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Evaluation of urine pneumococcal antigen test performance among adults in Western Kenya☆

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Abstract

When used in an area of rural western Kenya, the BinaxNOW® urine antigen test had a sensitivity of 67% (95% Confidence Interval [CI]: 43–85%) among 21 adults ≥15 years old with acute respiratory illnesses and pneumococcal bacteremia and a specificity of 98% (95% CI: 96–99%) among 660 adults ≥15 years old without fever or cough. The specificity of the test was not significantly affected by pneumococcal colonization, regardless of patients' HIV status, age, or sex. Use of the pneumococcal urine antigen test in clinical assessments of adults in Africa with acute respiratory illness is a viable option regardless of whether a patient is colonized by pneumococci, even among HIV-infected adults, although the moderate sensitivity of the urine antigen test indicates that the test is probably best used clinically as part of a panel with other tests that can detect pneumococci.

Keywords

Streptococcus pneumonia ; Pneumococcus; Nasopharyngeal colonization; HIV; Kenya; Africa; Urine pneumococcal antigen test

1. Introduction

Pneumococcal pneumonia is a major cause of mortality worldwide, causing hundreds of thousands of deaths annually (Lozano et al., 2012). Accurate diagnosis of *Streptococcus pneumoniae* as the cause of clinical pneumonia can guide treatment, and the BinaxNOW® pneumococcal urine antigen test offers a relatively quick, simple way of detecting pneumococcal infection (Dowell et al., 2001). However, the urine antigen test has previously been shown to be positive in some children colonized by pneumococci who do not have

☆The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention. Use of trade names is for identification only and does not imply endorsement by the Public Health Service or by the U.S. Department of Health and Human Services.

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clinical signs or symptoms of pneumonia (Adegbola et al., 2001; Dowell et al., 2001; Hamer et al., 2002). Few evaluations of the urine antigen test's performance have been conducted either in adults colonized by pneumococci who do not have symptoms of pneumonia (Marcos et al., 2003; Turner et al., 2011) or in developing countries (Boulware et al., 2007; Sinclair et al., 2013; Turner et al., 2011). Confidence in the test's accuracy in diagnosing pneumonia in developing countries and among adults colonized by pneumococci is important for its clinical utility in many contexts, particularly since pneumococcal colonization has been found to be as high as 25% among adults living in rural areas in Nigeria and Burma (Myanmar) and approximately 12% among adults with HIV in Spain (Adetifa et al., 2012; Marcos et al., 2003; Turner et al., 2011). To determine the utility of the urine antigen test among adults in developing countries, particularly in areas with high prevalence of both pneumococcal colonization and HIV infection, we assessed the sensitivity and specificity of the urine antigen test for pneumococcal acute respiratory illnesses in adults ≥15 years old in an area of rural western Kenya.

2. Materials and methods

To assess the performance of the urine antigen test in patients with acute respiratory illnesses, we collected urine and blood specimens from patients ≥15 years old with acute respiratory illness at the St. Elizabeth Lwak Mission Hospital (Lwak Hospital) between May 2007 and December 2010. This component of the study was conducted as part of a previously described population-based infectious disease surveillance program in which residents of 33 villages within 5 kilometers of Lwak Hospital in Asembo in Kenya's Nyanza province were eligible for free medical care at Lwak Hospital for most acute conditions, including all possible infectious diseases (Feikin et al., 2010, 2011, 2012). Clinical officers with specific training through the surveillance program examined and diagnosed patients. An acute respiratory illness was defined as cough, difficulty breathing, or chest pain combined with at least one of the following: documented axillary temperature ≥38.0 °C, oxygen saturation <90%, or hospitalization (Feikin et al., 2010). Blood specimens were inoculated into commercial blood culture bottles and incubated and continuously monitored in an automated BACTEC 9500 system using standard methodology (BACTEC™ Aerobic PLUS™, Becton Dickinson, Belgium) (World Health Organization, 2003). Urine specimens were collected and tested with the BinaxNOW® pneumococcal urine antigen test (Inverness Medical, Scarborough, Maine, USA) according to the manufacturer's instructions. All urine specimens were tested within four days of being collected.

