current Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines (2007), Penicillin G or amoxicillin would be used for the targeted treatment of SP[2]. We defined effectiveness in terms of the number of patients correctly classified. Thus the incremental cost effectiveness was given by the difference in cost of cultures and BinaxNOW-SP versus Cultures alone divided by the increase in the number of patients correctly classified due to the addition of BinaxNOW-SP to the work-up. This definition of effectiveness does not refer to the effectiveness in outcomes for the individual patient, either in terms of successful treatment of CAP or in terms of reducing their risk of nosocomial infections.

Figure 1 Model of patient flow for cost analysis



We used Monte Carlo simulation to capture the uncertainty of inputs to the model. We randomly drew 10000 values of the pooled sensitivity and specificity of the BinaxNOW-SP test, and pooled estimates of sensitivity and specificity of reference class A (blood, sputum, and at least one other culture) from our meta-analysis results. The prevalence rate of SP was assumed to be 30%. Prices of antibiotics were obtained from the MUHC pharmacy (see Table 3).

We considered the cost-effectiveness of first-line and alternate empiric treatment separately as the costs of the alternate empiric treatment is significantly more expensive. In each group we assumed that 300 out of 1000 CAP inpatients had SP pneumonia annually. Our primary interest was the incremental cost per case correctly classified. We also reported the number of correctly classified SP and non-SP patients and the total number of correctly classified patients. We also conducted sensitivity analyses using the more expensive alternative in targeted treatment (ampicillin) and alternative estimates for the prevalence of SP pneumonia.

We calculated the budget impact for an estimated 1700 patients, derived from a summary of respiratory admissions during the fiscal period 2008-2009 (Appendix 2). The uncertainty of the figure must be acknowledged, since this figure may include multiple admissions and transfers between ICU and non-ICU wards.

4. RESULTS

4.1. Health technology assessment reports/Systematic reviews

We identified a single systematic review of the performance of the BinaxNOW-SP test in adults with CAP or pneumonia[15], and no health technology assessments to date.

The systematic review, described in Boulware et al[15], included a total of 24 studies retrieved on a search of PubMed from 1950 to 2007. Most studies used one or more of blood culture, sputum Gram stain, or sputum culture as a reference standard. Pooled Mantel-Haenszel weighted means for sensitivity and specificity were 74% (95% CI 72%, 77%) and 94% (95% CI 93%, 95%), respectively, against an assumed single perfect reference standard. The authors were primarily interested in the use of the test in HIV-positive patients, and were concerned that in this population, recurrent CAP infection might lead to false positive test results. They concluded that testing with BinaxNOW-SP increases etiologic diagnosis by 23% (range 10%, 59%).

4.2. BinaxNOW-SP in clinical practice

Experts have expressed the belief that targeted treatment may be preferable to empirical therapy[2-4], and a large number of trials have compared specific treatments for pneumonia with each other[2]. The lack of available rapid tests has meant that historically there are few studies explicitly comparing a targeted treatment with an empirical treatment from the outset of therapy.

4.2.1. Randomized controlled trials of the impact of BinaxNOW-SP on clinical outcomes

Two RCTs[16, 17] provided a randomized comparison of clinical outcomes incorporating the BinaxNOW-SP test into the diagnostic process in hospitalized patients.

Falguera et al[16] randomized 177 patients to be treated with targeted therapy (88 patients) or empirical therapy (89 patients). All patients received empirical initial therapy. Those in the targeted therapy group who tested positive on a urinary antigen for either SP or *Legionella* were switched to targeted therapy (25 patients) once clinically stable (2-6 days). The initial therapy was beta-lactam plus macrolide or respiratory fluoroquinone (2-6 days) followed by amoxicillin (targeted group with positive BinaxNOW-SP), azithromycin (targeted group with positive Legionella urine test), or continued empirical therapy (empirical group, and targeted group patients with negative urine tests). All patients, therefore, received initial empirical therapy, targeted therapy was not administered from presentation, and was only administered in a minority of patients. The study patients had comparatively mild disease, with only one patient admitted to ICU. The outcomes of clinical interest were mortality, clinical relapse, admission to the ICU, incidence of adverse events, length of hospital stay and readmission. There was no statistically significant difference in clinical outcomes or adverse events; however, there were more relapses in the targeted therapy group (3/25 patients [12%] versus 3/152 patients [2%]).

Van der Eerden et al[17] randomized 303 patients with CAP to be treated with open-label pathogen-directed treatment (152 patients) or empirical broad spectrum antibiotic treatment (151 patients). Pathogen-directed treatment was determined by clinical presentation according to predetermined criteria, identification of organisms in Gram stain of sputum or pleural fluid, or positive urinary antigen for SP, as measured by BinaxNOW-SP or *Legionella*. Of the 262 evaluable patients, 92 had a definite or presumptive diagnosis of SP (49 in the pathogen-directed treatment group, 43 in the empirical treatment group). Outcomes for these patients were not individually described. The outcomes of clinical interest were length of stay, clinical failure (early and late), 30 day mortality, duration of antibiotics (IV and total), resolution of fever, adverse events, and quality of life. No significant difference was observed for the primary outcome of length of stay for either the intention to treat (ITT) or the evaluable patient population.

There were more deaths in the empirical treatment group in both the ITT and the evaluable populations, although the odds ratio (OR) itself was not statistically significant. In the ITT population, 22 (15%) of patients who received empirical treatment died, compared with 12 (8%) of those who received pathogen-directed treatment (OR 1.99, 95% CI 0.95, 4.18). Within the pathogen-directed treatment group itself, higher mortality was observed in patients treated according to results from rapid diagnostic testing (8 patients, 13%), than in those treated according to features at clinical presentation (syndromic approach, 2 patients, 3%). The significance of this observation is unclear, given the small numbers and secondary endpoint (ie, no statistical power).

4.2.2. Observational studies of the influence of BinaxNOW-SP on prescribing practice and clinical outcomes

Three observational studies looked at the influence of BinaxNOW-SP on prescribing patterns. Weatherall et al[18] saw no trend towards prescribing of narrower-spectrum antibiotics with knowledge of BinaxNOW-SP results, in an observational cohort study of 59 patients that among other outcomes measured whether BinaxNOW-SP influenced treatment decisions. Matta et al[19] conducted a prospective study of treatment adaptation in inpatients who had a BinaxNOW-SP test. Fifty-eight (58) of 233 patients with clinical CAP had a positive urine antigen test. Of these fifty-eight, twenty-two (38%) had a treatment change that was adapted to SP (amoxicillin), 14 had a change that was not directed to SP, and 20 had no change (results for 2 were unreported). Of the 175 patients with a negative urine antigen test, 6 were switched to broader-spectrum antibiotics. In a study of 278 patients, Segonds et al[20] found 32 with a positive BinaxNOW-SP test, as a result of which 11 (34%) additional patients received amoxicillin, 4 of whom received monotherapy. None of these studies, however, included interventions designed to direct or modify physician prescribing behaviour.

Two observational studies[21, 22] described the effect of BinaxNOW-SP on outcomes in hospitalized patients. Outcomes for subjects with SP whose treatment was modified in response to positive urinalysis results were comparable to those whose treatment was not adjusted, but the numbers of patients whose treatment was adjusted were in the minority: 41/171 (24%) cases of SP pneumonia in Sordé et al[21], and 10/44 (23%) in Kobashi et al[22]. In Sordé et al, 18 patients had improved targeted treatment and 23 had what they considered optimal targeted treatment.

Of note, in an ambulatory patient population with mild/moderate CAP (ie, milder disease than the subject of this review), Guchev et al[23] reported no significant difference in outcomes (treatment effectiveness or failure) in patients with positive BinaxNOW-SP treated with amoxicillin and negative BinaxNOW-SP treated with clairithromycin, or in the subgroup with known (diagnosed by culture and/or BinaxNOW) SP pneumonia.

In summary, the available evidence suggests that a positive result on the BinaxNOW-SP test results in use of targeted treatment only in a minority of patients, and there is no difference in clinical outcomes between patients treated by empirical or targeted treatment, with the caveat that studies were designed only to monitor physician behaviour rather than influence it, and the number of patients who were candidates for adjusted treatment and who were SP pneumonia cases was small.

4.2.3. Economic studies

A single study addressed the potential cost savings of implementing early targeted therapy for pneumococcal pneumonia[24] in patients with severe pneumonia. Costs were calculated for a cohort of 122 patients, 85 of whom had BinaxNOW-SP results available, with 23 positive for SP. Costs for targeted treatment of the SP patients with amoxicillin (three times daily) or penicillin G (6 times daily) were compared with those for empirical treatment with broad spectrum empirical antibiotic therapy (most expensive, least expensive, and average cost). When the cost of targeted therapy per patient was compared with the most expensive empirical regimen, cost savings per patient were €19.85 and €8.11 for targeted therapy of amoxicillin and penicillin G, respectively. However, when targeted therapy was compared with the average regimen, additional cost per patient was €8.56 and €20.30, for targeted therapy of amoxicillin and penicillin G, respectively. The authors concluded that BinaxNOW-SP offered no cost savings for their cohort. This study did not consider costs of nosocomial infections. In addition, the study by Falguera et al[16] described above compared costs per patient in the targeted (€1657.00) versus empirical therapy arms (€1617.20), with a difference of €39.80. This study involved urine testing for both SP and *Legionella* infection.

4.3. Review of diagnostic studies

The combined searches (see Section 3.1, Appendix 1) retrieved a total of 459 citations for text and abstract review. Commentaries, narrative reviews, paediatric studies, and studies of diagnosis of pneumonia of other aetiology were excluded.

