

Prevalence of Pneumococcal Serotypes in Adults Enrolled in a Phase 3 Trial that Evaluated the Efficacy and Safety of Oral Solithromycin (CEM-101) versus Moxifloxacin in Adults with CABP

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Abstract

Background: We investigated the prevalence and geographic distribution of *Streptococcus pneumoniae* (Spn) serotypes in patients from a randomized, double-blind Phase 3 trial to evaluate the efficacy and safety of oral solithromycin compared to oral moxifloxacin in the treatment of adults with CABP.

Methods: Key inclusion criteria included ≥18 years of age, chest x-ray showing lobar or multilobar infiltrates and consistent signs and symptoms. Spn was identified as an etiologic agent on the basis of blood or sputum culture, urine antigen testing (BINAX), sputum multiplex PCR (Unyvero™ by Curetis) and quantitative Spn PCR of nasopharyngeal (NP) swabs. Spn isolates recovered from patients by culture from blood, sputum, or nasopharyngeal (NP) swabs were serotyped by Quellung reaction.

Results: 860 patients were enrolled from 16 countries across Europe (52.1%), Latin America (12.3%), North America (23.7%) and South Africa (11.9%). The overall Spn diagnosis rate for the trial was 23%. Spn isolates from blood (N=16), sputum (N=72) or NP swab (N=79) from 123 unique patients were available for serotyping. With 3 exceptions, the serotype of blood or sputum Spn was the same as Spn from the nasopharynx. 35 different serotypes were detected, with serotype 3 as the most prevalent (10.6%), followed by 19F (7.3%) and 19A (5.7%). Overall, 43.9% of patients with serotyped Spn had types in the 13-valent pneumococcal conjugate vaccine (PCV13), 60.2% had types in the pneumococcal polysaccharide vaccine (PPSV23) and 38.2% had Spn not represented in either vaccine. The prevalence of patients with Spn serotypes contained in PCV13 and PPSV23 by region are shown below.

	Europe	Latin America	North America	South Africa
Number of Randomized Patients	448	106	204	102
Patients with any Pathogen Diagnosis, N (Rate)	257 (57.4%)	68 (64.2%)	84 (41.2%)	52 (51%)
Patients with Pneumococcal Pneumonia, N (Rate)	114 (25.4%)	32 (30.2%)	24 (11.8%)	27 (26.5%)
Patients with Serotyped Spn, N	79	15	13	16
PCV13	50.6%	73.3%	15.4%	25%
PPSV23	63.3%	86.7%	53.8%	43.8%

Conclusions: Since there was very good correlation between the serotypes in the NP and blood/sputum of CABP patients, NP swabs may be able to replace sputum cultures if a quantitative threshold diagnostic of pneumonia is met. 38.2% of patients had isolates not represented in the PCV13 or PPSV23 vaccines.

Introduction

Streptococcus pneumoniae is a lancet-shaped, gram-positive, facultative anaerobic bacterium that represents one of the most common (~20%) etiologic agents for community-acquired bacterial pneumonia (CABP). To date, over 90 different serotypes have been identified for this organism and a select group of serotypes, such as serotype 19A, is frequently implicated in pneumococcal disease. The rapid and widespread emergence of antibiotic resistant pathogens, such as multidrug-resistant *S. pneumoniae*, has resulted in a need for new antibiotics that have activity against the pneumococcus and other CABP pathogens.

Cempra conducted a randomized, double-blinded Phase 3 trial which evaluated the efficacy and safety of oral solithromycin (5 days) compared to the oral fluoroquinolone, moxifloxacin (7 days), for the treatment of adult patients with CABP. As pneumococcal vaccines are becoming widely used worldwide, including PCV13 (children) and PPSV23 (adults), this phase 3 trial presented us a unique opportunity to further evaluate the overall prevalence of pneumococcal types causing CABP, serotype prevalence by geographic region, and to study the correlation between the pneumococcal type isolated from the nasopharynx and those strains isolated from blood or sputum.

