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Universal hepatitis A vaccination in Brazil: analysis of vaccination coverage and incidence five years after program implementation

Vacinação universal contra hepatite A no Brasil: análise da cobertura vacinal e da incidência cinco anos após a implantação do programa

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ABSTRACT: *Introduction:* In 2014, Brazil introduced a universal immunization program against the hepatitis A virus (HAV) for children in the second year of life, using a single dose of inactivated virus vaccine. The objective of this study was to evaluate the vaccination coverage (VC) against HAV in Brazil, against the incidence of cases reported five years after the implementation of the program. *Methodology:* Secondary data were obtained by searching free access electronic sites of the Ministry of Health, Department of Informatics of the Unified Health System (*Departamento de Informática do Sistema Único de Saúde* – DATASUS), for incidence analysis and VC from 2014 to 2018. *Results:* VC ranged from 60.13 to 97.07%. The homogeneity of VC against hepatitis A did not reach the established goal throughout all states but for a few exceptions. After 2015, CV decreased in all regions of the country. Despite insufficient coverage, a concomitant reduction in the incidence of Hepatitis A took place throughout the country. The incidence rate fell from 3.29 to 0.80/100,000 between 2014 and 2018. However, there was an interruption in the pace of incidence fall between 2017 and 2018, which may be a consequence of insufficient VC. This phenomenon seems to be part of a widespread downward trend in vaccination effort across the country, also verified for other vaccines, such as poliomyelitis and measles, mumps and rubella vaccine. *Conclusion:* These figures suggest the need for implementing efforts to improve hepatitis A VC rates in the country.

Keywords: Hepatitis A. Incidence. Hepatitis A vaccine. Vaccination coverage.

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RESUMO: *Introdução:* Em 2014, o Brasil introduziu programa de imunização universal contra o vírus da hepatite A (HAV) para crianças no segundo ano de vida, por meio de dose única da vacina de vírus inativado. Este estudo teve como objetivo avaliar a cobertura vacinal (CV) contra o HAV no Brasil, diante da incidência de casos notificados cinco anos após a implantação do programa. *Metodologia:* Dados secundários foram obtidos pesquisando-se sítios eletrônicos de acesso livre do Ministério da Saúde, Departamento de Informática do Sistema Único de Saúde (DATASUS), para análise de incidência e CV. *Resultados:* A CV variou entre 60,13 e 97,07%. A homogeneidade da CV contra hepatite A nos estados ficou aquém da meta estabelecida. Após 2015, houve queda da CV em todas as regiões do país. Apesar da cobertura insuficiente, houve redução concomitante da incidência da hepatite A em todo o Brasil. A taxa de incidência caiu de 3,29 para 0,80/100 mil entre 2014 e 2018. No entanto, ocorreu diminuição da velocidade de queda da incidência entre 2017 e 2018, o que pode ser consequência dos percentuais insuficientes de CV. Esse fenômeno parece acompanhar tendência geral de enfraquecimento do esforço vacinal no país, verificado também para outras vacinas, como poliomielite e tríplice viral. *Conclusão:* Esses números sugerem a necessidade de esforços para melhorar as taxas de CV da hepatite A no país.

Palavras-chave: Hepatite A. Incidência. Vacina contra hepatite A. Cobertura vacinal.

INTRODUCTION

Hepatitis A is an acute viral infection with fecal-oral transmission prevalent worldwide, especially in countries with poor economic and sanitary conditions¹. The infection is usually asymptomatic or mild in childhood, rarely some cases can progress to acute liver failure and death².

In countries with better sanitary conditions, exposure to the hepatitis A virus (HAV) is less frequent, affecting people later in life¹. In Brazil, as in other emerging countries, a decrease in endemic levels of HAV infection has been demonstrated, attributable to the increasing urbanization of the population and to improvements in basic sanitation in the largest urban centers since the end of the last century, especially in the south-southeast of the country³. A population-based survey on seroprevalence of HAV infection, carried out between 2004 and 2009, involving individuals aged 5 to 19 years, living in the 27 Brazilian capitals, showed that the country had areas of intermediate (North, Northeast, Midwest, and Federal District) and low endemicity (Southeast and South)⁴.

In addition to improving health conditions, universal vaccination of children is an important tool to control the circulation of HAV and to decrease the incidence of the disease. HAV immunogens have been available since the 1990s, with the monovalent inactivated virus vaccine being the most widely used. Two doses are recommended, with the second application between 6 and 18 months after the first one, however the vaccine is very expensive, limiting its large-scale implementation to countries with better economic conditions^{5,6}.