Sixty-seven articles were retrieved for full-text review. Articles were excluded at this stage for the following reasons: did not report results of diagnostic accuracy, cost or clinical outcomes, did not include sufficient information to construct a full 2x2 diagnostic table for BinaxNOW-SP versus a reference standard in the case of diagnostic accuracy studies, did not report results on the patient group of interest, incorporated BinaxNOW-SP into the reference standard, tested only concentrated urine samples, or used samples frozen >1 year.

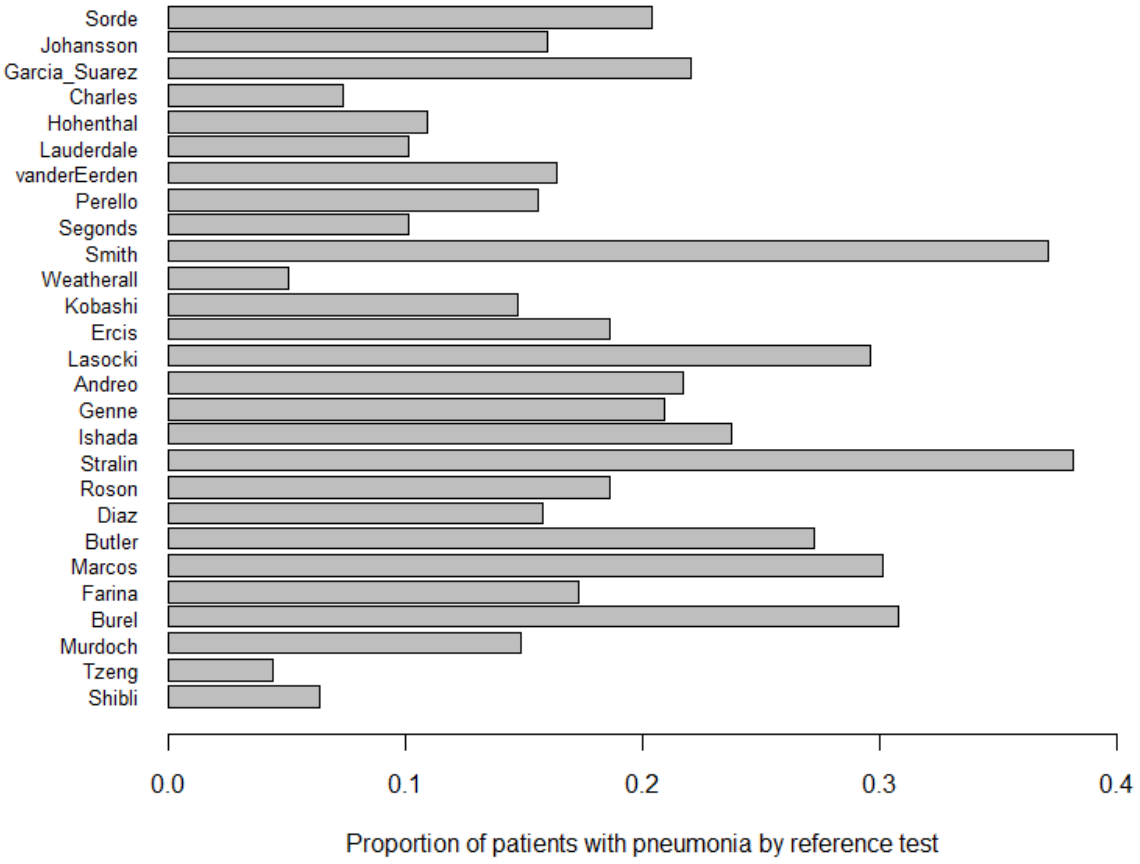
Twenty-seven studies[8-10, 18, 20-22, 25-44] provided sufficient information on the BinaxNOW-SP test performance in patients with CAP to contribute to a meta-analysis (see Section 4.4 for description of meta-analysis results). Study characteristics are summarized in

end-of-text Table 6, patient characteristics in end-of-text Table 7, and diagnostic 2x2 tables in end-of-text Table 8.

Four studies used blood culture alone as the reference standard (reference class C); 11 studies used blood culture and sputum gram stain/culture (a positive finding on either test indicated SP; reference class B); and 12 studies used blood culture, sputum gram stain/culture, and culture of at least one other respiratory site (a positive finding on any test indicated SP; reference class A) (End-of-text Table 6, end-of-text Table 8).

Patients were predominantly middle aged or elderly, with the exception of those with a significant representation of HIV-positive and AIDS patients (End-of-text Table 7). The mean/median age ranged from 43 to 79 years. The proportion of patients who were male ranged from 47% to 79%. The percentage to receive a diagnosis of SP pneumonia based on the reference standard in individual studies varied between 4.4% and 38.1% across studies (Figure 2). The most commonly-used measure of pneumonia severity was the proportion of patients with a pneumonia severity index (PSI) class IV or V, which ranged from 23 to 61%. One study reported on the test performance in a cohort of patients admitted to ICU. The prior use of antibiotics ranged from 16 to 76%, although the time-point of assessment varied across studies, eg, in the study that produced the upper figure[44], antibiotics were assessed at the time of urine collection, which was after admission. Not all studies reported pneumonia severity and antibiotic use.

Figure 2 Proportion of patients diagnosed with SP pneumonia based on the reference test in each study



Most studies made explicit the exclusion of those whose lung pathology proved to arise from other causes. Seven studies excluded patients with any significant degree of immunosuppression. The remaining studies did not exclude patients with immunosuppression, and one study[26] recruited only patients with HIV.

4.4. Meta-analysis of diagnostic studies

4.4.1. Choice of reference standard

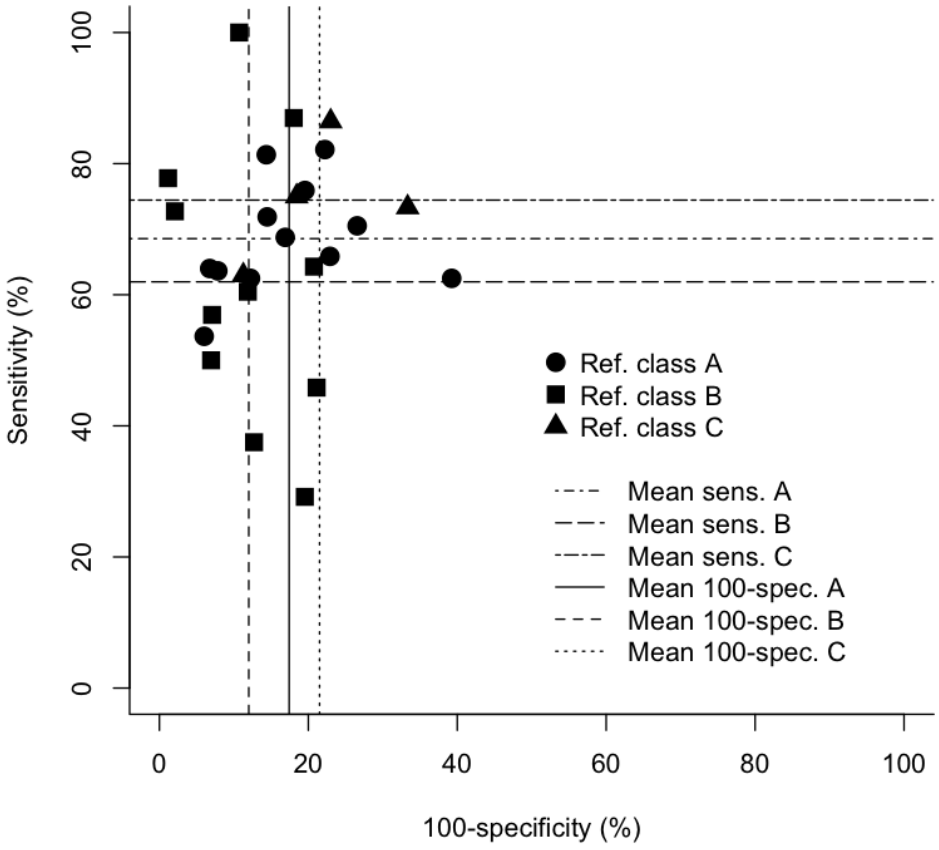
The 27 included studies varied in the detail and emphasis of their reporting, and we did not have the data available to construct a common reference standard. We therefore used the definition of SP from the individual studies. Where studies reported separate results for definite and probable SP pneumonia, we combined the results to create a single category of SP pneumonia. The three reference classes that resulted are listed in Table 2, with the studies that used them. Details of the individual studies are given in End-of-text Table 6.

Table 2 Reference class definition and included studies

Ref. class	Reference definition	Studies
A	Blood positive or sputum (smear or culture) positive or any other respiratory sample positive	Sordé, 2011[21]; Segonds, 2010[20]; Garcia-Suarez, 2007[32]; Lasocki, 2006[35]; Tzeng, 2006[36]; Lauderdale, 2005[37]; Ishida, 2004[9]; Róson, 2004[39]; Stralin, 2004[40]; Butler, 2003[41]; Marcos, 2003[10]; Burel, 2001[41]
B	Blood positive or sputum (smear or culture) positive	Shibli, 2011[27]; Charles, 2008[29]; Weatherall, 2008[18]; Diaz, 2007[31]; Kobashi, 2007[22]; Andreo, 2006[33]; Ercis, 2006[34]; Genne, 2006[8]; Van der Eerden, 2005[38]; Farina, 2002[42]; Murdoch, 2001[44]
C	Blood positive	Johansson, 2010[25]; Perello, 2010[26]; Smith, 2009[28]; Hohenthal, 2008[30]

There was no apparent relationship between the in-study reference standard and the sensitivity and specificity measured by the study (Figure 3; by convention, specificity in percents is plotted as 100-specificity). It is possible that variability due to other causes obscures the differences due to reference standard. Although analytically we treated all patients within a study as having potentially received all tests comprising that study's reference standard, the clinical reality is that they may not have done so. For instance, if a patient could not produce a sputum sample, then that information would not be available.

