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Changing trends in serotypes of *S. pneumoniae* isolates causing invasive and non-invasive diseases in unvaccinated population in Mexico (2000-2014)

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ABSTRACT

Objective: Introduction of pneumococcal conjugate vaccines (PCV) targeted against a limited number of serotypes substantially decreased invasive (IPD) and non-invasive pneumococcal diseases (NIPD) but it was accompanied by non-vaccine type replacement disease. After 9 years of introduction of PCV in Mexico, we analyze the evidence of the indirect effects on IPD and NIPD serotype distribution among groups not targeted to receive the vaccine.
Methods: From January 2000 to December 2014, pneumococcal strains isolated from IPD and NIPD cases from patients ≥5 years of age from participant hospitals of the SIREVA II (Sistema Regional de Vacunas) network were serotyped. A regression analysis was performed considering year and proportion of serotypes included in the different vaccine formulations (PCV7, PCV10 and PCV13). The slope was obtained for each regression line and their correspondent p-value. The proportion of each serotype in the pre-PCV7 and post-PCV7 periods was evaluated by $\chi 2$ test.
Results: From a total of 1147 pneumococcal strains recovered, 570 corresponded to the pre-PCV7 and 577 to the post-PCV7 periods. The proportion of vaccine serotypes included in the three PCV formulations decreased by 2.4, 2.6 and 1.3%, respectively per year during the study period. A significant increase of serotype 19A was observed in the post-vaccine period in all age groups.
Conclusions: A percentage of annual decline of serotypes causing IPD and NIPD included in PCV was detected among groups not targeted to receive the vaccine, probably due to herd effect. Considering pneumococcal serotype distribution is a dynamic process, we highlight the importance of surveillance programs.

Introduction

The widespread use of pneumococcal conjugate vaccines (PCV) has been very effective in the prevention of diseases caused by *Streptococcus pneumoniae* by reducing invasive (IPD) and non-invasive pneumococcal diseases (NIPD) in young children, especially when introduced as part of the national immunization programs. In the United States, introduction of heptavalent conjugated pneumococcal vaccine (PCV7) using a 4-dose schedule has resulted in significant reduction in IPD in vaccinated and unvaccinated populations due to herd protection, which has been found to be a very important factor in determining the cost-effectiveness of PCV programs;[1,2] Herd protection has been reported in other countries,[3–5] while in some others, these benefits have not been observed or have been partly offset by an increase in incidence of IPD caused by pneumococcal serotypes not included in any conjugate vaccine or non-vaccine types (NVT).[6,7]

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Three PCV formulations, 7-valent (PCV7: 4, 6B, 9V, 14, 18C, 19F and 23F serotypes), 10-valent (PCV10: PCV7 + 1, 5, 7F serotypes) and 13-valent (PCV13: PCV7 + 1, 3, 5, 6A, 7F and 19A serotypes) have been licensed using a 4-dose schedule (3 primary doses plus 1 booster, 3 + 1), 3 primary doses (3 + 0) or 2 primary doses plus a booster (2 + 1) depending on the country.[8,9] In Mexico, PCV7 became available in the private market in 2001. In 2006, it was introduced initially for children living in the poorest regions of the country with a 2, 4, 6 months (3 + 0) schedule; and universal vaccination for all Mexican children started in 2008 originally considering a 2 + 1 schedule. Unfortunately, because of financial constraints, during 2008 and 2009, only a two dose schedule was offered at 2 and 4 months of age.[10] Since 2010, the same three-dose schedule with PCV10 was implemented for children affiliated to the Instituto Mexicano del Seguro Social (IMSS), and PCV7 continued to be administered to the rest of the population [(children affiliated to the Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE) and children cared for at medical units affiliated with the Secretaria de Salud (SS)]. Finally, in 2011, PCV13 was gradually introduced in the universal immunization program (UIP) for children younger than 2 years of age with a 2 + 1 schedule. Non-conjugated 23-valent pneumococcal polysaccharide vaccine (PPV23: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F serotypes) was included in the UIP since 2006 for adults 65 years and older with a single dose and a second dose 5 years after the first one in case of any health risk. A study based on the National Health and Nutrition Survey in 2012 indicated that coverage for PCV7 was 80.8% for children below one year of age and 88% for children 15-23 months old.[11]

Recently, we showed significant changes in pneumococcal vaccine serotypes (VT) causing IPD in children younger than 5 years of age following PCV7 introduction in Mexico.[12,13] In this study, we analyze some evidence on the indirect effects of PCV introduction on IPD and NIPD among groups not targeted to receive the PCV vaccine.

