Evaluation of the direct and indirect impact on pneumonia hospitalization after almost a decade of the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine in Brazil

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ABSTRACT

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Introduction: Pneumococcal pneumonia is a leading cause of severe disease, leading to approximately 2.2 million hospital admissions in 2019 in Brazil. Since 2010, the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine was introduced in Brazil, as part of the National Immunization Program (NIP) with universal access, approximated coverage of 91.4% in 2019. Although studies from many countries are available, there is still a need to understand the effect of the vaccine introduction on the incidence of pneumonia hospitalizations in Brazil.

Methods: Data on hospitalization associated with the diagnosis of pneumonia in the population assisted by the Brazilian Public Health System were accessed to fit a time series analysis, which tested the main hypothesis of the influence of vaccination on the trends for the incidence of pneumonia hospitalizations.

Results: The post-vaccination period showed a negative trend, reducing 1.75, 0.16, and 0.11 cases per 100,000 inhabitants per month for the groups < 1, 1–4, and 5–9 years old, respectively. In individuals older than 20 years, the post-vaccination period has a positive trend, but not as great as compared trends before the vaccination period. These results indicate a protective herd effect in the older population, nine years after introducing the pneumococcal vaccine in the NIP.

Conclusion: Vaccination with pneumococcal conjugated vaccine reduces hospitalizations associated with pneumonia diagnosis in vaccinated and non-vaccinated populations in a sustained and progressive manner.

Keywords: *Conjugate vaccine; pneumonia; pneumococcal vaccine; herd immunity; PHiD-CV*

INTRODUCTION

Pneumococcal pneumonia remains as a leading cause of severe disease and death worldwide, mainly in the older adults and young children[1-7]. Respiratory illnesses were the fourth leading cause of hospitalizations at all ages in Brazil, with 1,190,950 hospital admissions and 98,190 associated deaths in 2019. In around 16.5% of children hospitalizations, pneumonia was the leading diagnosis in Brazilian children under five years old in 2019[8]. Among several etiological agents, *Streptococcus pneumoniae* is implied in 294,000 deaths among children aged form one to 59 months worldwide; 81% of these infections were linked to a pneumonia diagnosis[9].

In 2010, the 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) was introduced in Brazil as part of the National Immunization Program (NIP) with universal access by a 3 + 1

schedule in the second, fourth and sixth months of life, plus a booster dose between the 12th and 15th months of age, followed by the withdraw of the third dose after 2016. The PHiD-CV coverage via the Brazilian Health System increased from 24% in 2010 to an average of 91.4% from 2011 to 2019 (81.7% to 95.3% of coverage)[10].

Alicino et al. published a systematic review on the impact of the 10-valent pneumococcal conjugate vaccines in several countries, showing a 17% reduction in hospitalization rates for clinical pneumonia in children younger than five years[11]. In Brazil, a 12.6% reduction in hospitalizations in children under four years due to pneumonia has been observed two years after the PHiD-CV introduction[12]. Andrade et al. used data from 2005 to 2015, concluding that pneumonia hospitalization rates are lower after introducing the vaccine schedule for children and older age groups[13]. Although many studies are available, this large Brazilian database is unique and includes 18 years of data, nine of which with PHiD-CV was already completely introduced in the Brazilian NIP.

We aimed to use data from 2002 to 2019 to assess the temporal trend of all-cause pneumonia hospitalization incidence for vaccine-eligible and non-eligible age groups. We used publicly available data on pneumonia hospitalization obtained from the Brazilian Health System Informatics Department (DATASUS) via the Health Information section, testing the hypothesis of the interaction of the time trend before and after the vaccine introduction.

METHODS

Data source

Data for this study were accessed from an open-access governmental database: the Health System Informatics Department (DATASUS) via the Health Information section, accessed on August 30th, 2020[8]. The collected data correspond to a diagnosis (ICD-10) made at hospitalization, which is not changed independently of the course of the disease during hospital stay. Thus, the pneumonia code selected in this study is related to an early diagnosis accounting for all-cause pneumonia (virus, bacteria, or fungus). Data from 2002 to 2019 were used because after 2020 data was strongly influenced by the SARS-CoV-2 pandemic[14,15].