Information on the HIV status of individuals was collected using the results of a 2008 home-based testing initiative in which all persons ≥13 years old in the Asembo surveillance area were offered HIV testing, with 78% of eligible adults agreeing to be tested, as described previously (Dalal et al., 2013; Feikin et al., 2012). A person's HIV status, as determined from the home-based testing, was assumed to be the same throughout the study period.

We also collected urine specimens, oropharyngeal (OP) swab specimens, and nasopharyngeal (NP) swab specimens from non-hospitalized parents of young children; the parents were either HIV-infected or living in family compounds within which at least one HIV-infected parent resided. HIV-infected parents were identified through the 2008 home-

based testing initiative. Participants were included if they were ≥15 years old and living in the Asembo region of Kenya during October 29-December 23, 2009. This study was conducted as a sub-study of a previously described study examining adult pneumococcal carriage (Conklin et al., 2016). Specimens were collected at Lwak Hospital along with information on participants' demographics, current symptoms of respiratory illness, and possible risk factors for pneumococcal colonization. OP and NP swab specimens were transported to a laboratory in Kisumu, Kenya run by the Kenya Medical Research Institute (KEMRI) and the U.S. Centers for Disease Control and Prevention (CDC), and tested for pneumococci as previously described (Conklin et al., 2016; da Gloria Carvalho et al., 2010). Urine specimens were collected and tested in the same manner as for urine samples from the patients ≥15 years old with acute respiratory illness.

The KEMRI and CDC Institutional Review Boards reviewed and approved the protocols and consent forms for both the population based infectious diseases surveillance program and the adult pneumococcal carriage study, and written assent (for minors 15–17 years old in the acute respiratory illness surveillance program) or written informed consent was obtained from all participants.

Analyses were performed using SAS (version 9.3, Cary, NC). Binomial proportions with exact confidence intervals (CI) were calculated. Sensitivity was calculated as the proportion of adults who had positive urine antigen tests among those identified as having acute respiratory illnesses and pneumococcal bacteremia through the population based infectious diseases surveillance program (Feikin et al., 2012). The proportion of adults who had negative urine antigen tests among those identified as having acute respiratory illnesses and bacteria other than pneumococci detected in their blood was also calculated, but was not considered indicative of the test's specificity because of the possibility that positive urine antigen tests among this population could be due to co-infections with pneumococcus. Specificity was calculated as the proportion of adults with negative urine antigen tests among the adults tested for pneumococcal carriage who did not have fever or cough when the specimens were collected (Feikin et al., 2012). Participants were also categorized and analyzed by HIV-status (HIV-infected, HIV-uninfected, and HIV-unknown) based on the results of the 2008 home-based HIV testing initiative as well as by age, sex, and, for participants tested for pneumococcal carriage, pneumococcal carriage. Proportions with 95% confidence intervals which did not overlap were considered to be statistically significantly different.

3. Results

Of the 2,338 adults ≥15 years old diagnosed with acute respiratory illnesses at Lwak Hospital between May 2007 and December 2010, 1,230 had blood cultures performed and 532 had urine antigen tests performed. Twenty-one had both blood cultures positive for pneumococcal growth and a urine antigen test result (Table 1). One patient was HIV-infected (5%) (this individual was found to be HIV-infected before the acute respiratory illness that prompted the blood culture and urine antigen test), eight were HIV-uninfected (38%), and 12 were HIV-unknown (57%). The urine antigen test was positive in 14 of those 21 patients,

giving the test a sensitivity for blood culture confirmed pneumococcal disease of 67% (95% Confidence Interval [CI]: 43–85%).

In addition, 25 patients had both a urine antigen test result and blood cultures positive for growth of bacteria other than pneumococci, specifically 19 patients with non-typhi *Salmonella*, two patients with *Salmonella typhi*, two patients with *Staphylococcus aureus*, one patient with *Haemophilus influenzae*, and one patient with *Klebsiella oxytoca* (Table 2). Eight patients were HIV-infected (32%) (all of whom were found to be HIV-infected before the relevant acute respiratory illness), six were HIV-uninfected (24%), and 11 were HIV-unknown (44%) The urine antigen test was positive in four of the 19 patients with non-typhi *Salmonella* bacteremia and the one patient with *H. influenzae* bacteremia, resulting in the test being negative in 80% (95% CI: 59–93%) of the patients with bacteremia with other organisms detected. Of the five patients with bacteremia with other organisms and a positive urine antigen test result, one was HIV-infected, two were HIV-uninfected, and two were HIV-unknown.

