Published in final edited form as:
J Infect. 2007 October ; 55(4): 300–309.

RAPID DIAGNOSIS OF PNEUMOCOCCAL PNEUMONIA AMONG HIV-INFECTED ADULTS WITH URINE ANTIGEN DETECTION

David R Boulware, M.D., M.P.H., D.T.M. & H.[1], **Charles L. Daley, M.D.**[2], **Cynthia Merrifield, R.N.**[3], **Philip C. Hopewell, M.D.**[3], and **Edward N. Janoff, M.D.**[4]

1 *Division of Infectious Disease and International Medicine, Department of Medicine, University of Minnesota, MMC 250, 420 Delaware St. SE, Minneapolis, Minnesota 55455, USA*

2 *Division of Mycobacterial and Respiratory Infections, National Jewish Medical and Research Center, 1400 Jackson Street, Denver, Colorado 80206 USA*

3 *Division of Pulmonary and Critical Care Medicine, San Francisco General Hospital, University of California, San Francisco General Hospital, Box 0809, Bldg NH 2A2, San Francisco, California 94143, USA*

4 *Division of Infectious Disease, Department of Medicine, Colorado Center for AIDS Research, University of Colorado at Denver and Health Sciences Center, Box 168, SOM Room 1813, 4200 E 9th Ave., Denver, Colorado 80262, USA*

Abstract

Objectives—*Streptococcus pneumoniae* is the leading cause of bacterial pneumonia and associated bacteremia during HIV infection. Rapid diagnostic assays may limit inappropriate therapy.

Methods— Clinical signs and symptoms and sera and urine were collected prospectively from 70 adults with pneumococcal pneumonia, including 47 with HIV co-infection. Pneumococcal C-polysaccharide antigen was detected in urine using the Binax® immunochromatographic test (ICT). A systematic review of 24 published studies was conducted.

Results— Clinical symptoms, signs, and laboratory parameters except leukocytosis, were similar in HIV-infected and HIV-seronegative pneumonia. The performance of the urine antigen ICT was independent of HIV-status (sensitivity 81%, specificity 98%, positive (PPV) and negative predictive values (NPV) 98%, and 82%, respectively). The sensitivity of sputum Gram's stain was 58% [34/59] with sputum unable to be provided by 16%. The CRP response was identical in HIV-infected (mean ± SD) 133 ± 88 vs. seronegative 135 ± 104 mg/L (p=0.9). In the systematic review, the ICT performance revealed 74% sensitivity (95% CI: 72% to 77%) and 94% specificity (95% CI: 93% to 95%). Urine antigen testing increases etiologic diagnosis by 23% (Range: 10% –59%) when testing adults with community acquired pneumonia of unknown etiology.

Conclusions— Urinary antigen detection provides a credible rapid diagnostic test for pneumococcal pneumonia regardless of HIV-status. CRP response to acute infection is similar in HIV co-infection and increases diagnostic certainty.

Corresponding Author: David R Boulware, MD, DTM&H, Telephone: 612.624.9996, Fax: 612.625.4410, Email: Boulw001@umn.edu

There are no conflicts of interest.

Binax was not involved in the design and conduct of this study. We thank Binax® NOW for providing the test kits for the study."

Keywords

HIV; pneumonia; community acquired pneumonia; streptococcus pnuemoniae; pneumococcal; diagnosis; c-reactive protein; sensitivity

INTRODUCTION

Streptococcus pneumoniae is the leading cause of community acquired pneumonia (CAP), the 6th leading cause of death overall and the leading cause of infectious disease deaths.[1,2,3,4,5] In England and Wales, the rates of invasive pneumococcal disease are at near 10 per 100,000 general population.[6] Among HIV-infected adults, rates of CAP are 5–10 fold higher than in age-matched populations, and bacteremic pneumonia occurs 35–50 times more commonly.[7,8,9,10] Rates in an HIV population approach 0.4–8 per 100 patient years in the U.S. and 1–4 per 100 person years in Sub-Saharan Africa.[8,10,11,12] Despite the beneficial effects of HAART and the paediatric conjugate pneumococcal vaccination on the reducing the rates of CAP in the past decade, HIV-infected adults still comprise 24% of U.S. invasive pneumococcal disease and 28% of pneumonia deaths in British young-adults[13,14]

The persistently high incidence and morbidity of HIV-associated pneumococcal infections highlight the need for tools for rapid and accurate diagnosis. In part, this limitation is related to the suboptimal availability and poor quality of sputum specimens provided to laboratories.[15] Rates of pathogen detection in CAP are only 30–50%.[16,17,18] Musher et al. emphasized the importance of collecting adequate sputum specimens promptly, prior to antibiotic administration for diagnosis of pneumococcal pneumonia,[18] but such specimens are often neither sought nor provided.[15] Moreover, the decline in accessible microbiologic facilities in developed countries and the dearth of microbiological laboratories in much of the developing world, where the burden of HIV disease predominates, highlights the need for rapid diagnostic tests for *S. pneumoniae* infection at the point of care. The inability to establish specific aetiologic diagnoses leads expert panels to recommend broad-spectrum empiric antimicrobials for CAP. These well-intentioned efforts likely increase cost and facilitate the emergence of resistant organisms.

The Binax NOW® immunochromatographic test (ICT) is a rapid urine antigen test with reasonable performance characteristics among adults with clinical pneumonia.[19,20] However, immunocompromised persons, including those with HIV-infection, have been largely excluded from prior urine antigen studies. In this report we characterize the performance characteristics of this ICT among HIV-infected patients with documented *S. pneumoniae* pneumonia and bacteremia.

PATIENTS AND METHODS

Study population and setting

We prospectively enrolled 230 adult patients from a study of the natural history of pulmonary complications of HIV infection at San Francisco General Hospital during 1990–92, as previously described.[10,21,22] As a sub-study, urine was collected from 70 o these patients for urine antigen testing. After written informed consent, patients were selected for inclusion if they presented with pneumococcal pneumonia, defined by a compatible clinical scenario, a chest radiograph demonstrating parenchymal opacities, and microbiologic criteria. The microbiologic criteria included either: 1) *S. pneumoniae* cultured from a sterile site, i.e. blood, CSF, or tracheal aspirate; 2) acceptable sputum with Gram's stain revealing a predominance of Gram-positive cocci in pairs and chains at 1,000x magnification with or without a positive *S. pneumoniae* sputum culture. Sputum samples were considered acceptable with >25 WBC

and <10 epithelial cells per 400x field. Individuals were identified prospectively via microbiologic reporting.