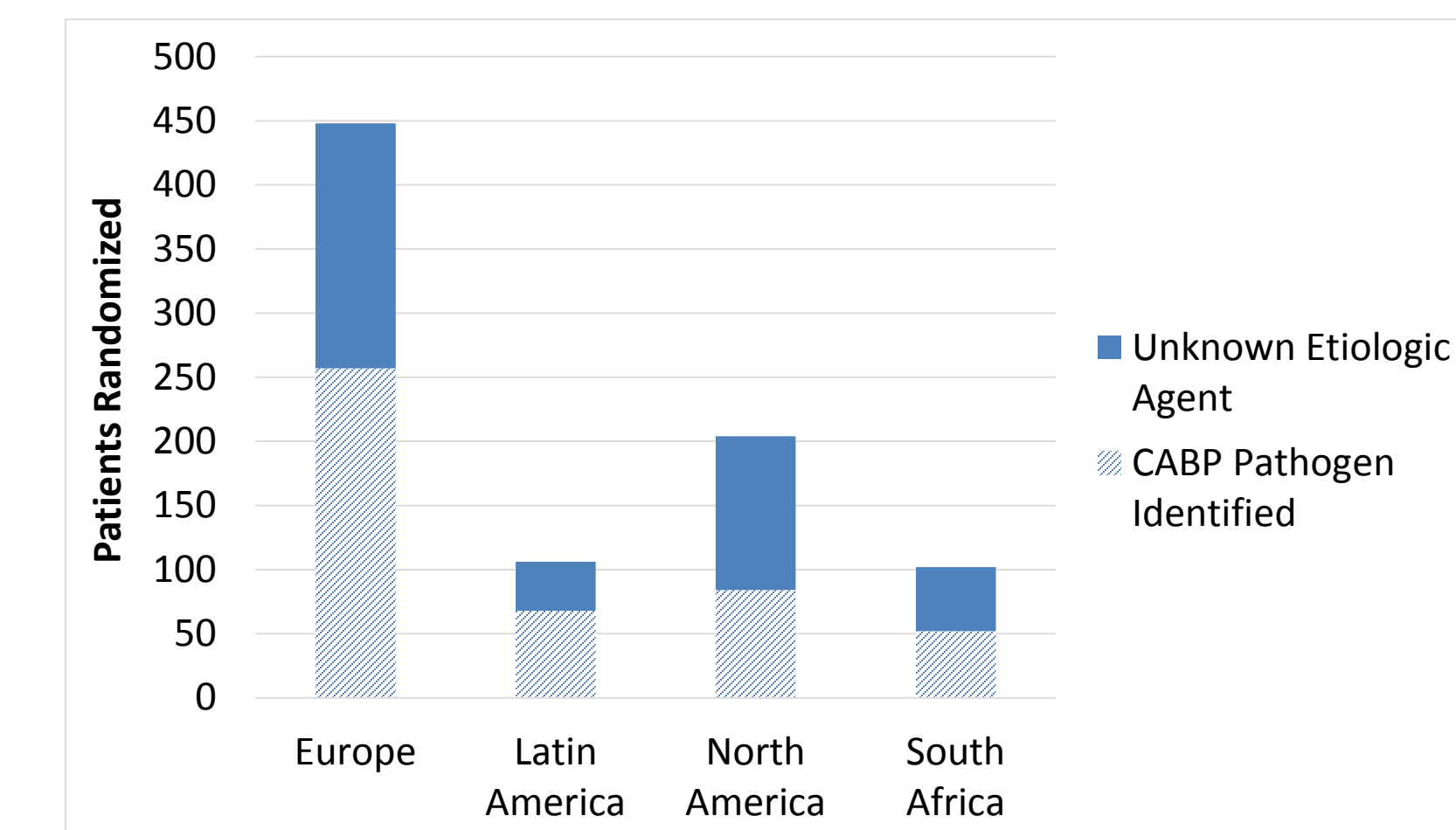
- PCV13 serotypes: 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F
- PPSV23 serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F

Methods

- Enrollment criteria included the following: ≥ 18 years of age; acute onset or worsening of at least 3 of 4 cardinal symptoms (cough, dyspnea, chest pain, and sputum production); must have fever or hypothermia, and/or physical exam findings consistent with CABP; chest radiograph with lobar or multi-lobe infiltrates; and no long-acting antibiotic use during the prior 7 days.
- Baseline microbiological evaluation included cultures of blood and sputum, detection of *S. pneumoniae* and *Legionella pneumophila* antigen in urine, *L. pneumophila* and *Mycoplasma pneumoniae* serologies (4-fold diagnostic rise in titers), quantitative real-time PCR and culture of nasopharyngeal swabs for *S. pneumoniae*, culture and PCR of oropharyngeal swabs for *M. pneumoniae*, and sputum multiplex PCR for lower respiratory pathogens (Unyvero™ by Curetis).
- Spn isolates recovered from patients by culture from blood, sputum, or nasopharyngeal (NP) swabs were serotyped by Quellung reaction using antisera produced by the Staten Serum Institute (SSI). Quellung reactions identify 91 pneumococcal serotypes, including all vaccine types.

