Original Article

Adverse events after pneumococcal vaccination*

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Abstract

Objective: To study the occurrence of adverse events after administration of a capsular polysaccharide vaccine against 23 pneumococcal serotypes in individuals for whom such vaccination is indicated. **Methods:** This was a prospective study, conducted in a general hospital in the city of Sumaré, Brazil, in which 152 individuals were evaluated after intramuscular vaccination with 0.5 mL of the Pneumo 23® vaccine. The study variable was subject complaint of at least one symptom forming a temporal nexus with the vaccine (appearing within 48 h after its administration). The subjects were evaluated at five to seven days after vaccination. The covariables age, gender and clinical profile were tested using the chi-square test and multiple logistic regression, with the level of significance set at 5%. **Results:** The age of the population ranged from 5 to 86 years (mean, 61.8 years). For nearly all (99%) of the subjects, the vaccination evaluated was their first dose of the vaccine. Events occurring at the injection site were reported in 36 subjects (23.7%). Of those 36 events, 24 (68%) were mild and had no repercussions for the daily activities of the subjects. Pain at the site of the injection was the most common symptom, being reported by 97.2% of the subjects. Erythema and localized edema were found in 6.3% and 5.1% of the subjects, respectively. Of the subjects evaluated, 12.8% reported general symptoms (malaise, fever, sleepiness and generalized pain). In the bivariate analysis, none of the covariables were found to present a statistically significant correlation with adverse events ($p > 0.20$). The same held true in the multivariate analysis. **Conclusion:** Although, the 23-valent pneumococcal vaccine provokes few reactions in the first dose, it is still rarely recommended in the region, even for patients at risk.

Keywords: Streptococcus pneumoniae; Pneumonia; Pneumococcal/prevention & control; Pneumococcal vaccines/adverse effects.

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Introduction

Vaccination for the prevention of *Streptococcus pneumoniae* infections in at-risk individuals has been adopted as a public health measure in various countries.[1,2] Clinical and epidemiological studies suggest that the 23-valent pneumococcal capsular polysaccharide vaccine is effective in preventing invasive disease caused by pneumococci, thereby decreasing the numbers of hospitalizations and deaths from pneumonia in several regions.[3-5] The antigens available in the vaccine induce the formation of specific antibodies, increasing the opsonization and the phagocytosis of *S. pneumoniae*. Some authors emphasize the limited effectiveness of the vaccine in immunocompromised patients with different responses according to age, genetic factors, nutritional factors, and clinical situation, as well as the short duration of its protection effect.[6-8] Despite the controversies on the immunobiological effectiveness in some clinical situations, it has been recommended for use in specific groups of individuals in various countries.[1,9-12]

The pneumococcal polysaccharide vaccine is still not widely used in at-risk patients in Brazil, although it is available in public hospitals and is formally indicated for patients with chronic diseases, such as diabetes, chronic bronchitis, emphysema, cardiopathy, asplenia, acquired immunodeficiency syndrome, renal insufficiency, and liver cirrhosis.[1,11]

Although concerns exist regarding the occurrence of adverse events in second doses given at intervals of less than five years, most studies consider the vaccine safe and minimally reactogenic.[1,10,14] In Brazil, there have been few studies of the occurrence of adverse events. The present study aims to analyze the occurrence of these events after administration of the vaccine in individuals for whom such vaccination is indicated in the microregion of the city of Sumaré, Brazil.

Methods

In November of 2004, a prospective investigation was conducted, involving 152 individuals who participated in the vaccination campaign against pneumococcal diseases (receiving the 23-valent vaccine), diphtheria and tetanus (adult-type combined diphtheria-tetanus vaccine) at the Sumaré State Hospital, a clinical referral center in the microregion of the city of Sumaré (630,000 inhabitants). The campaign lasted two days and had been previously disclosed in public hospitals and medical services throughout the region. General practitioners and specialists working at public hospitals received technical information and literature on the 23-valent vaccine on the occasion of the campaign. The vaccine against diphtheria and tetanus was also offered in order take advantage of the opportunity to administer this vaccine in those who took part in the campaign.

