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Effectiveness of influenza vaccination and its impact on health inequalities

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Background Since 1998, annual publicly funded campaigns for mass vaccination against influenza of the population aged 65 years or older have been performed in the city of São Paulo, Brazil. The effectiveness of the intervention was not assessed for its contribution to the reduction of influenza-attributable mortality. This study sought to compare the age-specific mortality (65 years or older) before and after the onset of yearly vaccination, and to assess the impact of the intervention on health inequalities in relation to inner-city areas.

Methods Official information on deaths and population allowed assessment of overall pneumonia and influenza mortality. Monitoring of outbreaks and the estimation of mortality attributable to influenza peaks used Serfling and ARIMA models. Rates were compared between 1998 and 2002, when vaccination coverage ranked higher than 60% among individuals aged 65 years or older, and 1993–97 (prior to vaccination).

Results Overall mortality due to pneumonia and influenza fell by 26.3% after vaccination. An even higher reduction was observed for mortality specifically attributable to influenza epidemics; the number of peaks of influenza mortality also decreased. Deprived areas of the city had a higher decrease of mortality by pneumonia and influenza during the vaccination period.

Conclusions Influenza vaccination contributed to reduce influenza-attributable mortality in this age group, and was associated with the reduction of inequalities in the burden of the disease among social groups. The concurrent promotion of health and social justice is feasible when there is political will and commitment to implement public health interventions with prompt and effective universal access.

Keywords Influenza, mortality, vaccination, socioeconomic factors, human development

Introduction

Most temperate countries of the Northern Hemisphere continually document the circulation and impact of influenza virus on morbidity. During the 1990s, influenza vaccination was stated to be one of the most cost-effective medical interventions aimed at the older adult population,[1] and a meta-analysis of vaccine efficacy concluded that influenza immunization was an indispensable part of the care for the elderly.[2] However, evidence on the usefulness of vaccination of seniors living in the community was subsequently appraised as barely modest by a systematic review,[3] which considered immunization recommendable for those living in long-term care facilities. In the USA, the Centers for Disease Control and Prevention also stated that vaccination was most effective among the elderly residing in nursing homes, despite acknowledging its beneficial overall effect on issues related to secondary complications, hospitalization and death.[4]

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For non-temperate, tropical countries, the burden of the disease is not well established and neither is the effectiveness of influenza vaccination.[1] This consideration accounts for the importance of monitoring influenza and vaccination in developing countries.

The surveillance of influenza in Brazil improved substantially after the 1990s, when the perspective of public-funded mass vaccination became feasible. Nationwide influenza immunization campaigns have been performed since 1999, with a large participation of the population;[5,6] this programme began 1 year earlier in São Paulo, the largest Brazilian city. Notwithstanding, the effectiveness of vaccination was not specifically appraised in the country.[7]

The implementation of health programmes may impact on previously existing health inequalities. The 'inverse equity hypothesis' was proposed to explain why inequalities in the burden of disease increase after public-health interventions are introduced.[8] According to this hypothesis, the overall improvement achieved may be concurrent to an increase in the gap between social groups, because those of higher socioeconomic position are benefited earlier than the poor. This hypothesis is consistent with the report of relevant variation of influenza vaccination coverage among sociodemographic strata in the USA.[9,10]

This study aimed at evaluating the effectiveness of the vaccination of the population aged 65 years or older against influenza in São Paulo, by estimating the reduction of mortality attributable to the disease before (1993–97) and after (1998–2002) the implementation of the campaign. It also aimed at assessing inner-city differences in the decline of mortality.

Methods

Study design

This study assessed trends and the distribution of pneumonia and influenza (P&I) mortality across inner-city areas. The study population comprised individuals aged 65 years or older that reside in São Paulo, Brazil.