Results

Figure 1: Patients Randomized by Region and Percent of Patients in which Etiologic Agent Was Identified

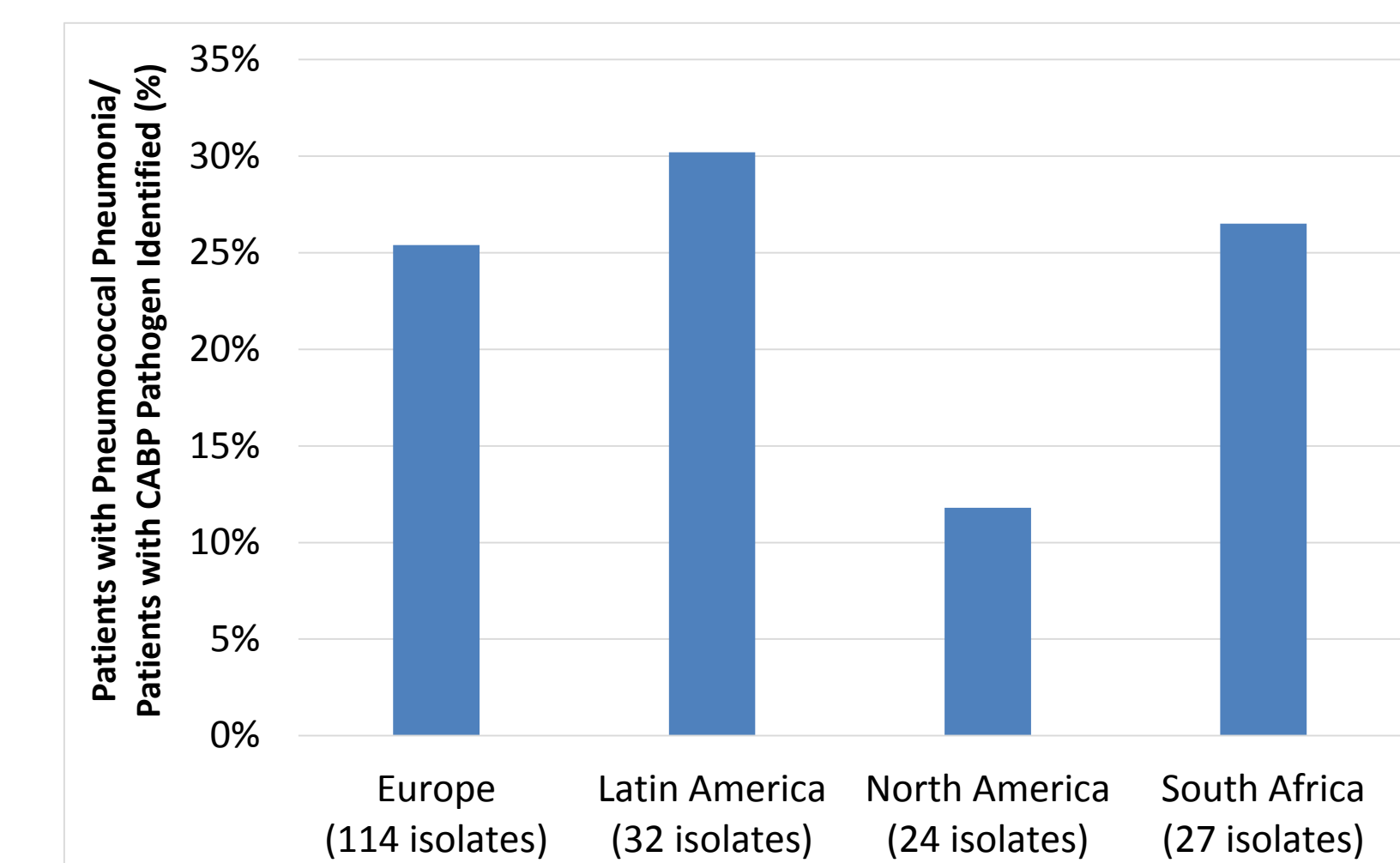


- The most frequently identified CABP pathogens in order of prevalence:

