Article

Impact of childhood and maternal vaccination against diphtheria, tetanus, and pertussis in Colombia

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Abstract

Background: In Latin America, there are few studies of the impact of vaccination against diphtheria, tetanus, and pertussis. We estimate the impact of infant and maternal vaccination on the incidence of these diseases in Colombia.

Design and methods: an interrupted time series study analyzing the incidence before and after of vaccination with DwPT (1975-2018) and with Tdap in pregnant women (2008-2018). A segmented regression model with negative binomial distribution estimated the change in level and trend of the predicted incidence ratio after vaccination in relation to the incidence if vaccination had not been started (IRR), using a Prais Winsten regression.

Results: The pertussis IRR decreased immediately after the start of childhood vaccination (0.91, p=0.51), but this was only significant (1.01, p<0.001) along with the trend per year, after the start of maternal vaccination (0.98, p<0.001). In the absence of vaccination, the incidence would not have been reduced. Neonatal tetanus had the highest rate of change with significant reduction -1.69 - CI 95%: -2.91, -0.48). The trend after vaccination was the highest with an annual reduction of 19% (0.81, p=0.001). The change in incidence of diphtheria was significant, although slow (-0.02 - CI 95%: -0.04, -0.004). The sustained effect in the post-vaccination period was smaller (0.95, p=0.79).

Conclusion: Childhood and maternal vaccination markedly reduced the incidence of pertussis and neonatal tetanus. It is necessary to maintain optimal vaccination coverage and surveillance, within an integrated elimination plan, which prevents the resurgence of these diseases.

Introduction

The COVID-19 pandemic has reminded humanity not only of the need to anticipate the development of technologies for new vaccine creation, but also the urgency of increasing access and coverage of vaccines that have been available for more than a century.[1] The resurgence of diphtheria, neonatal tetanus, and pertussis is a global concern following the mortality from diphtheria in unvaccinated children in Peru during the COVID-19 pandemic,[2] the resurgence of pertussis in the last decade,[3] and concern about the loss of progress in neonatal tetanus elimination.[4]

In Latin America there are few studies of the impact of vaccination. In Colombia, despite having an Expanded Program of Immunizations (EPI) since the mid-70s,[5] few have studied the temporal behavior of these diseases. In Argentina[6] and Colombia, the impact of maternal vaccination with Tdap on the burden of pertussis was analyzed through descriptive studies of incidence and mortality,[7] seroprevalence studies,[8] documentation of the neonatal tetanus elimination process from 1989 to 2005,[9] cost-benefit analysis of booster tetanus vaccination in adults,[10] and description of a diphtheria outbreak reported in 2000.[11]

In Colombia, childhood vaccination against diphtheria, tetanus, and pertussis (DwPT) began in 1980 through the EPI using a three-dose schedule (2, 4 and 6 months of age).[5,12] In 1996, two reinforcements were added at 18 months and 5 years. In 1990, vaccination with tetanus and diphtheria toxoid (Td) was initiated for women of childbearing age between 10 and 49 years to prevent diphtheria and neonatal tetanus.[5,12] Following the resurgence of pertussis in 2013, vaccination of pregnant women with acellular pertussis vaccine (Tdap) was introduced.[13] The maternal and neonatal tetanus elimination plan began in 1989 including vaccination with tetanus toxoid, improved surveillance, and promotion of safe delivery through umbilical cord care.[9]

This work seeks to quantify the population impact of vaccination against diphtheria, tetanus, and pertussis before (1973, 1975) and after (1980-2018) childhood DwPT vaccination, and before (2008-2012) and after (2013-2018) maternal vaccination with acellular vaccine (Tdap) by analyzing the temporal change in incidence in Colombia.

The baseline provided in this study can be informative for decision makers, in the country and the region, to compare the incidence in the future and achieve prioritization of these vaccines so that no one else suffers from these diseases in the 21st century.