Materials and methods

Surveillance of S. pneumoniae *and clinical isolates*

Since 1993, Mexico has been part of the SIREVA network, a laboratory-based surveillance Latin-American group, coordinated by the Pan American Health Organization (PAHO) that monitors pneumococcal infection. During the study period from January 2000 to December 2014, participant hospitals from the second and third level of attention throughout the country sent pneumococcal strains isolated from IPD and NIPD cases mainly from patients with an initial clinical diagnosis of meningitis, sepsis or pneumonia to the Laboratory of the Department of Vaccine Evaluation at the National Institute of Public Health (INSP, for its acronym in Spanish) in Cuernavaca, Morelos for serotyping. In order to analyze serotype distribution, four age groups were considered: children and adolescents from ≥5 to 17, adults 18-49, 50-64 and ≥65 years of age. The pre-vaccine period (pre-PCV7) was considered from year 2000 to 2007 and the post-vaccine period (post-PCV7) from 2008 to 2014.

Clinical definitions

Invasive pneumococcal disease (IPD) isolates were considered when *S. pneumoniae* was isolated from blood, cerebrospinal fluid (CSF) and/or pleural fluid. Non-invasive pneumococcal disease (NIPD) included those isolates from patients with probable pneumonia and isolates from non-sterile sites, such as the middle ear fluid obtained by tympanoscentesis and eye discharge. Bacteremic and/or complicated pneumonia was defined for those patients with clinical diagnosis of pneumonia[14] and positive culture from blood or pleural fluid. Probable pneumonia was defined by the treating physician by clinical and radiological criteria[15]; and included tracheal aspirate and/or bronchoalveolar lavage samples obtained with the bronchoscopic protected catheter brush and *S. pneumoniae* isolated as a single culture.

Bacterial procedures

Pneumococcal isolates were identified by standard procedures that included tests for bile solubility and optochin sensitivity. Pneumococcal isolates were serotyped by the Quellung reaction with type- and factor-specific antisera (Statens Serum Institut, Copenhagen, Denmark). Only one isolate from each patient was considered.

Statistical analysis

A database with information about site of isolation, diagnosis, age, year and pneumococcus serotype was elaborated. The information was analyzed every two years from 2003 to 2014; the years 2000-2002 were compacted into one by the number of samples. A simple linear regression model with fixed effect for time was performed considering every year and the percentage of the serotypes included or not in the different vaccine formulations. The slope from the years 2000-2007 was compared with the slope from years 2008-2014 by the Student t test. A second regression analysis was performed by compacting the years (every two years, except the first three); to assess the serotypes included in the vaccine (stratified by age group), the slopes and p-values were calculated. The proportion of each serotype in the pre-PCV7 and post-PCV7 periods was evaluated by χ^2 test and particularly for serotype 19A, by χ^2 trend test. The p values <0.05 were considered statistically significant. Statistical analyses were conducted using SPSS v 15.0 and Graphpad Prism 6 software.

Ethical statement

The study was submitted for Ethical approval and it was exempt by the Research Ethics Committee at the INSP considering it was performed with *S. pneumoniae* isolates that resulted from standard microbiological diagnostic procedures as requested by the treating physician. No additional biological specimens were taken for the purpose of this study. Specimens were anonymized and only data on year and month of birth, sex, type of specimen and hospital/laboratory were registered.

Results

Between January 2000 and December 2014, a total of 1147 pneumococcal strains were recovered from IPD and NIPD cases, 570 of them corresponded to the pre-PCV7 era and 577 to the post-PCV7 period. Their distribution by age group and clinical diagnosis is shown in Table 1. Clinical diagnoses were similar in both pre and post-vaccine periods except that an increase in sepsis/bacteremia cases during the post-PCV7 period was observed in ≥5 to 17 and 50–64 year old groups. A decrease in frequency in probable pneumococcal pneumonia was registered in the post-PCV7 period.