- S. pneumoniae* (23%)
- H. influenzae* (16%)
- L. pneumophila* (15%)
- M. pneumoniae* (9%)
- M. catarrhalis* (6%)
- S. aureus* (4%)

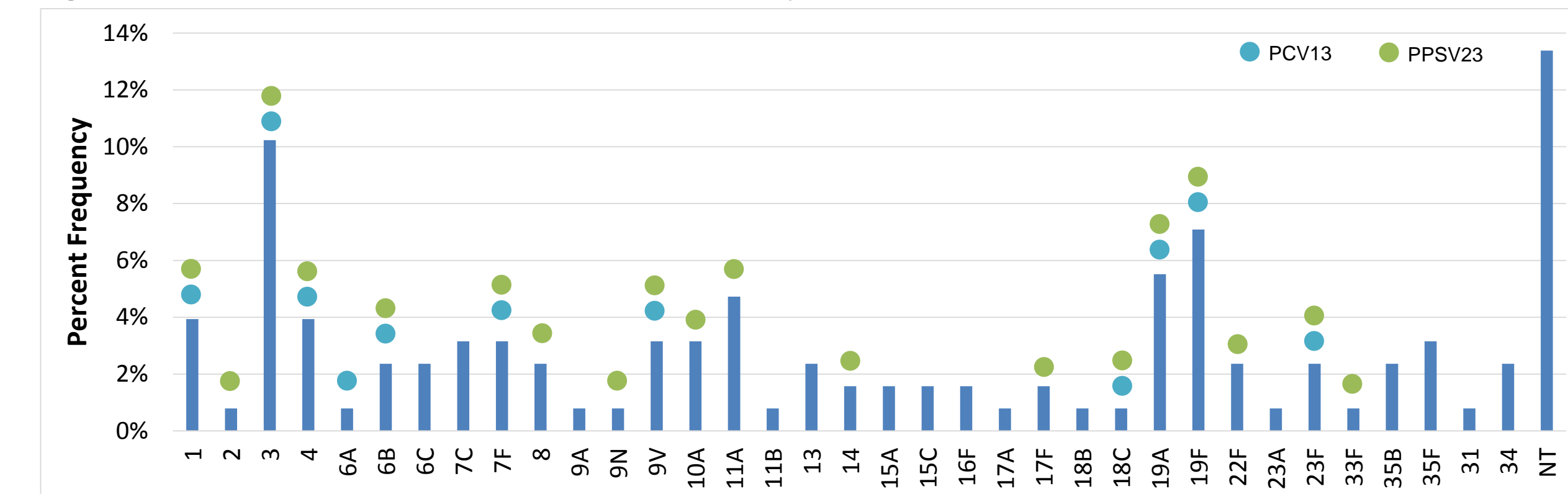
* Some patients had >1 pathogen

Figure 2: Rates of Pneumococcal Pneumonia Diagnosis by Region Among Patients with CABP Pathogen Identified



Results

Figure 3: Overall Distribution of *S. pneumoniae* Serotypes



- There was a total of 123 patients from whom 167 Spn isolates were available from different sources for serotyping.
 - 16 blood isolates
 - 72 sputum isolates
 - 79 NP swab isolates
- There were 127 unique Spn isolates based on serotype.
- Most common serotypes were:
 - 3 (10.6%)
 - 19F (7.3%)
 - 19A (5.7%)

