

In-Hospital Pneumococcal Polysaccharide Vaccination Is Associated With Detection of Pneumococcal Vaccine Serotypes in Adults Hospitalized for Community-Acquired Pneumonia

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During an etiology study of adults hospitalized for pneumonia, in which urine specimens were examined for serotype-specific pneumococcal antigen detection, we observed that some patients received 23-valent pneumococcal polysaccharide vaccine before urine collection. Some urine samples became positive for specific vaccine pneumococcal serotypes shortly after vaccination, suggesting false-positive test results.

Keywords. antigen; pneumococcal conjugate vaccine; pneumonia; serotype; urine.

After the successful introduction of pneumococcal conjugate vaccines in infants [1–3], a 13-valent pneumococcal conjugate vaccine (PCV13) was recommended for (1) US adults with high-risk conditions for pneumococcal disease in 2012 and (2) for all adults ≥ 65 years in 2014 [4].

Baseline burden estimates of community-acquired pneumonia (CAP) attributable to PCV13 serotypes in adults are needed to assess potential changes in pneumococcal pneumonia after

widespread vaccination of adults with PCV13. However, available diagnostic tests are limited in their sensitivity for pneumococcal detection.

We used novel urine antigen detection assays for identification of PCV13 serotypes in a large study of adults hospitalized with CAP [5]. We observed that some patients received 23-valent pneumococcal polysaccharide vaccine (PPV23) very early in their hospitalization, occasionally before collection of urine samples for pneumococcal detection studies. This was likely driven by hospital performance metrics to increase pneumococcal vaccination in eligible adults. Therefore, we sought to explore the impact of in-hospital PPV23 vaccination on serotype-specific urinary pneumococcal antigen detection results.

METHODS

Study Population

This study was nested within the Centers for Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community (EPIC) study conducted from January 2010 to June 2012. Adults were enrolled at 5 hospitals in Chicago, Illinois and Nashville, Tennessee. The study enrolled patients hospitalized with CAP who resided in specific catchment areas. Inclusion criteria are described in detail elsewhere but included those with signs, symptoms, and radiographic evidence of pneumonia. Patients with recent hospitalization, severe immunosuppression, and functionally dependent residents of chronic care facilities were excluded. Diagnostic samples, including urine, were systematically collected and tested for etiology per protocol. Aliquots were archived for additional studies. Vaccination history was self-reported and then confirmed through medical record review; this was supplemented with information from vaccine registries and nontraditional providers (when feasible). The study protocol was approved by the institutional review board of the participating institutions and the CDC [5].

Serotype-Specific Urinary Antigen Detection

We tested archived urine samples using recently described serotype-specific urinary antigen detection (SSUAD) assays [6, 7]. Individual reactions using monoclonal antibodies identified each of the 13 pneumococcal serotypes included in PCV13. These assays have excellent diagnostic performance relative to bacteremic pneumococcal pneumonia [6, 7]. The SSUAD assays are not available for clinical use but are increasingly used in research to assess pneumococcal etiology [6, 8].

Available aliquots of urine samples were sent to the Pfizer, Inc. laboratory for testing, without clinical data. This study

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was restricted to patients with urine samples tested with SSUAD, without taking into account results of other pneumococcal detection tests, which were published elsewhere [5].

Statistical Analysis

We first explored whether in-hospital vaccination with PPV23 could interfere with SSUAD detections in a convenience sample of patients with urine samples collected both before and after PPV23 administration. Previous studies have shown that PPV23 vaccination induces transient false-positive detections in BinaxNOW (Alere Inc., Waltham, MA), a pneumococcal urine antigen detection test used in clinical practice [9, 10]. However, SSUAD assays are more sensitive than the BinaxNOW test for identification of PCV13 serotypes [6, 8].

Because timing of PPV23 vaccination was not consistently available, we assessed the potential impact of vaccination with PPV23 on SSUAD detections by comparing SSUAD results from samples collected before the date of confirmed in-hospital vaccination with SSUAD results from samples collected on the same date or after vaccination. Descriptive statistics and comparisons of proportions were conducted with Stata 13 (StataCorp, College Station, TX).