Cases were defined as either 1) pneumococcal pneumonia or 2) pneumococcal bacteremic pneumonia. Exclusion criteria for this study included: lack of urine collection (n= 160) at hospital admission, nosocomial pneumonia or history of prior pneumococcal pneumonia, bacteremia, or hospitalization for *S. pneumoniae*. Control samples were obtained from 17 HIV + and 46 HIV− healthy ambulatory patients without clinical evidence of pneumococcal infection. An exclusion criterion for controls was the presence of an active, undiagnosed pulmonary infection at the study visit. Clinical characteristics as well as serum, urine, sputum and blood for culture were collected at time of diagnosis. C-reactive protein (CRP) was measured from collected serum by antigen-antibody agglutination (Abbott). Urine samples were immediately frozen and stored at −70°C for a median of 13.5 years. Convalescent urine was collected from 64% [45/70] one month after illness. The urine was collected with the express *a priori* intent for urine antigen testing; however, this was not possible until after August 31, 1999 when the current ICT became available.

Urine antigen detection

The Binax® NOW ICT (Binax Inc. Portland, Maine) was performed per the manufacturer's instructions.[23] Unconcentrated aliquots (1 mL) of urine were thawed to room temperature. Briefly, the manufacturer-provided swab was dipped into a gently swirled urine sample and inserted into the test device. The Binax ICT utilizes a colloidal gold-labeled antibody immobilized on a nitrocellulose membrane. When the device is closed, the sample is brought in contact with the test strip. Any pneumococcal antigen present binds with conjugated rabbit anti-C-polysaccharide *S. pneumoniae* antibody creating an antigen-antibody complex. A colorimetric reaction occurs when those complexes are captured by anti-*S. pneumoniae* antibodies immobilized on the sample line (i.e. positive) on the test device. Photography documented results at 15 minutes, and three masked readers read the results independently. This step was undertaken to determine inter-observer variability, previously suggested as a cause of variation in ICT performance.[24] Readers quantified test results based on their visual intensity as: negative (no detectable test band), weak positive (any visible test band <control band intensity), or strong positive (test band ≥control band intensity) [Appendix 1].

To exclude false negative reactions, all presumed false negative results (ICT negative but with bacteremic pneumococcal infection) were confirmed first by repeat urine ICT. In addition, the urine was acidified with buffered NH_4Cl to dissociate potential antigen-antibody complexes as previously described,[25] then pH neutralized, and the samples were re-tested.

Systematic Review

We identified and reviewed study design, performance characteristics and the microbiologic "gold-standard" used in 20 studies in adults from the PubMed database (1950–June, 2007) identified using the keywords Binax, urine antigen, and *Streptococcus pneumoniae* and 5 additional studies from cross-references. Selected studies showed heterogeneity in the populations and gold-standards used to assess the test, but most used standard sputum Gram's stain, sputum culture, and blood culture for diagnosis. In the published studies, when the ICT was tested in patients with pneumonia of unknown aetiology, this is reported separately. Following the STARD initiative recommendations, we present positive and negative likelihood ratios (LR+, LR−). Data were analyzed using Meta-DiSc software (v1.4).[26] Summary values of the test performance were calculated from pooled Mantel-Haenszel weighted means.

Data Analysis

The sensitivity and specificity of the Binax® urinary ICT for diagnosing pneumococcal infection was determined, stratified by HIV-status. A double blind was maintained with test performance, readers, and data analyses. Statistical analysis was performed with SPSS 14.0 (Chicago, IL). Continuous, normally distributed variables are expressed as mean ±standard deviation (SD) with comparisons via Student's *t*-test. For categorical variables, Fisher's exact test was used. For comparisons between inter-observer or multiple measurements, the Kappa statistic is presented. Statistical significance was defined as $P<.05$.

RESULTS

Diagnosis

Seventy pneumococcal infections occurred during the study (47 HIV+, 23 HIV−). Sixty infections were bacteremic pneumonia. Diagnostic methods of included sputum Gram's stain (n=34), sputum culture (n=32), and/or both bacteremia and sputum positive by either Gram's stain and/or culture (n=32) [Figure 1].

Clinical features of pneumococcal infection

Presenting symptoms included: cough, tactile fever, pleuritic chest pain and chills were present in ≥75% of each group (Table 1). The majority of patients with and without HIV infection showed symptoms at comparable frequencies. The median duration of symptoms prior to admission was 4 days (IQR: 2–5 days). Cough was present longer than other symptoms by 1.1 days (95% CI: 0.4–1.8 days; P=.0004). No patient reported receiving antibiotics in the 30 days prior to admission, including trimethoprim-sulfamethoxazole prophylaxis.

HIV-infected patients with pneumonia were equally likely to generate an inflammatory response to the infection (fever, elevated CRP), although the proportion with elevated neutrophil counts was lower (Table 2). Chest radiographs revealed parenchymal opacities in all patients. These opacities were multi-lobar in 44% [31/70] with bilateral involvement in 30% [21/70] of persons with pneumococcal pneumonia. The most commonly infected lobes included the left lower (n=37) and right lower (n=36) lung lobes. The frequency and distribution of infiltrates was similar regardless of HIV-status. The interval between collection of blood for culture and final identification of positive cultures averaged 2.1 ±1.2 days with 33% [24/60] formally identified on hospital day two or three. A majority of HIV-infected patients with pneumonia had advanced HIV disease (56% < 200 $CD4^+$ T cells/μL).

Sputum Specimens

Among pneumonia patients, sputum Gram's stains were obtained in 59 (84%) subjects, and acceptable sputum cultured in 57 (81%) subjects (Table 2). The sensitivity of the sputum Gram's stain was 58% (34/59) among all pneumonia patients and 51% (25/49) in bacteremic pneumonia. Only 37% (18/49) had sputum positive both by Gram's stain and positive by sputum culture among bacteremic pneumonia cases and 41% (22/54) among all pneumonia patients (Kappa=0.42). Sputum collected >24 hours after antibiotic therapy rarely yielded either a positive Gram's stain [4/12] or culture [4/11] compared with those collected within 24 hours of admission, 68% (30/44) for Gram's stain ($P=.03$). Timing of sputum collection was unavailable for three subjects. Over one-third of patients with bacteremic pneumonia submitting sputum had non-diagnostic sputum specimens (18/50; 36%) either by Gram's stain or culture and an additional 16% (10/60) of bacteremic pneumonias submitted no sputum sample, suggesting the need for an adjunctive diagnostic test at the point of care when making therapeutic decisions.