Individuals who took part in the campaign were revaluated in relation to whether such immunobiological protection was clinically indicated, and all gave written informed consent. The informed consent form was retained for further contact. By the fifth to seventh days after vaccination, individuals were contacted by telephone (or home visits if necessary) in order to investigate the occurrence of systemic and local (left arm) adverse events, possibly related to the 23-valent vaccine.

Complaints of adverse effects at the site of administration were investigated in the 152 individuals receiving the 23-valent vaccine, and systemic symptoms were investigated in the 78 individuals who received only this vaccine. Since both vaccines – against pneumococcal diseases and against diphtheria/tetanus – were offered, the systemic symptoms of the 74 individuals who received both vaccines were not considered. The research was approved by the Ethics in Research Committee of the State University at Campinas School of Medical Sciences (process no. 215/2005).

The 23-valent vaccine administered was Pneumo23® vaccine (lot X0056-1; Aventis Pasteur, Madrid, Spain), which was injected intramuscularly into the left arm in a dose of 0.5 mL. The vaccine against diphtheria and tetanus was administered in the right arm. The outcome measure was the complaint of at least one symptom related to the vaccination. Only local symptoms in the left arm with temporal connection with vaccination, that is, within 48 h after the administration of the vaccine, were considered.[1] The covariables investigated were as follows: age, gender, place of residence, clinical indication for the vaccine, and reporting having chronic diseases.

The local symptoms were classified as being of low, mild, or high intensity, based on patient reporting. The level of discomfort in performing daily activities, the use of medication, and the search for medical attention were taken into account,

although these perceptions can vary according to social and cultural conditions.

Statistical associations between the occurrence of symptoms and the covariables were identified using the chi-square test, considering a significance level of 5%. After the bivariate analysis, the multiple logistic regression model was adjusted considering as dependent variable the occurrence of at least one symptom, and c-variables were progressively tested (stepwise) in the model.[15] The Epi Info program, version 6.04, was used to build the database, and the Proc Logistic procedure of the Statistics Analysis System software was used for the multiple analysis.

Results

A total of 152 individuals were investigated, representing 76% of the 200 individuals who took part in the campaign. Of the 200 individuals, 47 were not found in three attempts, and one declined to complete the questionnaire. All 200 individuals were vaccinated against pneumococcal diseases, and 78 received only this vaccine (the 23-valent vaccine). In 36 (23.7%) of the 152 individuals evaluated, at least one local symptom was observed, possibly related to the vaccination against pneumococcal diseases. The local symptoms reported were pain, erythema, and edema. The profile of the individuals studied is shown in Table 1. Systemic symptoms were reported by 10 individuals (12.8%).

We observed that most of the vaccinated individuals (82; 53.9%) were women, and that most (57; 37.5%) were in the 60 to 69 years age bracket. The age of the studied population ranged from 5 to 86 years (mean, 61.8 years). Most of the individuals (61%) were referred by clinical practitioners from basic public health services or specialty outpatient clinics in the region.

Among the comorbidities, the most prevalent in the studied population was systemic arterial hypertension, which affected 82 patients (53.9%), followed by cardiopathy, which was observed in 46 cases (30.3%). Chronic obstructive pulmonary disease and other chronic pulmonary diseases were reported by, respectively, 16 (10.5%) and 25 (16.4%) of the individuals vaccinated, and only one patient presented renal insufficiency. Other diseases, such as cirrhosis and liver fibrosis, were reported by two individuals (1.4%). In addition, some diseases that do not formally constitute an indication for vaccination against pneumococcal diseases (vasculopathy, mental disorders, prostate diseases, and others) were reported, accounting for 14.4% of the sample (Table 1).

Table 1 - Profile of vaccinated patients investigated during the Sumaré State Hospital campaign, 2004.

	n	(%)
Gender		
Female	82	53.9
Male	69	45.4
Age (years)		
< 20	4	2.6
20-29	4	2.6
30-39	3	2.0
40-49	19	12.5
50-59	20	13.2
60-69	57	37.5
70-79	39	25.7
≥ 80	6	3.9
Comorbidities		
Arterial hypertension	82	53.9
Cardiopathy	46	30.3
Diabetes Mellitus	37	24.3
Pneumopathy*	25	16.4
COPD	16	10.5
Renal insufficiency	1	0.7
Other	24	15.8

More than one disease was reported per individual; COPD: Chronic obstructive pulmonary disease; *excluding COPD.

