

The Importance of 23-Pneumococcal Polysaccharide Vaccine in An Alzheimer's Cohort from the South of Brazil- A Retrospective Study

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ABSTRACT

Objective: Pneumonia is the leading cause of death in patients with dementia. The efficacy of the pneumococcal polysaccharide vaccine 23 (PPV23) in these patients is uncertain. This study aims to analyze the role of the PPV23 on preventing community pneumonia in Alzheimer's disease and Mixed Dementia patients.

Method: It is a retrospective cohort study. Vaccinated and non-vaccinated patients were compared for the following outcomes: diagnosis, hospitalization and death from pneumonia or all causes. Data on the characteristics of 510 individuals older than 60 years with the diagnosis of Alzheimer's disease or Mixed Dementia were collected at a public outpatient clinic in a city from the South of Brazil, from January 1, 2015 to December 31, 2018. **RESULTS:** From 510 individuals, 237 (46.5%) were vaccinated with PPV23 and 74 (14.5%) had all-cause pneumonia. There was no significant association between PPV23 vaccination and the risk of pneumonia or death.

Conclusion: No association between PPV23 and pneumonia or death in dementia patients was found in the studied population. This is the first study with PPV23 exclusively in dementia patients. Future and largest studies should be done to prove the efficacy of this vaccine in this population.

Keywords

Alzheimer's disease, Mixed Dementia, Pneumococcal Polysaccharide Vaccine 2, Pneumonia, Vaccination.

Introduction

Pneumococcal disease is a worldwide public health problem aggravated by increased pneumococcal resistance to essential antibiotics and the ease with which resistant serotypes progressively spread throughout the world [1]. The Global Burden Disease Study showed that there were 43.8 million individuals with dementia in the world in 2016, an increase of 20.2 million over 1990 [2]. According to the World Health Organization (WHO), pneumonia and other respiratory infections are the 4th cause of death worldwide and dementias are the 5th cause, and together they accounted for almost 5 million deaths in 2016 [3].

In addition to pneumonia being the leading cause of death in patients with dementia, with each infectious event or hospitalization these individuals decline cognitively and functionally, resulting in even greater decline of autonomy and functionality [4].^[1] The efficacy of PPV23 in the older population varies in studies, from 45-73% against invasive pneumococcal disease (meningitis, bacteremic pneumonia), between 48-64% against community pneumococcal pneumonia, and between 25-44.8% against all causes of pneumonia [5-7]. Studies have shown that efficacy is lower in the older persons and 5-year revaccination is recommended [7]. However, many studies have failed to demonstrate efficacy in the older people with chronic diseases [8-10]. A meta-analysis of randomized clinical trials published in 2016 pointed to several studies that have not shown PPV23 to be effective in preventing all-cause community-acquired pneumonia in the older population and found only one

study in Japan of institutionalized older adults that showed vaccine efficacy [5].

Although WHO recommends PPV23 for all people over 60 years of age, the importance of this vaccine exclusively on older people with Alzheimer's Disease or Mixed Dementia has not been evaluated in studies to date [11]. Therefore, knowing the impact of vaccination on pneumonia prevention in this older population with dementia is important in order to help reduce morbidity and mortality from this disease.

Materials and Methods

A retrospective study was done of all individuals older than 60 years with the diagnosis of Alzheimer's Disease or Mixed Dementia according to the Clinical Protocol and Therapeutic Guidelines of the Brazilian Ministry of Health (2017) based on the National Institute of Aging and Alzheimer's Association recommendations [12] cared at the Alzheimer Outpatient Clinic in Londrina, from January 1, 2015 to December 31, 2018. Information on gender, age, education, institutionalization, vaccination with PPV23, PCV13, Influenza and year of vaccination; diagnosis of AD or MD; severity of dementia by Clinical Dementia Rating (CDR), Mini Mental State Examination (MMSE) at the first consultation, 2017 and 2018; Katz Index for Daily Living Activities in 2017 and 2018; Body Mass Index (BMI) in the diagnosis, diagnosis of Chronic Lung Disease, current or recent smoking (last year), current or recent alcohol abuse (drink more than two cans of beer a day), presence of immunosuppressive condition (dialytic chronic kidney disease, cancer being treated, use of immunosuppressive dose corticosteroids such as prednisone >1mg/kg daily, diagnosis of HIV, splenectomies), if there were symptoms of delirium (agitation, aggressiveness), diagnosis of Hypertension, Diabetes Mellitus, history of Acute Myocardial Infarction and Stroke were extracted from electronic records. Outcomes of interest were diagnosis, hospitalization or death from pneumonia or all causes. The diagnosis of pneumonia was cough plus one of the following symptoms: dyspnea, chest pain or sputum; focal findings on chest physical examination and laboratory exams (CBC with leukocytosis) or chest x-ray with suggestive image, without identifying the etiological agent. The information was obtained by reviewing the electronic medical records of these patients and by telephone interview with the patient's caregivers. The cause of death was verified by telephone contact with the caregiver and information on the death certificates.