Significance for public health

Immunization and control of diseases in the process of elimination, such as neonatal tetanus and with a recent resurgence such as diphtheria and pertussis constitute a challenge for Colombia, the region, and the world. The impact of infant and maternal vaccination on reducing the incidence of diphtheria, tetanus, and pertussis in Colombia, has been reported in this study. Childhood and maternal vaccination markedly reduced the incidence of neonatal pertussis and tetanus. The change in incidence of diphtheria was significant before and after immunization, although slow. Public health efforts should focus on improving and sustaining maternal and child vaccination against diphtheria, tetanus and pertussis. Development of an integrated elimination plan is recommended for the three diseases based on the experience of neonatal tetanus.

Design and methods

This is a retrospective study of secondary sources that estimates the impact of childhood and maternal vaccination against diphtheria, tetanus, and pertussis by means of an interrupted time series analysis[14] with segmented regression to determine the change in magnitude and trend of incidence before and after the start of vaccination.

Data sources

The confirmed cases of these diseases were reported to the national epidemiological surveillance system "SIVIGILA",[15] whose notification is mandatory and standardized, following criteria defined by the National Institute of Health of Colombia (INS, or Instituto Nacional de Salud de Colombia in Spanish).[15] The time series comprised the period from 1973 for diphtheria[16,17] and from 1975 for all forms of tetanus and pertussis.[16,18] The neonatal tetanus analysis included annual data from 1981 to 2018.[16,19] The effect of the Tdap vaccine was analyzed with weekly pertussis data reported from 2008 to 2018.

Data on vaccination coverage were obtained from the databases of the Ministry of Health and Social Protection of Colombia.[20] This information was supplemented with other government publications.[16] The population denominators were obtained from the official databases of the National Administrative Department of Statistics (DANE, Departamento Administrativo Nacional de Estadística in Spanish).[21]

Statistical analysis

The interrupted series analysis determined the incidence level of the three diseases in each segment analyzed before and after the start of vaccination. The slope indicated the decreasing, ascending, or stable trend of the series. Changes in level indicated an immediate effect while changes in slope indicated a gradual or long-term effect. [14,22-24]

The analysis included: i) Data cleaning; ii) descriptive analysis of the temporal behavior of incidence, vaccination coverage, and characteristics of cases reported in the resurgence period of the three diseases. The rate of change and the dependence of the incidence rates per year were calculated (the rate of a given year depends on what happened in the immediately previous year) through a Prais Winsten regression;[22,23] iii) estimation of the series parameters using a segmented regression model with negative binomial distribution; iv) evaluation of the seasonal component in the 2008-2018 pertussis series; v) Estimation of the percentage reduction in the relative incidence IRR (ratio of the incidence predicted after of vaccination in relation to incidence if vaccination had not been started).[14,22-24]

The segmented regression model was as follows:

$$Yt=\beta_0+\beta_1 * time_t+\beta_2 * start\ of\ vaccination_t+\beta_3 * time\ after\ vaccination_t + e_t$$

where Y_t is the relative incidence IRR at time t, b_0 is the intercept or baseline of IRR at the beginning of the series. Time was coded as 0 (before vaccination) and 1 (after vaccination);[25] b_1 estimates the change in IRR level before the start of vaccination; b_2 estimates the immediate effect or change in the IRR level immediately after the start of vaccination (at the end of the prevalence period); b_3 estimates the sustained effect, or change in trend, in IRR per unit time after the start of vaccination compared to the previous trend; e_t is the random variability not explained by the model.

The time unit for the analysis of the impact of childhood vaccination was annual and that of maternal vaccination was weekly.

Data were analyzed with Stata® (ver. 14. Statistical Software: StataCorp LLC, College Station, TX, USA).

Ethical approval

This study was approved by the ethics committee of the "Héctor Abad Gómez" National School of Public Health of the University of Antioquia (session 204 of February 1, 2019, CEI Code 021-2019). It used anonymous data from official sources. The manuscript does not contain any individual person's data in any form.

Results

Vaccination coverage against DwPT increased gradually from the beginning of the EPI until the 1990s. Then, coverage varied, with a predominance of estimates lower than 80%, being lower between 1998-2000 (73-79%), and above 85% since 2003 (Figure 1). Tdap vaccination coverage in pregnant women increased from 72% in 2013 to 92% in 2018.