Figure 3 Individual study sensitivity and specificity (plotted as [100-specificity]), by reference class



4.4.2. Results of meta-analysis

Results of the Bayesian bivariate hierarchical meta-analysis and sensitivity analyses are given in Figure 4 and Figure 5. Using non-informative priors, the pooled sensitivity of BinaxNOW-SP was 74.0% (95% CrI 66.6%, 82.3%) and the pooled specificity was 97.2% (95% CrI 92.5%, 99.8%). The much wider 95% credible intervals around the predicted sensitivity 74.3% (95% CrI 48.8%, 90.9%) and specificity 97.2% (95% CrI 84.4%, 100.0%) in an individual study compared to the pooled sensitivity and specificity reflects the considerable heterogeneity among the 27 studies in these parameters.

Very similar results were obtained using informative prior distributions defined from the reference ranges given in Section 3.2, though the model with the non-informative prior had a better fit as indicated by the Deviance Information Criterion[45] (results not shown). For this reason, we chose to use the results from the analysis with non-informative priors in our calculation of cost-effectiveness, permitting the posterior distribution to reflect the data with minimal influence from the prior. None the less, the ordering and magnitude of the pooled estimates of sensitivity and specificity of the three reference

standards was similar to our prior information providing further support that our final model is reasonable: i) Reference class A: sensitivity 59.4% (43.9%, 76.3%), specificity 98.6% (95.1%, 99.8%), ii) Reference class B: sensitivity 56.2% (35.9%, 80.5%), specificity 97.4% (93.8%, 99.4%), iii) Reference class C: sensitivity 50.3% (24.6%, 78.8%), specificity 98.3% (91.2%, 99.8%). The pooled sensitivity of reference class C was somewhat higher than suggested by the prior information.

The observation of high heterogeneity led us to explore the effect of study characteristics on sensitivity and specificity. Meta-regression analyses that separated diagnostic from etiologic studies, prospective from retrospective studies, and studies within and outside North America or Europe (on the assumption that seasonal cycles and strains of SP, as well as hospital practice, would be similar within western institutions), gave similar results and no reduction of heterogeneity (Figure 4 and 5). We also considered the effect of institution type, with a subgroup analysis of studies conducted in institutions similar to MUHC's (large urban centre, tertiary care, or university associated). Though it appeared that there was less heterogeneity in diagnostic studies, in studies using a prospective design and in studies based in a university centre, there were no statistically significant differences in pooled sensitivity and specificity between the sub-groups. We also examined the effect of prior antibiotic use and average severity of pneumonia in the sub-groups of studies that reported these variables, but we did not find any significant effect. Therefore for the cost analysis we used the sensitivity and specificity estimates obtained from pooling across all 27 studies. For the sensitivity analysis we used the ranges of sensitivity and specificity predicted for an individual study.

Figure 4 Pooled sensitivity estimates from meta-analysis models

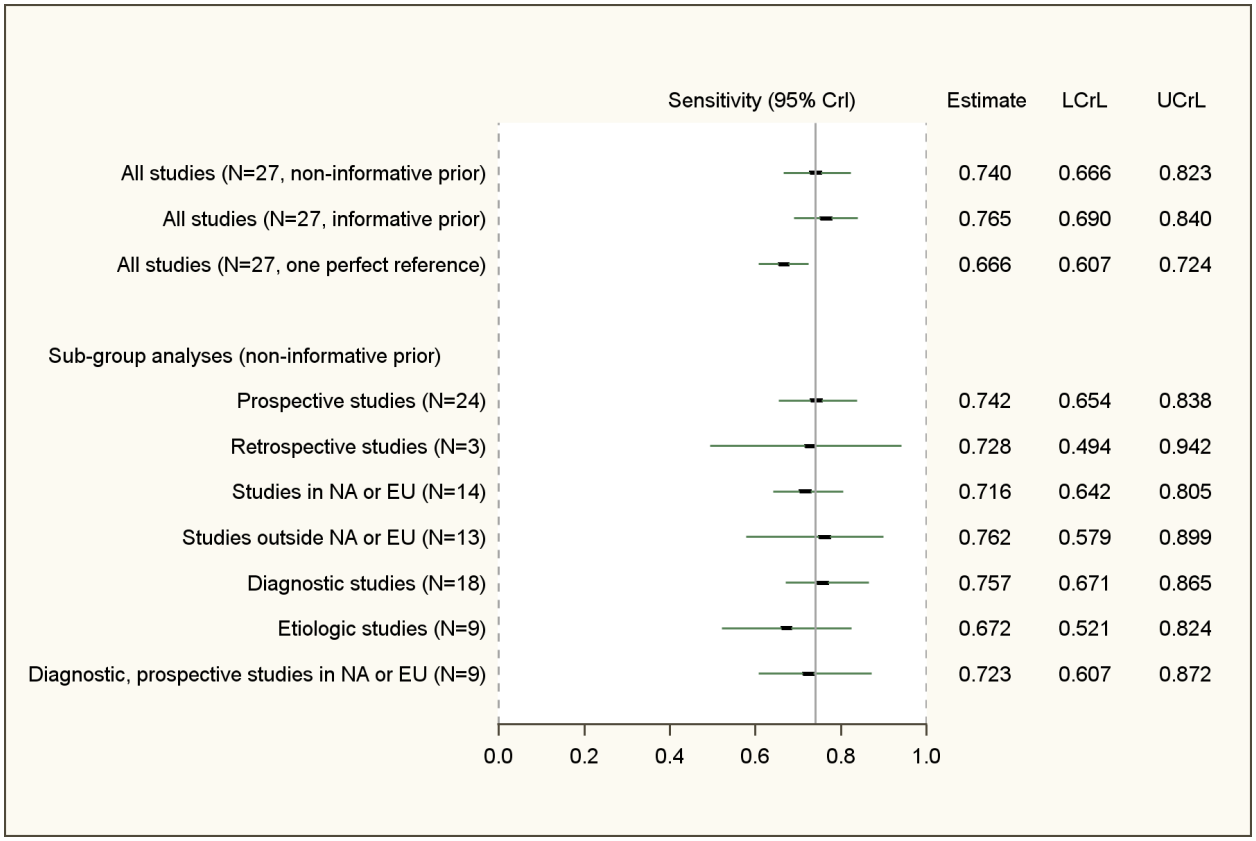
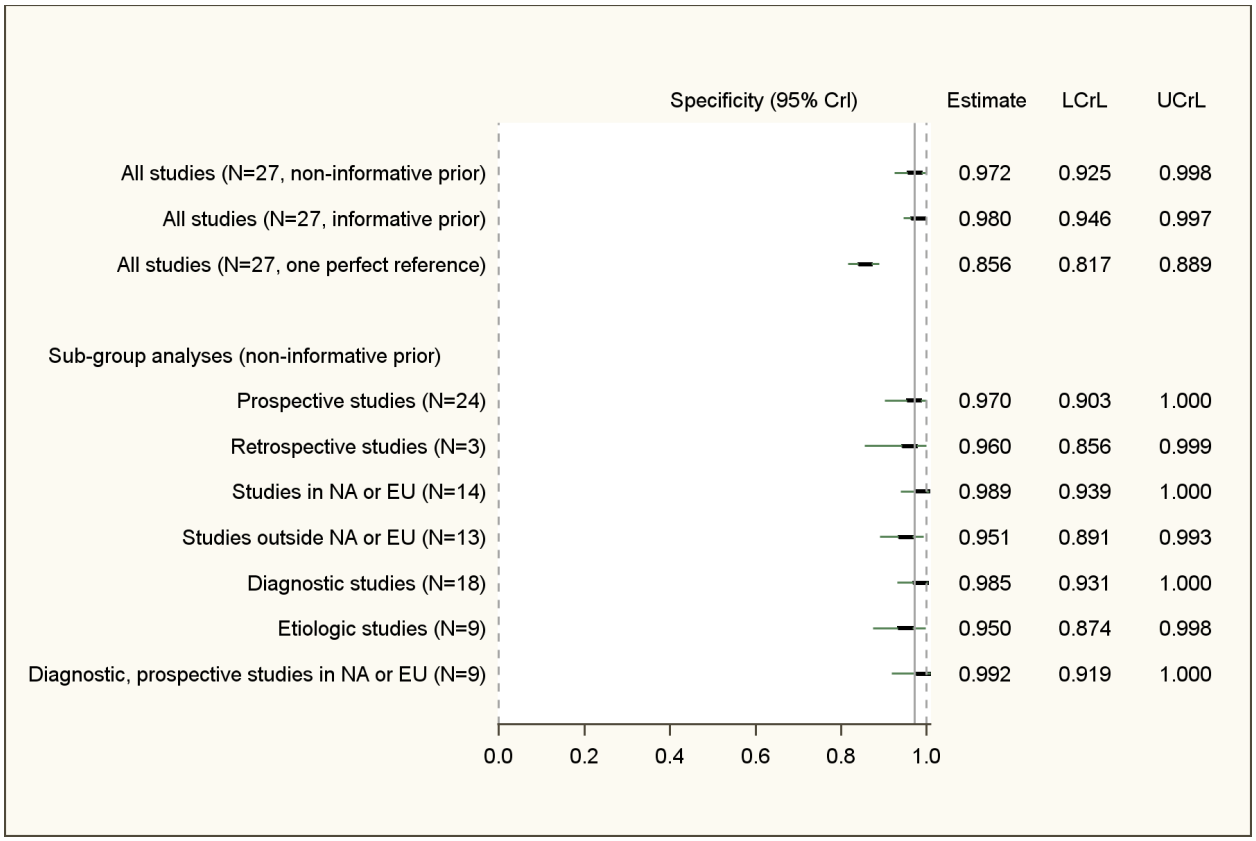


Figure 5 Pooled specificity estimates from meta-analysis models



We found that assuming all studies used the same gold-standard test would result in lower estimates of the pooled sensitivity and specificity of BinaxNOW-SP (Figures 4 and 5). We also conducted the analysis as though the references for each group of studies represented a “gold standard” with sensitivity of 100% and specificity of 100%. For the 12 studies in reference standard A, sensitivity was 68.5% (95% CrI 62.6%, 74.2%), and specificity was 84.2% (95% CrI 77.5%, 89.3%). For the 11 studies in reference standard B, sensitivity was 60.3% (95% CrI 46.4%, 74.4%), and specificity was 89.2% (95% CrI 82.5%, 94.4%). For the 4 studies in reference standard C, sensitivity was 76.7% (95% CrI 49.0%, 93.0%), and specificity was 79.6% (95% CrI 56.3%, 93.1%).