Means were compared between groups by Student's T test and the proportions by Fisher's exact test. Logistic regression models were created to test the association between vaccination and outcomes, with adjustment for confounding factors (diagnosis of Chronic Lung Disease, age and severity of dementia by CDR). We used the statistical package SPSS and the significance level set at 5%.

Ethics

Data collection was only carried out after approval by the Research Ethics Committee (CAAE 09535119.7.0000.0020).

This study is in accordance with the Helsinki Declaration.

Results

The sample consisted of 510 older patients, 65% female, and 53.5% with 1-4 years of education. The predominant age group was 80-89 years (47.3%) and the individuals who were vaccinated were older (81.08 ± 7.08 versus 78.63 ± 7.84 , $p = 0.01$). Of these, 88% had a diagnosis of AD and most were CDR I (47%), i.e. mild dementia. Less than half (46.5%) were vaccinated with PPV23, the majority for less than 5 years (98.8%) and 39.8% for less than 2 years. No individual was vaccinated with PCV13. A minority lived in nursing homes (2.4%), but being institutionalized favored vaccination ($p = 0.01$). Most were vaccinated against Influenza in 2018 (65.3%) and it was associated with PPV23 vaccination ($p = 0.01$). Few had Chronic Lung Disease (5.5%). Smokers represented 21.8% and 19% had a history of alcohol abuse. A total of 27.5% had a medical history of stroke or acute myocardial infarction and 30.8% were diabetic. Less than 1% had some disease or factor for immunosuppression. One third was eutrophic according to BMI (33.3%). There was no association between vaccination and worse cognitive performance (MMSE), functionality (ABVD) or delirium symptoms. Except for age, Influenza vaccination and institutionalization, there was no significant difference between the characteristics of the vaccinated and unvaccinated group. These features are arranged in the Table 1.

A total of 74 (14.5%) of the patients had all-cause pneumonia in the studied period, 61 (11.9%) were hospitalized, 26 (5%) died from pneumonia and 96 (18.8%) died from all causes. There was no significant association between vaccination with PPV23 and pneumonia diagnosis or death. There was significant association between vaccination and hospitalization for pneumonia in this first analysis ($p = 0.045$), as shown in Figure 1, and no difference in severity of dementia between the vaccinated or unvaccinated group who had been hospitalized.

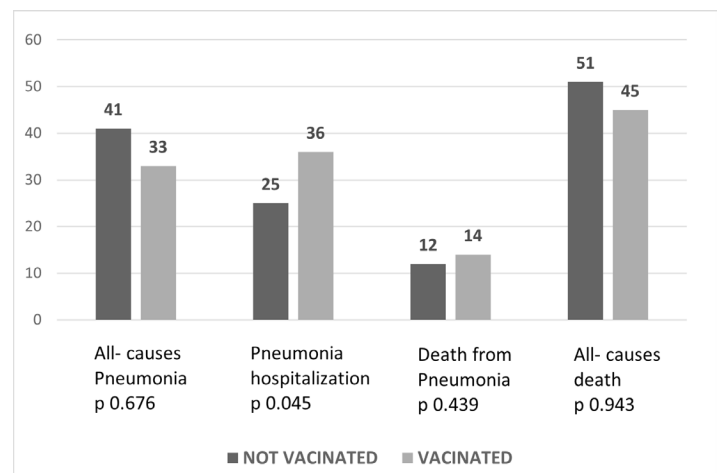


Figure 1: Number of cases of all-cause pneumonia, pneumonia hospitalization, death from pneumonia, and all-cause death in relation to PPV23 vaccination status.