With nearly 10 million inhabitants, this is one of the largest cities in Latin America, and capital of the most populous and industrialized Brazilian state. Throughout the last several decades, São Paulo has experienced a relevant improvement of life expectancy and health indicators.[11] Notwithstanding, intense inequalities affect the population and affluent and deprived areas co-exist in the town, resembling patterns of heterogeneous socioeconomic conditions at the country level. The geographic division of the city into 96 districts was established in 1991 by governmental agencies with the objective of delimiting regions with relatively homogeneous socioeconomic profile. These areas ranged from 8404 to 333 436 inhabitants, with an average of 108 690 inhabitants per district.[12]

Since 1998, a regular 2-week influenza vaccination campaign for the population aged 65 years or older has taken place in April, immediately before the cold season (May–August), and includes all public primary healthcare units. Intense involvement of media contributes to increased population coverage, corresponding to nearly 650 000 inhabitants vaccinated each year. No other age group was specifically targeted by the vaccination campaign.

Time-series analysis assessed P&I death rates for the city as a whole, and compared summarized values for periods with and without mass vaccination. The reduction of P&I mortality was assessed at the area level, and ecological correlations explored hypotheses related to this outcome.

Outcome variable and covariates, sources of information

Official information on mortality allowed the assessment of deaths (from 1988 to 2002) as stratified by gender, age and area of residence. Inclusion criterion was for deaths with underlying cause attributed to P&I; i.e. codes 480–487 of the International Classification of Diseases, 9th Revision—ICD-9[13] (used from 1988 to 1995) and J10–J18 ICD-10[14] codes (from 1996 to 2002). Censuses carried out in 1980, 1991, 1996 and 2000 supplied primary information for yearly and weekly inter-censal estimates of the population. Overall and district-level death rates (per 100 000 inhabitants) were adjusted by gender and two age groups (65–74 years, 75 and older) for both the temporal and the ecological assessment, thus avoiding the impact of differential population distribution on trends and spatial patterns.

The socioeconomic characterization of areas used the human development index, which summarizes information on income, instruction and longevity and was assessed by governmental agencies based on the most recent source of information on population, observing criteria established by the United Nations Development Program.[15] Additional covariates were: (i) the proportion of households in shantytowns;[16] (ii) the 'health index'[17] proposed and measured by the local health authority by compiling information on infant death rates and mortality due to tuberculosis and external causes; (iii) the per capita household income, measured in US dollars; (iv) illiteracy rates (census information for adults aged 25 years or older, corresponding to direct answer on the ability to read and write); (v) the proportion of head of households that completed high school and (vi) household crowding (average number of inhabitants per household), a proxy for socioeconomic status in Brazilian epidemiologic studies.[18]

The Respiratory Virus Laboratory of Institute Adolfo Lutz (WHO Collaborative Centre for Influenza in São Paulo) provided virological surveillance information regarding the correspondence between vaccine composition and most prevalent viral strains in each season. The State Health Department, the local health authority, informed yearly vaccination coverage, corresponding to the number of doses effectively given per inter-censal estimates of age-specific population.

Data analysis

The study of trends and seasonal patterns of P&I mortality used weekly death rates. Observed and estimated figures were compared, according to two classic methods for assessing mortality attributable to influenza epidemics. Both methods estimated weekly mortality for each year based upon information on observed mortality for the previous 5 years.

The first method was originally described by Serfling,[19] and is based on forecasts calculated by a regression equation involving harmonic terms. According to this method, $Y(t)$—mortality

