Vaccination Against the *Influenza* Virus and Mortality due to Cardiovascular Diseases in the City of Sao Paulo

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Summary

Background: The effect of vaccination against the influenza virus on the mortality due to cardiovascular diseases (CVD) remains controversial.

Objective: To analyze the mortality by CVD before and after the start of the vaccination against the Influenza virus in the city of Sao Paulo, Brazil.

Methods: We analyzed the mortality due to ischemic heart diseases (IHD), cerebrovascular diseases (CbVD) and external causes (EC) in the population of the metropolitan region of the city of Sao Paulo, Brazil, aged ≥ 60 years, before and after the start of the vaccination program against Influenza. The population estimates and mortality data were obtained, respectively, from the Brazilian Institute of Geography and Statistics (IBGE; www.ibge.gov.br) and from the Brazilian Ministry of Health (www.datasus.gov.br) for the period between 1980 and 2006. The risk of death was adjusted by the direct method, using the 1960 world standard population.

Results: The comparisons between the inclinations of the regression lines were similar for CbVD (p = 0.931) and EC (p = 0.941); however, for IHD (p = 0.022), a significant decrease was observed in the regression line of the post-vaccination period, when compared to the pre-vaccination period. A change in the tendency towards mortality after 1996 was significant only for the IHD (p=0.022), remaining unaltered for the CbVD (p=0.931) and EC (p=0.941).

Conclusion: The vaccination against the Influenza virus was associated with a significant decrease in the mortality due to IHD. (Arq Bras Cardiol 2009; 93(3) : 367-371)

Key Words: Cardiovascular diseases / epidemiology; myocardial ischemia; *influenza* vaccines; *influenza*, human.

Introduction

The cardiovascular diseases (CVD) are the main cause of death in the city of Sao Paulo. Of these, ischemic heart diseases (IHD) predominate over cerebrovascular diseases (CbVD). Both types of diseases have shown a decrease in mortality[1]. The main causes for this decrease are unknown. Improvement of the socioeconomic conditions and access to the health system can be possible explanations. The infection by the *Influenza* virus is associated with a higher mortality due to CVD[2-5]. Since 2006, the guidelines of the American Heart Association and the American College of Cardiology have recommended the vaccination against the *Influenza* virus in patients with atherosclerotic disease in general[6]. The recommendation is Class I (in which there is conclusive evidence or, in the absence of evidence, a consensus that the procedure is safe and useful/effective) with level of evidence B (data obtained based on a less robust meta-analysis, from a single randomized study or non-randomized studies). This recommendation was based on fact that patients with IHD present a higher risk of cardiovascular complications for the *Influenza*[7]. In turn, the European Society of Cardiology does not recommend the vaccination in patients with IHD or congestive heart failure, as adequate clinical trials are yet to be performed[8]. The vaccination is not recommended either in the secondary prevention of IHD by the Brazilian Society of Cardiology.

The present study aimed at analyzing the effect of the vaccination against the *Influenza* virus on the mortality due to CVD in the city of Sao Paulo, in individuals aged ≥ 60 years, which is the age range considered since 1996 for the vaccination campaigns against the *Influenza* virus.

Methods

We analyzed the mortality due to IHD, CbVD and external causes (EC) among the population of the metropolitan region of the city of Sao Paulo, Brazil, in individuals aged ≥ 60 years, before and after the start of the program of vaccination against the *Influenza* virus. The population estimates and mortality