Codes for "pneumonia," grouped in DATASUS as ICD J12 to J18, were used to select the main outcome data from January 2002 to December 2019. All non-pneumonia respiratory (ICD J00 to J99, minus ICD J12 to J18) hospitalizations were also collected and used in the time series analysis as a confounder variable (further explained in the statistical analysis section). The number of hospitalizations was evaluated in the "pneumonia" and "non-pneumonia-respiratory" groups. Subjects were divided into the group of vaccine-eligible population according to age strata: < 1, 1–4, 5–9 years old, and non-vaccine-eligible population according to age strata: 10–19, 20–59, 60–79, and ≥ 80 years old. Two researchers independently collected the information using a standard approach, while a third researcher checked data quality. Table 1 summarizes data collection.

Table 1: Research database collection, outcomes of interest, and case definitions considered in time series analysis. Brazil, 2002–2019.

Outcome of interest	Database	Description	Case definition
Total PNM hospitalizations	DATASUS	National database of hospitalizations in the public healthcare system	Admission coded as J12-J18 (ICD-10)
Total respiratory hospitalizations excluding PNM	DATASUS		All admission codes between J01-J99, minus J12-J18 (ICD-10)
Brazilian population projection 2000-2030	Brazilian Institute of Geography and Statistics	Absolute number informed	Year projection by sex and age
People with hospital health insurance	National Agency of Supplementary Health	Absolute number with quarter updates	Data informed by age and health insurance coverage

PNM: pneumonia; DATASUS: Health System Informatics Department of the Brazilian Ministry of Health.

Monthly and annual incidence admission per 100,000 inhabitants were calculated by dividing the number of hospitalizations by the official population estimation of specific age groups from the Brazilian Census of 2018 minus all people with private in-hospital health insurance coverage[16]. Brazilian National Agency of Supplementary Health (ANS), an open-access database, provides the number of inhabitants per age group with private health insurance[17]. Those subjects with private health insurance represent a small fraction of the population—higher income stratum—and were excluded from the denominator in the analysis once their hospitalizations were not included in DATASUS. The study was evaluated

and approved by the review board of the Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Brazil. Since DATASUS has no individual subject data information, our study was considered exempt from approval by the Research Ethics Committee by the institutional review board of PUCRS.

Statistical analysis

A dynamic linear time series regression was used to assess the monthly incidence of admissions for respiratory causes (outcome) from 2002 to 2019. A *dummy* variable (*vaccine*) was created to split the time series into pre-vaccination (2002–2009) and post-vaccination periods (2011–2019). The year of 2010 was considered a transition period and excluded from the time series analysis. The hypothesis tested was the time trend interaction and the vaccination effect on the outcome (i.e., hospitalization incidence). Considering $\beta_{time*vaccine}$ as the regression coefficient for interaction between time and vaccine, then:

$$\begin{cases} H_0: \beta_{time*vaccine=0} = \beta_{time*vaccine=1} \\ H_1: \beta_{time*vaccine=0} \neq \beta_{time*vaccine=1} \end{cases}$$

Where *vaccine*=0 stands for the pre-vaccination period and *vaccine*=1 stands for the post-vaccination period. If the test rejects the null hypothesis, the incidence trends significantly differ before and after the vaccine introduction. Non-respiratory admission causes and seasonality effect were used as adjustment confounders covariates. For ridding the model of autocorrelation[18], the outcome was included as a covariate in the model lagged two times (i.e., y(−2)). Time series regression was performed using the R package "dynlm"[19]. All analyses were performed in R Core Team version 4.0.2[20]; the data and scripts used are available on: https://github.com/eduardodefreitascosta/Pneumovacc