Figure 4: Frequency of pneumococcal vaccine-type serotypes by region

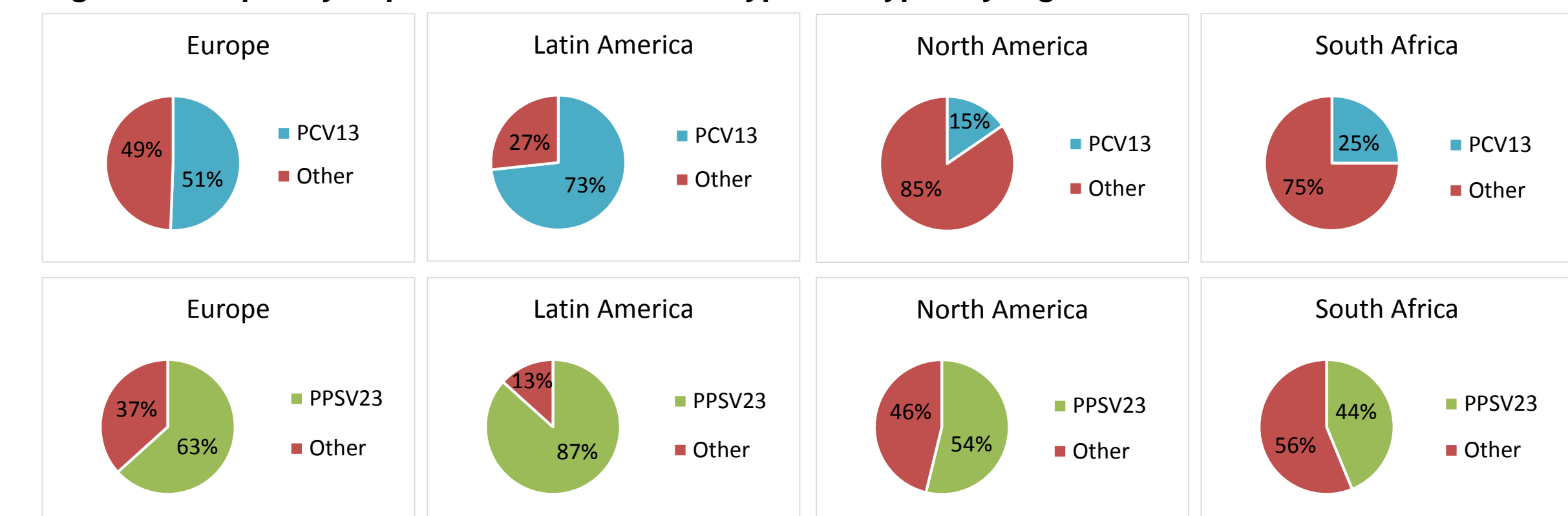


Figure 5: Pneumococcal density in CABP patients with strains isolated

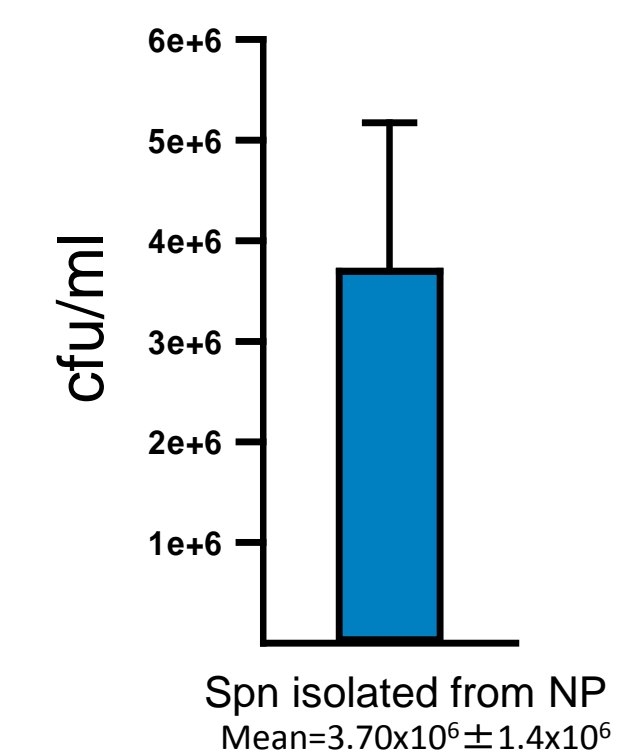


Table 1: Correlation of Serotypes between Isolates from Nasopharyngeal and Blood or Sputum Specimens

Total Patients with Spn Isolates, N	Patients with Identical Serotypes, N (%)	Patients with Different Serotypes, N (%)
123	120 (97.6%)	3 (2.4%)

- 3 Patients with different serotypes:
 - NP Isolate: 35F, Blood Isolates: NT, 2
 - NP Isolate: 18C, Sputum Isolate: 18B
 - NP Isolate: 35F, Sputum Isolate: 9A

Conclusions

- S. pneumoniae* was the most prevalent bacterial pathogen isolated in the Phase 3 CABP trial and a total of 35 different pneumococcal serotypes were identified.
- In European and Latin American countries, more than 60% of pneumococcal pneumonia cases were produced by PPSV23 serotypes.
- Overall, non-vaccine serotypes were found in greater than 38% of patients with CABP.
- We observed a very strong correlation between the pneumococcal serotype isolated from blood or sputum, utilized as definitive diagnoses of pneumococcal pneumonia, and those isolated from the nasopharynx of pneumococcal pneumonia patients.

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