Table 2 indicates the type and intensity of the principal symptoms at the site of application

Table 2 - Local symptoms reported after vaccination with the 23-valent vaccine, Sumaré State Hospital, 2004.

Symptoms	Intensity	n	%
Left-arm pain	Mild	25	71.4
	Moderate	8	22.9
	Severe	2	3.7
	Subtotal	35	100 (97.2)*
Left-arm Erythema	Mild	7	70
	Moderate	1	10
	Severe	2	20
	Subtotal	10	100 (6.6)*
Left-arm Edema	Mild	4	50
	Moderate	3	37.5
	Severe	1	12.3
	Subtotal	8	100 (5.5)*

More than one symptom was reported by some individuals; *percentage obtained considering the total of individuals with local symptoms (n = 36).

reported by the 36 patients. Low intensity local symptoms presented the highest incidence. Only five patients reported high intensity local symptoms, 2 reporting pain, 2 reporting erythema, and 1 reporting edema. Local pain was the most prevalent symptom, reported by 35 individuals, being of low intensity in 25 cases (15.8% of the vaccinated individuals). Although present, left-arm erythema and edema were less common, being reported by 10 (6.6%) and 8 (5.3%) patients, respectively.

Of the 36 individuals who reported some local complaint after vaccination, 11 (30.6%) reported having used medications at home. Only one individual sought medical attention (due to fever and malaise after vaccination).

In cases of local adverse event complaints, the duration of the reported symptoms was investigated. Table 3 shows that most patients reported symptoms of short duration, for an average of 1.5 days after vaccination, not exceeding two days in 83.3% of the cases. Only one individual (2.8%) complained of persistent and prolonged pain (for more than six days) at the site of application.

Of the 78 patients who were vaccinated only against pneumococcal diseases, 10 (12.8%) reported systemic symptoms after vaccination (Table 4). In 59% of the cases, the symptoms were reported by individuals older than 65 years of age. In 3 cases (3.8%), local and systemic systems were reported: in a 73-year-old man, local pain and edema were intense and were accompanied by malaise and chills; in a 40-year-old man, local pain was mild but was accompanied by headache and nausea; in a third case, pain and erythema were mild but were accompanied by fever, although no medication was used.

The bivariate analysis identified no associations between the occurrence of any local or systemic adverse event and any of the covariables studied ($p > 0.20$; Table 5), which was confirmed in the multiple logistic analysis.

Table 3 - Duration of local symptoms after pneumococcal 23-valent vaccination (n = 36), Sumaré State Hospital, 2004.

Duration of pain (days after vaccine)	n	%
< 1 day	7	19.4
1	13	36.1
2	10	27.8
3	5	13.9
6	1	2.8
Total	36	100.0

Table 4 - Systemic symptoms reported by individuals who received pneumococcal 23-valent vaccine only (n = 78), Sumaré State Hospital, 2004.

Symptoms*	n	%
At least one symptom	10	12.8
Malaise	5	6.4
Fever	2	2.6
Body pain	1	1.3
Chills	1	1.3
Headache	3	3.8
Nausea	1	1.3
Prostration and/or sleepiness	2	1.3

*More than one symptom was reported by some individuals.

Discussion

Although the campaign attendance was limited, we studied patients submitted to clinical follow-up evaluation at the basic health services and specialty clinics in the microregion who had never before been vaccinated against pneumococcal diseases. This fact suggests a low coverage of vaccination, considering that during annual vaccination campaigns against influenza, when vaccination against pneumococcal diseases is also offered, the doses did not reach 10% of the population that had sought medical attention as of 2005. There are no available data on the coverage of pneumococcal vaccination in Brazil. Although the coverage of the vaccine against influenza virus is adequate and increasing, the use of the pneumococcal vaccine in Brazil, as in other countries, is still quite limited.[7] In a study evaluating the reasons for the lack of demand for vaccination against pneumococcal diseases, one of the most

Table 5 - Bivariate analysis of the occurrence of local symptoms after pneumococcal 23-valent vaccine and covariables, Sumaré State Hospital, 2004.