Changing trends on pneumococcal VT as well as NVT throughout the study period considering IPD and NIPD cases are shown in Figure 1. Although starting from different values, the proportion of VT decreased in all age groups. PCV7, PCV10 and PCV13 serotypes decreased 2.4%, 2.6% and 1.3% on average per year, respectively. Decreases in the proportion of isolates included in PCV started in the pre-vaccination period, but when compared between the pre and post-vaccine periods, the decrease was more

Table 1
Clinical diagnosis of patients with invasive and non-invasive pneumococcal diseases.

AGE GROUPS (YEARS)	VACCINE PERIOD	CLINICAL DIAGNOSIS					TOTAL
		SEPSIS/BACTEREMIA	MENINGITIS	BACTEREMIC AND COMPLICATED PNEUMONIA	PROBABLE PNEUMONIA[†]	OTHERS[‡]	
		n (%)	n (%)	n (%)	n (%)	n (%)	n
≥5–17	Pre-PCV7	30 (16.5)	38 (20.9)	20 (11)	71 (39)	23 (12.6)	182
	Post-PCV7	77 (29.3)**	42 (16)	25 (9.5)	98 (37.3)	21 (8)	263
	Total	107 (24.1)	80 (18)	45 (10.1)	169 (38)	44 (9.9)	445
18–49	Pre-PCV7	41 (21.5)	26 (13.7)	16 (8.4)	89 (46.8)	18 (9.5)	190
	Post-PCV7	37 (26.7)	27 (19.4)	9 (6.5)	58 (41.7)	8 (5.8)	139
	Total	78 (23.7)	53 (16.1)	25 (7.6)	147 (44.7)	26 (7.9)	329
50–64	Pre-PCV7	13 (13.3)	11 (11.2)	7 (7.1)	58 (59.2)	9 (9.2)	98
	Post-PCV7	26 (28.3)*	10 (10.9)	13 (14.1)	35 (38)	9 (9.8)	93
	Total	38 (20)	21 (11.1)	20 (10.5)	93 (48.9)	18 (9.5)	190
>65	Pre-PCV7	11 (11)	9 (9)	10 (10)	68 (68)	2 (2)	100
	Post-PCV7	15 (18.1)	7 (8.4)	14 (16.9)	38 (45.8)**	8 (9.6)*	82
	Total	26 (14.2)	16 (8.7)	24 (13.1)	106 (57.9)	10 (5.5)	183
TOTAL	Pre-PCV7	95 (16.7)	84 (14.7)	53 (9.3)	286 (50.2)	52 (9.1)	570
	Post-PCV7	155 (26.9)**	86 (14.9)	61 (10.6)	229 (39.7)**	46 (8)	577
	Total	250 (21.8)**	170 (14.8)	114 (9.9)	515 (44.9)**	98 (8.5)	1147

* $p < 0.05$.
** $p = <0.01$.
[†] Probable pneumonia: was defined by the treating physician by clinical and radiological criteria[15]; and included tracheal aspirate and/or bronchoalveolar lavage samples obtained with the bronchoscopic protected catheter brush and *S. pneumoniae* isolated as a single culture.
[‡] Other clinical diagnosis: otitis, peritonitis, abscess, renal insufficiency and conjunctivitis (isolates from non-sterile sites like middle ear fluid, peritoneal fluid, abscess discharge and eye discharge).

pronounced in the post-PCV7 for the three formulations: 1.7 vs 3.2% for PCV7 (p = 0.280); 2.0 vs 3.6% for PCV10 (p = 0.136) and 1.1 vs 3.0% for PCV13 (p = 0.141), respectively. These differences were not statistically significant. The proportion of serotypes 1, 5 and 7F of PCV10 was 4.1% in the pre-PCV7 period and 3.6% in the post-PCV7 era, while the proportion for serotypes 3, 6A and 19A of PCV13 was 19.9% in the pre-PCV7 era and 31.7% in the post-PCV7 period ($p < 0.001$). Particularly for serotype 19A, the proportion of isolates during the pre-PCV7 was 4.7%, for the period (2008-2011), it was 10.1% and after the introduction of PCV13 (2012-2014), it was 14.6%) with $p < 0.0001$ (χ^2 trend test).