The reported cases per 100 000 inhabitants of the three diseases decreased considerably even before the start of vaccination and more markedly until the 1980-1990s, with variations by disease. The incidence of diphtheria gradually decreased until 1990 when there was a resurgence of cases between 1990-1995 and then in 2018 when eight cases were reported, all imported from Venezuela. The cases were men of different ages (one case was 3 years old, three cases were between 4 and 17 years old, two cases were between 18-29 years old, and two cases were between 30 and 40 years old), 75% (n=6/8) were hospitalized and 37.5% (n = 3/8) died. Tetanus of all forms, like neonatal tetanus, was progressively reduced from 1980 to 1995, subsequently observing a sustained decrease in incidence. Between 2008 and 2018, 28 cases of neonatal tetanus were reported. The cases had an average age of 14 days (*SD* ± 7) of these cases 64.3% (18/28) belonged to the urban area and 17.8% (5/28) to the rural area. Of those reported, 67.85% (19/28) were hospitalized and 25% (7/28) died. The incidence of pertussis decreased gradually until 1995 when it maintained a low incidence and then increased after the resurgence reported between 2011 and 2013 (Figure 1). Of the 14 809 cases reported between 2008 and 2018, 71% (n=10 519) occurred between 2011 and 2013, around 65% of the cases were reported in children under one year of age, especially those under two months. In the epidemic period from 2011 to 2013, the mean age and percentage of cases in those older than three years increased, compared to other periods. The time between onset of symptoms and health services visits was shorter during the epidemic period. After the start of maternal vaccination in 2014-2018, an increase in rural, hospitalized, and deceased cases was observed. Confirmation of pertussis was predominantly carried out by laboratory, except in the epidemic period when clinical confirmation increased. After the epidemic period in which maternal vaccination began, laboratory confirmation of cases was lower compared to the pre-epidemic period (Table 1).

As shown in Table 2, the maximum incidence range was higher for pertussis and neonatal tetanus in the pre-vaccination period, while it was higher for pertussis in the post-vaccination period. The rate of change shows a significant reduction for diphtheria and neonatal tetanus, with 2 000 and 169 000 cases annually, respectively. The rate of change of pertussis was more evident after maternal vaccination began, although not significant, and presented the highest dependence of incidence rates between years (corre-