Variable	χ^2	p	df
Gender	0.07	0.78	2
Age	2.85	0.72	5
Comorbidity	0.66	0.42	2
Diphtheria and Tetanus vaccine	0.02	0.89	2
City of residence	6.77	0.75	10
General symptoms	0	0.97	2

χ^2: chi-square test; df: degrees of freedom.

common was that people are afraid of the potential adverse events, as well as the lack of formal recommendations by physicians.[16]

The finding that local adverse events occurred in 23.7% of the individuals evaluated in the present study was similar to that found by some authors[17] and lower than those found by other authors, who reported rates of 30 to 50%.[10,14,18] These numbers can be influenced by the demographic, social, and cultural features of the studied population, as well as by the composition of the specific vaccine lot. One relevant fact is that severe adverse reactions were not observed among the studied patients, thereby confirming evidence in the literature of the fact that they are rare.[1,18,19]

Most local adverse reactions were reported as mild, not interfering with the daily activities of the patients. Most local and systemic events appear within the first 24 h after the vaccine administration and did not last more than 48 h. This pattern has been described in other studies.[1,13]

Our finding that systemic complaints after vaccination were reported by 12.8% of the individuals is similar to the 11.3% found in another study[17] involving revaccinated individuals and considerably higher than the approximately 2% reported in yet another study.[14] It is important to emphasize that the systemic symptoms observed in these patients were, for the most part, nonspecific (malaise, sleepiness, and prostration), mild, and reported by individuals of more than 65 years of age with chronic disease. It is possible that the individuals investigated attributed an excessive number of systemic symptoms to the 23-valent vaccine. However, fever, which is a more specific symptom, was reported by 2.6% of the individuals, which is similar to the percentage found by other authors.[17] Nausea has been reported as a possible postvaccination event in other studies.[17]

Almost all patients vaccinated in the campaign evaluated were receiving their first dose of the vaccine. Some authors reported a higher frequency of local adverse reactions in revaccinated individuals, specifically in those vaccinated at intervals of less than five years. Nevertheless, there is consensus that the occurrence of symptoms possibly related to vaccination or revaccination is not a contra-indication to immunobiological protection due to its benefits.[1,6,13,18]

Especially in immunocompromised individuals, some authors, in a systematic review of randomized clinical trials, have identified low effectiveness of the vaccine in 'high risk' patients, that is, patients with renal immunodeficiency, blood cancer, nephrotic syndrome, systemic lupus erythematosus, and alcoholism. However, among elderly individuals, as well as individuals with diabetes, chronic pulmonary disease, or cardiopathy, the immunological response has been evaluated as appropriate or compensatory due to the impact on the prevention of morbidity and mortality from invasive disease caused by *S. pneumoniae*.[13,14,21-23]

Among the patients analyzed, it was not possible to compare vaccinated and revaccinated individuals, since only one individual was revaccinated in the campaign, and that individual had been received the first dose more than five years prior. This result indirectly suggests the low coverage of the vaccination against pneumococcal diseases among patients with chronic diseases under clinical follow-up treatment in the region of Sumaré and for whom such vaccination is formally indicated.

In the present study, the 23-valent pneumococcal capsular polysaccharide vaccine was found to be minimally reactogenic in the first dose and was rarely recommended by physicians in the region under study. The disclosure of experiences confirming the minimal reactogenicity and safety of the 23-valent vaccine might stimulate basic health services and specialty clinics to vaccinate individuals for whom such vaccination is clinically indicated. Given the importance of formal recommendation of immunobiological protection by the physician, wider dissemination of such information among health professionals could improve the vaccination coverage. The implementation of strategies to identify such patients in hospitals and emergency rooms could favor an increase in the specific protection of at-risk groups.[24]

References

1. Center for Disease Control and Prevention. CDC. Prevention of pneumococcal disease: recommendation of the Advisory Committee on Immunization Practice (ACIP). MMWR Recomm Rep. 1997;46(RR-8):1-24.
2. Toniolo-Neto J, Weckx LW, Halker E, Lopes CH, de Menezes Succi RC, de Paiva TM, et al. Safety of simultaneous pneumococcal and influenza vaccination in elderly patients in Brazil. Drugs Aging. 1999;15 Suppl 1:43-5..