RESULTS

Observed incidences

The study had 6,086,826 and 5,895,278 pneumonia admissions, among all age groups, for pre-vaccine (2002–2009) and post-vaccine (2011–2019) periods, respectively. Among the vaccine-eligible population, we found 3,171,207 pneumonia hospitalization cases in the eight years of the pre-vaccine period and 2,253,107 during the nine years since the implementation of the vaccine program. Among age groups < 1, 1–4, and 5–9 years old, the mean incidence in the pre-vaccine period was 386.7, 141.7, and 31.1 cases per month per 100,000 inhabitants, respectively; reducing in the post-vaccine period to 308.4, 113.4, and 24.7 cases per month per 100,000 inhabitants, respectively (Figure 1).
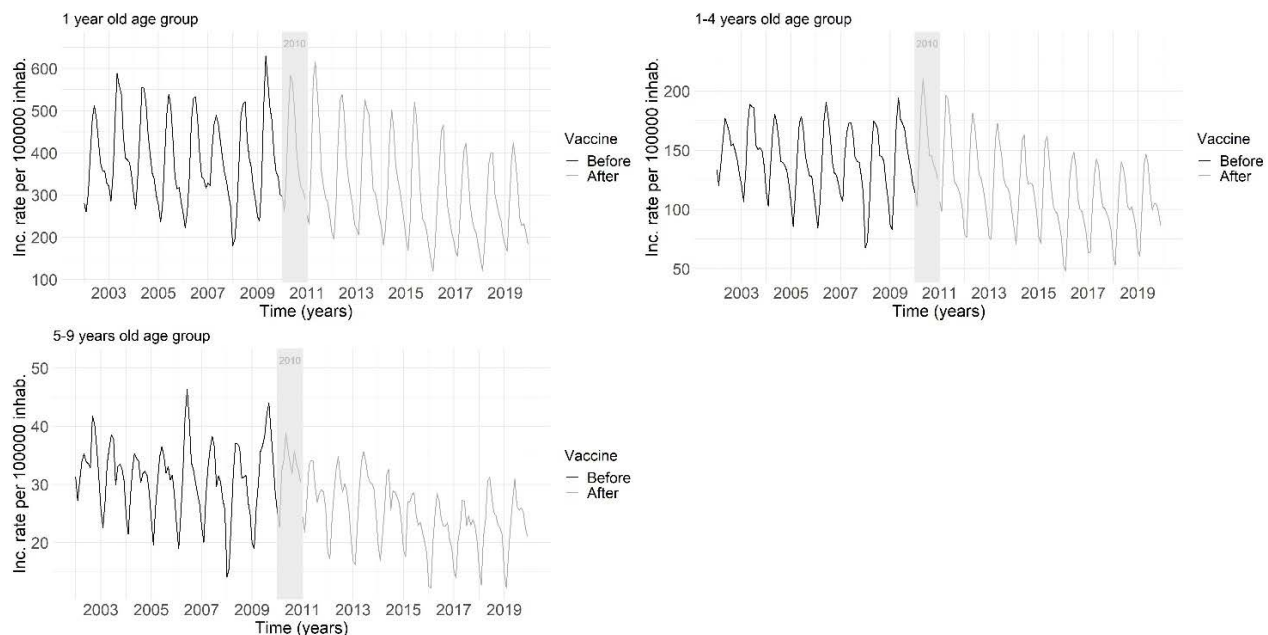

Figure 1: Observed pneumonia incidence hospital admissions over time among the vaccine-eligible population by groups in the period before (2002–2009) and after (2011–2020) the vaccination. The vertical grey bar corresponds to the year of vaccine introduction, 2010.

