Influenza vaccination in Brazil: rationale and caveats

Imunização contra Influenza no Brasil: racionalidade e desafios

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Keywords
Influenza. Influenza vaccine. Program evaluation. Immunization programs.

Abstract
Mass vaccination campaigns against influenza in the elderly have been conducted in Brazil since 1999. A search of the literature on influenza in Brazil indicated that data on disease burden are still scarce and inaccurate. Published data seem to indicate that vaccination has produced some impact in the southern and southeastern regions but not in other regions of Brazil. A discussion of the technical and scientific rationale for mass immunization against influenza is presented and it is argued that the current strategy has not taken into account potential differences in disease occurrence in different areas. It is suggested some epidemiological surveillance actions needed to address major concerns regarding mass influenza vaccination and its impact in Brazil.

Descritores
Influenza. Vacina contra influenza. Avaliação de programas. Programas de imunização.

Resumo
Campanhas de vacinação contra influenza na população idosa têm sido conduzidas no Brasil desde 1999. De acordo com levantamento da literatura realizada sobre influenza no Brasil, concluiu-se que dados sobre carga de doença são ainda escassos e imprecisos. Essas informações parecem indicar que a vacinação tem produzido algum impacto nas regiões Sul e Sudeste do País, mas não em outras regiões. Foram discutidas racionalidade técnica e científica para a imunização contra influenza, e argumentou-se que a atual estratégia de vacinação em todo o território nacional não levou em conta possíveis diferenças na ocorrência da doença causada por influenza entre as regiões do País. Foram sugeridas algumas atividades relacionadas à vigilância epidemiológica de influenza que se julgou necessárias para responder importantes questões referentes à vacinação e seu impacto no Brasil.

INTRODUCTION

Vaccination is generally considered a very important tool for disease control, and immunization programs are among the most successful interventions in public health. The package of vaccines recommended by the Expanded Program of Immunization (EPI) is well established as the basic set of immunization activities. As the growing number of licensed vaccines expands the available arsenal, policymakers face the decision on which vaccine should be included in immunization programs. Several aspects should be considered by program managers such as disease burden, vaccine protection, and economic aspects.[7] Although support for the implementation of public interventions is not always based on consensus, policymakers should base their decisions on technical grounds.[51]

It is recognized that the importance of influenza infection in tropical areas is poorly understood, and

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research addressing this topic should be stimulated.[39] However, it is not clear whether immunization as a result of vaccination for controlling annual epidemics plays a role in the preparedness against pandemics. There is no evidence so far that influenza vaccination led to a reduction in disease burden in tropical areas of Brazil, such as the Northern and Northeastern regions. In this scenario, immunization in tropical areas should be preceded by virus surveillance, assessment of disease burden and economic impact of annual influenza epidemics, as recommended by the 56th World Health Assembly on planning for preparedness for influenza pandemics and annual epidemics in the item regarding areas where there is no vaccination policy.[52]

The aim of the study is to present an analysis of the implementation of annual mass immunization campaign against influenza for people aged 60 years and older in Brazil focusing on its technical and scientific rationale. However, it is acknowledged the role of political will and government commitment as important elements in the decision making process. It is also acknowledged that progress has been made in influenza surveillance and control since public-funded mass immunization has started in Brazil. Still, the debate on principles for introducing new vaccines is thought to be valuable in the future.

ISSUES CONCERNING THE IMPLEMENTATION OF NEW VACCINES – THE CASE OF INFLUENZA

Some important technical issues guiding the decision making process for introducing new vaccines are: magnitude and distribution of the public health problem posed by the disease; availability of safe and efficacious vaccines; and social and economic implications of the intervention.[7]

DISEASE BURDEN: WHAT IS TO BE PREVENTED?

The clinical presentation of influenza is typically a syndrome comprising fever, myalgia, headache, severe malaise, non-productive cough, sore throat, and rhinorrhea, called "influenza-like illness".[5] In some individuals, influenza can cause severe disease, which often involves bacterial complications such as pneumonia, or exacerbation of underlying conditions such as pulmonary or cardiac disease.[5] Elderly population is a high risk group for severe complications of influenza, which lead to hospitalizations and deaths.[20] The association of influenza infection and severe illness in this population is inferred from the link between seasonal increase in morbidity and mortality rates of respiratory disease and detection of influenza virus in the absence of other viruses.[19] This evidence supports vaccination against influenza targeting elderly population and applied before seasonal peaks.