Urine antigen detection (ICT)

Among 70 cases of pneumococcal pneumonia, the urine ICT was positive in 81% (57/70), including 85% (51/60) of bacteremic pneumonias. The urine antigen performance was similar regardless of HIV status: 83% HIV+ vs. 78% HIV− (Table 2). Among control subjects without clinical evidence of current pneumococcal disease, the ICT showed positive results in none of 46 HIV-negative control subjects and 6% (1/17) HIV-infected control subjects. Overall, the urine antigen ICT sensitivity was 81% (95% CI: 71% to 89%) for pneumococcal infection, and specificity was 98% [62/63] (95% CI: 92% to 100%), with similar sensitivity among HIV-infected (83%) as seronegative (78%) persons. The urine antigen ICT LR+ was 51.3 (95% CI: 7.3 to 360), and the LR− was 0.19 (95% CI: 0.12 to 0.31). *S. pneumoniae* serotypes 1, 3, 4 (n=3), 9, 12 (n=3), 14 (n=4), 18, 19 (n=2), 20 (n=2), and 23 were detected by the Binax ICT. One bacteremic episode with serotype 16 yielded a false negative. There were no differences in urine antigen sensitivity based on the duration of symptoms nor on the time to positive blood culture (83% on hospital day ≤1 versus 87% on days ≥2). Proteinuria did not affect the ICT performance. The inter-observer validity was excellent with 99% agreement on the Binax ICT positivity among three readers.

False Negatives

Among patients with pneumococcal pneumonia, false negative results did not differ by clinical characteristics (symptom duration, fever), bacteremia, WBC count, or CRP level. Urine immune complexes were not responsible for false negative results as no new positive results were detected after urine acid dissociation of potential antibody-antigen complexes.

Antigen Clearance

Persistently positive results in convalescent samples collected at one month were detected in 40% (18/45) of pneumonia patients tested. Persistent antigen was more likely detected among those with initial strong positive results (58% [14/24]; RR 3.1, 95% CI: 1.4 to 6.9, P =.01) compared with those with initial weak positives (19% [4/21]) The frequency of persistent antigenuria at one month was comparable in pneumonia patients with and without HIV infection (40% [12/30] vs. 42% [6/14], respectively).

C-reactive protein

Results of CRP and ICT paralleled one another. Among patients with pneumonia, CRP was elevated (mean 132 ±93 mg/L, range 35–479 mg/L; 90% >40 mg/L). The frequency and magnitude of CRP responses were independent of HIV status (P=.6) (Figure 2). Using both tests together (Binax ICT and CRP >40 mg/L) increased the test performance modestly (Table 3) by raising the NPV (83% to 96%) and only slightly lowering the sensitivity (81% to 75%) compared with ICT alone. A negative Binax ICT and CRP <40 mg/L effectively excluded pneumococcal pneumonia (NPV 96%).

Systematic Review

Among the 25 published studies in HIV-negative adults, the pooled sensitivity for the Binax urine ICT was 74% (95% CI: 72% to 77%) and specificity 94% (95% CI: 93% to 95%) compared with traditional microbiology in adults with pneumococcal infection (Figure 3). The summary PPV is 79% (95% CI: 70% to 88%) and NPV is 92% (95% CI: 89% to 96%) using a gold standard of a positive sputum and/or blood culture with a consistent clinical syndrome. The LR+ for the ICT is 17 (95% CI: 11 to 26), and the LR− is 0.29 (95% CI: 0.24 to 0.39). Among the 17 studies testing the urine ICT test among pneumonias of unknown aetiology, an additional 23 ±14% were putatively diagnosed as *S. pneumoniae* pneumonia by urinary antigen testing (Table 4).

DISCUSSION

Among HIV-infected and seronegative patients with acute pneumococcal pneumonia, we demonstrate that *S. pneumoniae* infections can be diagnosed with reasonable sensitivity and excellent specificity with a simple test available at the point of care. Just as symptoms and signs of pneumococcal pneumonia are comparable regardless of HIV-status,[49] the Binax *S. pneumoniae* urine antigen test has comparable performance characteristics among both groups. This test may provide reliable, rapid diagnosis for pneumococcal infection in the absence of an acceptable sputum specimen or readily-accessible microbiologic facilities. The absence of microbiologic laboratories may be encountered not only in resource-limited regions, where HIV infection is prevalent, but also in primary care clinics, urgent visit centers, or after-hours in developed countries when trained microbiology technicians are unavailable.

An advantage of urine antigen testing is that prior antibiotics do not rapidly decrease the sensitivity of ICT.[18] Thus, patients having received antibiotics may still receive a specific diagnosis despite the rapidly diminishing yield of sputum examination. In the U.S., more rapid delivery of antibiotics is being encouraged. One U.S. Medicare quality improvement measure is the "number of pneumonia patients who received their first antibiotic dose within four hours from hospital arrival."[50] Antigenuria can persist for days to weeks after therapy, thereby enhancing the potential role of urine antigen detection for research purposes, such as vaccination trials.[28] Additionally, C-polysaccharide, the antigen detected in urine, appears to be cold stable at −70°C for extended periods (≥13 years in this study), a characteristic that will enhance epidemiologic studies.

Of greater consequence, false negative results occur in ≈20% of patients with pneumococcal pneumonia. Causes for false negative results include aetiologic misclassification, low levels of C-polysaccharide antigen present, or sequestration of the antigen by antibodies in serum or urine as immune-complexes. Misclassification, by inclusion of non-pneumococcal pneumonia cases, does not account for all the false negatives as 15% of bacteremic pneumonias yielded false negative urine antigen results. In our study, false negatives did not differ by duration of symptoms, temperature, WBC count, or CRP, thus "early" infection is an unlikely explanation. We hypothesize that sequestration of antigen-antibody immune complexes in serum may decrease antigen shedding into the urine and yield false negative results. In prior studies, urine concentration improves ICT sensitivity by 5–20% as low levels antigenuria may occur in some individuals.[20,28,29] Immune complexes were not present in the urine as acid dissociation did not improve detection. A broad array of different serotypes were detected in this study, thus the antigenic variability of the C-polysaccharide appears low. This is important as the previous latex agglutination urine antigen tests, which were based on the capsular polysaccharide, were limited in being serotype specific.[51]

In contrast to the high frequency of false positives in children,[52] false positive tests occurred in one HIV-infected adult control with a prior pulmonary infection of unknown aetiology. Sources of false positives are two-fold. First, *S. viridans* species of *S. mitis* and *S. oralis* contain the same C-polysaccharide as *S. pneumoniae*.[53] Second, antigen shedding continues for weeks as 40% in this study and 70% in a Spanish cohort had detectable urine antigen one month following illness.[20] This urine antigen test should not be used in persons with a recent pneumococcal infection. Marcos et al demonstrated that nasopharyngeal pneumococcal carriage in eight clinically stable HIV-infected adults, CD4 count unspecified, did not yield any false positive results.[20]

One difficulty with definitive CAP diagnosis is that there is no perfect gold standard for the aetiologic diagnosis. Even employing a range of diagnostic tests in an academic centre, a

specific aetiology cannot be determined in 50–70% of cases.[16,17,18] Because expectorated sputum samples were diagnostic in ≤60% of patients in this study, a new approach is necessary.

