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Impact of vaccination on influenza mortality in children <5 years old in Mexico

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ABSTRACT

Background: Influenza is a leading cause of respiratory tract infections among children. In Mexico, influenza vaccination was included in the National Immunization Program since 2004. However, the population health effects of the vaccine on children have not been fully described. Thus, we estimated the impact of influenza immunization in terms of mortality associated with this virus among children younger than 5 years of age in Mexico.
Methods: Mortality rates and years of life lost associated with influenza were estimated using national mortality register data for the period 1998–2012. Age-stratified and cause-specific mortality rates were estimated for all-cause, respiratory and cardiovascular events. Influenza-associated mortality was compared between the period prior to introduction of the influenza vaccine as part of the National Immunization Program (1998–2004) and the period thereafter (2004–2012).
Results: During the 1998–2012 winter seasons, the average number of all-cause, respiratory and cardiovascular deaths attributable to influenza were 1186, 794 and 21, respectively. Influenza-associated mortality was higher prior to the vaccination period than after influenza was included in the immunization program for all-cause (mean 1660 vs. 780) and respiratory (mean 1063 vs. 563) mortality, but no reduction was seen for cardiovascular mortality. The proportion of all-cause and respiratory deaths attributable to influenza was significantly lower in the post-vaccine period compared with the pre-vaccine period ($P < 0.001$), but no reduction was seen in the proportion of cardiovascular deaths. There was an average annual reduction of 66,558 years of life lost in the post-vaccine compared with the pre-vaccine period.
Conclusion: The introduction of influenza vaccination within the Mexican Immunization Program was associated with a reduction in mortality rates attributable to this virus among children younger than 5 years of age.

1. Introduction

During the past decades reduction of child mortality has been a major public health goal worldwide [1]. Despite current strategies for prevention and control, respiratory tract infections are still the leading cause of death in children under 5 years of age [2]. Viruses are among the most important agents associated with severe respiratory infections, with influenza and respiratory syncytial viruses being responsible for approximately 17% and 29% of pneumonia cases in young children, respectively [3].

Influenza virus infection causes significant morbidity and mortality globally [4]. In temperate regions, seasonal influenza occurs mainly during winter [5]. In the Northern hemisphere influenza circulation is rare prior to October, usually peaks in January or February, and is sporadic after April [5]. The annual attack rate in children is estimated at 20–30% [6]. In addition, young children have been reported to be at high risk for hospitalization associated with influenza [7,8]. Due to the relevance of the influenza epidemics on children, the Advisory Committee on Immunization Practice of the United States recommended the inclusion of the influenza vaccination in the routine immunization schedule in 2003 [9,10]; in Mexico, this vaccine was introduced in the National Immunization Program for children in 2004 [11]. Nevertheless, the efficacy and effectiveness of the vaccine is controversial because it depends on many factors: host age and immune status, match

Abbreviations: YLL, Years of life lost; P&I, Pneumonia and influenza.

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between the vaccine strain and the dominant season strain, presence of influenza virus mutations, among others [12–18]. Furthermore, there are few studies that assess the impact of influenza vaccination on child mortality.

Estimating the impact of influenza infection on mortality has been difficult mainly because a considerable number of cases are not identified as the cause of death resulting in an underestimation of the true effect of this virus [19]. Despite the increasing availability of tools to confirm the diagnosis of influenza, these are not yet used routinely in many countries in patients with respiratory illness. Moreover, deaths precipitated by influenza may also be attributed to underlying conditions and recorded in death certificates [20–22]. Thus, to estimate the impact of influenza, mortality attributed to this virus is frequently assessed through epidemiologic analyses [4]. Yet, the availability of such data for the Mexican population is limited. Therefore, in this study we estimated the mortality attributed to influenza in Mexican children under 5 years of age during the period encompassed between July 1998 and June 2012; to estimate the effect of the influenza vaccination, we compared mortality rates attributed to this virus between the period before (1998–2004) and after (2004–2012) the vaccination introduction in the childhood immunization schedule. Universal immunization in Mexican children was established in 2004 and, at that time, included infants 6–23 months of age [11]. The following year, the age group eligible for influenza immunization was increased to include all children 6–35 months of age. Starting in 2010, all children 6–59 months of age are included in the influenza immunization schedule. Finally, we also estimated the number of years of life lost (YLL) attributed to influenza during the full study period.

2. Material and methods

To estimate the mortality and YLL attributed to influenza, national mortality data which is publicly available at the General Direction of Health Information website (Ministry of Health) was used [23]. Information on the Mexican population by year and age group was obtained and retrieved from data generated by the National Institute of Statistics and Geography [24]. To compute the number of YLL we used the life expectancy by age group as reported by the World Health Organization [25].

