Evaluation of the Impact of a Single-Dose Hepatitis A Vaccination Program in Brazil: An Interrupted Time-Series Analysis

Bierrenbach AL[1], Choi Y[2], Batista PM[3], Serra FB[3], Parellada CI[3], Julian GS[4], Nakajima K[4], Moreira TNF[3]

[1]Instituto de Ensino e Pesquisa, Hospital Sírio-Libanês, São Paulo, SP, Brazil; [2]Merck & Co., Inc., Kenilworth, NJ, USA; [3]MSD Brazil, São Paulo, SP, Brazil; [4]IQVIA Brazil, São Paulo, SP, Brazil

Background

- A single-dose hepatitis A (hepA) vaccine (MSD) was introduced in the Brazilian National Immunization Program (NIP) for children aged 12-24 months in 2014 and extended to <5 years in 2017.[1-2] At a country level, the vaccination coverage in 2016, 2017, and 2018 was 71.6%, 78.5%, and 82.7%, respectively[3]

- The government's decision for HepA introduction was based on national epidemiological data showing that most cases occurred in children under 13 years old and the adoption of a single-dose schedule was due to competitive NIP fund allocation.[1] The overall incidence rate of hepA in Brazil has shown a downward trend, from 9.1/100,000 inhabitants in 2004 to 3.1/100,000 inhabitants in 2013
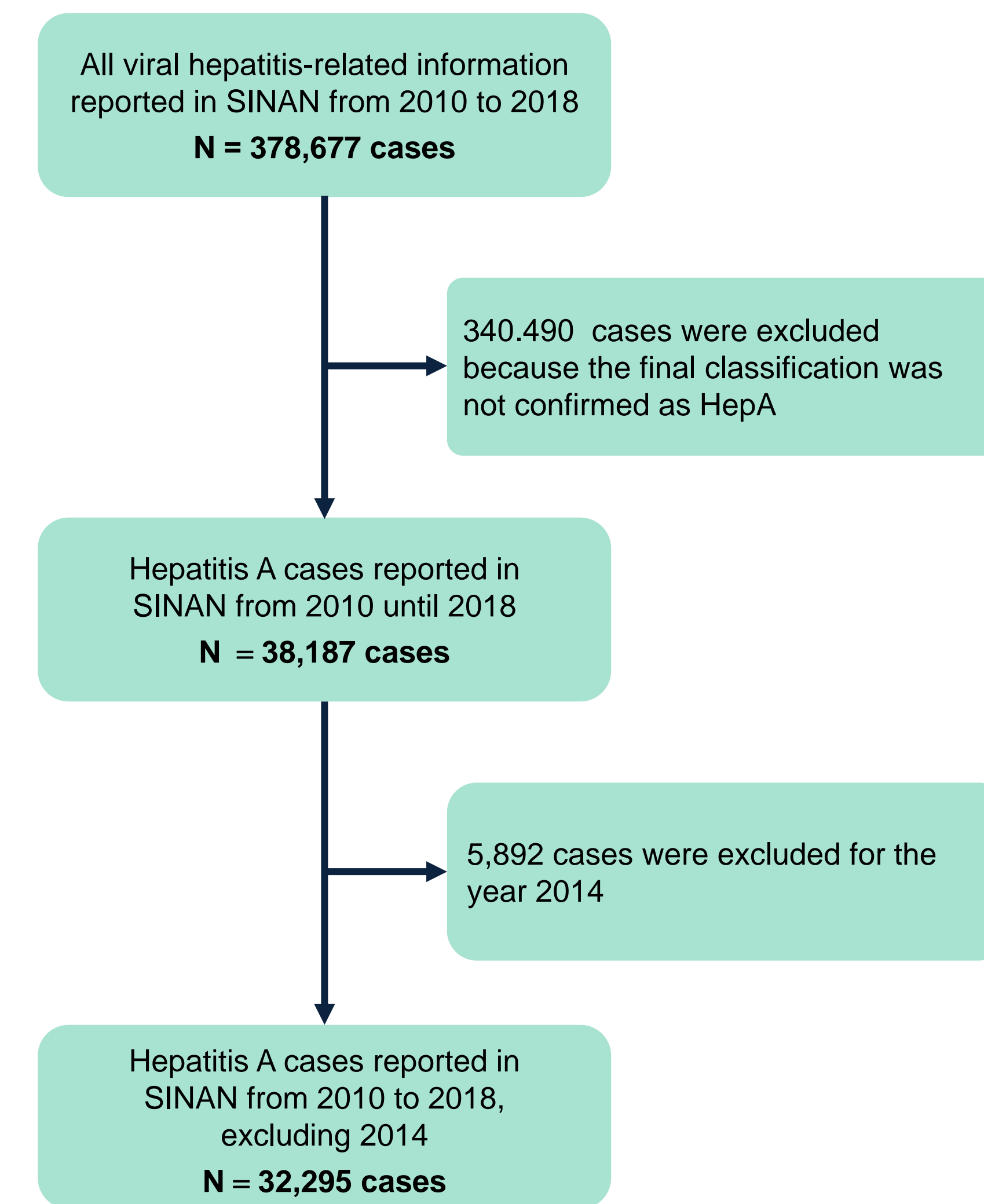
Objectives