With traditional microbiological techniques, a 24–48 hours delay typically precedes confirmation of the aetiologic diagnosis. In this study, the average for microbiologic results was 2.1 days. This diagnostic delay may prompt physicians to initiate and continue broader spectrum antimicrobial agents or order more diagnostic tests in the interim. With shorter hospitalizations now commonplace, physicians may be reluctant to narrow the antibiotic spectrum 2–3 days into therapy near time of discharge. As a result, broader, more expensive antimicrobial therapy may well be continued to complete a therapeutic course.

β-lactam antibiotics remain the mainstay therapy for pneumococcal infection and non-severe CAP.[54] In a meta-analysis of 18 trials with 6749 adults with non-severe CAP, treatment failure with β-lactams was identical to broader spectrum agents having atypical coverage (RR 0.97; 95% CI: 0.87 to 1.07).[54] Prompt aetiologic diagnosis within 15 minutes should promote narrow spectrum antibiotics, e.g. amoxicillin 1000mg three times daily, sparing broader spectrum, more expensive antibiotics, e.g. "respiratory" fluoroquinolones or azithromycin/ clarithromycin, in non-severe CAP.[55] The utility of rapid diagnosis-driven therapy at the point of care has been prospectively verified among military recruits.[56] The cost of Binax Now® ICT (~£15, US$30) outweighs the cost differential for 8 days of fluoroquinolones vs. amoxicillin (~£35, US$70).[57] The European and U.S. cost of the Binax ICT is still exponentially more expensive than what is practical for use in resource-limited areas.

For calculating the assay's specificity, controls without acute pulmonary infection were chosen. Among studies utilizing other non-pneumococcal CAP patients as controls, "false positives" are reported in up to 29%.[20,32,33,35] Because the frequency of the pneumococcal pneumonia is high in HIV selecting non-pneumococcal hospitalized CAP controls is difficult.[7,8] With such a high pre-test probability, a culture-negative CAP still has a high PPV for pneumococcal pneumonia. In this study, 47% [28/60] of bacteremic pneumonia did not have a positive sputum Gram's stain or culture. Even with viral pneumonias, mixed infections with pneumococcus may occur in up to one-third of children.[58]

Burel et al. have suggested that more work is required to establish the true specificity of the Binax® NOW test by studying its performance using urine from healthy subjects.[42] Other studies have used various controls with CAP of unknown aetiology or with positive serologic tests for Chlamydia, Mycoplasma, or Legionella to define the control group. Among HIV-infected patients without consistent history, clinical and laboratory features of pneumococcal pneumonia, "false positive" urine antigen detection may represent prior, recent CAP infection. In our study, we eliminated this confounder by utilizing controls without pulmonary infection. Although this choice of controls may be viewed as a limitation, confounding of results by a high rate of cases without a specific aetiologic diagnosis was avoided.

Conversely, whether these "false positives" represent actual false positives or mixed infections with unconfirmed *S. pneumoniae* is unclear. Emerging data suggest that even in viral childhood pneumonias, *S. pneumoniae* may contribute to symptoms as a co-pathogen.[58,59] These putative "false positives" lower the specificity and PPV in some studies reviewed.[33,45]

In summary, urine ICT is a useful rapid diagnostic test for *S. pneumoniae* pneumonia and bacteremia in adults with HIV-infection. The urine antigen ICT may be quite valuable for establishing an aetiologic diagnosis in the absence of traditional microbiological testing, such as outpatient or rural clinical settings, for research in resource-limited nations to determine appropriate point-of-care algorithms, or for epidemiologic studies. Use of the urine antigen in non-severe pneumonia is also promising to promote the use of narrower spectrum, less expensive antibiotics.[54,56]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank Claudine Fasching for technical and clinical support of the project. This work supported in part by National Institutes of Health (AI48796; P30-AI054907; AI39445; T32-AI055433; L30-AI066779), the Colorado Center for AIDS Research, and the Veterans Affairs Research Service.

References

1. Lim WS, Macfarlane JT, Boswell TC, et al. Study of community acquired pneumonia aetiology (SCAPA) in adults admitted to hospital: implications for management guidelines. Thorax 2001;56:296–301. [PubMed: 11254821]PubMed
2. Woodhead MA, Macfarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of the aetiology and outcome of pneumonia in the community. Lancet 1987;1:671–4. [PubMed: 2882091]PubMed
3. Kozak, LJ.; Owings, MF.; Hall, MJ. National Hospital Discharge Survey: 2002 annual summary with detailed diagnosis and procedure data. National Center for Health Statistics. Vital Health Stat. 2005 [Accessed Apr 10, 2007]. Available at: http://www.cdc.gov/nchs/data/series/sr_13/sr13_158.pdf
4. Bartlett JG, Mundy LM. Community-acquired pneumonia. N Engl J Med 1995;333:1618–1624. [PubMed: 7477199]PubMed
5. Brown PD, Lerner SA. Community-acquired pneumonia. Lancet 1998;352:1295–1302. [PubMed: 9788476]
6. Sleeman K, Knox K, George R, et al. Invasive pneumococcal disease in England and Wales: vaccination implications. J Infect Dis 2001;183:239–246. [PubMed: 11120930]PubMed
7. Nuorti JP, Butler JC, Gelling L, Kool JL, Reingold AL, Vugia DJ. Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. Ann Intern Med 2000;132:182–90. [PubMed: 10651598]PubMed
8. Feikin DR, Feldman C, Schuchat A, Janoff EN. Global strategies to prevent bacterial pneumonia in adults with HIV disease. Lancet Infect Dis 2004;4:445–455. [PubMed: 15219555]PubMed
9. Heffernan RT, Barrett NL, Gallagher KM, et al. Declining incidence of invasive Streptococcus pneumoniae infections among persons with AIDS in an era of highly active antiretroviral therapy. J Infect Dis 2005;191:2038–2045. [PubMed: 15897989]PubMed
10. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. N Engl J Med 1995;333:845–51. [PubMed: 7651475]PubMed
11. French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. Lancet 2000;355:2106–11. [PubMed: 10902624]PubMed
12. Kohli R, Lo Y, Homel P, et al. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER) study. Clin Infect Dis 2006;43:90–8. [PubMed: 16758423]
13. Flanery B, Heffernan RT, Harrison LH, et al. Changes in invasive pneumococcal disease among HIV-infected adults living in the era of childhood pneumococcal immunization. Ann Intern Med 2006;1444:1–9.PubMed
14. Simpson JC, Macfarlane JT, Watson J, Woodhead MA. A national confidential enquiry into community acquired pneumonia deaths in young adults in England and Wales. British Thoracic Society Research Committee and Public Health Laboratory Service. Thorax 2000;55:1040–5. [PubMed: 11083890]
15. Bartlett JG. Decline in microbial studies for patients with pulmonary infections. Clin Infect Dis 2004;39:170–2. [PubMed: 15307024]
16. Garcia Vazquez E, Mensa J, Martinez JA, et al. Lower mortality among patients with community-acquired pneumonia treated with a macrolide plus a beta-lactam agent versus a beta-lactam agent alone. Eur J Clin Microbiol Infect Dis 2005;24:190–5. [PubMed: 15782278]PubMed