When analyzed by age group (Figure 2), we observe statistically significant decreases in the proportion of PCV7 and PCV10 vaccine serotypes in all age groups except in those ≥65 years of age. Starting in 2011, a gradual annual decrease of IPD and NIPD caused by PCV13 VT was observed in the 18-49 age group from 68.2% in 2011, 55.6% in 2012 and 37% in 2013 with a slight increase in 2014 when PCV 13 VT caused 52.9% of pneumococcal diseases. In this group, the decrease of VT for all formulations was statistically significant. Considering only the age group of >65, where at least half of the population is vaccinated with PPV23,[16] no significant decrease was observed for serotypes included in PPV23. In the 50-64 age group, the proportion of annual decrease of PCV7 and PCV10 VT was 1.8% and 2.0%, respectively, with almost no change in PPV23 serotypes or non-vaccine types.

Considering individual serotypes (Figure 3), we observed an increase of serotype 19A in all age groups, especially in children among 5-17 years of age (p = 0.0047). A statistically significant

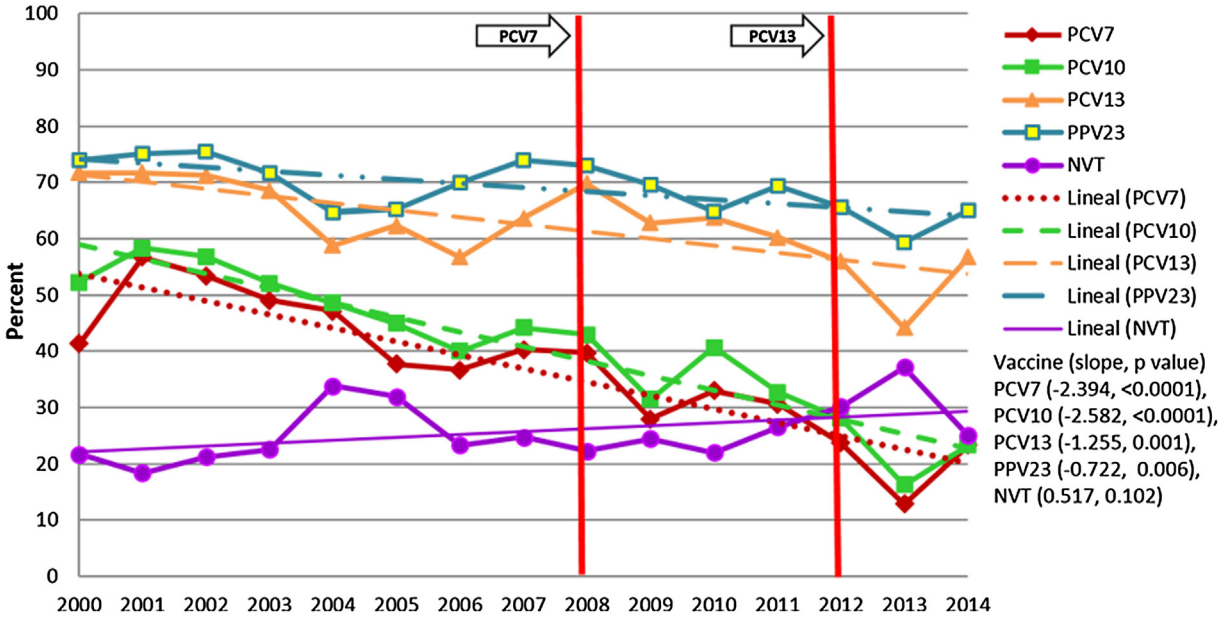

Figure 1. Trends of pneumococcal serotypes covered by PCV7, PCV10, PCV13 and PPV23 from 2000 to 2014.
NVT = Non-vaccine types.