- Primary objective: To assess the impact of universal hepA vaccination in children on hepA incidence in the population

- Secondary objective: To document healthcare resource utilization (HCRU) and costs associated with hepA outpatient procedures and hospitalization during the prevaccination (2010-2013) and postvaccination (2015-2018) periods

Methods

- We compared the incidence of hepA in the pre and postvaccination periods using case data from the Brazilian National Public Health Database (DATASUS) between January 2010 and December 2018

- For incidence rate evaluation, all confirmed hepA cases reported in the Brazilian National Epidemiologic Surveillance System (SINAN) were collected, and the case definition comprised individuals with positive IgM anti-HAV or detected HAV RNA or who met the clinical criteria and occurred in a person who had contact with laboratory-confirmed hepA prior to onset of symptoms (Figure 1)

- For the HCRU, all outpatient procedures and hospitalizations related to the ICD-10 codes B15, B15.0, and B15.9 were assessed from the outpatient information system (SIA) and inpatient information system (SIH), respectively

- For the interrupted time-series analysis, a generalized negative binomial linear model with linked logarithmic function was used to predict counterfactual hepA cases. To convert the monthly cases of hepA into a rate, the logarithmic function of the population divided by 100,000 was included as an offset variable, adjusting for any potential changes in the population over time. Data from the transition period (2014) were excluded

- The vaccination effect on hepA incidence rates was calculated per year after exponentiation of model coefficients (slope change) of both prevaccination (trend without vaccination effect) and postvaccination (trend with vaccination effect) periods. The immediate effect was the level change observed immediately after vaccine introduction

- The vaccine impact was assessed as the level change and as the counterfactual comparison with the prevaccination trend. A simulation bootstrap with 1,000 replications was used to estimate the total number of averted hepA cases, represented as median and percentiles 2.5% and 97.5%

- A descriptive analysis was performed to assess HCRU and related costs. The costs were converted from the local currency (Brazilian reais) to US dollars (exchange rate on August 24, 2020: 1 US$=5.59 reais)[4]

Figure 1. Sample Selection

All viral hepatitis-related information reported in SINAN from 2010 to 2018
N = 378,677 cases

340.490 cases were excluded because the final classification was not confirmed as HepA

Hepatitis A cases reported in SINAN from 2010 until 2018
N = 38,187 cases

5,892 cases were excluded for the year 2014

Hepatitis A cases reported in SINAN from 2010 to 2018, excluding 2014
N = 32,295 cases

Results

- Between 2010 and 2018 (excluding 2014), 32,295 hepA cases occurred across all ages
  - Among the NIP target children aged 1-4 years, hepA vaccination was associated with a level change reduction of 52.5% in cases (P<0.001) and a decrease in slope (-7.7% vs -67.6% per year for pre and post vaccination periods, respectively; Figure 2)
  - A similar trend was observed in non-target NIP children aged 5-14 years old, with a level change reduction of 57.1% in cases (P<0.001) and a decrease in slope (-3.4% vs -53.7% per year for pre and postvaccination periods, respectively)

- We observed a level change reduction of 62.7% (P<0.001) and 43.3% (P<0.001) in groups of 15-39 years old and ≥40 years old, respectively. However, there was an increase change in slope in the post-vaccination period (17.4% and 9.5% per year, respectively)