RESULTS

Population and Samples

Archived urine samples from 2026 adults hospitalized with CAP were available for SSUAD testing. Median age was 58

Table 1. Comparison of PCV13 Serotype Detections Relative to In-Hospital Vaccination With PPV23

	Patients With Samples Collected Before Confirmed In-hospital Vaccination or With Unknown In-hospital Vaccination Status (n = 1917)	Patients With Samples Collected on the Same Date or After Confirmed In-hospital Vaccination (n = 109)	All Samples (n = 2026)
At least a PCV13 serotype, % (n)	7% (136)	33% (36)*	8% (172)
Codetection of serotypes, % (n)	0.4% (8)	8% (9)*	0.8% (17)
Specific serotypes [†]			
Serotype 5	0.8% (15)	16% (17)*	2% (32)
Codetection(s) including serotype 5	0.3% (5)	6% (7)*	0.6% (12)
Serotype 19A	2% (33)	18% (20)*	3% (53)
Codetection(s) including serotype 19A	0.1% (2)	6% (6)*	0.4% (8)
Serotype 7F	1% (26)	0% (0)	1% (26)
Codetection(s) including serotype 7F	0.2% (3)	0% (0)	0.1% (3)
Serotype 23F	0.9% (17)	1.8% (2)	0.9% (19)
Codetection(s) including serotype 23F	0.2% (3)	0% (0)	0.1% (3)
Serotype 3	1% (28)	2% (2)	2% (30)
Codetection(s) including serotype 3	<0.1% (1)	0.9% (1)	0.1% (2)
Serotype 14	0.1% (2)	2.8% (3)*	0.2% (5)
Codetection(s) including serotype 14	0% (0)	2.8% (3)*	0.1% (3)
Serotype 18C	0.4% (8)	0% (0)	0.4% (8)
Codetection(s) including serotype 18C	0.1% (2)	0% (0)	0.1% (2)
Serotype 19F	0.1% (2)	0% (0)	0.1% (2)
Codetection(s) including serotype 19F	0% (0)	0% (0)	0% (0)
Serotype 1	0.1% (1)	0.9% (1)	0.1% (2)
Codetection(s) including serotype 1	0% (0)	0.9% (1)	0% (1)
Serotype 4	0.2% (3)	0% (0)	0.1% (3)
Codetection(s) including serotype 4	0% (0)	0% (0)	0% (0)
Serotype 6A	0.5% (9)	0% (0)	0.4% (9)
Codetection(s) including serotype 6A	0% (0)	0% (0)	0% (0)
All serotypes in former PCV7	1.7% (32)	4.6% (5)*	1.8% (37)
Codetection(s) including PCV7 serotypes	0.3% (5)	2.8% (3)*	0.4% (8)

Serotypes included in PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F); serotypes included in PCV13 (1, 3, 5, 6A, 7F, 19A and all PCV7 serotypes).

Abbreviations: PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine; SSUAD, serotype-specific urinary antigen detection.

* $P < .05$, for comparisons of SSUAD results from samples collected before the date of confirmed in-hospital vaccination with SSUAD results from samples collected on the same date or after vaccination.

[†] There were no detections of serotypes 6B or 9V.

years (interquartile range, 47–71), 51% were female, 55% were white, and 11% were Hispanic. The overall prevalence of confirmed new in-hospital vaccination with PPV23 was 11% (230 of 2026), including 9% of patients <65 years and 15% of ≥65 years. One hundred nine (5%) patients had urine samples collected for SSUAD testing on the same date or after confirmed in-hospital vaccination with PPV23.

Serotype-Specific Urinary Antigen Detection in Serial Samples Collected Before and After In-Hospital 23-Valent Pneumococcal Polysaccharide Vaccination

Serial urine samples were available for 46 patients. Among them, 3 patients with samples collected 1 day before vaccination and at least 1 sample collected after vaccination were identified. Samples from all 3 patients tested negative by SSUAD assays before PPV23 vaccination, but they were positive in at least 1 postvaccination assay. Two patients tested positive for serotype 5 and one for serotype 19A (Supplementary Figure 1). Four additional patients had received PPV23 vaccination in the week before hospitalization for CAP; 2 of them tested positive for serotype 19A through SSUAD, but no prevaccination samples were available for comparison. All 5 patients with positive SSUAD results had no evidence of pneumococcal infection in any other diagnostic test in the EPIC study, including blood cultures, respiratory sample cultures, and/or BinaxNOW urinary antigen detection [5].

We also identified 4 patients with >1 serotype detected through SSUAD testing with PPV23 vaccination and urine sample collection on the same date, and the exact times of PPV23 administration and sample collection were documented. Urine sample collection occurred 2.5–15 hours after PPV23 administration. Two patients had both serotypes 5 and 14 detected; and 2 patients had both serotypes 5 and 19A.

Detection of 13-Valent Pneumococcal Conjugate Vaccine Serotypes Relative to In-Hospital Vaccination With 23-Valent Pneumococcal Polysaccharide

Among patients with all their samples collected before confirmed in-hospital PPV23 vaccination or with unknown in-hospital vaccination, PCV13 serotypes were detected in 7% (136 of 1917) of patients. Serotype 5 was detected in 0.8% of patients, whereas 19A was detected in 2%. Eight patients (0.4%) had more than 1 serotype detected; 5 of them included serotype 5 (2 of these had codetection of 19A).