17. Apisarnthanarak A, Mundy LM. Etiology of community-acquired pneumonia. Clin Chest Med 2005;26:47–55. [PubMed: 15802165]PubMed
18. Musher DM, Montoya R, Wanahita A. Diagnostic value of microscopic examination of Gram-stained sputum and sputum cultures in patients with bacteremic pneumococcal pneumonia. Clin Infect Dis 2004;39:165–9. [PubMed: 15307023]PubMed
19. Smith MD, Derrington P, Evans R, et al. Rapid diagnosis of bacteremic pneumococcal infections in adults by using the Binax NOW *Streptococcus pneumoniae* urinary antigen test: a prospective, controlled clinical evaluation. J Clin Microbiol 2003;41:2810–3. [PubMed: 12843005]PubMed
20. Marcos MA, Jimenez de Anta MT, de la Bellacasa JP, et al. Rapid urinary antigen test for diagnosis of pneumococcal community-acquired pneumonia in adults. Eur Respir J 2003;21:209–14. [PubMed: 12608431]PubMed
21. Osmond DH, Chin DP, Glassroth J, et al. Impact of bacterial pneumonia and *Pneumocystis carinii* pneumonia on human immunodeficiency virus disease progression. Pulmonary Complications of HIV Study Group. Clin Infect Dis 1999;29:536–43. [PubMed: 10530443]PubMed
22. The Pulmonary Complications of HIV Infection Study Group. Design of a prospective study of the pulmonary complications of human immunodeficiency virus infection. J Clin Epidemiol 1993;46:497–507. [PubMed: 8501476]
23. Binax; Portland, ME: [Accessed Apr 10, 2007]. Binax NOW® Streptococcus pneumoniae Urinary Antigen Test Product Instructions. Available at: http://binax.com/uploads/strep_pneumo_pi_3_16_06_001.pdf
24. Hamer DH, Egas J, Estrella B, MacLeod WB, Griffiths JK, Sempertegui F. Assessment of the Binax NOW *Streptococcus pneumoniae* urinary antigen test in children with nasopharyngeal pneumococcal carriage. Clin Infect Dis 2002;34:1025–8. [PubMed: 11880971]PubMed
25. Amdahl BM, Rubins JB, Daley CL, Gilks CF, Hopewell PC, Janoff EN. Impaired natural immunity to pneumolysin during human immunodeficiency virus infection in the United States and Africa. Am J Respir Crit Care Med 1995;152:2000–4. [PubMed: 8520768]PubMed
26. Zamora J, Abraira V, Muriel A, Khan KS, Coomarasamy A. Meta-DiSc: a software for meta-analysis of test accuracy data. BMC Medical Research Methodology 2006;6:31. [PubMed: 16836745]
27. Andreo F, Dominguez J, Ruiz J, Blanco S, Arellano E, Prat C, Morera J, Ausina V. Impact of rapid urine antigen tests to determine the etiology of community-acquired pneumonia in adults. Respir Med 2006;100:884–91. [PubMed: 16226441]
28. Gutierrez F, Masia M, Rodriguez JC, et al. Evaluation of the immunochromatographic Binax NOW assay for detection of *Streptococcus pneumoniae* urinary antigen in a prospective study of community-acquired pneumonia in Spain. Clin Infect Dis 2003;36:286–92. [PubMed: 12539069] PubMed
29. Murdoch DR, Laing RT, Mills GD, et al. Evaluation of a rapid immunochromatographic test for detection of *Streptococcus pneumoniae* antigen in urine samples from adults with community-acquired pneumonia. J Clin Microbiol 2001;39:3495–8. [PubMed: 11574562]PubMed
30. Tzeng DH, Lee YL, Lin YH, Tsai CA, Shi ZY. Diagnostic value of the Binax NOW assay for identifying a pneumococcal etiology in patients with respiratory tract infection. J Microbiol Immunol Infect 2006;39:39–44. [PubMed: 16440122]PubMed
31. Sato N, Takayanagi N, Kurashima K, et al. [Usefulness of Streptococcus pneumoniae urinary antigen detection kit and the duration and intensity of reactivity with urinary antigen in patients with pneumonia] Japanese. Nihon Kokyuki Gakkai Zasshi 2004;42:247–52. [PubMed: 15069781] PubMed
32. Hashikita G, Yamaguti T, Tachi Y, et al. Examination about utility of a Streptococcus pneumoniae capsular antigen swiftness search kit urine in a pneumonia patient. Rinsho Biseibutshu Jinsoku Shindan Kenkyukai Shi 2005;16:153–61. [PubMed: 16536061]Japanese. PubMed
33. Ishida T, Hashimoto T, Arita M, Tojo Y, Tachibana H, Jinnai M. A 3-year prospective study of a urinary antigen-detection test for *Streptococcus pneumoniae* in community-acquired pneumonia: utility and clinical impact on the reported etiology. J Infect Chemother 2004;10:359–63. [PubMed: 15614462]PubMed