Among the non-vaccine-eligible population stratum, 2,915,919 and 3,6642,171 pneumonia hospital admissions were observed in all age groups in the pre-and post-vaccine periods, respectively. Incidence in the pre-vaccine period was 12.4, 15.8, 72.9, and 250.0 cases per month per 100,000 inhabitants. The post-vaccine period had a different incidence of 8.1, 12.4, 69.5, and 300.1 cases per month per 100,000 inhabitants for 10–19 years, 20–59 years, 60–79 years, and ≥ 80 years, respectively (Figure 2).
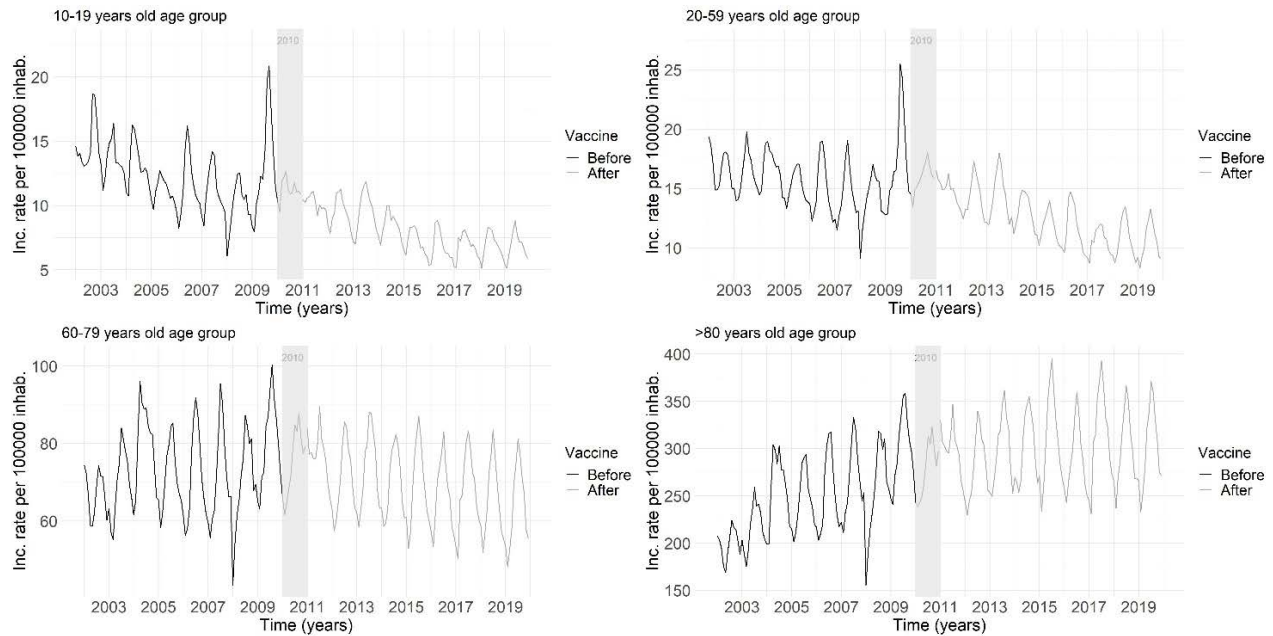

Figure 2: Observed pneumonia incidence hospital admissions over time among the non-vaccine-eligible population by groups in the period before (2002–2009) and after (2011–2020) the vaccination. The vertical grey bar corresponds to the year of vaccine introduction, 2010.

Time series analysis

For all vaccine-eligible population stratum age groups (i.e., up to 9 years old), the post-vaccination period showed a negative trend, reducing 1.75, 0.16, and 0.11 cases per 100,000 inhabitants per month for the groups < 1, 1–4, and 5–9 years old, respectively (Table 2).

Table 2: Slopes for the time trend before and after (interaction) the vaccine estimated in the multivariable time-series regression of pneumonia hospitalizations for all vaccine-eligible population stratum age groups.

	Regression coefficients*			
Age group	$\beta_{time \cdot vaccine=0}$	$\beta_{time \cdot vaccine=1}$	Standard Error	P-value
< 1 year old	0.780	−1.750	0.922	< 0.001
1–4 years old	0.860	−0.160	0.353	< 0.001
5–9 years old	0.055	−0.110	0.088	0.002

*Coefficient is the slope of the regression. i.e., it is the expected variation in the incidence per 100,000 inhabitants per month during the periods before ($\beta_{time \cdot vaccine=0}$) and after ($\beta_{time \cdot vaccine=1}$) the vaccine introduction.