- Across all age groups, 14,468 hepA cases were averted when compared to predicted counterfactual rates (Table 1)

- Overall, the hepA-related hospitalization rate dropped 64% after vaccine introduction, resulting in a cost reduction of 55%. The total number of outpatient procedures claimed among hepA-diagnosed patients dropped 18%, with 42% cost reduction (Table 2)

Figure 2. Time-Series Analyses of Hepatitis A Incidence Rate (IR).
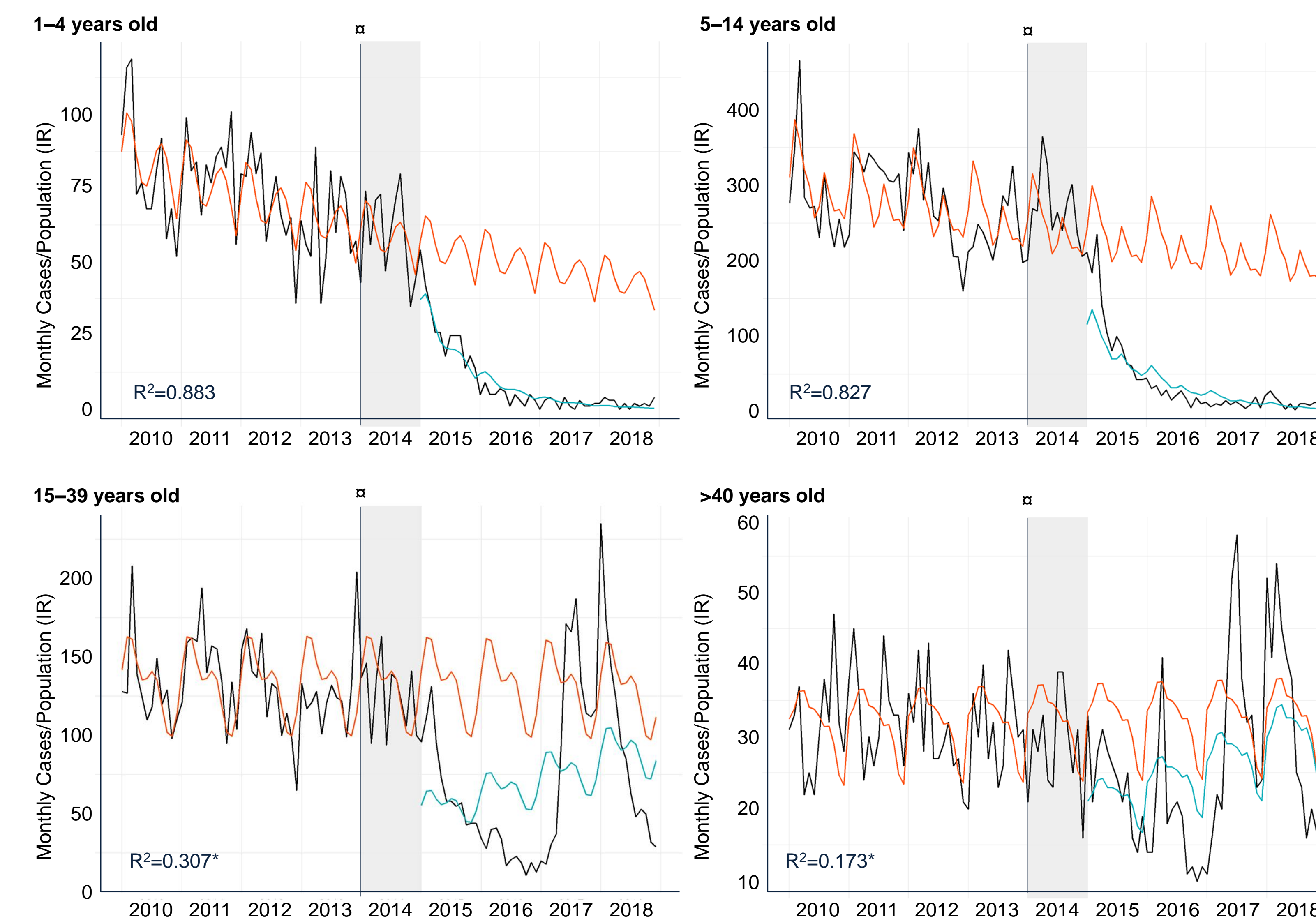
*Model affected by outbreak.
¤Year of hep A vaccine introduction in childhood NIP