4.5. Cost-effectiveness analysis

Table 3 shows the inputs to the economic model described in Section 3.3. The accuracy of BinaxNOW-SP and all cultures combined (Reference class A) were derived from our meta-analysis, and the costs of antibiotics were based on MUHC data. The pooled sensitivity and specificity estimates from the meta-analysis were used under the

assumption that we expected the performance of the test at the MUHC to resemble the average performance across studies. We used the same operating characteristics for all patients, although there have been conflicting reports in the literature about the impact of severity on sensitivity and specificity of BinaxNOW-SP, with some studies indicating better sensitivity in severe disease [30, 39, 46] and bacteremia[15, 39, 47-49], and others no influence [38, 40, 50]. Since either Penicillin G or ampicillin could be used for the targeted therapy, we arbitrarily selected the cheaper of the two, penicillin, as our base case, and used ampicillin in a sensitivity analysis. The recommended empirical treatment (ceftriaxone plus azithromycin) is only slightly more expensive than the empirical treatment. However, among ICU patients, the alternate empirical treatment (ceftriaxone plus moxifloxacin) is considerably more expensive than the targeted treatment (Penicillin G).

Table 3 Inputs to the economic model

	Value	Source
Efficacy		
Sensitivity of BinaxNOW-SP test, % Median (95% CrI)	74.0 (66.6, 82.3)	Meta-analysis
Specificity of BinaxNOW-SP test, % Median (95% CrI)	97.2 (92.5, 99.8)	Meta-analysis
Sensitivity of all cultures combined, % Median (95% CrI)	59.4 (43.9, 76.3)	Meta-analysis
Specificity of all cultures combined, % Median (95% CrI)	98.6 (95.1, 99.8)	Meta-analysis
True prevalence of SP pneumonia	0.30 (fixed value)	Assumption
Non-response rate of antibiotics used in UA positive & Culture negative branch	Uniform distribution (0.05, 0.15)	
Days of taking antibiotics	Uniform distribution (7, 14)	
Cost		
BinaxNOW-SP test	$38 per test (fixed value)	Micro department, JGH
Ceftriaxone (IV 2 g q 24h x 10 days)	$ 2.60 per day (fixed value)	MUHC pharmacy
Azithromycin (oral 500 mg q Day x 7 days)	$ 1.20 per day (fixed value)	MUHC pharmacy
Moxifloxacin (IV 400 mg q 24h X 10 days)	$ 25.13 per day (fixed value)	MUHC pharmacy
Ampicillin (IV, 2g per 6 hour x 10 days)	$ 7.04 per day (fixed value)	MUHC pharmacy
Penicillin G (IV 8-12 million units/day (given divided q 4 – 6 h) X 10 days)	$ 2.11/vial 10millions per day (fixed value)	MUHC pharmacy

Table 4 shows the results of the cost-effectiveness analysis based on first-line empirical treatment, and Table 5, the results of the cost-effectiveness analysis for the alternate empirical treatment among ICU patients.

Compared with cultures alone, using BinaxNOW-SP plus cultures significantly improves the overall sensitivity by identifying an additional 90/300 or 30% (95% CrI 17%, 41%) of SP patients. Conversely, since any positive test result in either test is considered to be SP, addition of BinaxNOW-SP reduces the specificity, increasing the number of false-positives by about 3% (95% CrI 0%, 7%). In a cohort of 1000 patients with suspected CAP and a true prevalence of 30% of SP pneumonia, this would translate into 90 additional SP pneumonia patients being diagnosed and 21 patients without SP pneumonia being false positive. The overall accuracy (patients correctly classified as either SP or non-SP) is increased by 7.2% (95% CrI 0.4%, 11.7%). In patients treated with first-line empirical treatment, this corresponds to an incremental cost per patient of $36, with an incremental cost per case correctly classified of $501. In ICU patients who receive the more expensive alternate empirical treatment, the increased accuracy corresponds to an incremental cost per patient of $4, and an increase in incremental cost per case correctly classified of $51.

For an estimated 1700 patients with CAP (based on admissions to MGH and RVH during 2008-2009), assuming a 30% prevalence of SP pneumonia and that 170 patients (10%) required ICU admission, routine use of BinaxNOW-SP plus cultures would represent a budget impact of $56,022 (95% CrI $52,938, $58,342) compared to testing for SP pneumonia with culture alone. Assuming test results determine prescribing practices, this would result in the targeted treatment of 457 patients.

Table 4 Cost-effectiveness of diagnosis by BinaxNOW-SP plus cultures versus cultures alone, for first-line empirical treatment in both ICU and non-ICU

	SP patients: N=300	Non-SP patients: N=700	All CAP patients: N=1000	Incremental N (%) of correct classification	Cost per patient ($)	Incremental cost per patient ($)	Incremental cost per case correctly classified
	N / % correctly classified	N / % correctly classified	N / % correctly classified	N / % correctly classified			
Culture test alone	179 (132, 231)/ 59.6 (44.0, 76.9)	691 (666, 699)/ 98.7 (95.2, 99.8)	867 (819, 921) / 86.7(81.9, 92.1)	--	32.90 (24.90, 42.60)	--	--
BinaxNOW-SP plus culture tests	269 (252, 284)/ 89.6 (83.9, 94.5)	670 (630, 693)/ 95.7 (90.0, 99.0)	938 (906, 960)/ 93.8(90.6, 96.0)	72 (4, 117) / 7.2 (0.4, 11.7)	69.10 (61.30, 78.70)	36.20 (35.70, 36.60)	501 (283, 2180)

All results are expressed as median (95% CrI).

Table 5 Cost-effectiveness of diagnosis by BinaxNOW-SP plus cultures versus cultures alone, for alternate treatment in ICU patients

	SP patients: N=300	Non-SP patients: N=700	All CAP patients: N=1000	Incremental N (%) of correct classification	Cost per patient ($)	Incremental cost per patient ($)	Incremental cost per case correctly classified
	N / % correctly classified	N / % correctly classified	N / % correctly classified	N / % correctly classified			
Culture test alone	179 (132, 231)/ 59.6 (44.0, 76.9)	691 (666, 699)/ 98.7 (95.2, 99.8)	867 (819, 921) / 86.7 (81.9, 92.1)	--	246.90 (168.70, 331.20)	--	--
BinaxNOW-SP plus culture tests	269 (252, 284)/ 89.6 (83.9, 94.5)	670 (630, 693)/ 95.7 (90.0, 99.0)	938(906, 960)/ 93.8(90.6, 96.0)	72 (4, 117) / 7.2 (0.4, 11.7)	250.80 (181.70, 327.70)	3.70 (-10.60, 14.60)	51 (0, 418)

All results are expressed as median (95% CrI).

4.5.1. Sensitivity analysis

If ampicillin rather than Penicillin G is used for targeted therapy, the incremental cost and incremental cost per case correctly classified are similar to those in the primary analysis.

We also tested the impact of the prevalence rate of SP on the incremental cost and incremental probability of correct classification (Figure 6, Figure 7). Incremental cost decreases with increasing SP pneumonia prevalence, as more patients receive the lower cost targeted therapy. For patients in the ICU receiving penicillin G as the targeted therapy, the median incremental cost is zero (no extra cost) at a prevalence rate of SP pneumonia around 34%. The incremental probability of correct classification increases with the increasing prevalence rate over the range explored, a trend resulting from the greater sensitivity of BinaxNOW-SP plus culture over culture.