CHARACTERISTICS	NOT VACCINATED n = 273 (53.5%)	VACCINATED n = 237 (46.5%)	p VALUE
Middle ages	78.63 (± 7.846)	81.08 (± 7.088)	0.01
Genre			
Female	182 (55%)	149 (45%)	0.41
Male	90 (50.6%)	88 (49.4%)	
Schooling			
Illiterate	89 (57.4%)	66 (42.5%)	0.24
≤4 years	134 (49.1%)	139 (50.9%)	
≤8 years	25 (58.1%)	18 (41.8%)	
High School	13 (76.4%)	4 (23.5%)	
College	9 (100%)	0 (0%)	
Dementia type			
Alzheimer	241 (53.7%)	208 (46.3%)	0.85
Mixed Dementia	32 (53.5%)	29 (46.5%)	
Dementia Stage			
CDR ^a I	138 (56.8%)	105 (43.2%)	0.27
CDR II	85 (48.9%)	89 (51.1%)	
CDR III	47 (52.8%)	42 (47.2%)	
Diabetes	91 (58%)	66 (42%)	0.15
Hypertension	179 (53.1%)	158 (46.8%)	0.85
Heart Attack/Stroke^b	80 (57.1%)	60 (42.8%)	0.32
Chronic Lung Disease^c	15 (53.6%)	13 (46.4%)	0.97
Smoking^d	55 (49.6%)	56 (50.4%)	0.38
Ethylism^e	47 (37.1%)	80 (62.9%)	0.30
Influenza Vaccine	164 (49.3%)	169 (50.7%)	0.01
Nursing Home^f	2 (16.7%)	10 (83.3%)	0.01
BMI^g			
Low weight	42 (53.8%)	36 (46.2%)	0.05
Normal weight	83 (48.8%)	87 (51.2%)	
Overweight	48 (67.6%)	23 (32.4%)	
Obesity	21 (70%)	9 (30%)	
Katz^h			
Dependent	19 (67.9%)	9 (32.1%)	0.29
Independent	162 (50.5%)	159 (59.5%)	
MMSEⁱ: mean at diagnosis	14.33 (± 4.903)	14.7 (± 5.285)	0.42
Immunosuppressive condition^j	2 (50%)	2 (50%)	
Delirium symptoms^k	26 (9.7%)	21 (8.9%)	0.87

Table 1: Population characteristics according to vaccination status for PPV23.

^a CDR: Clinical Dementia Rating

^b History of myocardial infarction or stroke

^c Diagnosis of Chronic Obstructive Pulmonary Disease , Asthma, Pulmonary fibrosis

^d Current or recent smoking (< 1 year)

^e Current or recent ethylism (< 1 year)

^f Living in a nursing home

^g Body Mass Index for elderly

^h Katz Scale- Basic Activities of Daily Living

ⁱ Mini -Mental State Exam

^j Dialytic chronic kidney disease, cancer being treated, use of immunosuppressive dose corticosteroids, diagnosis of HIV, splenectomized

^k Agitation, aggressiveness

However, the hospitalized group was older (83.2 ± 5.9 versus 79.3 ± 7.7 , $p < 0.01$) and there were more individuals with Chronic Lung Disease (21.4% versus 11.7%, $p < 0.01$). There was no significant difference in the multivariate analysis between vaccinated and unvaccinated for the diagnostic outcome and hospitalization for pneumonia when we controlled for age, CDR and Chronic Lung Disease, i.e., the association between vaccination and

hospitalization for pneumonia was lost in this second analysis, as shown in Table 2.