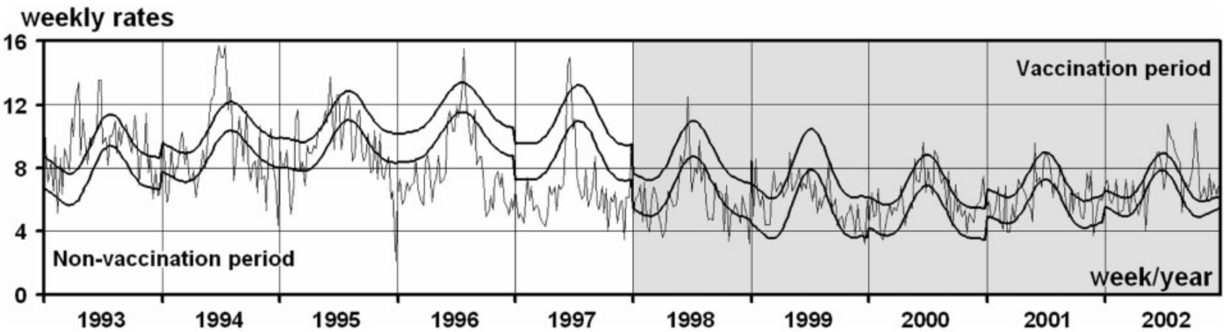

Figure 1 Time series for age-specific (>64 years) P&I mortality (per 100 000 inhabitants): weekly observed rates, forecast baseline and epidemic threshold (Serfling model) in São Paulo, Brazil: vaccination (1998–2002) and non-vaccination (1993–97) periods

estimated for the epidemiologic week 't'—is determined by least squares regression:

$$Y(t) = b0 + b1 \times t + b2 \times \cos 2\pi t/52 + b3 \times \sin 2\pi t/52 + b4 \times \cos 4\pi t/52 + b5 \times \sin 4\pi t/52 + \varepsilon$$

$b0$ being the intercept; $b1$ the slope (unstandardized coefficient) accounting for linear trend; $b2$–$b5$ the slopes accounting for seasonality and ε the regression error term. The estimation is subsequently improved by deleting observed mortality during epidemic weeks and refitting the equation.

The second method comprises a dynamic forecasting process using seasonal ARIMA models.[20] Observed death rates for epidemic weeks must be replaced by *ex post* forecasts, thus optimizing the modelling of mortality for subsequent weeks.

For both methods, the epidemic threshold was calculated by adding the estimated baseline to the product of 1.645 (the normal distribution z-value corresponding to a 95% probability of non-higher figures) and the standard deviation of forecasts. Influenza outbreaks are acknowledged when observed death rates exceed the epidemic threshold for at least two consecutive weeks. Excessive mortality refers to the difference between weekly rates observed during epidemic weeks and corresponding *ex post* forecasts.

Figures related to the vaccination and non-vaccination periods were subsequently compared for the city as a whole, and for each district. Ecological correlations considering the association between the proportional decrease of mortality and area-level socioeconomic indices used the Spearman's correlation coefficient.[21] Exclusively for descriptive purposes, the proportional decrease of mortality was classified by the k-means cluster analysis.[22] This procedure differentiates groups of areas with a relatively homogeneous profile of proportional reduction of mortality. Resulting profiles were comparatively classified as 'absent', 'lower', 'medium' and 'higher' levels of reduction. Statistical data analysis used the SPSS 8.0 1997 software (SPSS Inc. Headquarters, Chicago, IL, USA).

Results

Seasonal variation of mortality was graphically displayed and quantitatively assessed by fitting its baseline and epidemic threshold (Figure 1). Higher figures were reported for the cold season each year both before and after vaccination.

Nearly 63% of the population aged 65 years or older and living in the city were vaccinated each year. Vaccine composition broadly matched the most prevalent viral strains during the whole study period, except for 2002, when a larger mismatch between vaccine composition and the most prevalent viral strains was reported (Table 1).

P&I mortality decreased prior to vaccination (1996–97), a further reduction was acknowledged after the onset of vaccination (Figure 1, Table 2). The inter-period comparison indicated an overall decline of 26.3% in death rates. This figure corresponds to an overall decrease of 1341 deaths throughout the 5 years of vaccination.

The number of epidemic periods and the associated mortality excess decreased during vaccination, regardless of the method for seasonality modelling. During the 10-year follow-up, 20 outbreaks were assessed by the Serfling method, 15 by ARIMA. Weeks were concordantly classified as 'epidemic' and 'non-epidemic' by both methods in 86.5% of the study period.

The reduction of mortality attributable to influenza outbreaks during vaccination amounted to 47.4% (Serfling model) and 88.0% (ARIMA model) in comparison with the preceding period (Table 3). These figures correspond to an overall decrease of 194 (Serfling) and 583 (ARIMA) deaths attributable to influenza during 1998–2002, as compared with 1993–97.