34. Watanuki Y, Takahashi H, Ogura T, Miyazawa N, Tomioka T, Odagiri S. Usefulness of urinary antigen and sputum Gram stain for rapid diagnosis of pneumococcal respiratory infections. Kansenshogaku Zasshi 2005;79:13–9. [PubMed: 15717478]Japanese. PubMed
35. Honore S, Trillard M, Ould-Hocine Z, Lesprit P, Deforges L, Legrand P. [Contribution of urinary pneumococcal antigen detection combined with the research of legionella antigen for diagnosis of pneumonia in hospitalized patients] French. Pathol Biol 2004;52:429–33. [PubMed: 15465259] PubMed
36. Stralin K, Kaltoft MS, Konradsen HB, Olcen P, Holmberg H. Comparison of two urinary antigen tests for establishment of pneumococcal etiology of adult community-acquired pneumonia. J Clin Microbiol 2004;42:3620–25. [PubMed: 15297507]PubMed
37. Roson B, Fernandez-Sabe N, Carratala J, et al. Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. Clin Infect Dis 2004;38:222–6. [PubMed: 14699454]PubMed
38. Payeras Cifre A, Llado Ferrer B, Ramis Morell F, et al. [Usefulness of a new fast technique for detection of pneumococcal antigen in the diagnosis of community pneumonia] Spanish. Rev Clin Esp 2003;203:521–25. [PubMed: 14599391]PubMed
39. Farina C, Arosio M, Vailati F, Moioli F, Goglio A. Urinary detection of Streptococcus pneumoniae antigen for diagnosis of pneumonia. New Microbiol 2002;25:259–63. [PubMed: 12019736]PubMed
40. Domínguez J, Galí N, Blanco S, et al. Detection of *Streptococcus pneumoniae* antigen by a rapid immunochromatographic assay in urine samples. Chest 2001;119:243–249. [PubMed: 11157611] PubMed
41. Genne D, Siegrist HH, Lienhard R. Enhancing the etiologic diagnosis of community-acquired pneumonia in adults using the urinary antigen assay (Binax NOW). Int J Infect Dis 2006;10:124–8. [PubMed: 16290014]PubMed
42. Burel E, Dufour P, Gauduchon V, Jarraud S, Etienne J. Evaluation of a rapid immunochromatographic assay for detection of *Streptococcus pneumoniae* antigen in urine samples. Eur J Clin Microbiol Infect Dis 2001;20:840–1. [PubMed: 11783708]
43. Kobayashi T, Matsumoto T, Tateda K, et al. [Evaluation of *Streptococcus pneumoniae*-urinary antigen detection kit in patients with community acquired pneumonia] Japanese. Kansenshogaku Zasshi 2002;76:995–1002. [PubMed: 12607345]PubMed
44. Le Monnier A, Carbonnelle E, Zahar JR, et al. Microbiological diagnosis of empyema in children: comparative evaluations by culture, polymerase chain reaction, and pneumococcal antigen detection in pleural fluids. Clin Infect Dis 2006;42:1135–40. [PubMed: 16575731]PubMed
45. Briones ML, Blanquer J, Ferrando D, Blasco ML, Gimeno C, Marin J. Assessment of analysis of urinary pneumococcal antigen by immunochromatography for etiologic diagnosis of community-acquired pneumonia in adults. Clin Vaccine Immunol 2006;13:1092–7. [PubMed: 17028212] PubMed
46. Ercis S, Ergin A, Sahin GO, Hascelik G, Uzun O. Validation of urinary antigen test for Streptococcus pneumoniae in patients with pneumococcal pneumonia. Jpn J Infect Dis 2006;59:388–90. [PubMed: 17186959]PubMed
47. Lasocki S, Scanvic A, Le Turdu F, Restoux A, Mentec H, Bleichner G, Sollet JP. Evaluation of the Binax NOW Streptococcus pneumoniae urinary antigen assay in intensive care patients hospitalized for pneumonia. Intensive Care Med 2006;32:1766–72. [PubMed: 16957905]PubMed
48. Diederen BM, Peeters MF. Rapid diagnosis of pneumococcal pneumonia in adults using the Binax NOW Streptococcus pneumoniae urinary antigen test. Int J Infect Dis 2007;11:284–5. [PubMed: 17236801]PubMed
49. Janoff EN, Breiman RF, Daley CL, Hopewell PC. Pneumococcal disease during HIV infection. Epidemiologic, clinical, and immunologic perspectives. Ann Intern Med 1992;117:314–24. [PubMed: 1637028]PubMed
50. Centers for Medicare & Medicaid Services. Quality Measures Management Information System. [Accessed Jan 20, 2007]. Available at: https://www.qualitynet.org/qmis/measureDetailView.htm?measureId=10280

51. Scott JA, Hannington A, Marsh K, Hall AJ. Diagnosis of pneumococcal pneumonia in epidemiological studies: evaluation in Kenyan adults of a serotype-specific urine latex agglutination assay. Clin Infect Dis 1999;28:764–9. [PubMed: 10825036]PubMed

52. Dowell SF, Garman RL, Liu G, Levine OS, Yang YH. Evaluation of Binax NOW, an assay for the detection of pneumococcal antigen in urine samples, performed among pediatric patients. Clin Infect Dis 2001;32:824–5. [PubMed: 11229853]PubMed

53. Gillespie SH, McWhinney PH, Patel S, et al. Species of alpha-hemolytic streptococci possessing a C-polysaccharide phosphorylcholine-containing antigen. Infect Immun 1993;61:3076–7. [PubMed: 8514415]PubMed

54. Mills GD, Oehley MR, Arrol B. Effectiveness of beta lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis. BMJ 2005;330:456. [PubMed: 15684024]PubMed

55. BTS guidelines for the management of community acquired pneumonia in adults - 2004 update. [Accessed May 5, 2007]. Available at: http://www.brit-thoracic.org.uk/

56. Guchev IA, Yu VL, Sinopalnikov A, et al. Management of nonsevere pneumonia in military trainees with the urinary antigen test for Streptococcus pneumoniae: an innovative approach to targeted therapy. Clin Infect Dis 2005;40:1608–16. [PubMed: 15889358]PubMed

57. Drug topics red book: pharmacy's fundamental resource. Montvale (NJ): Medical Economics; 2004.

58. Madhi SA, Klugman KP. Pneumococcal Vaccine Trialist Group. A role for *Streptococcus pneumoniae* in virus-associated pneumonia. Nat Med 2004;10:811–813. [PubMed: 15247911] PubMed

59. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. Vaccine Trialists Group. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med 2003;349:1341–8. [PubMed: 14523142]PubMed