In contrast, among 109 patients with urine samples collected on the same date or after confirmed in-hospital vaccination with PPV23, PCV13 serotypes were detected in 33% (36 of 109). Serotype 5 was detected in 16% of patients, and serotype 19A was detected in 18%. Nine patients (8%) had more than 1 serotype detected; 7 of them included serotype 5 (4 of these were codetected with 19A). All of these detections were significantly more common than detections in patients with samples

collected before confirmed in-hospital PPV23 vaccination or with unknown in-hospital vaccination (Table 1). Detections of other serotypes were less frequent. There were no detections of serotypes 6B or 9V.

Among 121 patients who received in-hospital vaccination with PPV23 and had urine samples collected before the date of confirmed vaccination, there were 9 (7%) detections and no codetections; all of those were PCV13 serotypes (19A [2], 3 [2], 6A [1], and 7F [4]).

DISCUSSION

Our study indicates that PPV23 vaccination may impact the detection of pneumococcal serotypes in urine samples collected postvaccination. For SSUAD assays, this phenomenon seemed to favor the detection of certain serotypes such as 5 and 19A. Therefore, future assessments of the distribution of pneumococcal serotypes among adults hospitalized with CAP using SSUAD assays need to account for recent vaccination with PPV23.

Serotypes 5 and 19A were overrepresented among detections that occurred after PPV23 vaccination. Serotype 5 is a known but infrequent cause of invasive pneumococcal disease (IPD) in the United States, whereas serotype 19A is a frequent cause of IPD [1]. It is interesting to note that serotype 5 was detected concurrently with other serotypes in a number of samples. Although the amount of purified pneumococcal capsular antigens is the same for each one of the 23 serotypes included in PPV23, the cutoff values to define SSUAD assay positivity vary for different serotypes (range, 1.7–330.5 serotype-specific pneumococcal polysaccharide units per milliliter [PnPS U/mL]) [7]. The purified pneumococcal polysaccharides included in PPV23 may differ in their physical properties from the polysaccharides used for the development of SSUAD assays, but we noted that several serotypes commonly detected alone or in combination in our study are included in PPV23 and had low cutoff positivity values in SSUAD assays (positivity cutoff values for both serotypes 5 and 19A are <10 PnPS U/mL) [7]. These low thresholds for positivity may lead to preferential detection of those serotypes in samples collected soon after PPV23 administration.

The high sensitivity of SSUAD and other assays may facilitate the detection of small antigen amounts derived from recent vaccination. Previous studies have documented false-positive results induced by recent pneumococcal vaccination using BinaxNOW in urine samples [9, 10]. Likewise, transient false-positive detections of viral surface antigens in serum have been reported after hepatitis B vaccination [11]. Furthermore, false-positive results for influenza using sensitive molecular amplification techniques have been described for nasal samples collected in clinics where live-attenuated influenza vaccines had been previously administered [12]. This phenomena has

also been demonstrated where pertussis was detected by polymerase chain reaction and represented contamination from vaccine recently administered in the clinic setting [13]. Therefore, potential sources of sample contamination should be carefully scrutinized, especially when using highly sensitive assays.

From 2002 to 2014, in-hospital vaccination of eligible patients with PPV23 was a standardized performance metric for US hospitals [14]. Although current clinical guidelines for pneumonia management recommend vaccination at discharge [15], we noted that many patients received PPV23 shortly after hospital admission. Additional studies should be specifically designed to determine (1) the clinical implications of early in-hospital PPV23 vaccination and (2) whether vaccination early in the course of a severe infection stimulates optimal vaccine responses.

This study has limitations. First, although validation studies of SSUAD assays have shown excellent sensitivity and specificity relative to bacteremic pneumonia [6,7], no gold standard exists for identification of pneumococcal infections among patients with nonbacteremic pneumococcal pneumonia. Second, the number of patients with serial urine samples available for testing was small. Third, although we were able to illustrate scenarios in which PPV23 vaccination seemed to lead to false-positive SSUAD detections, some information about the dates and timing of PPV23 administration for other patients may be missing or incomplete. Although active efforts were made to obtain vaccination data, vaccination status and timing could not be confirmed in several patients. Additional studies that correlate the timing of PPV23 (or PCV13) vaccination with SSUAD testing results would be useful to fully characterize these initial observations.

CONCLUSIONS

In summary, our observations suggest that PPV23 vaccination can cause false-positive detections of pneumococcal serotypes in urine samples tested through SSUAD assays, favoring the preferential detection of certain serotypes. Caution is warranted when interpreting results from the SSUAD assays in the setting of recent PPV23 vaccination. Furthermore, additional studies are needed to fully characterize the clinical implications of early in-hospital PPV23 vaccination.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Supplementary Material

Supplementary material is available online at Open Forum Infectious Diseases (<http://OpenForumInfectiousDiseases.oxfordjournals.org/>).

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