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data for ICH, CbVD and EC were obtained, respectively, from the Brazilian Institute of Geography and Statistics (IBGE; www.ibge.gov.br) and from the Brazilian Ministry of Health (www.datasus.gov.br) for the period between 1980 and 2006. The population estimates were obtained from the censuses of 1980, 1991 and 2000; from the count of 1996 and the intercensus projections of 1981 to 2006. The deaths, from 1980 to 1995, were classified according to the ICD-9, at the 9th Review Conference of the International Classification of Diseases (ICD), from 1975, of which standards were adopted by the 20th World Health Assembly. At the ICD-9, the codes for the population from 1980 to 1995 were: from 410 to 414 for IHD, from 430 to 438 for CbVD and from E470 to E56 for EC. The mortality from 1996 to 2006 was classified by ICD-10: codes from 120 to 125 for IHD, from 160 to 169 for CbVD and from V01 to Y98 for EC. The risk of death was adjusted by the direct method, using the 1960 world standard population.[9] The data of mortality per 100,000 inhabitants and the percentage variations were analyzed in the general population, in individuals aged ≥ 60 years regarding the pre-vaccination period, between 1980 and 1995 and after the start of the vaccination period, between 1996 and 2006. The EC were used as the control group, as the effect of the vaccination against the *Influenza* virus on the mortality due to EC is practically zero. Two methods were used: the simple linear regression for the analysis of the coefficients of mortality of the pre- and post-vaccination periods and the comparison between the inclinations of the linear regression lines between the periods regarding the respective diseases. The analysis was performed using the program Primer of Biostatistics, version 4.02.

Results

Table 1 presents the tendencies of the risk of death due to IHD, CbVD and EC among the population of the metropolitan region of Sao Paulo, from 1980 to 2006. Between 1980 and 2006, we observed a significant decrease in the mortality due to IHD (-36.1%), CbVD (-47.7%) and EC (-12.4%). The simple linear regression analysis showed respectively, for IHD, CbVD and EC, a decreasing tendency in the initial mean standardized coefficient for the period of 489.21 ($p = 0.378$), 541.56 ($p = 0.037$) and 111.21 ($p = 0.611$), with a decline of -2.03, -8.24 and increase due to EC of 0.26 deaths per 100,000 inhabitants per year. In the pre-vaccination period, between 1908 and 1995, we observed a slight a non-significant decrease in mortality due to IHD (-9.3%) and EC (-8.5%), but a significant decrease in mortality due to CbVD (-31.4%). The simple linear regression analysis showed respectively, for IHD and EC, a non-significant decreasing tendency of the initial standardized coefficient for the period of 517.42 ($p = 0.151$) and 122.69 ($p = 0.414$), with a decline of -1.49 and -0.29 deaths per 100,000 inhabitants per year. However, for this same period, we observed a significant decrease of the initial standardized coefficient for CbVD for the period of 645.18 ($p < 0.0001$), with a decline of -13.32 deaths per 100,000 inhabitants per year. For the post-vaccination period, between 1996 and 2006, we observed a significant decrease in mortality due to IHD (-30.2%) and CbVD (-25.3%); however, the decrease in mortality due to EC (-1.2%) was significantly lower. The simple linear regression analysis showed respectively, for IHD and CbVD, a significant decrease in the initial standardized coefficient for the period of 529.71 ($p < 0.0001$) and 491.44 ($p < 0.0001$), with a decline of -17.55 and -14.55 deaths per 100,000 inhabitants per year. However, we observed a mean standardized coefficient for EC for the period of 105.89 ($p=0.542$), with a slight decline of -0.49 deaths per 100,000 inhabitants per year. The comparison between the inclinations of the regression lines showed they were similar for CbVD ($p = 0.931$) and EC ($p = 0.941$); however, for the IHD, we

Table 1 – Risk of death, per 100,000 inhabitants, due to ischemic heart diseases (IHD), cerebrovascular diseases (CbVD) and external causes (EC) and the percentage variations (PV%) of the pre- (1980-1995) and post-vaccination (1996-2006) periods among the population aged ≥60 years in the metropolitan region of Sao Paulo – 1980-2006