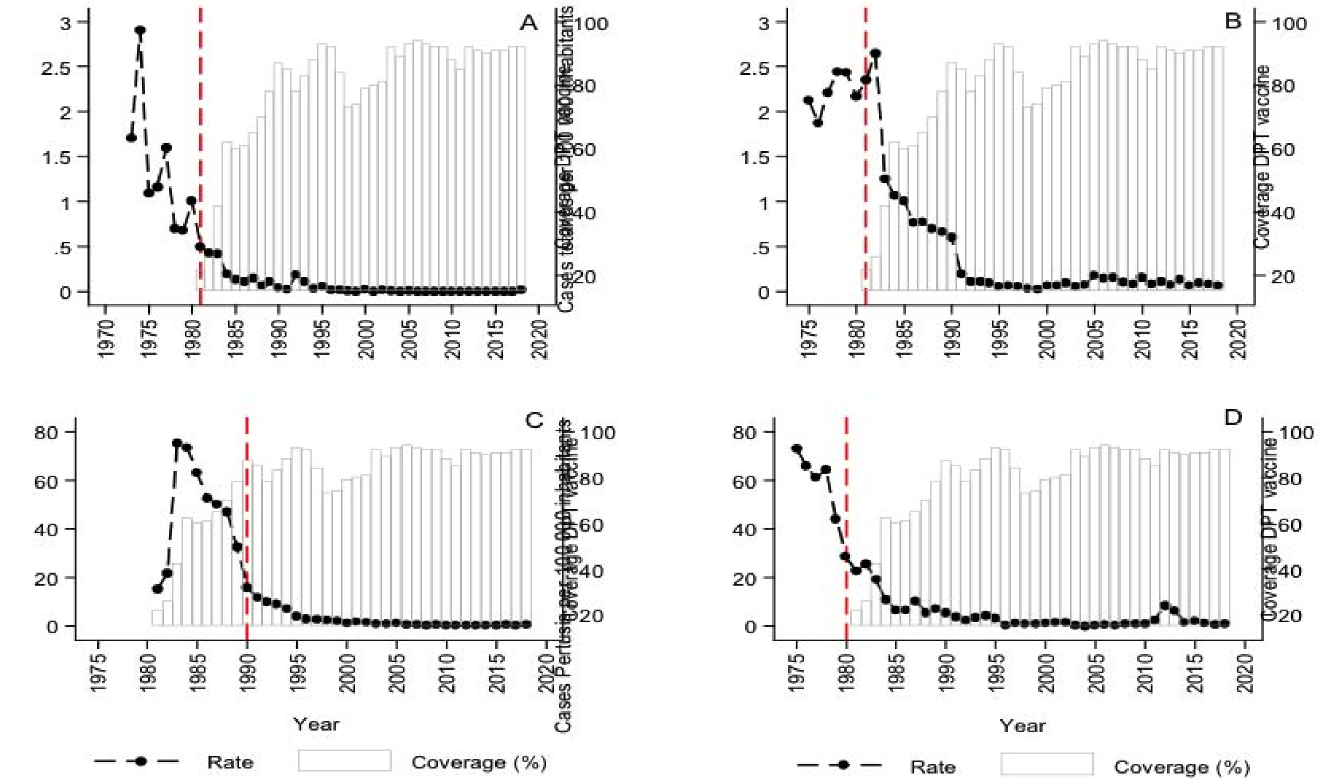

Figure 1. Number of new cases per 100 000 inhabitants notified of diphtheria, all forms tetanus, neonatal tetanus, pertussis and percent coverage of immunization with DwPT in Colombia.

Table 1. Demographic and clinic features of the cases of pertussis in Colombia from 2008 to 2018.

Variable	2008-2010	2011-2013	2014-2018	Total
Age: mean (min-max)	3.8 (0-86)	5.2 (0.1- 88)	3.3 (0.1- 84)	4.9 (0.1- 88.9)
Symptom onset and consultation: average (min-max)	5.4 (1-54)	3.5(2 - 48)	4.4 (1-51)	4.2 (1- 54)
	n (%)	n (%)	n (%)	n (%)
Age				
<2 months	442 (37.46)	3900 (37.08)	1303 (41.89)	5645 (38.11)
2-6 months	244 (20.68)	1951 (18.55)	771 (24.79)	2966 (20.02)
6-12 months	51 (4.32)	688 (6.54)	261 (8.39)	1000 (6.75)
>1-3 years	289 (24.49)	1361 (12.94)	443 (14.24)	2093 (14.13)
4-6 years	42 (3.56)	518 (4.92)	61 (1.96)	621 (4.19)
7-14 years	54 (4.58)	840 (7.99)	88 (2.82)	982 (6.6)
15-89 years	58 (4.92)	1261 (11.99)	183 (5.88)	1502 (10.14)
Gender				
Female	587 (49.75)	5269 (50.09)	1570 (50.48)	7426 (50.14)
Male	593 (50.25)	5250 (49.91)	1540 (49.51)	7383 (49.85)
Area				
City center	1003 (85.00)	8783 (83.50)	2463 (79.19)	12249 (82.71)
Countryside	94 (7.97)	727 (6.91)	262 (8.42)	1083 (7.13)
Rural area	83 (7.03)	1009 (9.59)	385 (12.37)	1477 (9.97)
Hospitalization				
Yes	322 (27.29)	6421 (61.04)	2462 (79.16)	9205 (62.15)
No	858 (72.71)	4098 (38.96)	648 (20.83)	5604 (37.84)
Mortality				
Yes	16 (1.36)	161 (1.53)	63 (2.02)	240 (1.62)
No	1164 (98.64)	10356 (98.45)	3046 (97.94)	14566 (98.35)

lation of 0.91) (Table 2). Table 3 shows the magnitude of change in IRR for the three diseases. The mean predicted rate before the start of vaccination compared to the mean predicted rate at baseline (β_1) decreased (*1-IRR*), for diphtheria in 14%, pertussis in 9%, neonatal tetanus in 4%, and all forms of tetanus in 3%.