Discussion

This retrospective study portrays the reality of an older population attended at a Brazilian public outpatient clinic. Although the PPV23 has existed for over 30 years, it was found that not even

Models	Pneumonia Hospitalization		Pneumonia	
	OR (CI 95%)	p value	OR (CI 95%)	p value
Model 1 (PPV23 vaccine)	1.734 (1.007; 2.985)	0.047	0.987 (0.548; 1.478)	0.676
Model 2 (Model 1 + age)	1.523 (0.876; 2.648)	0.136	0.788 (0.478; 1.309)	0.370
Model 3 (Model 2 + CDR ^a e CLD ^b)	1.474 (0,841; 2,584)	0.175	0.778 (0.470; 1.297)	0.355

Table 2: Multivariate analysis for pneumonia and pneumonia hospitalization between vaccinated compared to non-vaccinated PPV23.

^aClinical Dementia Rating

^bChronic Lung Disease (Chronic Obstructive Pulmonary Disease , Asthma, Pulmonary fibrosis)

half of this population had been vaccinated. Since this vaccine requires a physician prescription, it is assumed that doctors should be better informed about the indications. It was also observed that no individual had been vaccinated with PCV13, most likely because this vaccine was only very recently being provided free of charge in Brazil (2019).

In 2014 the Advisory Committee on Immunization Practices (ACIP) published recommendations for the use of PCV13 and PPV23 in adults > 65 years and reported that there was no consistent evidence on the effectiveness of PPV23 alone in preventing community pneumonia in the older population [13].

The efficacy of isolated pneumococcal 23 vaccine in preventing pneumonia in the older people with Alzheimer's disease or mixed dementia is yet to be proven. In a randomized clinical trial conducted in Japan's nursing home published in 2010 in a sample of 1.100 older people, of these 349 with cerebrovascular disease, there was a 63.8% reduction in the incidence of pneumococcal pneumonia per 1000 / person year and 44.8% reduction of all-cause pneumonia [6]. The prospective CAPAMIS cohort study conducted in Spain and published in 2014 only demonstrated efficacy of the PPV23 vaccine in the subgroup of older people who received the vaccine in a time shorter than the previous 5 years with a 25% reduction in pneumonia for all causes in the vaccinated group. This study had a sample of 27204 individuals > 60 years old, 801 with dementia [7].

There are some hypotheses why the present study could not demonstrate an association between vaccination and the occurrence of pneumonia, one of which is that the study time period wasn't long enough (39.2% were vaccinated in a period shorter than the previous two years). We cannot infer whether the results would remain negative if the patients had taken the PCV13 prior to PPV23, because there is evidence that immunogenicity increases, especially in this population where the immune response is reduced [14,15]. The CAPITA study, a randomized clinical trial published in 2015 involving 84496 adults older than 65 years of age showed 75% efficacy of PCV 13 against IPD and 45% efficacy in preventing bacteremic and nonbacteremic pneumococcal pneumonia, but showed no efficacy in preventing all-cause pneumonia in the older people [16]. Subsequently, in this study, a NNT of 634 (95% CI: 386-1.675) was calculated [17].

There was a significant association between vaccination and pneumonia hospitalization, which could not be verified after adjusting for age and the severity of dementia. There are studies reporting increases in some pneumococcal serotypes not contemplated in pneumococcal vaccines following the introduction of PCV7 and PCV 13, in the childhood vaccination schedule [18]. A study conducted in England showed that there was a reduction in the incidence of IPD caused by serotypes present in PCV7 and PCV 13, but increased the incidence of IPD by serotypes 8, 12F and 9N [19]. Another possibility is that this population, due to socioeconomic conditions and oral hygiene, associated with the presence of swallowing disorders, were hospitalized mainly due to aspiration pneumonia, which would have other etiological agents involved, such as aerobic and anaerobic gram negative enterobacteria [20,21].

Our study showed limitations such as the under diagnosis of subclinical cases or other potential benefits from the PPV23 as a prevention of meningitis and bacteremic pneumonia.

On the other hand, our study also showed positive initiative, for so far as is known, it is the first study that evaluates vaccination with PPV23 in older population diagnosed with Alzheimer's and mixed dementia.

Conclusion

Pneumonia is the leading cause of death in patients with Alzheimer's disease and Mixed Dementia. The data from this study was not able to demonstrate an association between vaccination with PPV23 and prevention of all-cause community pneumonia. Future studies should explore the causes, contributing factors and impact of pneumonia prevention in this older population with dementia.

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