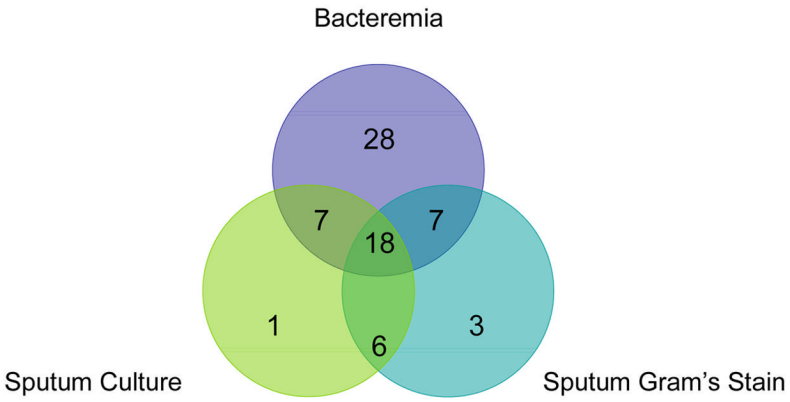

Figure 1.
Distribution of the microbiologic determination of pneumococcal pneumonia

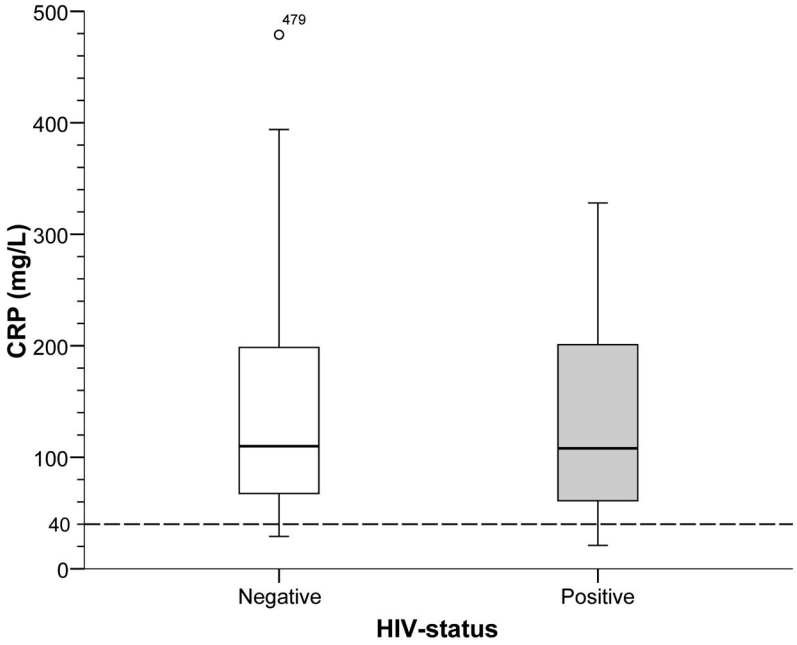

Figure 2.
CRP Response among patients with pneumococcal pneumonia by HIV-status

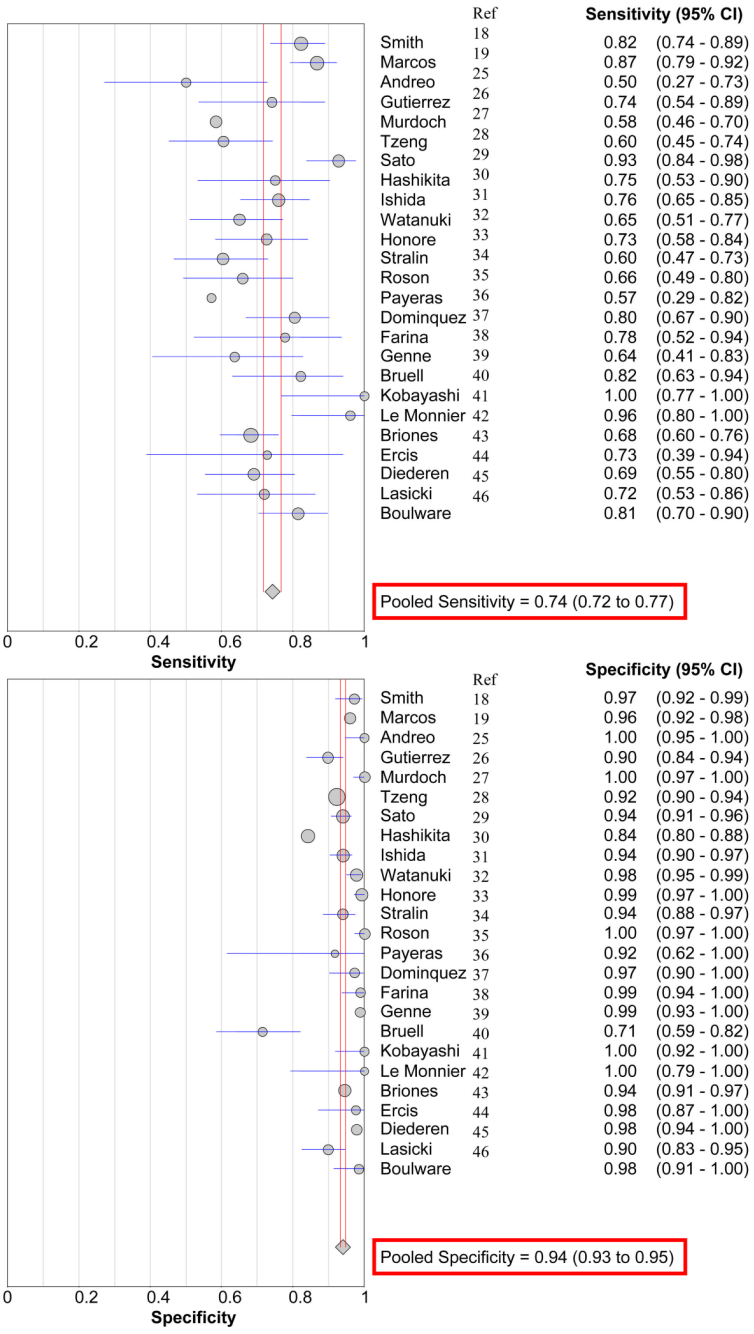

Figure 3.
Forest plot of the sensitivity and specificity of Binax urine antigen ICT performance.

Table 1

Clinical characteristics of patients with pneumococcal pneumonia and control subjects.