The immediate effect (β_2) in *IRR* for all diseases ranged between 25% and 78%, although this effect was statistically significant only for pertussis and neonatal tetanus (Figure 2).

Table 2. Summary measures of incidence by disease and period of immunization, speed of change and dependency per year, Colombia.

Diseases/ Vaccine	Pre-immunization period	Post-immunization period	Pre-immunization period (minimum-maximum)°	Post-immunization period (minimum-maximum)°	Speed of change per year Coeff. (95% CI)	Incidence dependence per year
Diphtheria	1973 – 1980	1980 – 2018	0.67 - 2.90	0 - 0.49	-0.02 (-0.04; 0.004)*	0.59
Tetanus all forms	1975 – 1980	1980 – 2018	1.87- 2.44	0.02- 2.65	-0.03 (-0.08; 0.03)	0.89
Neonatal tetanus	1980 – 1989	1989 – 2018	15.23 -75.3	0.26-15.8	-1.69 (-2.91; -0.48)*	0.76
Pertussis (DwPT)	1975 – 1980	1980 – 2018	44.1 - 72.9	0.10- 28.5	0.15 (-0.56; 0.86)	0.87
Pertussis (Tdap)	2008 – 2013	2013 – 2018	0.1 - 32.8	0.03- 62.2	-0.19	0.91

°Incidence x 100,000 inhabitants/neonatal tetanus incidence x 100,000 live births; *$p<0.05$; **$p<0.0020$; ***$p<0.008$.

Table 3. Interrupted time series (ITS) based on the trends of diphtheria, tetanus and pertussis incidence rates, Colombia.

Diseases/vaccine	Terms of the model	IRR	p-value	95% CI
Diptheria 1973-2018	Slope of the line before immunization (β_1)	0.86	0.274	0.66 - 1.13
	Sustained effect (β_3)	0.95	0.797	0.66 – 1.37
Tetanus all forms 1975-2018	Slope of the line before immunization (β_1)	1.03	0.862	0.75 – 1.41
	Sustained effect (β_3)	0.85	0.327	0.61 – 1.18
Neonatal tetanus 1981-2018	Slope of the line before immunization (β_1)	1.04	0.526	0.93 – 1.15
	Sustained effect (β_3)	0.81	0.001	0.72 – 0.91
Pertussis 1975-2018	Slope of the line before immunization (β_1)	0.91	0.518	0.67 – 1.22
	Sustained effect (β_3)	0.98	0.901	0.72 – 1.33
Maternal 2008-2018	Slope of the line before immunization (β_1)	1.01	<0.001	1.01 – 1.02
	Sustained effect (β_3)	0.98	<0.001	0.98 – 0.99