The major benefit expected from vaccination in elderly population is a reduction of severe cases. Mild disease, absenteeism and loss of productivity are usually not considered major aims for vaccinating this population. It is important to note that influenza infection is not the only risk factor related to seasonal outbreaks of severe respiratory disease in elderly population.[14,18,37,38] Furthermore, influenza infection does not always indicate detectable increase in the number of clinical cases.[6]

Influenza vaccination will only reduce the incidence of respiratory disease related to influenza infection. This component of respiratory morbidity corresponds to the epidemiological measure of potential impact known as "population attributable fraction," which can be interpreted as the proportion of the incidence of a disease in a population attributed to a specified factor.[25] This measure is a function of two factors: (1) magnitude of the incidence of influenza infection; and (2) magnitude of the association between influenza infection and morbidity and mortality due to respiratory diseases. This association is chiefly measured by the excess morbidity and mortality during seasonal periods and the concomitant detection of influenza virus, and not just by the incidence of respiratory disease.[19] A high incidence of pneumonia in elderly population does not necessarily mean that influenza virus plays an important role in the disease burden related to these cases.

VACCINE PROTECTION

To address the issue of vaccine protection the concepts of efficacy and effectiveness must be clarified. Vaccine efficacy is the percent reduction in the incidence of a disease among vaccinated compared to unvaccinated individuals under controlled conditions, and often based on laboratory confirmed cases.[8,34] These study results can not be taken straightforwardly as indicating the effect of influenza vaccination under routine conditions, i. e., in health care units or mass immunization campaigns. Sub-optimal conditions prevail in routine or campaign immunization settings and vaccination in such a context is likely to have a lesser impact than that observed in efficacy studies. It should be noted that most studies on influenza vaccine were conducted among healthy young adults and the estimates of vaccine efficacy were for influenza-like disease,[34] not for severe cases. Efficacy estimates have ranged from 70% to 90% in

laboratory confirmed cases. At least three clinical trials conducted among elderly people found vaccine efficacy between 60% and 67% in laboratory confirmed influenza-like illness,[15,21,45] not in severe cases leading to hospitalizations or death.

Differently, vaccine effectiveness is the percent reduction in the incidence of a disease among vaccinated compared to unvaccinated individuals under routine conditions, and may include cases regardless of laboratory confirmation, that is, non-influenza cases.[8,34] Most studies estimating vaccine effectiveness among elderly people were observational. The estimate of vaccine effectiveness depends greatly on the outcome of interest. For example, in the meta-analysis carried out by Gross et al,[22] vaccine protection ranged from 50% for pneumonia to 67% for death. A study conducted in United Kingdom among individuals aged 64 years or more showed a 21% vaccine effectiveness against hospitalizations for acute respiratory disease (with no reduction in hospital admissions outside influenza seasons).[29] In a retrospective cohort study conducted in the Netherlands, no effect of vaccination was found on the contact rate of general practice during a mild epidemic period, and during an influenza epidemic the workload was reduced only in patients with cardiovascular or diabetic disease.[49] Result generalization depends on the comparability of aspects such as vaccine storage and delivery, routine case definition, coverage rate, and contribution of influenza to disease burden. Furthermore, vaccine effectiveness also depends on antigenic match between the vaccine and circulating strains.

HEALTH ECONOMIC EVALUATIONS

In all societies, there are usually several health problems contending for limited resources, which make policymakers to set priorities in fund allocation. Ideally, the decision making process should use available information from health economic evaluation (HEE).[2,12,27] HEE assesses the existing balance between resources and health outcomes, assisting in comparing and choosing interventions based on their benefits and available funds. There is a wide range of different types of evaluations, which can be carried out even before the implementation of a vaccination program.[2] The outcomes can be appraised to represent preferences and priorities according to different viewpoints: society, government, and individual. In Brazil, HEE can generate crucial information, given the diversity in performance of health services, economic and epidemiological profiles, which imply different costs and priorities across the country.

Many HEE on influenza vaccination in elderly people concluded that vaccination was a cost-saving measure.[10,16,17,26,33,35,36,44] However, these results should be treated with great caution as they are very sensitive to differences in medical care and vaccination costs, and to the proportion of cases of severe respiratory disease related to influenza in each context. For example, if influenza occurs throughout the year without a seasonal pattern (as it seems to be in some Brazilian states), and is not importantly associated with hospitalization among elderly people, then vaccination against influenza may not be a cost-saving measure from a societal point of view.[17] As another example, Allsup et al[1] conducted a randomized trial aimed to assess the cost-benefit of vaccination and concluded that vaccination among healthy people aged 65-74 years has not led to lower costs in primary care units in England and Wales.[1]

INFLUENZA VACCINATION IN BRAZIL

Mass immunization against influenza in Brazil started in 1999, at first targeting 11 million individuals aged 65 years or more. In 2000, the age limit was shifted to 60 years old. National immunization campaigns achieved a vaccination coverage rate ranging from 71.8% to 87.3%.[48] One of the major conditions that seemed to have favored the implementation of vaccination against influenza in Brazil was the success of the Brazilian National Immunization Program (PNI) of infant recommended vaccination. Only a mature immunization program could face the challenges posed by influenza vaccine: the need for yearly immunization in mass campaigns, and for achieving high coverage rates in a subset of the adult population using a vaccine that cannot be stockpiled because of annual changes in their composition.