The decline of mortality was not homogeneous in the city, and the k-means cluster analysis classified areas into four levels of mortality reduction (Table 4). Few districts (9) did not present a reduction in mortality, 30 districts had a lower reduction level (12.2%, in average), 35 districts presented medium reduction (29.1%) and 20 districts had a higher reduction (46.9%). Two peripheral, predominantly rural and sparsely populated districts were excluded, on account of their reduced number of age-specific deaths by P&I.

At the area level, the proportional reduction in mortality correlated (Spearman's correlation coefficient = +0.57) with death rates assessed for the former period, indicating that areas with higher prior levels of P&I mortality underwent a more intense decline after the onset of vaccination. Therefore, the decline of mortality was concurrent with a reduction in disparity of its distribution.

Table 1 Correspondence of vaccine composition and most prevalent viral strains in each year; proportion of vaccinated among the elderly. São Paulo, Brazil, 1998–2002

Year	Most prevalent viral strains	Vaccine composition	(%) Vaccinated
1998	A/Sydney/05/97(H3N2)	A/Wuhan359/95(H3N2)	
	B/Beijing/184/93	B/Beijing/184/93	Not available
	A/Bayern07/95(H1N1)	A/Bayern07/95(H1N1)	
1999	A/Sydney/05/97(H3N2)	A/Beijing/262/95(H1N1)	
	B/Beijing/184/93	A/Sydney/05/97(H3N2)	57.1
	A/Bayern(H1N1)	B/Beijing/184/93	
2000	A/NewCaledonia/20/99(H1N1)		
	A/Sydney/05/97(H3N2)	A/Moscow/10/99(H3N2)	
	A/Panama/2007/99(H3N2)	A/New Caledonia/20/99(H1N1)	67.6
	A/Johannesburg/82/99	B/Beijing/184/93	
	A/Moscow/10/99(H3N2)		
	B/Shichuan/379/99		
	B/Beijing/184/93		
2001	A/Panama/2007/99(H3N2)	A/Moscow/10/99(H3N2)	
	A/NewCaledonia/20/99(H1N1)	A/New Caledonia/20/99(H1N1)	66.8
	B/Shichuan/379/99	B/Sichuan/379/99	
2002[a]	A/Panama/2007/99(H3N2)		
	B/HongKong/330/2001		
	B/HongKong/135/2002	A/Moscow/10/99(H3N2)	
	B/Brisbane/32/2002	A/New Caledonia/20/99(H1N1)	61.3
	B/Shichuan/379/99	B/Sichuan/379/99	
	B/Shizuoka/05/2001		
	B/Victoria variant		

[a]Larger mismatch between vaccine composition and most prevalent viral strains.

Table 2 P&I age-specific (>64 years) observed mortality (per 100 000 inhabitants) in São Paulo, Brazil, before (1993–97) and during vaccination (1998–2002)

Year	Number of deaths	Proportional mortality ratio	Yearly death rates
Before vaccination			
1993	2557	8.9%	484.1
1994	2628	9.1%	484.0
1995	2674	9.0%	479.0
1996	2383	7.6%	415.3
1997	2039	6.3%	341.7
Average	2456	8.2%	440.8
During vaccination			
1998	1967	6.5%	317.1
1999	2015	6.1%	312.4
2000	2076	6.3%	309.5
2001	2240	6.8%	321.2
2002	2642	7.8%	364.3
Average	2188	6.7%	324.87
Inter-period reduction (%)	10.9	18.1	26.3

Table 3 Number of outbreaks and associated death excess in São Paulo, Brazil, before (1993–97) and during vaccination (1998–2002), using two models of forecasting outbreaks

	Baseline (Serfling) model		ARIMA model	
Year	Number of outbreaks	Death excess (per 100 000)	Number of outbreaks	Death excess (per 100 000)
Non-vaccination period				
1993	3	30.9	2	17.7
1994	2	23.4	2	19.0
1995	4	7.0	7	37.2
1996	0	0.0	3	19.2
1997	1	3.9	1	5.6
Total	10	65.3	15	98.8
Vaccination period				
1998	0	0.0	0	0.0
1999	1	3.2	1	2.1
2000	2	4.3	4	4.7
2001	3	4.8	1	1.1
2002	4	24.1	1	4.0
Total	10	36.3	7	11.9
Inter-period reduction (%)	0.0	47.4	53.3	88.0