Figure 6 Relation between incremental cost (Canadian $) and prevalence of SP pneumonia in ICU patients receiving alternate therapy

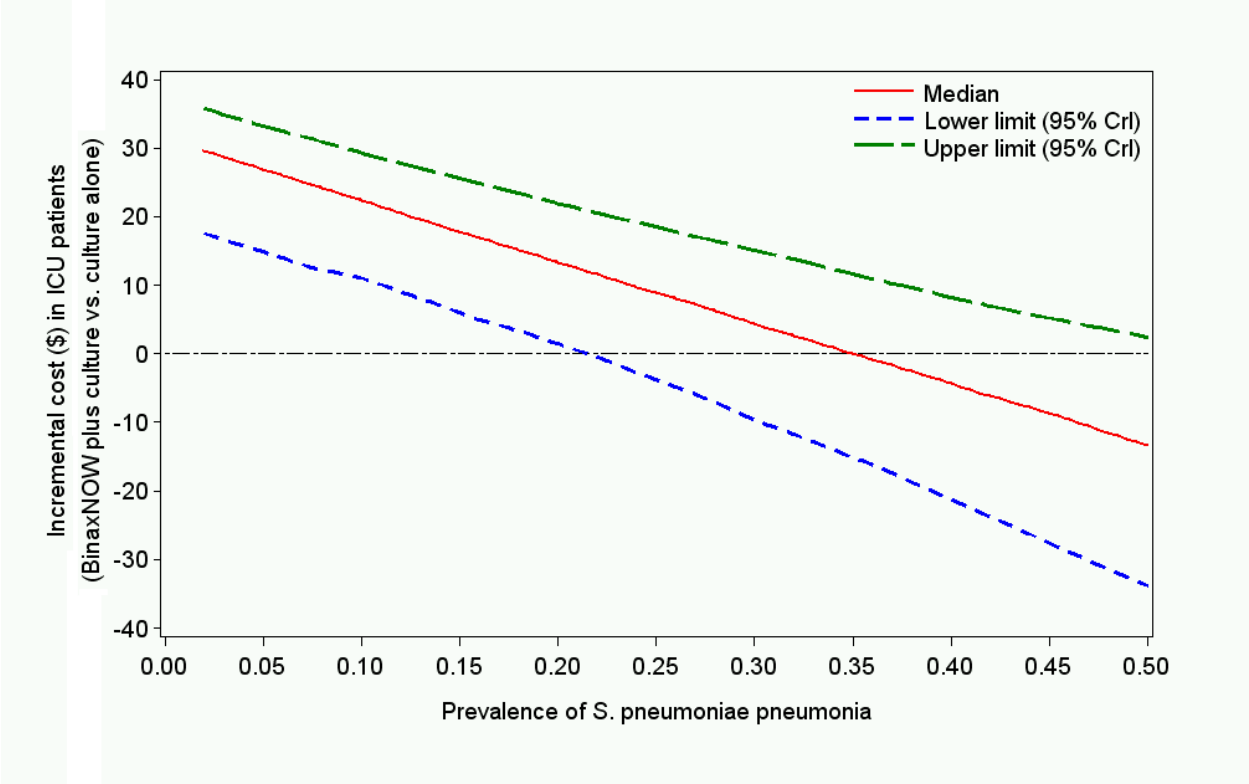
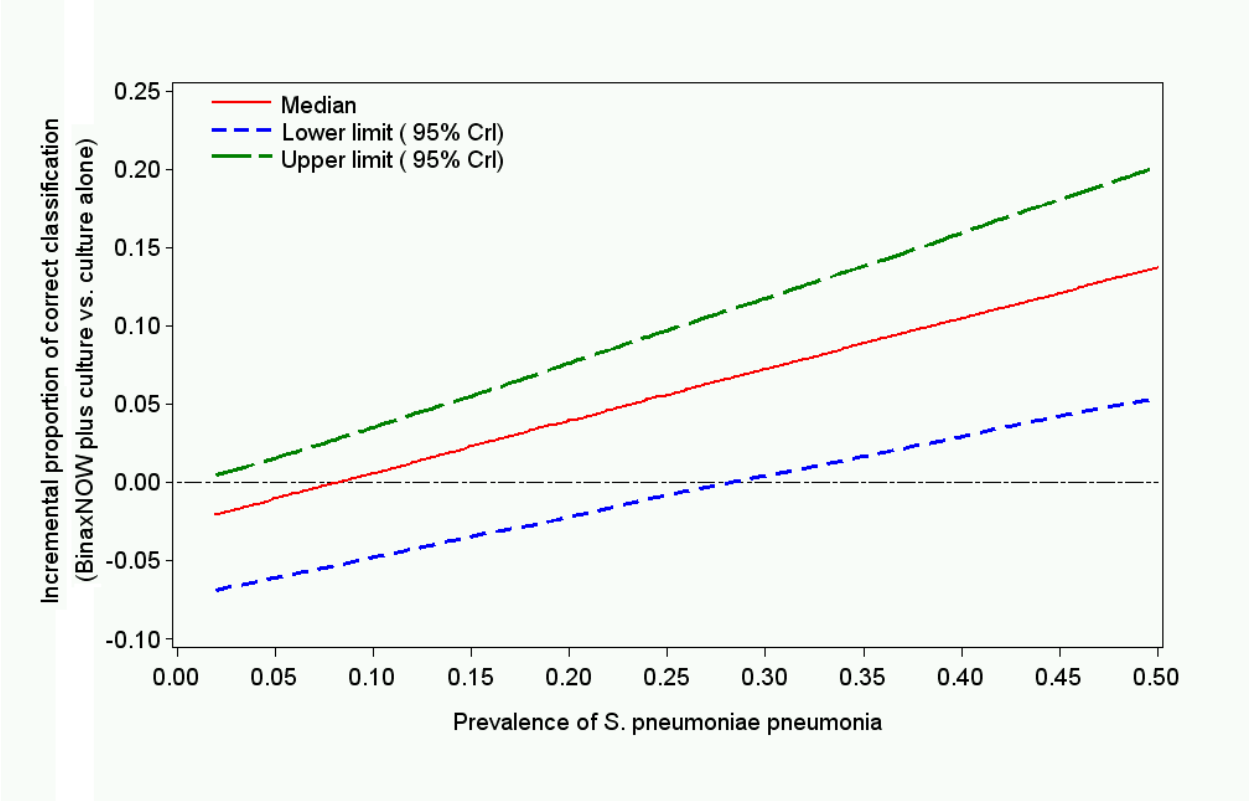


Figure 7 Relation between incremental proportion of correctly classified patients and prevalence of SP pneumonia



5. DISCUSSION

Our systematic review identified 27 studies evaluating the diagnostic accuracy of BinaxNOW-SP for detection of SP pneumonia. Using a meta-analysis model that adjusted for the lack of a perfect reference test, we estimated the pooled sensitivity of BinaxNOW-SP to be 74.0% (95% CrI 66.6%, 82.3%) and the pooled specificity to be 97.2% (95% CrI 92.5%, 99.8%). We estimated that the addition of BinaxNOW-SP to the work-up increases the percentage of SP patients who receive a bacteriological diagnosis by 30% and increases the percentage of correctly classified patients by 7.2% (0.4%, 11.4%). Based on the pooled estimates of sensitivity and specificity and the assumption that the prevalence of SP pneumonia is 30%, our cost-analysis showed that the addition of BinaxNOW-SP to cultures (cultures are required to provide antibiotic sensitivity data) would increase the incremental net cost per patient by $36 for non-ICU patients and by $4 for ICU patients when following the treatment guidelines of the MUHC Pharmacy.

5.1. Results and comparison with the literature

5.1.1. Diagnostic meta-analysis

A previous meta-analysis by Boulware et al[15] based on 24 studies and assuming a single perfect reference test estimated that the pooled sensitivity of BinaxNOW-SP was 74% (95%CI 72%, 77%) and the pooled specificity was 94% (95% CI 93%, 95%). In comparison, our estimate of the pooled specificity was significantly higher. The prediction intervals for both sensitivity and specificity based on our model are much wider as we accounted for between-study heterogeneity and the imperfect nature of the reference test.

Our meta-analysis and that by Boulware had 16 studies in common. However, our extracted numbers did not agree with theirs for all studies, as they included only those cases in which etiology had been established (excluding those with an unknown organism), and we included all those with clinically suspicious CAP whether an infectious aetiology was determined or not. Boulware et al[15] used cases without pulmonary infection as the control group for estimation of specificity, whereas we calculated both sensitivity and specificity from the single group of patients with suspected CAP.

5.1.2. Cost analysis

Like Oostherheert et al[24] our analysis also found that the cost savings due to introducing BinaxNOW-SP were possible only when the empirical treatment was much more expensive than the targeted treatment.

5.2. Limitations of our analysis

5.2.1. Diagnostic meta-analysis

As with any meta-analysis, our results are affected by the quality of the individual studies that we included. We discuss here some of the sources of bias within individual studies and their possible impact.

Risk of bias within each study

Selection bias

Table 9 summarizes risk of bias across individual studies, according to criteria described by the Cochrane Collaboration (see table footnote). Studies generally recruited a representative patient spectrum, and the majority were prospective and recruited consecutive patients. In seven studies verification either was or may have been incomplete (status unclear), and the description did not allow us to eliminate risk of bias.

Blinding

As the BinaxNOW-SP test results could be obtained within 15 minutes of obtaining a urine sample, and culture results would not be available for 24-48 hours, there was the risk of unblinded interpretation of culture results. For three studies, the authors either stated that interpretation was blinded, or the timing as described ensured it. For the remainder, blinding status was unclear. Given that culture is an established method, it is unlikely that knowledge of BinaxNOW-SP test results influenced interpretation of culture result. However, where urine samples were stored, frozen, or transported for later testing (5 studies), it is possible that interpretation of equivocal urine tests might have been influenced by knowledge of the culture results, although descriptions of experience with the tests suggests that there should be few such results.

Misclassification of subjects

For BinaxNOW-SP, the literature has identified the following sources of potential false positive results in adult patients: Cross-reaction with other organisms [35], persistent positive signal from a recent SP infection[15, 49, 51], presence of a mixed infection with another bacterial or viral organism, recent vaccination against SP (there were no reports of the actual risk, but several studies restricted enrolment by patients vaccinated immediately prior) and prior antibiotic treatment.