STUDIES ON INFLUENZA IN BRAZIL

A literature search was conducted in data bases LILACs (Latin-American and Caribbean Health) and PUBMED between May-June 2003 (and reviewed in August 2004). The articles were short-listed to include only those with data on adult population obtained from the 1980s and onwards. There may be other studies but if so they were not published and thus were not available to be reviewed.

Several serological surveys were conducted in adult populations, mostly based on specific sub-populations such as students[28] and patients attending health services.[9,13,24,32,46] It is worth noting that only one was a population-based study,[50] and all of these studies, except two,[9,46] were conducted in the Southern parts of the country. More recently, Paiva et al[41] showed the circulating virus strain without estimating vac-

cine efficacy. As most study populations came from specific sub-groups, generalization for a community at large had many pitfalls. These studies were very helpful in determining the circulating virus strains but did not contribute to assess either disease burden or the clinical attack rate of influenza.

There were some studies aimed to assess the impact of influenza vaccination. Paiva et al[42] described an outbreak of acute respiratory disease in a city of the Southeastern state of São Paulo in 1999, in which most cases were among individuals younger than 14 years old, but there is no reference of rates by age group. In that study population, the 1999 influenza campaign (before the outbreak) achieved a 72.4% coverage rate among those aged 65 years or more, and no case was observed in this age group. The latter suggested to the authors that vaccination elicited high protection against respiratory disease. However, vaccine effectiveness was not estimated.

Gutierrez et al[23] described a retrospective cohort study conducted in a reference service in the city of São Paulo. This study aimed to assess whether the occurrence of respiratory disease in elderly population was different between those vaccinated and those unvaccinated against influenza in the 1999 campaign. There were no apparent differences related to the proportions of individuals who reported hospitalization, hospitalization for respiratory diseases, and antibiotics use (a proxy for bacterial infection and pneumonia). This finding could be due to lack of study power, but there was no description of such an estimate or sample size calculation. However, it was observed a statistically significant difference related to the number of episodes of influenza-like illness: vaccinated subjects had a lower mean number of episodes (1.5) than those unvaccinated (2.25). As these results were expressed in terms of mean values, they cannot be translated into vaccine effectiveness (percent reduction in incidence).

Brondi et al[3] reported a decrease in hospital admission rates observed after vaccination in the Southern and Southeastern regions of Brazil, but not in other regions. According to this study, the number of hospitalizations from pneumonia and chronic pulmonary obstructive disease in individuals in the vaccinated age group decreased in these regions in comparison to the period 1995-1998. Silvestre[48] also showed a 19.1% reduction in hospitalizations for pneumonia between June-August of the period 1999-2001 in comparison to the same period a year before the launch of the mass vaccination campaign. This reduction did not occur in age groups outside the target population. Unfortunately, these results were representative of the entire country and whether this reduction occurred in tropical areas was not showed, and the southern and southeastern regions were certainly overrepresented. Therefore, it is not possible to say this result can be generalized for the entire country.

Mixeu et al[31] reported a randomized trial among healthy adults members of a Brazilian airline company and observed a 33% vaccine effectiveness for episodes of any severe flu-like illness and reduction in absenteeism.[31] However, these results can not be applied to vaccination targeting elderly people.

Economic assessments of mass immunization against influenza are scarce. Burckel et al[4] reported the only health economic evaluation carried out but it included only healthy workers and its results could not be applied to elderly people.

CAVEATS ON THE DECISION MAKING PROCESS OF IMPLEMENTING MASS IMMUNIZATION OF THE ELDERLY AGAINST INFLUENZA IN BRAZIL

Reliable data are often unavailable to guide the decision making process in specific contexts, and the decision may be based on expertise judgment and literature review. However, caution should be exercised in using evidence from published results on influenza vaccine to analyze the Brazilian context. First, virus surveillance conducted in Brazil has demonstrated that influenza virus circulates in the country, and has shown the viral strains prevailing in specific settings.[40] However, this virus surveillance has neither contributed substantially to assess disease burden nor to assess the clinical attack rate of influenza. Second, most studies on influenza vaccine were conducted in the Northern Hemisphere, in countries with temperate climate where influenza peaks of incidence occur during the winter (influenza season). In those studies, influenza is recognized as an important cause of severe disease among elderly, leading to excess morbidity and mortality. At most, these results could be cautiously generalized to South and Southeast regions of Brazil, which have temperate climates. In Brazil, a large proportion of the population live in tropical areas, mainly in the Northeast and North regions, and there are around 4,880,000 inhabitants aged 60 years or older.[30]