For all non-vaccine-eligible population stratum age groups, the interaction between vaccination and the time trend was significant (p < 0.05), except for the 10–19 years old group, which was in a reducing trend even before the implementation of the vaccine (Table 3). In age groups older than 20 years, the post-vaccination period has a positive trend, but not as great as compared trends before the vaccination period. Thus, the number of cases after vaccination is still increasing, but at a slower rate than before the vaccine inclusion in the NIP.

Table 3: Slopes for the time trend before and after (interaction) the vaccine estimated in the multivariable time-series regression of pneumonia hospitalizations for all non-vaccine-eligible population stratum age groups.

	Regression coefficients*			
Age group	$\beta_{time \cdot vaccine=0}$	$\beta_{time \cdot vaccine=1}$	Standard Error	P-value
10–19 years old	−0.010	0.006	0.028	0.312
20–59 years old	0.147	0.013	0.057	< 0.001
60–79 years old	1.326	0.197	0.501	< 0.001
> 80 years old	4.199	1.366	1.277	< 0.001

*Coefficient is the slope of the regression. i.e., it is the expected variation in the incidence per month per 100,000 inhabitants during the periods before ($\beta_{time \cdot vaccine=0}$) and after ($\beta_{time \cdot vaccine=1}$) the vaccine introduction.

DISCUSSION

We presented a long-term assessment of the universal use of PHiD-CV among vaccinated and non-vaccinated populations, stratified by age, on the incidence of pneumonia-related hospitalizations, excluding the pandemic period. Although the literature correctly describes the positive and protective effects of the PHiD-CV introduction, especially among vaccinated children[12,13,21-23], this study provides strong additional evidence on the direct and herd-sustained effects of PHiD-CV in a NIP, in a nine-years period.

The data we presented is consistent with similar ecologic studies and reinforces the finding of PHiD-CV direct impact. A systematic review and meta-analysis evaluating PHiD-CV and PCV-13 showed the following declines for community-acquired pneumonia hospitalization: 17% for children < 24 months and 9% for those aged from 24 to 59 months[11]. In another systematic review, direct vaccine effectiveness in pneumococcal pneumonia in Latin America varied from 7.4% to 84.6%[24]. In Brazil, a significant impact in children < 12 months, 12–23 months, and 2–4 years old was already reached five years after vaccine implementation, with a significant decrease in the incidence of pneumonia hospitalizations and relative reductions of 13.9%, 22.2%, and 17.6%, respectively[13].

The lack of detectable effects for adolescents is not fully understood[25,26]. A hypothesis is that, as this age group constitutes the healthiest individuals in the population, the herd effect is not significant. The trend of pneumonia hospitalization for adolescents decreased even before 2010, which can be explained by the socioeconomic developments, improving quality of life in Brazil[27]. Our study also describes a significant protective effect in individuals above 20 years old. Although not vaccinated, those age groups benefit from the acquired immunity in younger individuals. Children act as pneumococcal carriers and immunity in early age possibly leads to less exposure and, consequently, lower spread throughout the community via droplets by sneezing or close contact[27-30].

Our study has limitations mostly related to its ecological design. First, there is a possible pneumonia misdiagnosis at admission and the absence of an etiologic diagnosis; however, these limitations do not hamper the observed changes of pre- versus post-vaccination periods. Second, there was no information on clinical conditions, treatment, or outcomes available in the database. Also, the main public health action implemented in Brazil during the study period against pneumonia was the PHiD-CV vaccine Program; HiB vaccination started in 2002, and seasonal influenza vaccination was already routinely offered to high-risk groups.

