



STUDY PROTOCOL

Rationale and Methods of the Study Protocol: *Streptococcus pneumoniae* Serotypes in Adults 18 Years and Older with Radiographically-Confirmed Community-Acquired Pneumonia (CAP)

Ronika Alexander¹, Paula Peyran², Julio Ramirez², Wesley H. Self³, Carlos Grijalva⁴, Francis Counselman⁵, Gregory Volturo⁶, Heidi Kabler⁷, Luis Ostrosky-Zeichner⁸, Richard Wunderink⁹, Robert Sherwin¹⁰, Senen Pena Oliva², Thomas File¹¹, Timothy Wiemken¹², Sharon Gray¹, Michael Pride¹, Kimbal D. Ford¹, Qin Jiang¹, and Raul Isturiz¹

Affiliations:

- ¹ Pfizer, Inc. Collegeville, Pennsylvania
- ² Division of Infectious Diseases, University of Louisville, Louisville, Kentucky
- ³ Department of Emergency Medicine, Vanderbilt University Medical Center, Nashville, Tennessee
- ⁴ Department of Health Policy, Vanderbilt University Medical Center, Nashville, Tennessee
- ⁵ Department of Emergency Medicine, Eastern Virginia Medical School, Norfolk, Virginia
- ⁶ Department of Emergency Medicine, University of Massachusetts Medical School, Worcester, Massachusetts
- ⁷ eStudysite Clinical Research, Las Vegas, Nevada
- ⁸ McGovern Medical School, Houston, Texas
- ⁹ Feinberg School of Medicine, Northwestern University, Chicago, Illinois
- ¹⁰ Department of Emergency Medicine, Wayne State University, Detroit, Michigan
- ¹¹ Summa Health, Northeast Ohio Medical University, Akron, Ohio
- ¹² Department of Epidemiology and Population Health, University of Louisville, Louisville, KY

©2017, The Authors



DOI: 10.18297/jri/vol1/iss4/8

Received Date: October 10, 2017

Accepted Date: October 17, 2017

Website: <https://ir.library.louisville.edu/jri>

Abstract

This study was an active, prospective surveillance study of adults 18 years and older hospitalized with community-acquired pneumonia (CAP) due to *Streptococcus pneumoniae* conducted at 21 hospitals in ten cities across the United States. This report describes the surveillance methodology applied between October 7, 2013 and September 30, 2016, including the identification and description of surveillance areas and populations at-risk for CAP hospitalization for estimation of incidence rates for selected study sites.

Introduction and Rationale

Community-acquired pneumonia (CAP) continues to be a one of the leading causes of morbidity and mortality worldwide [1-3]. The prevalence of *Streptococcus pneumoniae* in CAP, especially non-bacteremic pneumococcal CAP, is likely underestimated due to a lack of sensitive diagnostic assays [4]. A traditional etiologic approach to subjects with CAP requiring hospitalization includes obtaining blood and/or sputum cultures. Although cultures are highly specific, their sensitivity is low [5]. Despite difficulty in identifying etiologic agents associated with CAP, *S. pneumoniae* was estimated to cause nearly 600,000 cases of pneumonia among United States (U.S.) adults >18 years of age in 2004, of which approximately 50% occurred in subjects aged >65 years and older [6].

In 2000, a 7-valent pneumococcal conjugate vaccine (PCV7) was introduced into the U.S. infant immunization program. This vaccine was replaced in 2010 with a 13-valent pneumococcal conjugate vaccine (PCV13). This vaccination program has had

a well-documented and significant public health impact among those vaccinated [1, 7-12], and unvaccinated children and adults have benefited from indirect (herd) protection derived from the program [13, 14]. However, most of this indirect effect has been reported for invasive pneumococcal disease; the impact in non-invasive pneumonia is not entirely understood.

One screening method for detecting infection by *S. pneumoniae* is the BinaxNOW[®] kit provided by Alere[™]. This commonly used rapid assay tests for the presence of pneumococcal C-polysaccharide (C-PS) antigens in the urine using an immunochromatographic membrane test kit. The sensitivity of this assay is documented by the manufacturer as 86% for bacteremic pneumococcal pneumonia [15]. While the BinaxNOW[®] assay detects C-PS antigen, which is present in all *S. pneumoniae* strains; it does not distinguish among different pneumococcal serotypes.