Of the 973 adults tested for pneumococcal carriage, 664 denied having fever or cough at the time of specimen collection, and 660 of these provided a urine specimen. The urine antigen test was negative in 645 of those 660 adults, giving the test an overall specificity of 98% (95% CI: 96–99%) (Table 3). The specificity of the urine antigen test among 244 pneumococcal-colonized adults who denied having fever or cough at the time of specimen collection (97% [95% CI: 94–99%]) was similar to its specificity among 416 non-colonized adults who denied having fever or cough at the time of specimen collection (98% [95% CI: 97–99%]).

Among a total of 364 HIV-infected adults without fever or cough, the test had a specificity of 97% (95% CI: 93–100%) among those colonized with pneumococci (n=149) and 98% (95% CI: 95–99%) among those not colonized with pneumococci (n=215). The test specificity was similar across groups with different HIV and carriage status (Table 3). The specificity of the urine antigen test was also similar among colonized and non-colonized adults of different sexes and age groups, although some of the groups analyzed, particularly colonized adults ≥45 years old, were relatively small.

4. Discussion

While a previous study in Thailand has indicated that the urine antigen test has a 97% specificity in asymptomatic refugee women from Burma (Myanmar) of Karen ethnicity colonized by pneumococci (Turner et al., 2011), to our knowledge this is the first study that has assessed both the sensitivity and specificity of the test in a developing country as well as its specificity in HIV+ adults who are particularly likely to be colonized by pneumococci (Gill et al., 2008; Grijalva and Edwards, 2006). The test's overall sensitivity of 67% in our study was not significantly different from the sensitivity of 74.0% (95% CI: 66.6–82.3%) found by a meta-analysis of the urine antigen test's performance in detecting pneumococcal community acquired pneumonia in developed countries (Sinclair et al., 2013). Similarly, our finding that the test had an overall specificity of 98% is comparable to the specificity of 97.2% (95% CI: 92.7–99.8%) found by the same meta-analysis of the test's performance

in developed countries. These results suggest that the BinaxNOW® pneumococcal urine antigen test can perform similarly in developing and developed countries.

In addition, the specificity of the urine antigen test was markedly higher among pneumococcal colonized Kenyan adults without fever or cough than the 45%, 46%, and 78% specificities found for the test among pneumococcal colonized children without fever or cough in the Gambia (Adegbola et al., 2001), China (Dowell et al., 2001), and Ecuador (Hamer et al., 2002), respectively. These findings may indicate that the urine antigen test is more reliable for confirming pneumococcal pneumonia in colonized adults than in colonized children. The difference in the specificity of the test between adults and children might be due in part to higher colonization density in the latter (Roca et al., 2012).

Although the urine antigen test was negative for only 80% of the 25 patients with acute respiratory illnesses who had blood cultures that detected bacteria other than pneumococci, many of these patients may have had co-infections with pneumococci and the pathogens that were isolated from blood. Non-typhi *Salmonella* infections with respiratory symptoms in Africa have been often noted to involve co-infections with pneumococci (Feasey et al., 2012), and *H. influenzae* bacteremia has occasionally been linked with pneumococcal co-infections (Laupland et al., 2011). Furthermore, pneumococcal pneumonia is known to often not result in detected bacteremia (Feikin et al., 2012; Scott et al., 2000), so co-infections might have been missed. Previous studies in Spain have found that the urine antigen test has a specificity of 96% or 97% in patients with a diagnosis of non-pneumococcal pneumonia (Dominguez et al., 2001; Sorde et al., 2011), and our findings are consistent with those results if four or five of the patients with acute respiratory illnesses and bacteremia with organisms other than pneumococci also had co-infections with pneumococcus.

This study has a number of limitations. The HIV status of many study participants was unknown, and some adults who were HIV-uninfected in 2008 may have become HIV-infected by the time they were evaluated for this study. However, all study participants found to be HIV-infected in 2008 were still HIV-infected when they were evaluated for this study. In addition, the sensitivity of the urine antigen test was based on a relatively small number of cases and applies to severe (bacteremic) pneumonia. Furthermore, unlike some previous studies, we did not assess cultures of sputum specimens or other respiratory specimens (for example, pleural fluid) as part of our case definition of pneumococcal disease. However, the sensitivity of the urine antigen test in Asembo was consistent with the sensitivity estimated from other studies that used only blood cultures positive for pneumococci as the reference standard for pneumococcal disease (sensitivity: 76.7% [95% CI: 49.0–93.0%]) (Sinclair et al., 2013).