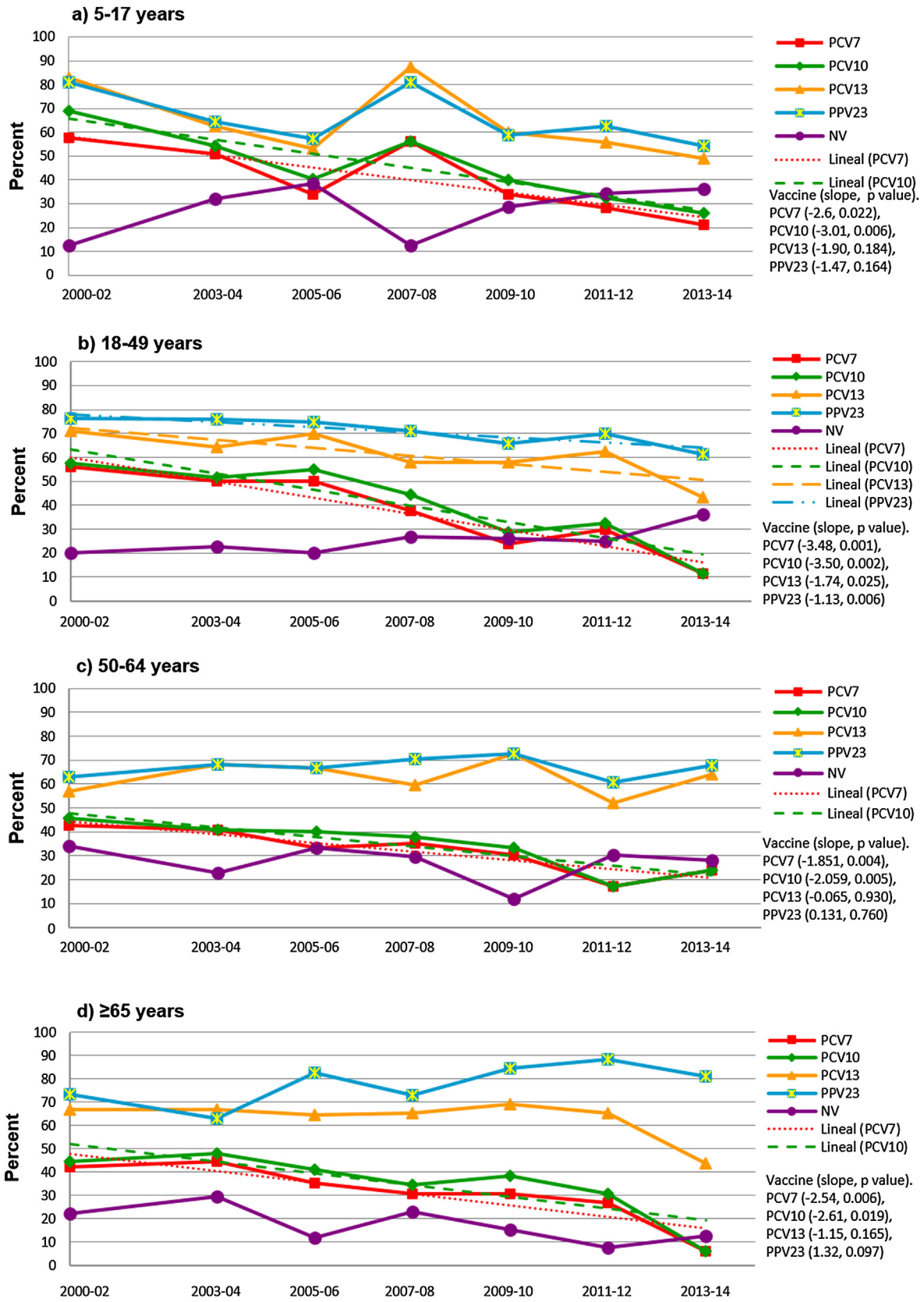

Figure 2. Distribution of pneumococcal serotypes covered by PCV7, PCV10, PCV13 and PPV23 according to age groups from 2000 to 2014.
NVT = Non-vaccine types; only trends with $p < 0.05$ are shown.

decrease was observed for some of the PCV7 serotypes, particularly serotype 6B in the 5-17 and 18-49 age groups. Serotype 19F significantly decreased ($p \leq 0.05$) only in the children and adolescent group and serotypes 14 and 23F presented a sharp