More recently, a Luminex technology-based multiplex urinary antigen detection (UAD) assay has demonstrated the ability to simultaneously detect 13 different *S. pneumoniae* serotype-specific capsular polysaccharides in human urine [16]. These

*Correspondence To: Ronika Alexander
Work: Address: Pfizer Inc. 500 Arcola Road, 5th Floor Bldg D
Collegeville, PA 19426
Work Email: <mailto:Ronika.Alexander@pfizer.com>

polysaccharides correspond to the 13 serotypes in PCV13 (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F). A notable advantage of this UAD assay is its ability to combine multiple distinct beads, each conjugated to a different serotype-specific monoclonal antibody, in a single well with the urine to be tested. This allows the detection of all 13 polysaccharides simultaneously using only a small sample volume. The UAD assay has demonstrated greater sensitivity than culture or BinaxNOW® urinary antigen detection and excellent specificity in a convenience sample obtained from 776 subjects with radiographically confirmed CAP [16], and in a separate prospective study of adults with radiographically-confirmed pneumonia [17]. In a study conducted in 2010, the use of the UAD assay helped to demonstrate PCV7 associated serotypes were still prevalent among adults aged ≥50 years with CAP, representing 26.6% of all *S. pneumoniae* serotypes detected [19]. Nevertheless, the burden of both non-invasive and invasive pneumococcal disease in adults with pneumonia after the introduction of PCV13 remains unclear.

To provide more contemporary information about the proportion of radiographically-confirmed CAP in adults (≥18 years old) caused by *S. pneumoniae*, a large epidemiological study was undertaken. Pneumococcal serotypes were identified using the serotype-specific UAD assay and standard culture methods. Serotype distribution was estimated for the total population and incidence was calculated at selected sites. In this report we describe the methodology of the study design, including the specifics of subject selection and study procedures.

Objectives

The primary objective of this study was to estimate the proportion of pneumonia cases caused by PCV13 *S. pneumoniae* serotypes among adults ≥18 years of age hospitalized with radiographically-confirmed pneumonia. Secondary objectives included: 1. Description of the full distribution of detected *S. pneumoniae* serotypes; 2. Estimation of the incidence rate of CAP overall and CAP caused by *S. pneumoniae* (SP+ CAP) for sites where a population denominator could be established; and 3. Description of the differences in detection of *S. pneumoniae* by culture, BinaxNOW® and UAD assay.

Study Design

This prospective, multicenter, surveillance study was conducted at 21 hospitals in 10 geographically dispersed U.S. cities between October 7th, 2013 and September 30th 2016. The institutional review board (IRB)/independent ethics committee (IEC) at each participating site reviewed and approved the protocol and informed consent form before any subjects provided consent.

Inclusion criteria

Subjects 18 years of age and older who presented to a study hospital were eligible for enrollment if they met the following criteria: 1) the presence of 2 or more of the following a) fever (oral temperature > 38°C/100.4°F or tympanic temperature >38.5°C/ 101.2°F) or hypothermia (<35.5°C) within 24 hours of enrollment b) chills or rigors c) pleuritic chest pain d) cough e) sputum production f) dyspnea g) tachypnea h) malaise i) abnormal auscultatory findings; 2) radiographic finding consistent with pneumonia (chest radiograph or chest computed tomography scan obtained no more than 72 hours prior to study

enrollment); and 3) able and willing to provide urine samples for diagnostic evaluation.

Exclusion criteria

Subjects were excluded from the study if they: 1) were transferred from another inpatient healthcare facility after already being hospitalized for 48 hours or more; 2) had a diagnosis of hospital acquired pneumonia (ie, developed signs and symptoms of pneumonia after being hospitalized for 48 hours or more); and 3) were previously enrolled in this study within the past 30 days.

Enrollment Sites

This study enrolled subjects from 21 hospitals in 10 US cities (Akron, OH, Chicago, IL, Detroit, MI, Louisville, KY, Nashville, TN, Norfolk, VA, Houston, TX, Las Vegas, NV, San Diego, CA and Worcester, MA) (Table 1). Pneumonia incidence was calculated at sites which were able to establish a population denominator: Louisville, KY (nine hospitals), Nashville, TN (one hospital) and Chicago, IL (one hospital).