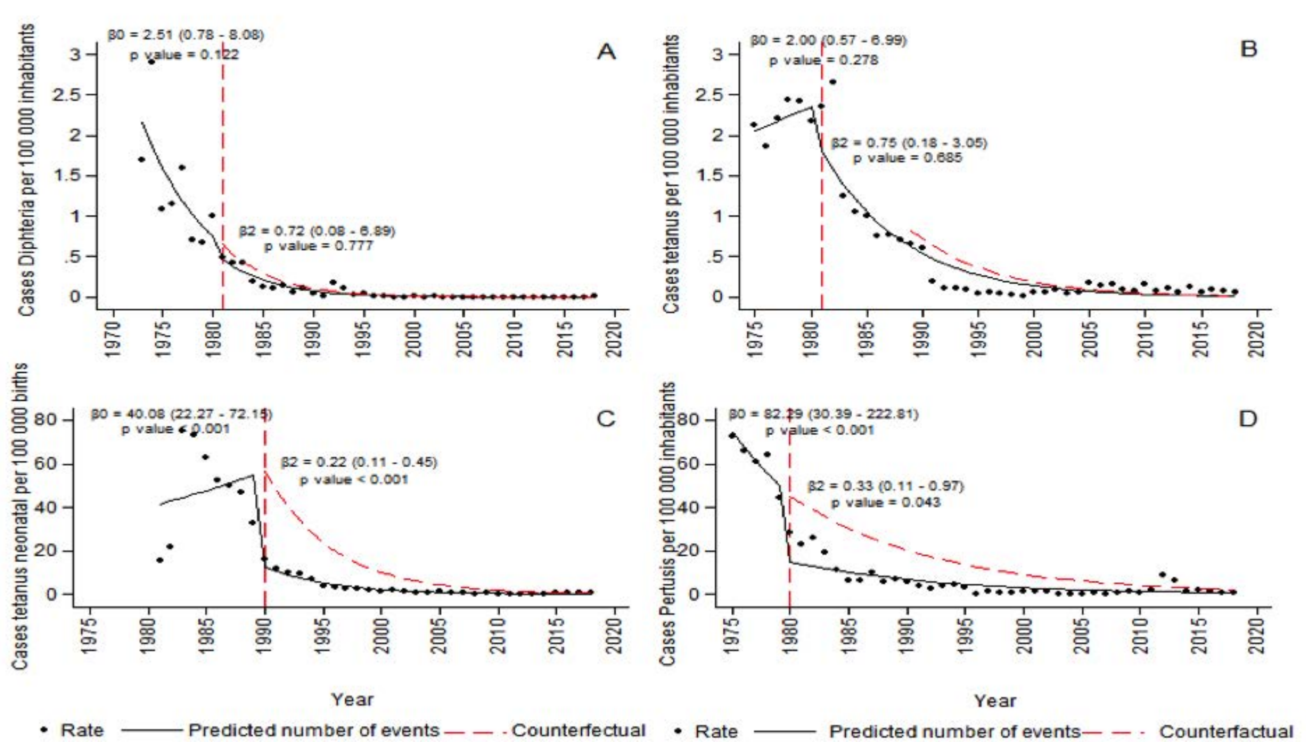

Figure 2. Reported and predicted incidence of the diphtheria, tetanus and pertussis with interrupted time series analysis, Colombia

Regarding the sustained effect (β_3) of the intervention, an annual reduction in *IRR* of 19% was observed for neonatal tetanus, 15% for all forms of tetanus, 5% for diphtheria, 2% for pertussis after infant and maternal vaccination (Table 1).

Figure 2 shows that, if the vaccination program had not been implemented, the diphtheria rate would have a similar magnitude between what was reported and what was predicted (29 *vs* 31). All forms of tetanus (63 *vs* 74) and neonatal tetanus (20 *vs* 13) show marked incidence rate reductions. Pertussis would have had an increased incidence rate if vaccination had not been implemented (20 *vs* 12) (Figure 2).

Discussion

This study detected the reduction in temporal trend in diphtheria, tetanus, and pertussis incidence more markedly after the introduction of vaccination with DwPT in 1980 and Tdap in 2013.

Vaccination coverage with DwPT increased gradually since 1980, but was below 80% between 1998-2002, possibly related to the shortage of biologicals and the reorganization of the provision of health services after the reform of the Colombian health system,[5,26] a situation that may be more critical in some municipalities due to disparities in vaccination coverage.[27] Although maternal vaccination coverage increased gradually in 2018, in 2020 it presented a global figure of less than 80%, after the COVID-19 pandemic.[20]

This study estimated that pertussis incidence would not have been reduced if there had not been massive vaccination of children and significant maternal vaccination. However, it is necessary to monitor the temporal evolution of the disease for a longer period and to intensify disease control due to the resurgence observed between 2011-2013, the low trend magnitude after maternal vaccination compared to the pre-vaccination period, and the high per year correlation of annual incidence dependence. The resurgence of pertussis reported worldwide has been explained by different factors including the loss of vaccine immunity over time and the reduction in vaccination coverage.[28,29] Although the effectiveness of maternal vaccination has been widely studied,[8,30,31] there is a need to strengthen epidemiological surveillance of pertussis and develop new approaches based on hospital reporting, to avoid late consultation, complications, and death. In our study, a percentage increase in hospitalization and mortality, higher frequency of cases in the dispersed rural area, and lower laboratory confirmation of cases were observed after the epidemic period compared with the epidemic period. The characteristics of pertussis cases reported during the resurgence in Colombia were similar to those in published works[32] in terms of the higher frequency of cases in children under two months of age and the occurrence of cases in adolescents and adults, whose atypical symptoms make diagnosis difficult.