Secular trends and seasonality could also have biased our findings. However, our results include 18 years of analyses and differences after PHID-CV introduction. These findings are still significant even after adjusting for both secular trends and seasonality, as well as the non-pneumonia respiratory group as a confounder in the multivariate analysis. Moreover, due to the adjusted analysis of a vast 18-years database, we believe that our study provides strong evidence of the protective PHiD-CV impact, despite the aforementioned limitations. This study demonstrates consistent and sustained direct and indirect effects for all age groups with a sustained reduction in the incidence of all-cause pneumonia hospitalization during the nine years of follow-up after vaccine introduction. Our results provide important evidence about the major impact of the pneumococcal conjugate vaccine on public health.

REFERENCES

1. Drijkoningen JJC, Rohde GGU. Pneumococcal infection in adults: burden of disease. *Clin Microbiol Infect*. 2014;20(Suppl 5):45-51.

2. Tricarico S, McNeil HC, Cleary DW, Head MG, Lim V, Yap IKS, et al. Pneumococcal conjugate vaccine implementation in middle-income countries. *Pneumonia (Nathan)*. 2017;9:6.

3. Troeger C, Forouzanfar M, Rao PC, Khalil I, Brown A, Swartz S, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory tract infections in 195 countries: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Infect Dis*. 2017;17(11):1133-61.

4. le Roux DM, Zar HJ. Community-acquired pneumonia in children – a changing spectrum of disease. *Pediatr Radiol*. 2017;47(11):1392-8.

5. Zar HJ, Andronikou S, Nicol MP. Advances in the diagnosis of pneumonia in children. *BMJ*. 2017;358:j2739.

6. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax*. 2012;67(1):71-9.

7. Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. *Bull World Health Organ*. 2008;86(5):408-16.

8. Ministério da Saúde (BR). *Informações de saúde (TABNET Win 3.2)*: morbidade hospitalar do SUS [Internet]. Brasília, DF: Ministério da Saúde; [cited 2023 Jan 16]. Available from: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sih/cnv/niuf.def

9. Wahl B, O'Brien KL, Greenbaum A, Majumder A, Liu L, Chu Y, et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000–15. *Lancet Glob Health*. 2018;6(7):e744-57.

10. Ministério da Saúde (BR). *Informações de saúde (TABNET Win 3.2)*: Imunizações - Cobertura - Brasil [Internet]. Brasília, DF:

Ministério da Saúde (BR). c1994 - [cited 2021 Apr 11]. Available from: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?pni/cnv/cpniuf.def

11. Alicino C, Paganino C, Orsi A, Astengo M, Trucchi C, Icardi G, et al. The impact of 10-valent and 13-valent pneumococcal conjugate vaccines on hospitalization for pneumonia in children: a systematic review and meta-analysis. *Vaccine*. 2017;35(43):5776-85.

12. Scotta MC, Veras TN, Klein PC, Tronco V, Polack FP, Mattiello R, et al. Impact of 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) on childhood pneumonia hospitalizations in Brazil two years after introduction. *Vaccine*. 2014;32(35):4495-9.

13. Andrade AL, Afonso ET, Minamisava R, Bierrenbach AL, Cristo EB, Morais-Neto OL, et al. Direct and indirect impact of 10-valent pneumococcal conjugate vaccine introduction on pneumonia hospitalizations and economic burden in all age-groups in Brazil: a time-series analysis. *PLoS One*. 2017;12(9):e0184204.

14. Friedrich F, Ongaratto R, Scotta MC, Veras TN, Stein RT, Lumertz MS, et al. Early impact of social distancing in response to Coronavirus Disease 2019 on hospitalizations for acute bronchiolitis in infants in Brazil. *Clin Infect Dis*. 2021;72(12):2071-5.

15. Araujo OR, Almeida CG, Lima-Setta F, Prata-Barbosa A, Colleti J Jr. The impact of the novel coronavirus on Brazilian PICUs. *Pediatr Crit Care Med*. 2020;21(12):1059-63.