3. Shapiro E, Berg AT, Austrian R, Schroeder D, Parcells V, Margolis A, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med, 1999;325(21):1453-60.
4. Christenson B, Lundbergh P. Hedlund J. Örqvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in adults aged 65 years or older: a prospective study. Lancet. 2001;357(9261):1008-11.
5. Gomes L. Fatores de risco e medidas profiláticas nas pneumonias adquiridas na comunidade. J Pneumol. 27(2): 97-114.
6. Rubins J, Janoff EN. Pneumococcal disease in the elderly: what is preventing vaccine efficacy? Drugs Aging, 2001;18(5):301-11.
7. Wagner C, Popp W, Posch M, Vlasich C, Rosenberger-Spitzy A. Impact of pneumococcal vaccination on morbidity and mortality of geriatric patients: a case-controlled study. Gerontology. 2003;49(4):246-50.
8. Watson L, Wilson B, Waugh N. Pneumococcal polisaccharide vaccine: a systematic review of clinical effectiveness in adults. Vaccine. 2003;20(17-18):2166-73.
9. Guerrero M, Kruger S, Saitoh A, Sorvillo F, Cheng KJ, French C, Beall G. Pneumonia in HIV-infected patients: a case-control survey of factors involved in risk and prevention. AIDS. 1999;13(14):1971-5.
10. Whitney CG. Preventing pneumococcal disease. ACIP recommends pneumococcal polysaccharide vaccine for all adults age > or = 65. Geriatrics. 2003; 58(10):20-2, 25.
11. Zimmerman RK, Middleton DB, Smith NJ. Vaccines for persons at high risk due to medical conditions, occupation, environment, or lifestyle, 2003. J Fam Pract. 2003;52(1 Suppl):S22-35.
12. Nichol KL, Baken L, Wuorenma J, Nelson A. The health and economic benefits associated with pneumococcal vaccination of elderly person with chronic lung disease. Arch Intern Med. 1999;159(20):2437-42.
13. Törling J, Hedlund J, Konradsen HB, Örtqvist A. Revaccination with the 23 valent pneumococcal polysaccharide vaccine in middle-aged and elderly persons previously treated form pneumonia. Vaccine. 2003; 22(1):96-103.
14. Fine MJ, Smith MA, Carson CA, Meffe F, Sankey SS, Weissfeld LA, et al. Efficacy of pneumococcal vaccination in adults. Arch Intern Med. 1994;154(23): 2666-77.
15. Daniel WW. Biostatistics. A foundation for analysis in the health sciences. 6th ed. New York: Wiley, 1995.
16. Moura M, Silva LJ. Pesquisa de opinião sobre as campanhas de vacinação contra a influenza no estado de São Paulo. Bol Epidemiol Paul. 2004;4(1):8-10.
17. Lackner TE, G Hamilton R, J Hill J, Davey C, Guay DR. Pneumococcal polysaccharide revaccination: immunoglobulin g seroconversion, persistence, and safety in frail, chronically ill older subjects. J Am Geriatr Soc. 2003;51(2):240-5.
18. Moylett EH, Hanson IC. Mechanistic actions of the risks and adverse events associated with vaccine administration. J Allergy Clin Immunol. 2004;114(5):1010-20; quiz 1021.
19. Jackson LA, Benson P, Sneller VP, Butler JC, Thompson RS, Chen RT, et al. Safety of revaccination with pneumococcal polysaccharide vaccine. JAMA. 1999;281(3):243-8.
20. Sankilampi U, Honkanen PO, Pyhala R, Leinonen M. Associations of prevaccination antibody levels with adverse reactions to pneumococcal and influenza vaccines administered simultaneously in the elderly. Vaccine. 1997;15(10):1133-7.
21. Shapiro ED, Berg AT, Austrian R, Schroeder D, Parcells V, Margolis A, Adair RK, Clemens JD. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med. 1991;325(21):1453-60.
22. Fletcher TJ, Tunnicliffe WS, Hammond K, Roberts K, Ayres JG. Simultaneous immunization with influenza vaccine and pneumococcal polysaccharide vaccine in patients with chronic respiratory disease. BMJ. 1997;314(7095):1663-5.
23. Smith SA, Poland GA. Use of influenza and pneumococcal vaccines in people with diabetes. Diabetes Care. 2000;23(1):95-108.
24. Stack SJ, Martin DR, Plouffe JF. An emergency department-based pneumococcal vaccination program could save money and lives. Ann Emerg Med. 1999;33(3):299-303.