Table 1. Details of 21 enrolling hospital centers

Institution Name	City	State	Setting	Number of Adult Beds
Sentara Norfolk General Hospital	Norfolk	VA	Not-for-profit community based teaching hospital	500
Sharp Grossmont Medical Center	La Mesa (San Diego)	CA	Community Hospital	532
Sharp Chula Vista Medical Center	Chula Vista (San Diego)	CA	Community Hospital	343
Tri-City Medical Center	Oceanside (San Diego)	CA	Community Hospital	397
Northwestern University Feinberg School of Medicine	Chicago	IL	Urban Academic/teaching Not-for-Profit Hospital	854
University of Louisville Hospital	Louisville	KY	Urban Academic/teaching Not-for-Profit Hospital	384
Robley Rex VA Medical Center	Louisville	KY	Teaching Hospital	109
Jewish Hospital	Louisville	KY	Community Hospital	412
Saint Mary & Elizabeth Hospital	Louisville	KY	Community Hospital	298
Norton Hospital	Louisville	KY	Community Hospital	859
Norton Brownsboro Hospital	Louisville	KY	Community Hospital	127
Norton Audubon Hospital	Louisville	KY	Community Hospital	432
Norton Suburban Hospital	Louisville	KY	Community Hospital	373
Baptist Hospital East	Louisville	KY	Community Hospital	468
UMASS Memorial Medical Center	Worcester	MA	Academic Hospital	779
Detroit Receiving Hospital	Detroit	MI	Academic Urban Medical Center	248
Sinai-Grace Hospital	Detroit	MI	Academic Urban Medical Center	299
Sunrise Hospital and Medical Center	Las Vegas	NV	Community Hospital	638
Summa Health System	Akron	OH	Community-based teaching hospital	542
Vanderbilt University Medical Center	Nashville	TN	Academic Hospital in urban setting	906
University of Texas Medical School at Houston	Houston	TX	Not for profit, University-affiliated tertiary care center	733

Incidence surveillance sites

Louisville

The surveillance area for Louisville is Jefferson County, located in the northwest region of the state of Kentucky. All nine hospitals providing adult hospitalization for pneumonia were included in this study. The adult census population of Louisville was used as the denominator for incidence rate calculations, while the numerator was derived from the number of Louisville residents hospitalized for CAP. The annual population incidence rate per 100,000 adults was estimated for this catchment area. Although all eligible cases were identified, approximately 20% of patients did not consent to participate in the study (Table 2).

This 20% of unconsented CAP patients will be factored into the numerator for this site.

The comprehensive management group in Louisville included over 60 team members performing functions that spanned all aspects of study management. The overall accountability remained with the Principal Investigator, however daily operations were led by the coordinating center manager. Study related activities were stratified into four categories: 1) compliance/administration, 2) data science/infrastructure, 3) clinical operations and 4) laboratory/biorepository operations. The compliance and administration group managed budgets, payments, invoicing, IRB approvals, issues of informed consent, and compliance with all federal, state, local and university study conduct requirements. The data science and infrastructure group was responsible for maintaining security of the data during collection, transmission, and storage, management of data quality monitoring meetings, development and implementation of the Data Security Plan, and implementing real-time reporting of enrollment across the coordinating center. The clinical operations team was responsible for the development of Standard Operating Procedures (SOPs) for clinical operations, the manual of operations, development of data collection forms and training in their use, study team management and training, ensuring adequate supply of materials needed for daily operations, establishing tools for assessment of coordinators as well as testing procedures and processes. Laboratory and biorepository operations developed the process for specimen collection, analysis, and tracking and documented receipt, shipment, and storage of study specimens.

Chicago and Nashville

The surveillance centers for Nashville and Chicago are located at Vanderbilt University Medical Center and Northwestern Memorial Hospital, respectively. Each represents only one of multiple hospitals in the Nashville and Chicago regions, respectively. Both are large urban hospitals serving adult general medical and surgical patients. For the Nashville site, patients were enrolled from 9 counties around Nashville area (Cheatham, Davidson, Dickson, Montgomery, Robertson, Rutherford, Sumner, Trousdale, and Williamson). Eight other hospitals in the area treat adult pneumonia. Thus, the cases enrolled at this site did not represent all cases in this catchment area (nine counties); however estimations of incidence were performed by applying market share estimation. The Tennessee Hospital Discharge Data System (HDDS) database was used to determine the percentage (market share) of CAP hospitalizations contributed by Vanderbilt University hospital among the total hospitals within the nine counties. All hospitals in Tennessee are required to report discharge diagnoses for each hospitalization, emergency department visit and outpatient clinic visit to the HDDS system.

The incidence from the Chicago site was also calculated using the market share method. COMPdata-Illinois Health and Hospital Association provided the market share for Northwestern Memorial Hospital pneumonia hospitalizations among Cook County residents [19]. Approximately 32% of CAP patients did not provide consent for enrollment in the study. This will be factored into the incidence calculation for this site.