Year	IHD	CbVD	EC
1980	555.53	679.77	123.37
1981	528.65	635.1	112.76
1982	494.64	595.36	117.47
1983	489.48	590.38	133.01
1984	489.31	558.3	125.93
1985	500.69	566.52	109.95
1986	483.5	528.1	123.26
1987	516.58	490.22	121.68
1988	522.59	544.14	123.22
1989	510.56	506.07	123.11
1990	497.76	506.64	120.92
1991	492.34	457.93	123.9
1992	491.08	453.31	112.91
1993	510.51	468.67	125.6
1994	488.42	464.81	113.38
1995	503.8	466.38	112.93
PV%1980-1995	-9.31183	-31.3915	-8.46235
1996	508.72	475.69	109.34
1997	508.59	477.63	114.93
1998	482.2	452.37	103.72
1999	476.6	477.87	107.44
2000	422.3	385.09	91.03
2001	407.16	366.44	98.52
2002	388.97	374.42	88.94
2003	395.23	352.98	98.96
2004	379.09	381.05	102.54
2005	344.2	346.25	108.54
2006	355.09	355.48	108.04
PV%1980-2006	-36.0809	-47.7058	-12.426
PV%1996-2006	-30.1993	-25.2707	-1.18895

observed a significant decrease in the post-vaccination period line when compared with the line of the pre-vaccination period. (Figure 1).

Discussion

The present study verified a significant association between the start of the vaccination program against the *Influenza* virus and a marked and constant decrease in mortality due to IHD among individuals aged ≥ 60 years in the metropolitan region of the city of Sao Paulo. However, the tendencies of mortality due to CbVD and EC remained unaltered. The mortality due to CbVD maintained a decreasing trend, whereas the mortality due to EC remained stable. The analysis of previous epidemiological data showed a concrete association between the IHD and epidemics caused by the *Influenza* virus[10]. Previous studies have demonstrated a decrease in mortality due to IHD after vaccination against the flu; however, the follow-up period of these studies was short. Gurfinkel et al[11], during a six-month follow-up, observed a mortality rate of 2% in the group that had been vaccinated and 8% in the control group [OR 0.25; (95%CI: 0.07 to 0.86); p = 0.01]. Death, myocardial infarction or hospitalization due to acute coronary syndrome (ACS) occurred in 11% of vaccinated patients and in 23% of the individuals from the control group[11]. These authors demonstrated the continuing beneficial effects of vaccination during a one-year follow-up of the same population[12]. Ciszewski et al[13], in a randomized, double-blind, placebo-controlled study, analyzed the incidence of coronary events in 658 patients with stable coronary artery disease (CAD) during a 12-month follow-up (confirmar com o autor). The authors found an incidence of 6.02% of coronary events in the vaccinated group against 9.97% in the placebo group [HR = 0.54; (95%CI: 0.29–0.99), p = 0.047].

Two important points must be observed in these studies: a single dose of vaccine was used and the beneficial effects of the vaccination were not limited to *influenza* epidemic period. The decrease in the incidence of coronary events was even higher at the final months of the study. Therefore, the effect of repeated doses of vaccine in the population is unknown. Thus, our study might be indicative and the result of the repeated doses of vaccine in the population, as it showed a constant decrease in mortality due to IHD after the start of the vaccination program, which can suggest a cumulative effect on mortality.

In the United States, only 43% of the healthcare area workers were vaccinated between 2003-2004[14]. This result was similar to that observed in 2006 in Hospital das Clínicas of the School of Medicine of the University of Sao Paulo, a public health institution with almost 20,000 employees working in the healthcare area, after an intensive campaign of information and assistance[15].

The vaccinal coverage among elderly individuals in the United States was of approximately 70%[16]. The percentage of vaccinated individuals in the cities of Sao Paulo and Belo Horizonte was similar, with a strong adherence on the part of the elderly, as observed in previous studies[17-19], which makes the analysis of the influence of vaccination on the mortality due to CVD a more consistent one. According to the Secretary of Health of the city of Sao Paulo, in 2006, the adherence was of 70.3% in individuals aged between 60 and 64 years, which was higher than that of the previous year, of 68.3%. The vaccinal coverage of the population aged ≥65 years was of 82.9%[16].