Demographic	HIV-infected *S. pneumoniae* Pneumonia	HIV-negative *S. pneumoniae* Pneumonia	HIV-infected Control Subjects	HIV-negative Controls
No. of patients	47	23	17	46
Age (mean ± SD)	35 ± 6	38 ± 7	34 ± 6	42 ± 15
Sex (M:F)	39 : 8	18 : 5	12 : 5	29 : 17
Intravenous drug use	21 (45%)	11 (48%)	11 (64%)	0%
Smoking, current[‡]	72%	86%	79%	
MSM	26 (55%)[*]	1 (4%)	6 (35%)	0%
$CD4^+$ T cells/μL (mean ±SD)	218 ± 207	593 ± 316	360 ± 230	
$CD4^+$ T cells <200/μL (%)[§]	27 (56%)	5 (22%)	6 (33%)	
Clinical Symptoms & Signs				
Cough	93%	95%	28%	N/A[†]
Fever (subjective)	90%	89%	11%	N/A
Pleural pain	91%	80%	0%	N/A
Chills	74%	83%	0%	N/A
Haemoptysis	51%	36%	0%	N/A
Temperature >38°C	63%	71%	0%	N/A

[*] $p<05$

Numbers (%) unless otherwise specified. MSM = men who have sex with men

[†] Clinical symptoms and signs were not collected from HIV-negative controls.

[‡] Tobacco status known for 43 HIV-positive with pneumonia, 21 HIV-negative with pneumonia, 14 HIV-controls, and 1 HIV-negative control.

[§] 7 HIV pneumonia patients and 3 HIV controls patients were being treated with zidovudine (AZT) monotherapy.

Table 2

Presenting Laboratory Findings:

Laboratory Parameters	Pneumococcal Pneumonia: HIV-infected (n = 47)	Pneumococcal Pneumonia: HIV-negative (n = 23)	Healthy: HIV-infected Controls (n = 17) ‡
Haematologic parameters			
WBC cells × 10^6/μL (mean ± SD)	11.0 ± 6.9 *	15.6 ± 6.6	4.7 ± 1.7
WBC >15 cells × 10^6/μL	31% *	54%	0%
Absolute neutrophil count ×10^6/μL(mean ± SD)	8.9 ± 5.9 *	14.4 ± 7.2	2.9 ± 1.3
CRP mg/L (mean ± SD) §	133 ± 88	135 ± 104	5 ± 6
CRP > 40 mg/L §	90%	96%	1%
Microbiology			
Bacteremia	41 (87%)	19 (83%)	-
Diagnostic Sputum Gram's Stain †	57% [24/41]	56% [10/18]	-
Unable to provide acceptable sputum †	7 (15%)	6 (26%)	-
Sputum culture % [positive / acceptable † collected]	55% [22 / 40]	59% [10/17]	-
Binax Urine Antigen positive	39 (83%)	18 (78%)	1 (6%) **

* p<.05 compared with HIV-seronegative patients with pneumococcal pneumonia

** The frequency of Binax positive urine antigen was 0% [0/46] in HIV-seronegative control subjects for whom other laboratory values were not available.

† Diagnostic sputum Gram's stain had a predominance of Gram positive cocci in pairs/chains in acceptable sputum. An acceptable sputum specimen for culture had >25 WBC and <10 epithelial cells per 400x field.

‡ Data obtained for CRP from 90 HIV+ controls, WBC values from 63 HIV+ controls.

§ CRP normal reference value <8 mg/L

Table 3

Performance of Diagnostic Methodologies

Test	Number of Samples	Number Positive	Sensitivity %	Specificity %	PPV %	NPV %
Sputum Gram's Stain	59	34	58	100*	100*	--
Sputum Culture	57	32	56	100*	100*	--
Binax Urine Antigen	70	57	81	98	98	83

*By inclusion definition; in a clinical setting, the specificity is not 100% due to potential *S. pneumoniae* colonization.

Table 4

Review of Binax Immunochromatographic urinary antigen test performance in adults

Study	N	Methodology	Clinical Scenario	Gold Standard Microbiology technique	Sensitivity %	Specificity %	PPV %	NPV %	Additional Yield % †
Smith [19]	213	P	Bacteremia	Blood culture	82	97	97	84	N/A
Marcos [20]	295	P	CAP, 68 HIV Controls	Blood or sputum culture	87	96	94	91	25
Andreo [27]	34	P	CAP	Blood, sputum culture	50	100	100	87	9
Gutierrez [28]	183	P	CAP	Blood or sputum*	70	90	85	98	26
Murdoch [29]	192	P	CAP	Blood or sputum culture	58	100	100	80	23
Tzeng [30]	859	P	CAP	Blood or sputum culture	64	92	27	98	10
Sato [31]	384	P	CAP	Blood culture	93	94	77	98	42
Hasikita [32]	372	P	CAP	Blood or sputum*	75	84	25	98	16
Ishida [33]	349	P	CAP	Blood or sputum*	76	94	91	83	39
Watanuki [33]	313	P	CAP	Sputum Gram's stain	65	98	86	93	N/A
Honore [34]	304	R/P	Pneumonia	Blood or sputum*	77	98	95	95	59
Strålin [35]	191	P	CAP	Blood or sputum culture	60	94	86	74	N/A
Rosón [36]	173	P	CAP	Sputum Gram's stain	66	100	100	99	26
Payeras [37]	163	P	CAP	Sputum culture	57	92	42	95	15
Dominquez [38]	122	R	Pneumonia	Blood or sputum*	80	97	95	87	25
Farina [39]	104	P	CAP	Blood or sputum*	78	99	93	96	N/A
Genne [40]	103	P	CAP	Blood or sputum*	64	99	93	91	24
Bruell [41]	91	P	CAP	Blood, sputum, pleural fluid	82	71	62	90	22
Kobayashi [42]	58	P	CAP	Blood or sputum*	100	100	100	100	57
Le Monnier [43]	41	P	Empyema	Pleural fluid culture, PCR	96	100	100	94	N/A
Briones [44]	566	P	CAP	Blood or sputum*	68	88	64	90	26
Erics[45]	52	R	CAP	Blood or sputum*	73	98	89	93	N/A
Diederen[46]	194	R	CAP	Blood or sputum*	69	98	93	88	N/A
Lasocki[47]	140	R	ICU	Blood, Sputum, BAL	72	90	68	92	12
Boulware	133	P	HIV CAP	Blood or sputum*	81	98	98	83	N/A
Total	5629				74	94	79	92	23

Totals reflected pooled data;

Methodology: P = Prospective, R = Retrospective

CAP=community acquired pneumonia; Pneumonia= CAP + nosocomial pneumonia; sputum* = Gram's stain and culture

† Represents the additional percent yield in aetiologic diagnosis made when testing the Binax urine antigen among pneumonias without an aetiologic diagnosis.