Table 2. Estimated catchment area denominator and market share for incidence calculations

	Chicago*	Nashville*	Louisville**
Year 1 date	Oct. 2013-Sept. 2014	Nov. 2013-Oct. 2014	June 2014-May 2015
Market share ages 18-64 years	4.57%	14.20%	100%
Market share ages 65+	3.64%	7.23%	100%
Year 2 date	Oct. 2014-Sept. 2015	Nov. 2014-Oct. 2015	June 2015-May 2016
Market share ages 18-64 years	4.30%	13.39%	100%
Market share ages 65+	3.47%	6.38%	100%

*Adjusted for an estimated 32% non-consented rate.

**Adjusted for a 20% non-consented rate.

Subjects

Subjects with suspected pneumonia who provided written informed consent were screened for inclusion in the study. Subjects were actively identified during normal day to day procedures at participating centers. Subject recruitment included at a minimum a daily review of the emergency department and admission records for potential subjects, as well as doctor-to-doctor communication regarding the study. Subjects identified outside of normal daily procedures were also contacted, evaluated and recruited on the following calendar day.

Sites used for the estimation of incidence employed several approaches to ensure complete identification of all patients meeting study criteria. In Louisville, the Clinical Research Coordinating Center at the University of Louisville Division of Infectious Diseases operationalized the project across all nine participating hospitals. Adult patients presenting to participating hospitals with the following conditions were assessed via electronic medical records (EMR) for inclusion in the study: respiratory failure, congestive heart failure, aspiration, stroke, urinary tract infection, confusion, and altered mental status. Initial radiographic findings were reviewed for patients meeting any of the criteria. Patients with findings consistent with pneumonia were approached for inclusion in the study.

Eligible patients presenting in Nashville were identified electronically utilizing the EMR system at Vanderbilt University Medical Center (StarPanel®). The system was programmed to alert the study team of chest x-ray and CT findings potentially consistent with pneumonia. Research team members stationed in the emergency department were then dispatched to further evaluate patients for inclusion. In Chicago, individual research coordinators screened hospital admission records daily for patients meeting inclusion criteria. Identified patients were subsequently contacted for further evaluation for study inclusion.

Study Procedures

Results of chest imaging (X-ray or CT scan) performed per the standard of care were recorded. Images obtained within 72 hours prior to the signing of informed consent could be used in addition to those obtained at the time of hospitalization. Upon confirmation of eligibility, further information was collected, including demographic information, pneumonia severity index (PSI) and medical history (including chronic obstructive pulmonary disease [COPD], asthma, congestive heart failure [CHF], coronary artery disease, chronic kidney disease, diabetes and liver disease, immunosuppressive therapy, autoimmune disease, HIV/AIDS, solid and hematologic tumors and organ

transplantation). Self-reported vaccination status was collected for influenza (within the previous year) and pneumococcal vaccine exposure (within the previous five years).

Urine was collected via micturation as soon as possible following the signing of the informed consent. Urine samples were frozen and stored for subsequent UAD and BinaxNOW® testing. If a blood culture was not obtained as standard of care, it was performed by the study team within 24 hours of study enrollment. Available results of blood and respiratory cultures (sputum, tracheal aspirate, bronchial washing, pleural fluid, etc.), including antibiotic susceptibility testing, were recorded. *S. pneumoniae* isolates obtained from the sites were sent to a central laboratory for confirmation of the pathogen and serotype identification.

Assessments

Subjects had a final diagnosis recorded based on available data, including both study and standard of care exams, procedures and tests through hospital discharge or hospitalization day 10, whichever occurred first. Principal investigators confirmed whether the subject had clinical and radiographically confirmed pneumonia and recorded the subjects' vital status. A final assessment was conducted to determine subject vital status at 30 days post-enrollment, either by phone call or follow-up as standard of care.

Urine assays

The BinaxNOW® antigen test is a rapid assay for the qualitative detection of *S. pneumoniae* antigen in the urine of patients with pneumonia [20]. The UAD is a validated limit assay with defined positivity cut-off limits and is based on the ability of individual serotype-specific monoclonal antibodies to detect the polysaccharides of the 13 serotypes covered by PCV13 in urine.

Statistics

Sample Size Determination

The primary objective of this study was to estimate the proportion of adults hospitalized with CAP infected with a PCV13 *S. pneumoniae* serotype. Sample size determination was based on the 95% confidence interval around this proportion. With a sample size of 216 subjects at each site and an expected proportion of 0.10, an approximate 95% confidence interval will be ± 0.04 at a given site.