Recent antibiotic use is known to reduce the diagnostic yield of cultures[2, 11], with SP blood cultures sensitive even to a single dose of antibiotic[2]. In the absence of an effect on BinaxNOW-SP this would increase the rate of false positives and decrease specificity. For cultures, the usual reason for false positive findings is contamination of the sample. This is not expected in samples of body fluids that are normally sterile, for instance blood, but may occur in samples from the respiratory tract. Some studies differentiated between definite and possible SP, with the former being restricted to samples from normally-sterile sites. For the purposes of this analysis, we combined the two, which potentially increased false positive reference tests.

Subgroup analyses in individual studies found decreased sensitivity of BinaxNOW-SP in patients who had received prior antibiotic treatment in some studies[9, 35, 38, 40], but not in others[9, 35, 39, 52]. In those studies that reported prior antibiotic treatment, the proportion of patients who received antibiotics prior to study entry ranged from 16% to 70%.

Sources of error within the meta-analysis

Study heterogeneity

The breadth of the credible intervals around the mean sensitivity and specificity calculated from the pooled meta-analysis, and especially from the predicted value for a new finding, suggests considerable statistical heterogeneity. We conducted sub-group analyses in an attempt to explain heterogeneity due to study design (prospective vs.

retrospective), study purpose (diagnostic vs. etiologic study) and study location (university affiliated hospital vs. other), but did not find any statistically significant differences. We also examined the effect of prior antibiotic use and average severity of pneumonia in the sub-groups of studies that reported these variables, but we did not find any significant effect.

Validity of the model

We used a more sophisticated meta-analysis model than has previously been reported in the literature for this application. Compared to more naive diagnostic meta-analysis models, ours allowed for: i) correlation between sensitivity and specificity across studies, ii) heterogeneity in BinaxNOW-SP performance between studies due to observed study-level covariates as well as unexplained variation, iii) imperfect nature of the reference standard, iv) 3 different types of reference standards in individual studies, and v) heterogeneity in the performance of each type of reference standard across studies. We carried out a series of sensitivity analyses, particularly examining the effect of using informative and non-informative prior distributions for the reference test sensitivity and specificity. The final selected model was one that fit the data the best in terms of the Deviance Information Criterion (DIC) statistic[45].

Our model makes the simplifying assumption that the results of BinaxNOW-SP and the reference test are independent within the sub-group of SP pneumonia patients and the sub-group of non-SP pneumonia patients. This assumption would be violated if there was a patient characteristic, e.g. severity of pneumonia, that caused a correlation between the two tests so that severe cases of SP pneumonia are more likely to be positive on both tests. Such a correlation would result in lower estimates of sensitivity and specificity than those we report. We felt it was not possible to adjust for conditional dependence appropriately due to the lack of patient level data from each study**.** Therefore, it should be noted that the values of sensitivity and specificity we report are estimates that are sensitive to our model, which, though reasonable, cannot be proven to be correct.

5.2.2. Cost analysis

The cost analysis was based on the guideline-recommended use of antibiotics, and did not attempt to model the impact of targeted prescribing on putative reduction of *Clostridium difficile* associated diarrhea or development of antibiotic resistance.

6. CONCLUSIONS

- There is currently no evidence that the introduction of BinaxNOW-SP influences physicians' prescribing habits. Observational studies examining this question were inconclusive.
- Our meta-analysis shows that addition of BinaxNOW-SP to the diagnostic work-up of patients with suspected CAP may, in addition to providing an earlier bacteriological diagnosis, result in an increase in the percentage of SP pneumonia cases diagnosed by 30% (95% CrI 17%, 41%). This would be, accompanied by a smaller increase in the percentage of false-positive cases 3% (95% CrI 0%, 7%). Note that the credible intervals around these estimates are very wide due to the heterogeneity in sensitivity and specificity estimates across individual studies.
- Assuming that BinaxNOW-SP does influence prescribing practice, our cost-analysis showed that the addition of BinaxNOW-SP to the work-up will result in an incremental net cost of $36.2 (95% CrI $35.7, $36.6) per patient in a regular ward and $3.7 (95% CrI -$10.6, $14.6) per patient in the ICU, despite cost-savings from using targeted treatment. It should be noted that our estimates ignore the possible decrease in cost due to reduced risk of nosocomial infections. Cultures will continue to be required to provide information about antibiotic resistance.
- For 1700 patients with pneumonia (estimated admissions to MGH and RVH over one year), assuming that 170 (10%) required ICU admission, that represents a budget impact of $56,022 (95% CrI $52,938,$58,342). Assuming test results determine prescribing practices, this would result in the targeted treatment of 457 patients.
- The limited evidence available suggests that this change of therapy would produce no measurable benefit to the individual patient. We do not presently have the information to quantify the indirect benefits of improved antibiotic stewardship.

7. RECOMMENDATIONS

We recommend that Binax-NOW not be used in the routine testing of patients suspected of community acquired pneumonia. Any use that takes place should be carried out within a protocol, to be determined by the Departments of Microbiology and Infection Control, with the objective of defining the value of this

test. This issue should be reviewed in one year at which time usage and value of this test should be reviewed.

TABLES

Table 6 Design and outcome of studies reporting diagnosis of *S pneumoniae* community acquired pneumonia using BinaxNOW

Reference	Patients, country	CAP definition	Strep pneumonia	
			Definite	Probable
Sordé, 2011[21]	Hospitalized adults ≥ 16 y with CAP, admitted. Spain.	Clinical signs/symptoms with pulmonary infiltrate on CXR	blood+ or pleural fluid+ or PCR (pleural fluid)+	sputum+
Johansson, 2010[25, 53]	Hospitalized adults with CAP. Sweden.	Clinical signs/symptoms with pulmonary infiltrate on CXR	blood+ or pleural fluid+ or bronchiolar lavage+ or BinaxNOW-SP+	sputum+
Perello, 2010[26]	Hospitalized adults with HIV. Spain.	By criteria of Infectious Diseases Society of America.	blood+	ND
Segonds, 2010[20]	Hospitalized adults >18 years with BinaxNOW-SP test. France.	Not provided	blood+ or pleural fluid+	sputum+ or bronchial lavage+ or BinaxNOW-SP+
Shibli, 2010[27]	Adults ≥18 years with CAP, admitted to hospital. Israel.	Clinical signs/symptoms of LRTI with pulmonary infiltrate on CXR	ND	ND
Smith, 2009[28]	Hospitalized adults with blood+ CAP; hospitalized adults with CAP, blood-. UK.	Clinical signs/symptoms with pulmonary infiltrates on CXR	blood+	clinical CAP with specific features
Charles, 2008[29]	Hospitalized adults >18 years with CAP. Australia.	Clinical signs/symptoms with pulmonary infiltrate CXR	blood+ or sputum+ or BinaxNOW-SP+	sputum+ (without gram stain+)
Hohenthal, 2008[30]	Hospitalized adults ≥16 years with CAP. Finland.	Clinical signs/symptoms with pulmonary infiltrate on CXR	blood+ or pleural fluid+	BinaxNOW-SP+ or sputum+
Weatherall, 2008[18]	Adults >14 years with CAP. Australia.	Clinical diagnosis of pneumonia with CXR infiltrate	ND	ND
Diaz, 2007[31]	Hospitalized adults ≥16 y with CAP. Chile.	Clinical signs/symptoms with pulmonary infiltrate on CXR	blood+ or BinaxNOW-SP+	sputum+

Reference	Patients, country	CAP definition	Strep pneumonia	
			Definite	Probable
Garcia-Suarez, 2007[32]	Adults with serious community acquired bacterial infection, SP pneumonia subgroup. Spain.	Clinical signs/symptoms with pulmonary infiltrate on CXR	blood+ or pleural fluid+	sputum+, tracheal aspirate+
Kobashi, 2007[22]	Adults >15 years with CAP, admitted to hospital. Japan.	Clinical features c/w pneumonia, plus CXR with infiltrate.	blood+ or pleural fluid+ or sputum+	ND
Andreo, 2006[33]	Adults ≥16 years with CAP, admitted to hospital. Spain.	Clinical signs/symptoms with pulmonary infiltrate on CXR and treatment with antibiotic	blood+ or pleural fluid+ or transthoracic needle aspirate+ or BinaxNOW-SP+	sputum+
Ercis, 2006[34]	Adults with CAP, admitted to hospital. Turkey.	Clinical signs/symptoms (no diagnostic imaging)	blood+ or sputum+	ND
Genne, 2006[8]	Adults >18 years with CAP, admitted to hospital. Switzerland.	Clinical signs/symptoms with pulmonary infiltrate on CXR	blood+ or sputum or micro+ from resp	ND
Lasocki, 2006[35]	Adults with CAP, admitted to ICU. France.	Clinical signs/symptoms with pulmonary infiltrate on CXR	blood+ or sputum+ or micro+ from resp tract	ND
Tzeng, 2006[36]	Adults with RTI symptoms. Taiwan.	LRTI defined as clinical symptoms with CXR showing pulmonary involvement	blood+ or pleural fluid+ or sputum+	ND
Lauderdale, 2005[37]	Hospitalized adults >16 y with CAP. Taiwan.	Clinical signs/symptoms with pulmonary infiltrate on CXR	blood+ or pleural fluid+ or (sputum+ AND BinaxNOW-SP+)	sputum+ or BinaxNOW-SP+
Van der Eerden, 2005[38]	Hospitalized adults ≥ 18 y with CAP. Denmark.	Clinical signs/symptoms with pulmonary infiltrate on CXR.	blood+ or pleural fluid+ or pleural fluid antigen+	sputum+ or BinaxNOW-SP+
Ishida, 2004[9]	Adults >15 years hospitalized with CAP. Japan.	Clinical signs/symptoms with pulmonary infiltrate on CXR	blood+ or pleural fluid+	sputum+
Róson, 2004[39]	Adults with CAP, admitted to hospital. Non-severe	Acute resp illness plus CXR with infiltrate.	blood+ or sputum+	ND