5. Conclusions

Based on these findings, use of the pneumococcal urine antigen test on adults in Africa with acute respiratory illness is a viable option for diagnosis regardless of whether a patient is colonized by pneumococci, even among HIV-infected adults. The urine antigen test's high specificity suggests that a positive result should be considered reliable and should prompt treatment for pneumococcal disease by clinicians among the adult population in

developing countries. However, the urine antigen test's moderate sensitivity indicates that the test is probably best used clinically as part of a panel with other tests which can detect pneumococci but may be logistically more complicated, such as blood cultures, in order to maximize the probability of correctly identifying pneumococcal disease.

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Table 1

Sensitivity of BinaxNOW® Urine Pneumococcal Antigen Test among 21 Adults with Acute Respiratory Illness* and Pneumococcal Bacteremia, Asembo, Kenya.

Patient characteristics:	Positive Tests/Total Tests Performed	%	(95% CI)
Total	14/21	67	(43–85)
HIV-infected	6/8	75	(35–97)
HIV-uninfected	0/1	0	(0–98)
HIV Unknown	8/12	67	(35–90)
Aged15–30 Years	7/9	78	(40–97)
Aged 31–45 Years	5/6	83	(36–100)
Aged >45 Years	2/6	33	(4–78)
Male	7/13	54	(25–81)
Female	7/8	88	(47–100

* Individuals had cough, difficulty breathing, or chest pain combined with at least one of the following: documented axillary temperature ≥38.0 °C, oxygen saturation <90%, or hospitalization

Table 2

Proportion of BinaxNOW® urine pneumococcal antigen test results that were negative among 25 adults with acute respiratory illness* and blood cultures positive for organisms other than pneumococci, Asembo, Kenya.

Patient characteristics and pathogens:	Negative Tests/Total Tests Performed	%	(95% CI)
Total	20/25	80	(59–93)
Salmonella non-typhi**	15/19	79	(54–94)
Salmonella typhi	2/2	100	(16–100)
Staphylococcus aureus	2/2	100	(16–100)
Haemophilus influenzae	0/1	0	(0–98)
Klebsiella oxytoca	1/1	100	(2–100)

*Individuals had cough, difficulty breathing, or chest pain combined with at least one of the following: documented axillary temperature ≥38.0 °C, oxygen saturation <90%, or hospitalization

**11 of the 19 patients with non-typhi *Salmonella* had *Salmonella* Group B while the other eight had *Salmonella* Group D. All of the positive urine antigen test results were from patients with *Salmonella* Group B.

Table 3

Specificity of BinaxNOW® urine pneumococcal antigen test among adults without fever or cough, Asembo, Kenya.

	All adults (N = 660)			Adults colonized with pneumococci in nasopharynx or oropharynx (N = 244)			Adults not colonized with pneumococci in nasopharynx or oropharynx (N = 416)		
Patient characteristics:	**Negative Tests/Total Tests Performed**	**%**	**(95%CI)**	**Negative Tests/Total Tests Performed**	**%**	**(95% CI)**	**Negative Tests/Total Tests Performed**	**%**	**(95% CI)**
Total	645/660	98	(96–99)	236/244	97	(94–99)	409/416	98	(97–99)
HIV-infected	356/364	98	(96–99)	145/149	97	(93–99)	211/215	98	(95–99)
HIV-uninfected	105/109	96	(91–99)	29/31	94	(79–99)	76/78	97	(91–100)
HIV Unknown	184/187	98	(95–100)	62/64	97	(89–100)	122/123	99	(96–100)
Aged15–30 Years	298/307	97	(95–99)	127/133	95	(90–98)	171/174	98	(95–100)
Aged 31–45 Years	305/311	98	(96–99)	102/104	98	(93–100)	203/207	98	(95–99)
Aged >45 Years	42/42	100	(92–100)	7/7	100	(59–100)	35/35	100	(90–100)
Male	222/223	100	(98–100)	74/74	100	(95–100)	148/149	99	(96–100)
Female	423/437	97	(95–98)	162/170	95	(91–98)	261/267	98	(95–99)

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