Analyses

The primary study analysis population was comprised of subjects meeting all inclusion criteria, with a final diagnosis of CAP, and no evidence of pneumococcal vaccination within 30 days prior to enrollment. A subject with SP+CAP was defined as a patient meeting criteria for CAP and with *S. pneumoniae* identified by UAD, BinaxNOW®, or cultures. The primary endpoint of this study was the proportion of subjects with clinically (confirmed diagnosis of CAP at final assessment) and radiographically-confirmed CAP who had any of the *S. pneumoniae* serotypes from the PCV13 vaccine based on the UAD assay or culture. This proportion was summarized for all sites with 95% confidence interval using the exact method.

The proportion of subjects with PCV13 vaccine type (VT) and non-vaccine type (non-VT) *S. pneumoniae* was summarized by site and geographic region in the full analysis population. To

examine the differences in detection by the different methods, the proportion of subjects with detection of *S. pneumoniae* by culture, BinaxNOW®, and UAD assay were summarized by method (among patients with tests performed). Serotype distribution of *S. pneumoniae* isolates was described by determining the proportion of subjects for each of the *S. pneumoniae* serotypes. Antibiotic resistance rates of *S. pneumoniae* isolates were also determined.

Incidence

For sites with well-defined catchment areas, annual pneumonia incidence rates per 100,000 at risk population were estimated. All incidence rates were computed separately, as well as an annualized rate of the two study years combined. The numerators for each of the incidence rate calculations were the respective numbers of cases during the designated time periods as operationalized in the case definitions; the denominators were the corresponding estimated population figures provided by the US census bureau. Ninety-five percent confidence intervals, based on the Poisson distribution were computed for all incidence rates. Incidence rates were also computed for key-sub-groups (e.g., age and gender).

Discussion

This is the largest surveillance study for *S. pneumoniae* CAP among hospitalized adults in the U.S. with the ability to measure non-invasive pneumococcal disease and identify causal serotypes. The results of this prospective study will provide epidemiologic information concerning the current burden of CAP due to *S. pneumoniae*, including the current distribution of pneumococcal serotypes and their incidence based on population surveillance. Previous analyses of *S. pneumoniae* incidence [2, 21] in CAP have been performed in the U.S.; however, they were conducted before widespread use of PCV13 in children, and before the increasing use of PCV13 among adults seen in recent years. Current data on *S. pneumoniae* serotype distribution in CAP are also limited, as few studies have measured both non-invasive and invasive disease utilizing non-culture methods to identify *S. pneumoniae* in adults.

Importantly, the population surveillance conducted in the Louisville sites provides virtually complete capture of the population at risk for CAP in this area, and therefore yields an incidence rate representative of 100% of the market share in the Louisville area. Market share methodologies for the estimates of incidence in Chicago and Nashville hospital sites (~5-15% market share at one hospital in each location) may yield incidence rates affected by potential differences in patient population at each hospital in the catchment area and an inability to capture the entire population at risk.

In conclusion, the novel methodology of this study allows for a more accurate estimation of the current incidence of PCV13-isolates among hospitalized patients with CAP in the United States via the use of the UAD assay. In addition, information on non-PCV13 serotypes is being gathered via culture methods, along with each subject's PCV13 vaccination status. This may have implications both for evaluation of PCV13 vaccine effectiveness and non-vaccine serotypes likely to be of increasing importance in the near future.

Acknowledgements: Editorial support was provided by Scott Vuocolo, PhD (Pfizer). The authors wish to acknowledge the contribution of Scott Overcash to the study and manuscript.

Funding Source: This study was funded by Pfizer, Inc.