In tropical and subtropical areas, circulation of influenza viruses occur throughout the year.[53] Indeed, a seasonal pattern is less pronounced in tropical areas, such as the North and Northeast Brazil, and the absence of seasonal peaks of respiratory diseases in these regions raises other questions. First, how can it be

assumed that influenza-related disease burden is important in such areas since there is no recognizable excess of morbidity and mortality? One could argue that the available data are on hospitalizations and there may still be severe cases unreported. However, these data are not available either. Second, seasonal peaks of influenza-related diseases, which occur in temperate areas, indicate a temporal concentration of cases, and provide the opportunity to maximize vaccine effectiveness. In the northern regions of Brazil, seasonal peaks may not be apparent or may occur in the rainy season, which does not coincide with the winter in Southern regions. Mass immunization campaigns have been conducted nationwide during the weeks preceding the influenza season in the South and Southeast, which is not the optimum period of the year for immunization in the Northern and Northeastern regions. But even if the timing for implementing vaccination in such regions is "adjusted", there is still the case of no temporal concentration of cases, and it is reasonable to anticipate that vaccine impact on reducing disease burden will be much less than expected.[17] In fact, Brondi et al[3] have not observed an impact in the Northern regions of Brazil.

Support for the implementation of public interventions is not always based on consensus. As for influenza, the recent debate on the decision of Ontario government (Canada) to expand influenza vaccination in 2000[11,47] revealed the different views of manufacturers representatives and scholars and worked as a good example of lack of consensus on how to implement such vaccination. On one hand, it was argued that there was already convincing evidence on the vaccine efficacy and its cost-effectiveness, and on the importance of being prepared for an influenza pandemic.[47] On the other hand, it was argued that there were neither predictions on the impact of such vaccination nor estimates of disease burden related to influenza, nor studies aimed to assess whether it was the best way to allocate resources.[11]

In conclusion, it is agreed that virus surveillance is important as the rationale for surveillance of a worldwide infection with potential for pandemics are long well recognized.[19,39,43] But one should recast the question: if no reduction in disease burden is observed in all Brazilian regions, is the current annual vaccination nationwide justifiable? Policymakers often have to make decisions despite the uncertainty of the benefits of public interventions.[51] It is worth reminding that in the 1990's vaccines against hepatitis B and rubella were introduced in public health services in different periods in Brazilian states based on regional epidemiological and programmatic data. With the same rationale, it may be justifiable to reexamine mass immunization against influenza in the northern parts of the country.

THE ROLE OF INFLUENZA EPIDEMIOLOGICAL SURVEILLANCE

Given such considerations, it is envisaged three major activities of the influenza surveillance system to address questions to guide the decision making process in health policy.

First, it is necessary to better determine the burden of the influenza-related diseases.[39] This task implies not only identifying prevailing viral strains and ascertaining antigenic vaccine match but also estimating the contribution of influenza to morbidity and mortality in different regions.

Second, it is necessary to demonstrate whether influenza vaccination through immunization campaigns has been able to reduce disease burden and, if so, where this was achieved. Establishing the areas where vaccination is effective is particularly important where climate conditions and epidemiologic profile of respiratory diseases among elderly people differ from those of temperate settings. This is a challenging task given that influenza may have seasonal distribution, the proportion of severe respiratory disease related to influenza varies with age, and large-scale vaccinations were already implemented. All these factors imply methodological difficulties such as:

(1) the simple comparison of hospitalization rates before and after vaccination in short time-series may be limited to show vaccine impact, given natural and temporal variations in disease occurrence. Preliminary evidence of the impact of immunization against influenza on elderly population needs further analysis since available data on hospitalizations may be unreliable as the records are generated for billing purposes. Moreover, hospital admission is taken as a proxy of disease severity but regional differences in access to health care and in care seeking behavior may hamper comparability across regions;
(2) as occurrence and severity of influenza-related diseases varies with age, hospitalization rates among those aged below 60 years (outside vaccination target population) cannot be used to indicate disease occurrence in the target population, neither for the rates among unvaccinated individuals nor for the temporal variations;
(3) vaccination coverage rate and contribution of influenza to hospitalization rates vary in different regions, implying that any assessment should be undertaken and reported separately for each geographical area rather than for the whole country,

given that the South and Southeast regions are over represented.

Third, economic evaluations are essential to rank priorities for immunization across states, considering vaccine high costs and differences in the economic burden from other compelling diseases and their control programs.

These actions require the partnership of research centers to be better managed. The result of time and resources invested in such actions are invaluable considering that the effort to start and maintain additional vaccination activities are substantial, and once started, it is very difficult to justify its discontinuation to the community.

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