The number of deaths that occurred during each epidemiological week throughout the study period was retrieved from the mortality register. Data were stratified by age and analyzed using six different groups (<6 months, 6–11 months, 12–23 months, 24–35 months, 36–<60 months and 0–60 months). In addition to all-cause deaths (all ICD-10 codes), cause-specific mortality for two outcomes was analyzed, including respiratory (J00-J99 ICD-10 codes) and cardiovascular (I00-I99 ICD-10 codes) deaths.

Mortality attributed to influenza was estimated for each winter season (i.e. between week 27 of a given year and week 26 of the following year) using Serfling cyclical regression models [26,27]. To establish baseline mortality, we identified the best estimates based on the periods in the absence of influenza activity, through regression methods to establish α, $\beta1$, $\beta2$, $\beta3$ for the following basic equation $Y = \alpha + \beta1t + \beta2\sin(2\pi t/52.14) + \beta3\cos(2\pi t/52.14) + \varepsilon$ and the weekly recorded death numbers. Excess mortality was calculated as the observed minus predicted mortality during the weeks included in each influenza epidemic period.

Influenza epidemic periods were defined based on pneumonia and influenza (P&I) mortality (J09-J18 ICD-10 codes) for the Mexican population. The onset of the epidemic period was defined as the first of three consecutive weeks in which P&I mortality was greater than the upper 95% confidence limit of the mean mortality for the winter season, and the end of the epidemic period was defined as the last week when P&I mortality was above the upper 95% confidence limit of the mean which was followed by three consecutive weeks with mortality lower than the 95% confidence limit. The weekly mortality due to P&I in the Mexican population during the 1998–2012 period revealed a seasonal pattern. The pattern observed during 2009 was exceptional due to the occurrence of the influenza A(H1N1)pdm09 virus pandemic. The weekly mortality due to P&I and influenza epidemic periods is shown in Fig. 1. Because the vaccine composition prior to the start of the influenza A(H1N1)pdm09 pandemic did not include this viral strain, we excluded the data of the first pandemic wave (epidemiological weeks 14 and 19 of 2009) and the 2009–2010 winter season from our analysis. Once the influenza epidemic periods were defined, the baseline mortality was subtracted from the observed mortality for each week included in the epidemic period, to determine the number of excess deaths. The number of excess deaths during each week of the epidemic period was added up to obtain the excess mortality for each season. This calculation was carried out for each age group, and for every mortality cause of death (all cause, respiratory and cardiovascular). We computed the age-specific mortality rates using the number of excess deaths and the estimated population for each year. Finally, we compared the average mortality between the pre and post-vaccination periods. Statistical comparisons between the study periods were carried out using chi-square tests. Analyses were carried out using OpenEpi software [28].

For the YLL calculation we multiplied the deaths attributable to influenza for each age group, cause of death, and season by the life expectancy of the specific age group [27,29]. No discounting was used for YLL of calculation. Then, the YLL means for the pre and post-vaccine periods were compared.

3. Results

Overall, our analysis included 509,215 cases (all-cause mortality), of which 53,988 (10.6%) corresponded to respiratory and 6793 (1.33%) to cardiovascular deaths. The estimated influenza-attributable mortality for all causes, as well as for respiratory and cardiovascular causes is shown in Table 1; mean annual number of all cause, respiratory and cardiovascular influenza-attributable deaths were 1186, 794 and 21, respectively.

To analyze the effect of the introduction of the influenza vaccine to the National Immunization Program, the number of deaths attributable to influenza in each age group was divided into two periods (pre-vaccine and post-vaccine periods). The mean number of all cause, respiratory and cardiovascular influenza-attributable deaths during the pre-vaccine and post-vaccine periods are presented in Table 2. Age-specific mortality rates attributable to influenza per 100,000 population, by study period, are presented in Table 3. A reduction in all-cause and respiratory mortality rates was observed for children under 24 months of age in the post-vaccine period, but there were no significant trends in cardiovascular mortality rates. Overall, a reduction of 53% in all-cause influenza-associated mortality was registered.

Because an important decrease in infant mortality has occurred in Mexico during the past 10-years including, but not limited to, mortality due to respiratory infections, we also assessed the mortality associated to influenza as the percentage of all deaths that occurred in children <5 years of age (for all causes, respiratory causes and cardiovascular causes). The mean proportions of mortality attributable to influenza during the pre-vaccine and post-vaccine periods are shown in Table 4. A reduction in the proportions of deaths attributable to influenza was observed for all-cause mortality in children aged <24 months of age ($P < 0.001$), and for respiratory mortality among those aged <12 months ($P \leqslant 0.001$).