Countries that have instituted mass vaccination against HAV (Argentina, Belgium, China, Greece, Israel, Panama, the United States, and Uruguay) have seen a marked reduction in the incidence of the disease. The declines occurred regardless of the vaccine brand used in the programs, the number of doses administered, the target age at the first vaccination, which ranged from 12 to 24 months, or the vaccination coverage achieved (range from 25 to 96.8%). After their introduction, the percentage reduction in the incidence of the conditions was 88% in Argentina, > 95% in Israel, 93% in Panama, and 96% in Uruguay⁵.

In 2005, Argentina was the first country to apply the monovalent HAV inactivated virus vaccine to the children's vaccination calendar, with a single-dose schedule, for 12-month-old children. The single-dose scheme was a way to reduce costs. This decision was adopted in studies with high humoral response rates after the first dose of the vaccine^{7,8}. The World Health Organization (WHO), based on experiences like this, recommends that countries with less financial resources considered to adopt the alternative single-dose scheme⁹.

In 2014, the National Immunization Program (*Departamento de Informática do Sistema Único de Saúde* – PNI), of the Brazilian Ministry of Health (*Ministério da Saúde* – MS), implemented a vaccination program against hepatitis A similar to the Argentinian one, providing a single dose of the inactivated virus monovalent vaccine. Vaccination started in the second half of 2014. At that time, the target was children between 15 and 24 months of life. In 2017, the PNI expanded vaccination for children under five years of age, to reach those who were not vaccinated at the beginning of the program^{6,10}.

The single dose regimen of the monovalent HAV inactivated virus vaccine may be the solution for many developing countries^{5,9}. There is already evidence that children vaccinated by the national program achieve a high rate of seroconversion with just one dose¹¹, although it is extremely important to evaluate the programs that adopted this vaccine scheme^{5,6}.

In addition to epidemiological analyzes of incidence, the evaluation of immunization programs is also carried out by monitoring vaccination coverage (VC). These indicators represent an important tool for operational and impact assessment on immunization programs ^{12,13}.

Knowledge of the extent of VC in children is of paramount importance for epidemiological surveillance actions, as it allows the identification of the portion of individuals susceptible to immune-preventable diseases, in addition to improving the strategies of mass immunity as an effective barrier to stop their transmission¹².

The VC is measured by the percentage of individuals vaccinated and calculated for each type of vaccine, according to a specific geographic space, target population, and year considered. Mostly, the target population used to calculate infant vaccination coverage takes into account the number of live births, obtained from the Live Birth Information System (*Sistema de Informação Sobre Nascidos Vivos* – SINASC). The goals of VC are established according to the target population and scheme of each vaccine. For inactivated hepatitis A vaccine, vaccination of > 95% of the target population (one year old children) is considered adequate^{12,13}.

VC, in addition to being adequate, needs to be homogeneous. Homogeneity is an indicator of efficiency and performance of the PNI and is characterized by obtaining rates of

70% or more of the municipalities of a state, which managed to reach the VC target for a given vaccine^{12,13}.

Thus, in order to assess hepatitis A vaccination coverage in Brazil and its relationship with the incidence of new cases reported, a retrospective analysis of these indicators was carried out five years after the program was implemented (2014 to 2018).

METHODS

The VC data, already calculated and available in percentages, were obtained from the official website of the MS on April 20th, 2019¹⁴.

The tabulation covered the national scope, filtering the data by region, states and municipalities¹⁴. The extracted information was exported to Excel files (version 2013) to be later analyzed. The data update on the website dates back to April 10th, 2019.

Following the PNI analysis parameters, the VC results in regions and states were grouped into: up to < 49.99%; between 49.99 and 94.99%, and > 94.99%.

As for homogeneity, the results were described according to the parameter of 70% or more of the municipalities of the states with adequate VC^{13} .

The number of new confirmed cases of hepatitis A was extracted from the Notifiable Diseases Information System (*Sistema de Informação de Agravos de Notificações* – SINAN), available on the website of the Informatics Department of the Unified Health System (*Departamento de Informática do Sistema Único de Saúde* – DATASUS)¹⁶. The tabulation covered information between 2014 and 2018 by region and state. After the tabulation, the numbers were exported to an Excel file (2013 version) for performing incidence rate calculations. The rate was calculated by the number of new confirmed cases of hepatitis A, according to laboratory criteria (Anti-HAV IgM reagent) or epidemiological clinic, per year of notification and place of residence divided by the total population of the same year and the same place, the result multiplied by 100,000.