Table 4 P&I mortality, inter-period decrease and socioeconomic indices for four groups of areas (clustering of districts). São Paulo, Brazil, before (1993–97) and during vaccination (1998–2002)

Inter-period decrease of death rates	No decrease $n = 9$	Lower decrease $n = 30$	Medium decrease $n = 35$	Higher decrease $n = 20$
Proportional decrease, area-level average (%)	–2.8	12.2	29.1	46.9
Standard deviation (%)	3.9	5.5	4.8	6.8
Socioeconomic indices				
Human development index	0.58	0.58	0.55	0.51
Health index	0.71	0.66	0.57	0.51
Per capita household income (US$)	287.9	344.8	164.8	99.9
Household crowding (inhabitants per household)	3.3	3.2	3.4	3.5
Households in shantytowns (%)	2.8	3.3	6.1	11.6
Illiteracy rate (older than 24 years) (%)	4.1	4.3	5.8	6.8
High-school graduated (head of the household) (%)	43.4	46.2	36.5	32.9

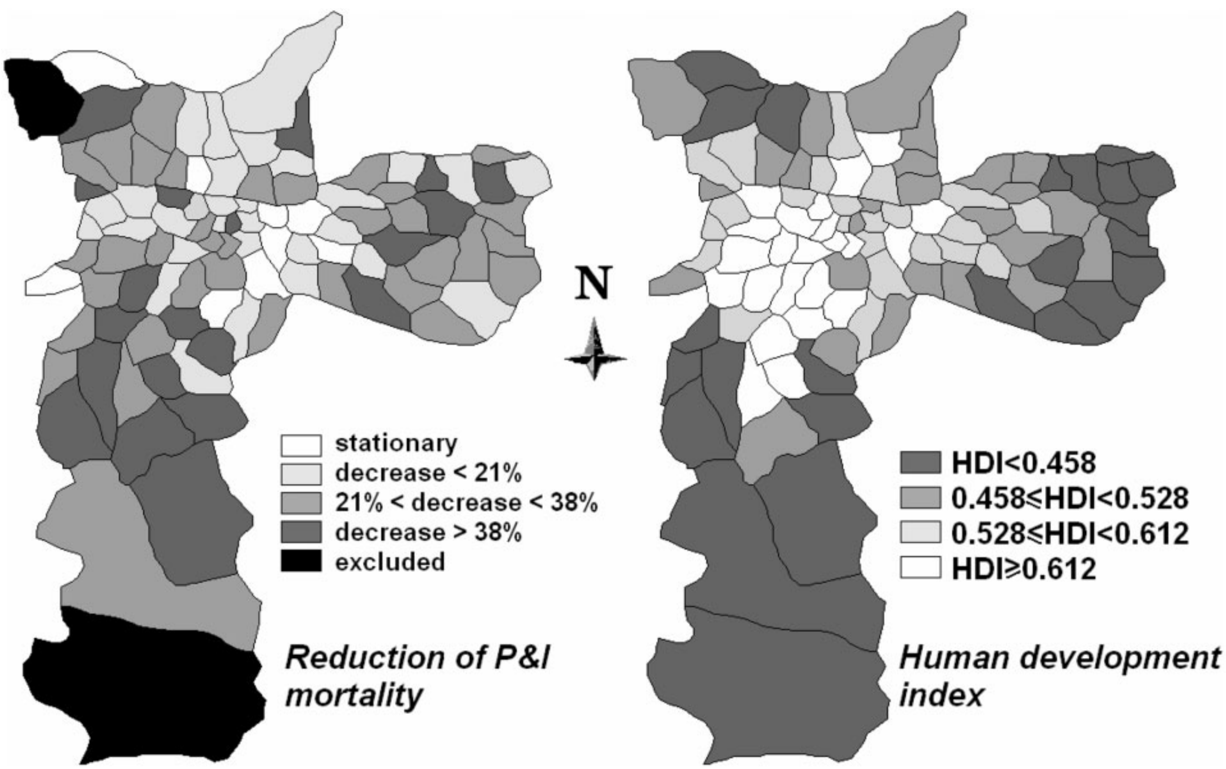

Figure 2 Maps for the cluster analysis of the inter-period decrease of P&I mortality of elders between the vaccination (1998–2002) and non-vaccination (1993–97) periods, and for the human development index (quartiles) in the city's districts