References

1. Angoulvant F, Levy C, Grimprel E, Varon E, Lorrot M, Biscardi S et al. Early impact of 13-valent pneumococcal conjugate vaccine on community-acquired pneumonia in children. *Clin Infect Dis*. 2014 Apr;58(7):918–24.
2. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM et al.; CDC EPIC Study Team. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *N Engl J Med*. 2015 Jul;373(5):415–27.
3. Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. *Lancet*. 2015 Sep;386(9998):1097–108.
4. Said MA, Johnson HL, Nonyane BA, Deloria-Knoll M, O'Brien KL, Andreo F et al.; AGEDD Adult Pneumococcal Burden Study Team. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. *PLoS One*. 2013;8(4):e60273.
5. Rosón B, Carratalà J, Verdaguier R, Dorca J, Manresa F, Gudiol F. Prospective study of the usefulness of sputum Gram stain in the initial approach to community-acquired pneumonia requiring hospitalization. *Clin Infect Dis*. 2000 Oct;31(4):869–74.
6. Huang SS, Johnson KM, Ray GT, Wroe P, Lieu TA, Moore MR et al. Healthcare utilization and cost of pneumococcal disease in the United States. *Vaccine*. 2011 Apr;29(18):3398–412.
7. Ben-Shimol S, Givon-Lavi N, Leibovitz E, Raiz S, Greenberg D, Dagan R. Near-elimination of otitis media caused by 13-valent pneumococcal conjugate vaccine (PCV) serotypes in southern Israel shortly after sequential introduction of 7-valent/13-valent PCV. *Clin Infect Dis*. 2014 Dec;59(12):1724–32.
8. Knoll MD. Preliminary Estimates of Adult Pneumococcal Disease Burden in the United States in the Post 13-valent pneumococcal conjugate vaccine (PCV-13) Era. 10th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD-10); June 26-30; Glasgow, Scotland 2016.
9. Loughlin AM, Hsu K, Silverio AL, Marchant CD, Pelton SI. Direct and indirect effects of PCV13 on nasopharyngeal carriage of PCV13 unique pneumococcal serotypes in Massachusetts' children. *Pediatr Infect Dis J*. 2014 May;33(5):504–10.
10. Pilišvili T, Gierke R, Farley MM, Schaffner W, Thomas AR, Reingold A et al., editors. Direct and Indirect Impact of 13-valent Pneumococcal Conjugate Vaccine (PCV13) on Invasive Pneumococcal Disease (IPD) in the U.S. Era. 10th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD-10); June 26-30; Glasgow, Scotland 2016.
11. Chan KC, Subramanian R, Chong P, Nelson EA, Lam HS, Li AM et al. Pneumococcal carriage in young children after introduction of PCV13 in Hong Kong. *Vaccine*. 2016 Jul;34(33):3867–74.
12. Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med*. 2015 Mar;372(12):1114–25.
13. Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study. *Lancet Infect Dis*. 2011 Oct;11(10):760–8.
14. Davis SM, Deloria-Knoll M, Kassa HT, O'Brien KL. Impact of pneumococcal conjugate vaccines on nasopharyngeal carriage and invasive disease among unvaccinated people: review of evidence on indirect effects. *Vaccine*. 2013 Dec;32(1):133–45.
15. BinaxNow® [package insert]. Scarborough, ME: Alere Scarborough, Inc.; 2012.
16. Pride MW, Huijts SM, Wu K, Souza V, Passador S, Tinder C et al. Validation of an immunodiagnostic assay for detection of 13 *Streptococcus pneumoniae* serotype-specific polysaccharides in human urine. *Clin Vaccine Immunol*. 2012 Aug;19(8):1131–41.
17. Pride MW, Huijts SM, Wu K, Souza V, Passador S, Tinder C et al. Validation of an Immunodiagnostic Assay for the Detection of 13 *S. pneumoniae* Serotype-Specific Polysaccharides in Human Urine. *Clin Vaccine Immunol*. 2012;19(8):1131–41.
18. Sherwin RL, Gray S, Alexander R, McGovern PC, Graepel J, Pride MW et al. Distribution of 13-valent pneumococcal conjugate vaccine *Streptococcus pneumoniae* serotypes in US adults aged ≥50 years with community-acquired pneumonia. *J Infect Dis*. 2013 Dec;208(11):1813–20.
19. Sherwin RL, Gray S, Alexander N, McGovern P, Graepel J, Pride MW, Purdy J, Jr TM. Distribution of PCV13-serotype *Streptococcus pneumoniae* in Adults Aged ≥ 50 Years Presenting to Select US Hospitals with Radiographically-Confirmed Community-Onset Pneumonia. *ID Week*, San Diego. 2012 Oct
20. COMPdata Informatics. Available from: <https://www.compdatainfo.com/About-Us.aspx>
21. Lasocki S, Scanvic A, Le Turdu F, Restoux A, Mentec H, Bleichner G et al. Evaluation of the Binax NOW *Streptococcus pneumoniae* urinary antigen assay in intensive care patients hospitalized for pneumonia. *Intensive Care Med*. 2006 Nov;32(11):1766–72.
22. Broulette J, Yu H, Pyenson B, Iwasaki K, Sato R. The incidence rate and economic burden of community-acquired pneumonia in a working-age population. *Am Health Drug Benefits*. 2013 Sep;6(8):494–503.