The observed impact of vaccination on pertussis incidence is similar to that reported in several studies. In Colombia, a study evaluated the effect of maternal vaccination on pertussis incidence and mortality in children under one year of age in Bogotá D.C., using data from the surveillance system-notified cases, and found a reduction between 54 and 87.5% of the cases in the different age groups. In Argentina,[6] authors estimated the impact of the maternal acellular pertussis vaccine in reducing the burden of childhood morbidity using data from the surveillance system, taking into account areas with high and low Tdap coverage and comparing the incidence before and after vaccination. These authors reported a 51% relative reduction (95% CI: -67%, -35%; p =0.001) in the incidence of pertussis, in areas where vaccination coverage was high.[6] In China, authors reported a significant reduction in diphtheria, tetanus, and pertussis incidence just after the implementation of the DwPT vaccination program.[32]

With respect to diphtheria, a greater reduction in incidence was observed even before the start of vaccination, which could be related to the improvement of socioeconomic conditions of the population. After the start of vaccination, a significant, albeit slow, change in incidence was observed between the pre- and post-vaccination period. The sustained effect on incidence in the post-vaccination period was modest and not significant.

Diphtheria incidence, as reported worldwide, increased between 1985-1995.[3] Following the resurgence of cases in 2018 in Colombia and other Latin American and Caribbean countries, concerns have been raised about the reemergence of this and other vaccine-preventable diseases due to population displacement and the inability to sustain optimal vaccination coverage in both migrant and recipient populations. New approaches such as identification of susceptible groups through seroprevalence studies and intensification of vaccination and epidemiological surveillance in populations in social conflict and with limited access to health services are needed to avoid cases occurrence.[33] The incidence of neonatal tetanus presented the most notable reduction in level and trend after the start of vaccination, which coincides with other authors who showed a 94% reduction in neonatal tetanus incidence in Colombia from 1989 to 2005.[10] The detected effect could be due to vaccination reinforcement with integrated measures of surveillance and umbilical cord care within the maternal and neonatal elimination plan.[34]

This study has several limitations. It was not possible to have the incidence data for 2019-2020 as it is in the process of being updated, nor the monthly incidence data and vaccination coverage before the start of the EPI. These data, like census information, are permanently reviewed by the country's health and demographic authorities and in this work, they were refined and contrasted with different sources of information, using official figures.

In conclusion, childhood and maternal vaccination markedly reduced the incidence of neonatal pertussis and tetanus in Colombia. Development of an integrated elimination plan is recommended for the three diseases based on the experience of neonatal tetanus. In this plan, ensuring the stability of vaccination program health and workers should be a priority along with epidemiological surveillance that allows maintaining optimal vaccination coverage, continuously monitoring the behavior of the diseases, developing new approaches to prevent the re-emergence of these diseases, and sustaining the achievements made.

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Key words: Incidence; immunization programs; interrupted time series analysis; diphtheria-tetanus-pertussis vaccine.

Contributions: All the authors made a substantive intellectual contribution. All the authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: The authors declare that no conflict of interest.

Funding: This work was financed by COLCIENCIAS Departamento Administrativo de Ciencia, Tecnología e Innovación Colciencias-Minciencias (699-2018) in Spanish) and the National School of Public Health "Héctor Abad Gómez", University of Antioquia, Colombia.

Informed consent: The manuscript does not contain any individual person's data in any form.

Ethical approval and consent to participate: This study was approved by the ethics committee of the National School of Public Health "Héctor Abad Gómez" of the University of Antioquia (session 204 of February 1, 2019, CEI Code 021-2019). It used anonymous data from official sources.

Availability of data and material: The data used to support the findings of this study are available from the corresponding author upon request.

Patient consent for publication: Not applicable

Ethics approval: not applicable: No experiments utilizing animals or humans were undertaken in this study.

Received for publication: 30 August 2021.
Accepted for publication: 22 September 2021.

Journal of Public Health Research 2022;11:2588
doi:10.4081/jphr.2021.2588

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