Several mechanisms of the coronary events are triggered by the *influenza*[3,20-25]. The infection by the *Influenza* virus can favor hemodynamic, atherogenic and thrombogenic alterations that lead to the instability of the atherosclerotic plaque and cause the acute coronary syndromes. The hemodynamic alterations can be caused by fever and dehydration[3] and the thrombogenic alterations can be intensified by the immunoinflammatory processes associated with the viral infection and, occasionally, with bacterial infections[20-25].

The data of the present study demonstrate the potential direct and indirect beneficial effects for the process of atherosclerosis. However, in spite of a similar physiopathology with the IHD, the effect of vaccination on the decrease in mortality due to CbVD was little evident. The difference might be the result of the impact of the control of systemic arterial

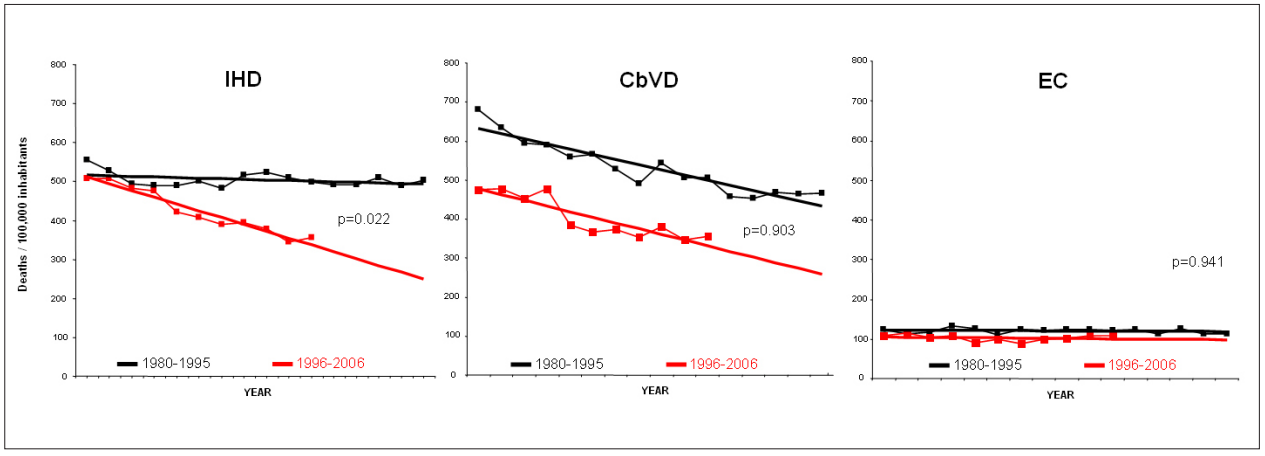

Figure 1 - Comparison between simple linear regressions of mortality due to ischemic heart diseases (IHD), cerebrovascular diseases (CbVD) and external causes (EC) for the pre- (black lines) and post-vaccination (red lines) periods among the population aged ≥ 60 years in the metropolitan region of Sao Paulo – 1980-2006.

hypertension, a main risk factor for CbVD[26]. As it is the most important risk factor and also the most prevalent one among the high-risk population for CbVD, the decrease in or control of blood pressure levels will have more impact on the decrease of mortality due to CbVD, masking possible effects of the vaccination or other interventions in this population[27,28].

The present study analyzed the mortality due to CVD in a population aged ≥60 years. However, previous studies have shown that younger individuals can benefit even more from the vaccination against the *Influenza* virus, with a consequent decrease in or significant prevention of deaths[29,30]. Therefore, from the point of view of the CVD, the vaccination of younger individuals can have an even higher impact on the decrease of mortality due to IHD.

This study has limitations and the main one is that it is an observational study in which the cause-and-effect association is questionable. As the decrease in ACS was previously shown in a prior study[13], it is quite likely that the vaccination also contributes to decrease the mortality due to IHD, in spite of the possibility of biases such as primary healthcare assistance and information campaigns for the control of the main risk factors for the IHD.

Conclusion

Although it remains a controversial subject, the annual vaccination program against the *Influenza* virus must be encouraged in individuals older than 60 years, in an additional attempt to reduce mortality due to IHD.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any post-graduation program.

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