— Monthly number of hepA cases observed over the study period
— Predicted trend based on pre-hepA vaccination monthly cases
— Predicted trend based on post-hepA vaccination monthly cases

Table 1. Number of Observed, Predicted Counterfactual, and Averted Hepatitis A Cases in the Post-hepA Vaccination Period (2015-2018), According to Age Group

Age Groups	Observed	Predicted Counterfactual	Averted Cases Media	Averted Cases Percentiles (2.5%-97.5%)
<12 months	88	404	316	288; 336
1-4 years old	423	2,375	1,952	1,855; 2,023
5-14 years old	1,925	10,427	8,502	8.062;.8,857
15-39 years old	3,495	6,302	2,807	2,488; 3,025
≥40 years old	1,255	1,575	320	262; 371
Total	7,186	21,654	14,468	13,395; 15,138

Table 2. Descriptive Comparison of Overall Healthcare Resource Utilization and Costs Between Pre- (2010-2013) and Post-hepA Vaccination Periods (2015-2018)

Healthcare Resource	Pre-hepA Vaccination	Post-hepA Vaccination	% Change
Hospitalization rate[a]	0.071	0.026	-64%
Hospitalization cost	$289,173.46	$130,677.16	-55%
Number of outpatient procedures	1,894	1,551	-18%
Outpatient procedure costs	$7,599.06	$4,372.52	-42%

[a]Hospitalization rate per 10,000 inhabitants

Discussion

- This is the first study that considered the baseline downward trend observed in the prevaccination period in Brazil on hepA

- The counterfactual comparison with the postvaccination trend was significantly different for children under 14 years old (P<0.001). Considering both groups of 15-39 years old and ≥40 years old, we observed a level change reduction of 62.7% (P<0.001) and 43.3% (P<0.001), respectively. However, there was an increase change in slope in the postvaccination period (17.4% and 9.5% per year, respectively)

- The increased number of cases observed in older age groups was associated with the 2017-2018 outbreak in the Southeast region. Based on local epidemiological reports, this sudden increase in hepA cases was associated with the men who have sex with men (MSM) population, who are not eligible in the Brazilian NIP to receive the vaccine. Even though this outbreak episode minimized the impact of the universal childhood immunization program against hepA, there was a significant reduction in hepA cases associated with the vaccine

- Regarding HCRU, in the postvaccination period, there were no cases of fulminant hepatitis in the target population for vaccination. This was also reflected in the reduction of hepA-related HCRU and costs, showing a positive economic burden reduction

Limitations

This study has some limitations related to the database used for data extraction:

- The incidence rate of hepA may be underestimated, as it was calculated considering only the cases notified by SINAN

- Since the outpatient and inpatient information systems are intended for billing purposes, ascertainment of outcome may not be complete. For example, low complexity procedures related to hepA infection may not be billed, resulting in outcome misclassification. If this outcome misclassification is pronounced in the pre-vaccination period, the impact of NIP can be under-estimated

Conclusion

- In Brazil, the single-dose hepA vaccine universal childhood program effectively reduced hepA incidence, HCRU, and associated costs in vaccinated and in some nonvaccinated age groups. This trend should continue to be monitored over time.

References

1. Brazil Ministry of Health. Informe técnico da Introdução da vacina adsorvida hepatite A (inativada). Brasília, June 2014. Available from: http://www.saude.gov.br/images/pdf/2015/junho/26/Informe-t--cnico-vacina-hepatite-A-junho-2014.pdf

2. Brazil Ministry of Health. Manual dos centros de Referência para imonobiológicos especiais, 5th edition. Brasília, 2019. Available from: https://sbim.org.br/images/calendarios/manual-centros-referencia_imunobiologicos-especiais-5ed-web.pdf´

3. Programa Nacional de Imunização. Available from: https://http://tabnet.datasus.gov.br/cgi/tabcgi.exe?pni/cnv/DPniuf.defhttp://tabnet.datasus.gov.br/cgi/tabcgi.exe?pni/cnv/DPniuf.def

4. Banco Central do Brasil. Conversão de moedas. Available from: https://www.bcb.gov.br/estabilidadefinanceira/historicocotacoes

https://bit.ly/3aBgx7j