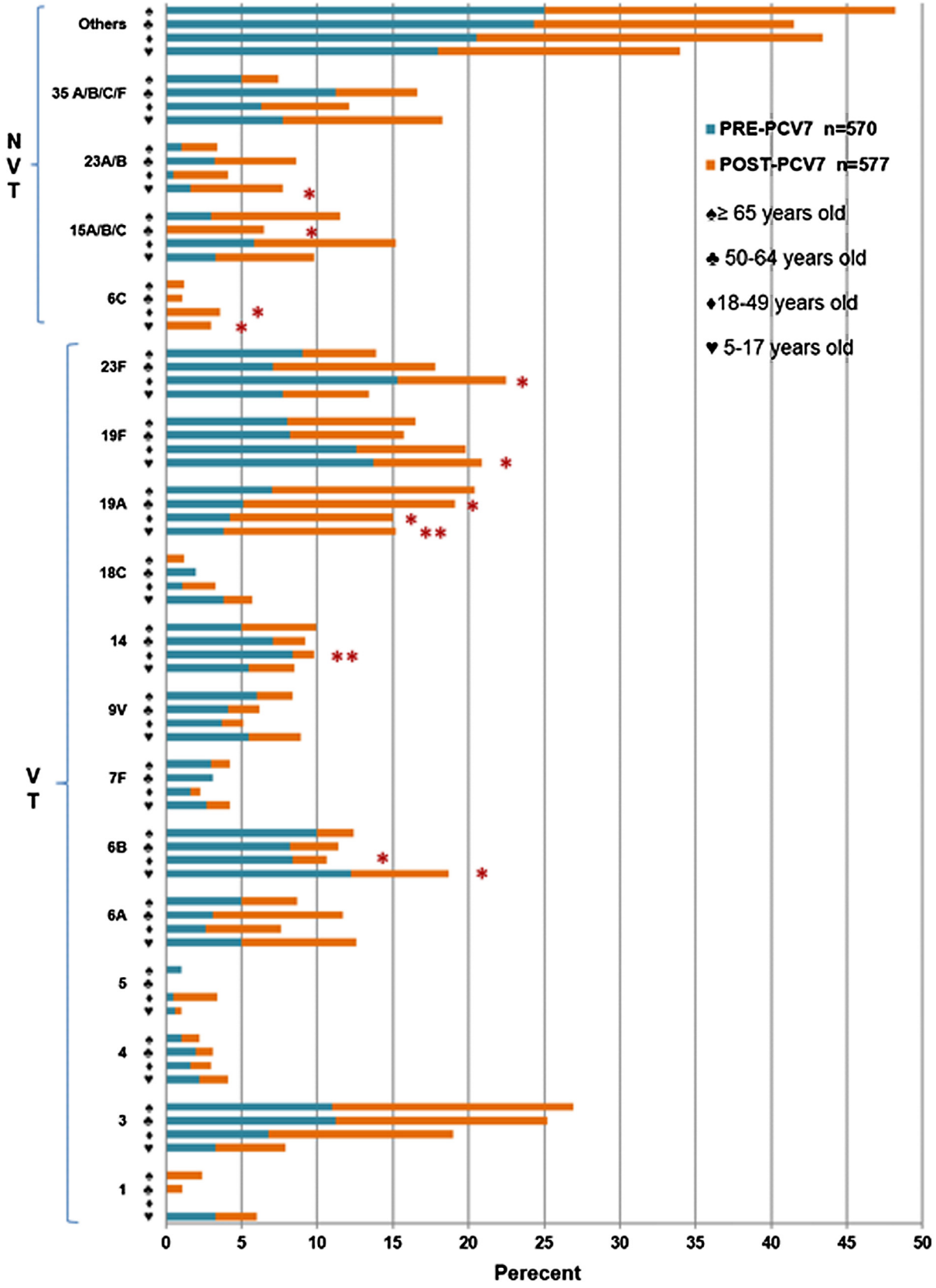

Figure 3. Pneumococcal serotype distribution according to age group before and after introduction of PCV7 in Mexico (2000-2014).
*$p \leq 0.05$, **$p \leq 0.001$; VT are those included in PCV13
Others (Serotypes: 13, 20, 21, 29, 31, 34, 42, 10A, 10F, 11A, 11F, 12F, 18A, 18F, 19C, 28A, 7C, 9A, 9L, 9N, 2, 8, 38, 10B, 16F, 17F, 19B, 22F, 24F, 7B and non-typable).

decrease in the 18-49 age group. An important statistically significant increase in serogroups 15 and 23 was observed in the post-PCV7 period. Other serotypes not included in any PCV, also increased in the post-PCV7 period and serotypes 6C and 22F appeared for the first time in the post-PCV7 period. Serotype 3 was the most important type isolated from adults older than 50 years of age and the proportion of isolates was higher in the post-PCV7 period. We detected 50 different capsular types and 39 non-typable serotypes among the isolates.