Areas with a lower reduction in mortality mostly occupied the central portion of the city, a region presenting improved socioeconomic standing. As to districts presenting medium and higher reduction in mortality, their localization mostly encompassed deprived regions of the city, which occupy peripheral areas, in addition to some once prosperous but now decadent central neighbourhoods (Figure 2).

The inter-period decrease of P&I mortality correlated with the human development index and supplementary figures of socioeconomic status (Table 3). In general, districts with a higher decrease of P&I mortality overlapped deprived areas, i.e. those districts with a poorer profile of human development. Negative correlations were observed for the human development index (−0.32), the health index (−0.27), income (−0.26) and proportion with complete high school education (−0.27). Positive correlations were observed for household crowding (0.34), proportion of households in shantytowns (0.45) and illiteracy rate (0.37).

Discussion

This study reported a relevant reduction of P&I age-specific mortality during the vaccination period. This study also assessed the reduction in mortality attributable to influenza epidemics, an observation corroborated by both methods of forecasting these outbreaks. Focused on one city, and assessing deaths associated with peaks of influenza, the current study adds evidence of advantages of vaccination in a non-temperate, tropical region.

The favourable impact of influenza vaccination on public health outcomes is consistent with studies reporting substantial benefits of vaccination for outcomes related to morbidity and mortality in the South American and the international context.[23–25] The advantageous effect of this intervention in Brazil was already reported by studies using alternative analytical schemes.[26,27] The countrywide number of pneumonia-related hospitalizations among persons aged 65 years or older decreased by 19.1% between June and August (winter) of the 1999–2001 period, in comparison with the same season of the year that preceded vaccination; a reduction that did not occur for age groups outside the target population.[27]

Two classical tools of time-series analysis allowed forecasting excess of P&I mortality. Results by both methods converged to conclude that vaccination was associated with the reduction of influenza-attributable mortality. Despite not having compared the methods' reliability, we observed that most of their results were concordant. While performing such comparative analysis, Choi and Thacker[20] reported advantages for the use of ARIMA, which allowed for more dynamic forecasting, while Serfling's models would be more influenced by previous levels of mortality. Despite this observation, Serfling's models present an interesting graphic interface, and governmental agencies in the USA continue to apply this method for the appraisal of influenza-attributable mortality.[28,29] Nonetheless, alternative statistical approaches for automated monitoring of influenza sentinel surveillance data continue to be studied.[30,31] This consideration accounts for the current option of concurrently assessing seasonal patterns of P&I mortality by two methods of time-series analysis.

Serfling and ARIMA models were respecified each year, using the five preceding years as input for respecification. Alternatively, the respecification of models after each outbreak might improve the dynamics of forecasting. This analytical option would demand a greater computational effort, and was not currently performed. This observation accounts for a former limitation of this assessment.

A further, but not less important limitation of the study refers to the comparability of data coded by different revisions of the International Classification of Diseases. The Pan American Health Organization acknowledges that despite retaining an analogous structure and basic categories for the reporting of P&I deaths, ICD-10 revised ICD-9 selection rules for the classification of underlying cause of death, thus permitting pneumonia and bronchopneumonia to be considered as terminal complications of malignant neoplasms, malnutrition, serious injuries, paralysis and communicable diseases.[32] This modification can lead to a reduction in pneumonia and bronchopneumonia deaths, and a consequent increase in the aforementioned disorders. In Canada, pneumonia deaths were heavily reduced (46.8%) by ICD-10 implementation;[33] in Spain, the concurrent register by both ICD revisions in 1999 allowed a 10.4% decrease.[34]

Likely effects of the change of classification schemes were identified in São Paulo, as P&I deaths fell by 10.9% in 1996, when ICD-10 was adopted. Notwithstanding, the onset of vaccination in 1998 was followed by an even higher decrease of P&I mortality, which could not be explained exclusively by the modification of the classificatory scheme. Furthermore, no seasonal variation is estimated to the effect of ICD-10 implementation, and the hypothesis that the assessment of influenza mortality peaks in the city would have withstood this modification cannot be ruled out.