Reference	Patients, country	CAP definition	Strep pneumonia	
			Definite	Probable
	immunosuppression. Spain.			
Strålin, 2004[40]	Adults with CAP, admitted to hospital. Denmark.	Acute illness, consolidation on CXR, clinical signs/symptoms.	blood+ or sputum+ or nasopharynx+	ND
Butler, 2003[41]	Adults with febrile respiratory illness; subgroup with CAP. US.	Clinical signs/symptoms with pulmonary infiltrate on CXR	blood+ or culture+ from normally sterile body site	sputum+ and CXR consolidation
Marcos, 2003[10]	Adults ≥18 y with CAP, admitted to hospital. Spain.	Clinical signs/symptoms with pulmonary infiltrate on CXR.	blood+ or pleural fluid+ or TBAS+ or BAL+	sputum+
Farina, 2002[42]	Adults with CAP, hospitalized. Italy.	Clinical signs/symptoms with pulmonary infiltrate on CXR.	blood+ or respiratory specimen+	ND
Burel, 2001[43]	Adults with CAP, admitted to hospital. France.	"Clinical and radiological evidence of CAP"	blood+ or sputum+ or BAL+ or trach aspirate+ or pleural fluid+ or latex agglutination+	ND
Murdoch, 2001[44]	Adults with CAP, admitted to hospital. New Zealand.	Clinical signs/symptoms with pulmonary infiltrate on CXR.	blood+ or sputum+	ND

Abbreviations: blood+, positive blood culture; sputum+, positive Gram stain and/or sputum culture; pleural fluid+, positive culture from pleural fluid; nasopharynx+, positive culture from the nasopharynx; BAL+, positive culture from bronchiolar lavage; respiratory+, positive culture from any respiratory sample; BinaxNOW-SP+, positive urinary BinaxNOW-SP test (to be included in the meta-analysis, studies had to report sufficient detail to separate these results into true and false positives).

CAP, community acquired pneumonia; CXR, chest X-ray; ND, not defined; RTI, respiratory tract infection.

Table 7 Patient characteristics in studies reporting diagnosis of *S pneumonia* community acquired pneumonia using BinaxNOW

Reference	Age (mean) (Years)	Gender M / F % / %	Severity PSI IV+V %	Prior antibiotics %	Immuno-suppressed %
Sordé, 2011[21]	64	67 / 33	58.2		20.3
Johansson, 2010[25]	61	51 / 49		22	
Perello, 2010[26]	43	65 / 35	Apache-II≥12 48%		100
Segonds, 2010[20]					
Shibli, 2010[27]	58	58 / 42			Excluded
Smith, 2009[28]	63; 67 (med)				
Charles, 2008[29]	65	61 / 39	53.5	31	Excluded
Hohenthal, 2008[30]	50	52 / 48	23	29	Excluded
Weatherall, 2008[18]	79 (med)	56 / 44	40	26	
Diaz, 2007[31]	66	52 / 48	61	33	Excluded
Garcia-Suarez, 2007[32]	60	64 / 36			
Kobashi, 2007[22]	62	71 / 29	26	45	12
Andreo, 2006[33]	59	70 / 30		26	Excluded
Ercis, 2006[34]	18-86	64 / 36			7
Genne, 2006[8]	68	57 / 43	PSI (mean) 106		
Lasocki, 2006[35]	69	66 / 34	SAPS-II (med) 46	70	
Tzeng, 2006[36]					
Lauderdale, 2005[37]	56	64 / 36		16	1.2
Van der Eerden, 2005[38]	64	54 / 46	44.3	26	Excluded
Ishida, 2004[9]	65	65 / 35	27		
Róson, 2004[39]	66	71 / 29	35	18	
Strålin, 2004[40]	71	53 / 47	39	27	
Butler, 2003[41]	45	70 / 30			Excluded
Marcos, 2003[10]	50	79 / 21			21
Farina, 2002[42]					
Burel, 2001[43]					
Murdoch, 2001[44]	68 (med)	51 / 49		76	

Age is mean age unless otherwise indicated

Table 8 Results for studies reporting diagnosis of *S pneumonia* community acquired pneumonia using BinaxNOW-SP

Reference	N CAP[a]	True positive[b]	False positive[c]	False negative[d]	True negative[e]	Reference class
Sordé, 2011[21,f,g]	474	55	81	23	224	A
Johansson, 2010[25,h]	184	17	16	10	126	C
Perello, 2010[26,h]	129	11	27	4	54	C
Segonds, 2010[20,f]	278	16	15	9	207	A
Shibli, 2011[27]	126	3	15	5	103	B
Smith, 2009[28,f,h,i]	159	51	23	8	77	C
Charles, 2008[29,f,g]	885	37	58	28	762	B
Hohenthal, 2008[30,f,h]	384	27	54	9	239	C
Weatherall[18,], 2008	59	3	6	0	50	B
Diaz, 2007[31,f]	176	7	25	17	103	B
Garcia-Suarez, 2007[32,f,j]	268	48	30	11	179	A
Kobashi, 2007[22,f]	156	20	24	3	109	B
Andreo, 2006[33,f]	107	10	5	10	67	B
Ercis, 2006[34,k]	59	8	1	3	47	B
Lasocki, 2006[35]	108	23	11	9	65	A
Genne, 2006[8,k]	67	9	11	5	42	B
Tzeng, 2006[36,l]	747	21	56	12	658	A
Lauderdale, 2005[37,f,g,m]	448	11	24	5	118	A
Van der Eerden, 2005[38,f,g]	262	26	26	17	193	B

[a] Number of patients with community acquired pneumonia recruited into the study
[b] Number of patients with positive findings for both BinaxNOW-SP and the reference test
[c] Number of patients with negative reference test but positive BinaxNOW-SP test
[d] Number of patients with positive reference test but negative BinaxNOW-SP test
[e] Number of patients with negative findings for both BinaxNOW-SP and the reference test
[f] Definitive and probable SP pneumonia were combined into a single category of SP pneumonia.
[g] Authors' definition of SP included a positive BinaxNOW-SP result. Patients diagnosed solely on the basis of a positive BinaxNOW-SP were treated as false positive results in our analysis.
[h] Complete data to construct a 2x2 table provided only for positive blood culture as a reference standard.
[i] Results for the total number of CAP cases derived from the summation of the authors' categories "Pneumococcal bacteremia, With pneumonia" and "Nonbacteremic Pneumonia, Combined subtotal"
[j] Results from the total number of CAP cases derived from the summation of the authors' categories "Pneumococcal infection, Pneumonia", "Pneumococcal infection, Probable pneumococcal pneumonia", "Nonpneumococcal infections, Pneumonia", and "Unknown etiology pneumonia".
[k] Data used from those patients with CAP. Data from control patients omitted.
[l] Data used for those patients with lower respiratory tract infections (LRTIs)
[m] Analysis restricted to a subset of patients with complete data.

Reference	N CAP[a]	True positive[b]	False positive[c]	False negative[d]	True negative[e]	Reference class
Ishida, 2004[9,f]	349	63	52	20	214	A
Róson, 2004[39]	220	27	41	14	138	A
Stralin, 2004[40]	215	44	8	38	125	A
Butler, 2003[41,f]	149	25	42	15	65	A
Marcos, 2003[10,f]	398	75	34	45	244	A
Farina, 2002[42]	104	14	1	4	85	B
Burel, 2001[43]	91	23	14	5	49	A
Murdoch,2001[44]	420	33	87	39	325	B

Table 9 Risk of bias in studies reporting diagnosis of *S pneumonia* community acquired pneumonia using BinaxNOW

Reference	Representative patient spectrum?[a]	Acceptable ref. standard?[b]	Acceptable time between tests?[c]	No partial verification?[d]	No differential verification?[e]	No incorporation ?[f]
Sordé, 2011[21]	Yes	No (A)	Yes: both as part of diagnostic workup.	Unclear - 129/474	Unclear	Yes (data separable)
Johansson, 2010[25]	Yes	No (C)	Yes, within 1 day	Yes	Yes	Yes
Perello, 2010[26]	No - all HIV	No (C)	Yes: sample at admission	Unclear - 96/129	Unclear	Yes
Segonds, 2010[20]	Yes	No (A)	Unclear: timing not given	Unclear - 247/278	Unclear	Yes (data separable)
Shibli, 2010[27]	Yes	No (B)	Yes: sample at admit	Yes	Yes	Yes
Smith, 2009[28]	Yes	No (C)	Unclear: blood obtained within 24h abx start	Yes	Yes	Yes
Charles, 2008[29]	Yes	No (B)	Unclear: within 48h	Yes	Yes	Yes (data separable)
Hohenthal, 2008[30]	Yes	No (C)	Unclear	Unclear	Yes	Yes
Weatherall, 2008[18]	Yes	No (B)	Yes	Yes	Yes	Yes
Diaz, 2007[31]	Yes	No (B)	Unclear: time of BinaxNOW-	Yes	Yes	Yes

[a] Was the spectrum of patients representative of the patients who will receive the test in practice?
[b] Was the reference standard likely to classify the target condition correctly? The letter in brackets indicates the reference class.
[c] Was the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
[d] Did the whole sample or a random selection of the sample, receive verification using the intended reference standard?
[e] Did patients receive the same reference standard irrespective of the index test result?
[f] Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?