16. Instituto Brasileiro de Geografia e Estatística. *Projeções da população* [Internet]. Brasília, DF: IBGE. c1980 - [cited 2021 Feb 16]. Available from: https://www.ibge.gov.br/ estatisticas/sociais/populacao/9109-projecao-da-populacao.html?edicao=21830&t=resultados

17. Agência Nacional de Saúde Suplementar. *Dados gerais* [Internet]. Rio de Janeiro: ANS; [cited 2021 Feb 16]. Available from: https://www.ans.gov.br/perfil-do-setor/dados-gerais

18. Keele L, Kelly NJ. Dynamic models for dynamic theories: the ins and outs of lagged dependent variables. *Polit Anal*. 2006;14(2):186-205.

19. Zeileis A. *dynlm*: Dynamic Linear Regression [Internet]. [place unknown]: CRAN R; 2019 [cited 2021 Feb 16]. Available from: https://CRAN.R-project.org/package=dynlm

20. R Core Team. *R*: A language and environment for statistical computing [Internet]. Vienna: R Foundation for Statistical Computing; 2020 [cited 2021 Feb 16]. Available from: https://www.r-project.org/.

21. Hortal M, Estevan M, Meny M, Iraola I, Laurani H. Impact of pneumococcal conjugate vaccines on the incidence of pneumonia in hospitalized children after five years of its introduction in Uruguay. *PLoS One*. 2014;9(6):e98567.

22. Izu A, Solomon F, Nzenze SA, Mudau A, Zell E, O'Brien KL, et al. Pneumococcal conjugate vaccines and hospitalization of children for pneumonia: a time-series analysis, South Africa, 2006–2014. *Bull World Health Organ*. 2017;95(9):618-28.

23. Jayasinghe S, Menzies R, Chiu C, Toms C, Blyth CC, Krause V, et al. Long-term impact of a "3 + 0" schedule for 7- and 13-valent pneumococcal conjugate vaccines on invasive pneumococcal disease in Australia, 2002-2014. *Clin Infect Dis*. 2017;64(2):175-83.

24. Oliveira LH, Camacho LAB, Coutinho ESF, Martinez-Silveira MS, Carvalho AF, Ruiz-Matus C, et al. Impact and effectiveness of 10 and 13-valent pneumococcal conjugate vaccines on hospitalization and mortality in children aged less than 5 years in Latin American countries: a systematic review. *PLoS One*. 2016;11(12):e0166736.

25. Griffin MR, Zhu Y, Moore MR, Whitney CG, Grijalva CG. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *N Engl J Med*. 2013;369(2):155-63.

26. Richter L, Schmid D, Kanitz EE, Zwazl I, Pöllabauer E, Jasinska J, et al. Invasive pneumococcal diseases in children and adults before and after introduction of the 10-valent pneumococcal conjugate vaccine into the Austrian national immunization program. *PLoS One*. 2019;14(1):e0210081.

27. Schuck-Paim C, Taylor RJ, Alonso WJ, Weinberger DM, Simonsen L. Effect of pneumococcal conjugate vaccine introduction on childhood pneumonia mortality in Brazil: a retrospective observational study. *Lancet Glob Health*. 2019;7(2):e249-56.

28. Kislaya I, Rodrigues AP, Sousa-Uva M, Gómez V, Gonçalves P, Froes F, et al. Indirect effect of 7-valent and 13-valent pneumococcal conjugated vaccines on pneumococcal pneumonia hospitalizations in elderly. *PLoS One*. 2019;14(1):e0209428.

29. Vadlamudi NK, Chen A, Marra F. Impact of 13-pneumococcal conjugate vaccine among adults: a systematic review and meta-analysis. *Clin Infect Dis*. 2019;69(1):34-49.

30. Tsaban G, Ben-Shimol S. Indirect (herd) protection, following pneumococcal conjugated vaccines introduction: a systematic review of the literature. *Vaccine*. 2017;35(22):2882-91.