Theoretical serotype coverages for IPD for the different vaccine formulations throughout the study period are: PCV7 (34.8%), PCV10 (41.2%), PCV13 (63.1%) and PPV23 (76.1%). For NIPD they are: PCV7 (38.5%), PCV10 (40.1%), PCV13 (61.5%) and PPV23 (72.6%).

Discussion

The most important finding of this study is the annual decrease in proportion of serotypes included in PCV causing IPD and NIPD among people not targeted to receive the vaccine. This is even more marked when stratifying by age groups, where adults from 18 to 49 years of age show a strong decrease, particularly after the introduction of PCV13. This group is the one most benefited by PCV introduction, suggesting possible herd protection. These effects are in accordance with reductions of IPD and NIPD among children and adults published in several parts of the world.[17–21]

We did not observe changes in the proportion of pneumococcal isolates causing meningitis during the study period. However, a significant increase was observed regarding sepsis/bacteremia cases in the post-PCV7 period, particularly in children 5-17 years old. This change could be the result of an increased awareness of IPD among clinical microbiologists and infectious diseases physicians, particularly after the introduction of PCV.

Previously, it has been shown that children younger than 5 years of age, vaccinated with a complete schedule or at least two doses of PCV7, displayed a 91% reduction of risk of getting sick due to serotypes included in PCV7 compared to unvaccinated children in Mexico. The same age group showed an 89% reduction of risk of death due to IPD among vaccinated children and there was a gradual increase in serotypes not included in PCV7, mainly due to 19A[12] with a concomitant increase in antimicrobial resistance.[22] In this study, including the population not targeted for vaccination with PCV, we observed a statistically significant increase of serotype 19A in all study groups, except in adults ≥65 years old. While it may be early to expect PCV13 herd effects, this study does not indicate a trend to a decrease in this serotype, in contrast to other studies where an important reduction has been observed after PCV13 introduction.[23,24] The high proportion of current IPD and NIPD caused by serotype 19A in Mexico may be a decisive factor in determining vaccine policies. A significant increase was observed in other serotypes after the introduction of PCV7: 15A, 15B and 15C in age group 50-64 years and 23A, and 23B in children among 5-17 years old. Similar results have just been published by van der Linden et al. in Germany.[21] Serotype 22F, though it was first isolated after introduction of PCV7, has not significantly increased either in children or adults after PCV introduction as observed in other countries.

Decreases in the proportion of isolates included in PCV started in the pre-vaccination period, which implies that other factors triggered the decrease of IPD and NIPD in Mexico. These factors include improvement of quality care for primary attention in children and adolescents[25,26] as well as vitamin A supplementation during vaccine weeks in children age 6 months to 4 years of age[27,27] Other factors like incomplete vaccine schedules without a booster dose during a two year period or low vaccine coverage, particularly for the booster dose, might be responsible for the limited decrease of VT observed when compared to other countries.

Data generated from passive laboratory surveillance has limitations. Particularly, there may be a low sensitivity because not all hospitals participate and send their information, and laboratory-based reports could remain incomplete. Despite this limitation, these data remain useful because they could be used primarily for monitoring trends in disease occurrence, as in this study, and could provide a basis for public health decisions. Data generated from the passive laboratory surveillance SIREVA has provided valuable and important information regarding trends of pneumococcal serotype changes in Latin America.[28]

Although this study was not designed to evaluate herd immunity, the frequency analysis of the main clinical forms of IPD and NIPD suggests that the decrease in frequency of serotypes causing disease included in the PCV is secondary to herd effect. The importance of herd effect in the cost-effectiveness of PCV programs has to be taken into consideration for optimal vaccine use. Continued surveillance, along with detailed nasopharyngeal carriage studies, will be important to determine the impact of PCV13 on pneumococcal diseases in these age groups, and also to monitor the evolution of causative serotypes.

Conflicts of interest

None.

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Competing interests

The authors declare that they have no competing interests.

Appendix

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