Reference	Representative patient spectrum?[a]	Acceptable ref. standard?[b]	Acceptable time between tests?[c]	No partial verification?[d]	No differential verification?[e]	No incorporation ?[f]
			SP not given			
Garcia-Suarez, 2007[32]	Yes	No (A)	Yes: samples drawn day 1	Yes	Yes	Yes
Kobashi, 2007[22]	Yes	No (B)	Unclear: BinaxNOW-SP at "acute stage"	Yes	Yes	Yes
Andreo, 2006[33]	Yes	No (B)	Unclear: urine stored frozen	Unclear - 92/107	Unclear	Yes (data are separable)
Ercis, 2006[34]	Yes	No (B)	Yes	Unclear - 52/59	Unclear	Yes
Genne, 2006[8]	Yes	No (B)	Unclear: taken at admit, but allowed up to 6 days.	Yes	Yes	Yes
Lasocki, 2006[35]	No - ICU	No (A)	Unclear: ICU	Yes	Yes	Yes
Tzeng, 2006[36]	Yes	No (A)	Unclear	Yes	Yes	Yes
Lauderdale, 2005[37]	Yes	No (A)	Unclear: urine stored frozen	Unclear – subset with all tests	Yes	Yes
Van der Eerden, 2005[38]	Yes	No (B)	Yes: sample at admission	Yes	Yes	Yes
Ishida, 2004[9]	Yes	No (A)	Yes	Yes	Yes	Yes
Róson, 2004[39]	Yes, but minority ambulatory	No (A)	Unclear	Yes	Yes	Yes
Stralin, 2004[40]	Yes	No (A)	Unclear: urine stored frozen	Yes	Unclear	Yes
Butler, 2003[41]	Yes	No (A)	Unclear	Yes: 147/149	Yes	Yes
Marcos, 2003[10]	Yes	No (A)	Yes	Yes	Yes	Yes
Farina, 2002[42]	Yes	No (B)	Unclear	Yes	Yes	Yes
Burel, 2001[43]	Yes	No (A)	Unclear	Yes	Yes	Yes
Murdoch, 2001[44]	Yes	No (B)	Yes	Yes	Yes	Yes

Table 9 (cont) Risk of bias in studies reporting diagnosis of *S pneumonia* community acquired pneumonia using BinaxNOW

Reference	Index results blinded?[a]	Ref. results blinded?[b]	Same clinical info?[c]	Uninterpretable results explained?[d]	Withdrawals explained?[e]
Sordé, 2011[21]	Unclear	Yes	Yes	None described	No
Johansson, 2010[25]	Unclear	Unclear	Yes	None described	All tested
Perello, 2010[26]	Yes	Unclear	Unclear	None described	No
Segonds, 2010[20]	Unclear	Unclear	Unclear	None described	No
Shibli, 2010[27]	Unclear	Unclear	Yes	None described	All tested
Smith, 2009[28]	Yes: "tested prospectively"	Unclear	Unclear	None described	All tested
Charles, 2008[29]	Unclear: within 48h	Unclear	Yes	None described	All tested
Hohenthal, 2008[30]	Unclear	Unclear	Yes	None described	All tested
Weatherall, 2008[18]	Yes: tested in ED	Unclear	Yes	None described	All tested
Diaz, 2007[31]	Unclear	Unclear	Yes	None described	All tested
Garcia-Suarez, 2007[32]	Unclear: samples were stored	Yes	Yes	None described	All tested
Kobashi, 2007[22]	Yes: stated	Unclear	Yes	None described	All tested
Andreo, 2006[33]	Unclear: urine frozen	Unclear	Unclear	None described	No
Ercis, 2006[34]	Unclear	Unclear	Yes	None described	No
Genne, 2006[8]	Unclear: timing?	Yes	Yes	None described	All tested
Lasocki, 2006[35]	Unclear: timing?	Unclear: ICU, so possible	Unclear:	None described	All tested

[a] Were the reference standard results interpreted without knowledge of the results of the index test? Were the index test results interpreted without knowledge of the results of the reference standard?
[b] Were the index test results interpreted without knowledge of the results of the reference standard?
[c] Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
[d] Were uninterpretable/ intermediate test results reported?
[e] Were withdrawals from the study explained?

Reference	Index results blinded?[a]	Ref. results blinded?[b]	Same clinical info?[c]	Uninterpretable results explained?[d]	Withdrawals explained?[e]
		later investigations	timing?		
Tzeng, 2006[36]	Unclear	Unclear	Yes	None described	All tested
Lauderdale, 2005[37]	Unclear: samples were stored	Unclear	Yes	None described	No - stated did not have samples
Van der Eerden, 2005[38]	Unclear	Unclear	Yes	None described	All tested
Ishida, 2004[9]	Yes: tested at admit	Unclear	Yes	None described	All tested
Róson, 2004[39]	Unclear	Unclear	Yes	None described	All tested
Stralin, 2004[40]	Yes: explicitly stated	Yes	Yes	Yes: described equivocal	All tested
Butler, 2003[41]	Unclear: frozen urine	Unclear	Yes	None described	All but 2 tested
Marcos, 2003[10]	Unclear	Unclear	Yes	None described	All tested
Farina, 2002[42]	Unclear	Unclear	Yes	None described	All tested
Burel, 2001[43]	Unclear	Unclear	Yes	None described	All tested
Murdoch, 2001[44]	Unclear: transported for testing	Unclear	Yes	None described	All tested

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APPENDICES

Appendix 1 Search strategies

Search 1 used plain text in PubMed and OVID, mapped to keywords, and did not attempt to narrow to diagnostic studies.

```
pneumonia.mp AND ((bacterial antigens.mp. or Antigens, Bacterial/) AND
urin$.mp) OR binax.mp OR urine antigens.mp)
with limits (language EN, FR; humans; age (adult, all NOT child)
```

Use of wildcards was also explored in OVID, to expand the search:

```
pneumococc$ AND ((urin$ AND antigen$) OR (BinaxNOW OR Binax))
```

Search 2 as designed by a reference librarian, used a diagnostic subheading

```
EMBASE 1996 to 2011 Week 16
1 exp antigen/ 563036
2 exp urine/ 20974
3 binax.mp. 242
4 binaxnow.mp. 33
5 exp bacterial polysaccharide/ 2842
6 or/1-5 585560
7 exp Streptococcus pneumoniae/ 18847
8 6 and 7 1325
9 exp pneumonia/di, ep [Diagnosis, Epidemiology] 22179
10 exp pneumococcal infection/di, ep [Diagnosis, Epidemiology] 803
11 exp diagnosis/ 2022744
12 exp pneumonia/ 93882
13 exp pneumococcal infection/ 3983
14 or/12-13 95231
15 11 and 14 32173
16 9 or 10 or 15 42572
17 8 and 16 197
18 limit 17 to yr="2000 -Current" 180
19 limit 18 to (english or french) 168
20 limit 19 to animals 8
21 19 not 20 160
22 limit 21 to (embryo or infant or child or preschool child <1 to 6 years>
or school child <7 to 12 years>) 28
23 limit 22 to (adolescent <13 to 17 years> or adult <18 to 64 years> or
aged <65+ years>) 11
24 21 not 22 132
25 23 or 24 143
26 from 25 keep 1-143 143
```

EMBASE 1996 to April Week 2 2011

Database(s): Ovid MEDLINE(R) without Revisions 1996 to April Week 2 2011

Search Strategy:

```
# Searches Results
1 exp Antigens, Bacterial/ur [Urine] 254
2 exp Antigens, Bacterial/ 60973
3 exp Urine/ 6322
4 2 and 3 66
5 exp Antigens/ 438453
6 exp Polysaccharides, Bacterial/ 42109
7 5 and 6 41873
8 binax.mp. 124
9 binaxnow.mp. 20
10 or/1-9 444781
11 exp Streptococcus pneumoniae/im, ip [Immunology, Isolation &
Purification] 4409
12 10 and 11 1062
13 exp Pneumonia/di, ep [Diagnosis, Epidemiology] 8763
14 exp Pneumococcal Infections/di, ep [Diagnosis, Epidemiology] 2963
15 13 or 14 11009
16 12 and 15 233
17 limit 16 to (english or french) 211
18 limit 17 to yr="2000 -Current" 187
19 limit 18 to animals 3
20 18 not 19 184
21 limit 20 to ("newborn infant (birth to 1 month)" or "infant (1 to 23
months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)")
114
22 limit 21 to ("all adult (19 plus years)" or "adolescent (13 to 18
years)") 55
23 20 not 21 70
24 22 or 23 125
```

Medline In-Process & Other Non-Indexed Citations April 27, 2011

```
1 binax.mp. 9
2 binaxnow.mp. 4
3 antigen*.mp. 10030
4 pneumo*.mp. 6160
5 3 and 4 233
6 streptococcus.mp. 1757
7 urin*.mp. 8971
8 6 or 7 10701
9 5 and 8 54
10 1 or 2 or 9 60
11 limit 10 to (english or french) 57
12 limit 11 to yr="2000 -Current" 43
```

Searches were combined in a reference manager database, filtered for duplicate entries, and then reviewed for inclusion/exclusion criteria.

Appendix 2 Patients admitted with pneumonia to RVH and MGH, fiscal years 2008-2009

	Respiratory admissions	Diagnosed with pneumonia	Diagnosed with SP
RVH (ICU)	915	342	4
RVH (non-ICU)	726	466	12
RVH (total)	1641	808	16
MGH (ICU)	972	410	26
MGH (non-ICU)	781	482	21
MGH (total)	1753	892	47
TOTAL	3394	1700	63