Vaccination of seniors tends to rank lower coverage than the vaccination of infants. Some of them feel too frail to be vaccinated and fear for adverse effects of vaccination.[35] Others feel too safe, and deny the need of the vaccination shot.[36] The likelihood of being vaccinated has been appraised in terms of socioeconomic status.[37] The proportion of age-specific population vaccinated each year in São Paulo can be considered high, and may be even higher than documented, because healthcare facilities continue to administer shots after the 2-week campaign. Furthermore, the underlying health status and limitations of functional status were described as confounders for the association between influenza vaccination and mortality.[38,39] Uncertainties on this matter and the mismatch of vaccine formulation in 2002 also limit the current assessment, although its acknowledgement is consistent with the identification of a larger number of epidemics during that year.

The current observation of seasonal variation of influenza outbreaks is consistent with the variation of temperature and outcomes of mortality in the city.[40] This observation reinforces the need to perform mass vaccination before the cold season each year, and adds evidence to earlier assessments of the circulation of influenza virus in the city.[41,42] This result must be carefully interpreted, because infection by the influenza virus is not the only factor associated with seasonality of severe respiratory disease among the elderly.[43,44]

The proportional reduction of P&I mortality in each district of the city allowed identification of a geographical pattern for this outcome. Areas presenting lower or no reduction mostly occupied the central portion of the city, a region with improved socioeconomic status. The localization of districts presenting medium and higher reduction in mortality mostly refers to deprived regions of the city. This observation suggests that population segments living in poorer areas of the city benefited the most from vaccination.

Few studies assessed influenza vaccination in terms of socioeconomic stratification. In particular, these studies appraised differentials of vaccination rates while the impact of vaccination on incidence or mortality across socioeconomic groups remains extensively unknown. In the USA, the odds of being vaccinated were reported to be higher for Whites than for Blacks and Hispanics,[9,10] and for elders with higher educational attainment.[45] In the Brazilian context, however, a more equitable profile of vaccination was observed, and studies applied to different towns in the State of São Paulo reported an absent association between the likelihood of being vaccinated and socioeconomic status,[35] or an inverse correlation, with lower-income and unschooled elders presenting higher odds of being vaccinated.[46]

The observation of a higher reduction in mortality in poorer areas reinforces the premise of an equitable profile of vaccination in the city. However, vaccination rates were not assessed at area level, and the number of P&I deaths (65 years or older) in each district was not high enough to allow the assessment of seasonality at area level. Therefore, the current assessment of geographic patterns exclusively refers to the overall mortality (65 years or older) by P&I, and no inferences can be drawn at individual level.

Vaccination against influenza was associated with a relevant reduction in the overall and excessive P&I mortality, and with the reduction of health inequalities. Overcoming the inverse equity hypothesis[8] is feasible, when there is political will and commitment to implement public-health interventions with prompt and effective universal access, a statement corroborated by the previous assessment of another health programme in the city.[47] Overall effective and contributing to reduce health inequalities, the influenza vaccination in São Paulo was identified as an achievable strategy to the concurrent promotion of health and social justice.

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Conflict of interest: None declared.

KEY MESSAGES

- Pneumonia and influenza mortality reduced by 26.3% among individuals aged 65 years or older after the launch of a large-scale, cost-free vaccination campaign against influenza.
- Vaccination was associated with an even higher reduction in mortality specifically attributable to influenza epidemics in the city.
- Vaccination may have contributed to the reduction of inequalities in health, because the reduction of pneumonia and influenza death rates was higher in areas with a poorer profile of socioeconomic indices and prior mortality by the disease.
- The concurrent promotion of health and social justice is feasible when there is political will and commitment to implement public health interventions with prompt and effective universal access.

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