The number used in the denominator to calculate the incidence rate was based on population estimates from the Brazilian Institute of Geography and Statistics (*Instituto Brasileiro de Geografia e Estatística* – IBGE), available on the DATASUS website¹⁷.

RESULTS

In Brazil, from August 2014 to December 2018, a total of 11,397,607 children under 2 years of age were vaccinated with a single dose of the inactivated virus vaccine against monovalent HAV (Vaqta™ Ped/Adol, Merck Sharp & Dohme — approximately 25 U of HAV antigen).

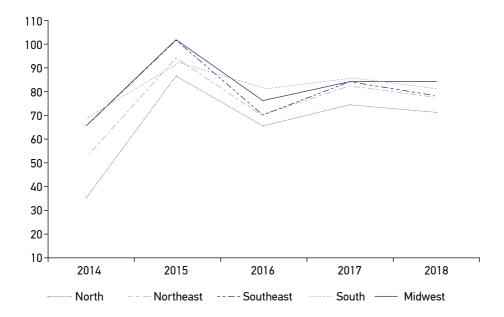
The VC of the inactivated hepatitis A vaccine in Brazil varied between 60.13 and 97.07%, in the observed period. In 2014, there was a higher VC in the South Region (70.72%),

followed by the Southeast Region (66.90%). The lowest coverage was in the North Region (36.25%). In 2015, VC was between 86.67 and 101.63%. From 2016 to 2018, the average VC in the regions did not exceed 87% (Figure 1).

When considering states, in 2014, seven states had VC of up to 49.99% (Acre, Amazonas, Pará, Amapá, Maranhão, Rio Grande do Norte, and Paraíba). The other 19 states, as well as the Federal District, had VC between 49.99 and 94.99%. In 2015, the Federal District and 11 states had VC between 49.99 and 94.99%, and the other 15 states had VC above 94.99% (Rondônia, Amazonas, Roraima, Ceará, Pernambuco, Alagoas, Sergipe, Minas Gerais, Rio de Janeiro, São Paulo, Paraná, Santa Catarina, Rio Grande do Sul, Mato Grosso do Sul, and Mato Grosso). In 2016, the 26 Brazilian states registered VC between 49.99 and 94.99%. Only the Federal District recorded VC above 94.99%. In 2017, all states had VC between 49.99 and 94.99%, with the exception of Ceará, which had VC above 94.99%. In 2018, all states registered VC between 49.99 and 94.99% (Table 1).

The homogeneity of hepatitis A CV in Brazil varied between 14.04 and 62.30%. In the years 2014, 2016, and 2018, no state reached the percentage of \geq 70%. In 2015, six states reached \geq 70%: Espírito Santo, Mato Grosso do Sul, Minas Gerais, Paraná, Rondônia, and São Paulo. In 2017, only Ceará reached the target of \geq 70%.

The incidence rate of hepatitis A in Brazil, during the period evaluated, varied between 3.29 and 0.47 cases per 100,000 inhabitants. In the same period, this rate was between 17.18



^{*}Expressed as a percentage and calculated by the number of doses applied to children aged one year old, in the year and region evaluated, divided by the population of live births from the previous year in the same place.

Figure 1. Vaccination coverage* against hepatitis A according to the regions of Brazil, 2014–2018.

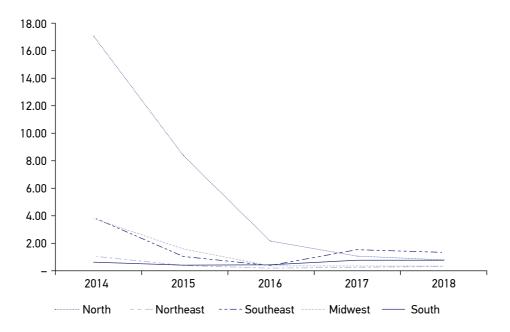
Table 1. Hepatitis A vaccination coverage* according to the Brazilian states, 2014 to 2018.

State (abbreviation)	2014	2015	2016	2017	2018	
Acre (AC)	11.52	73.22	60.42	69.47	74.81	
Alagoas (AL)	52.93	98.05	72.88	91.37	85.92	
Amapá (AP)	38.02	88.47	87.09	69.18	68.82	
Amazonas (AM)	44.12	97.74	68.07	79.92	77.37	
Bahia (BA)	61.83	94.42	60.53	76.15	69.15	
Ceará (CE)	57.84	102.26	94.11	96.24	88.94	
Distrito Federal (DF)	82.97	74.69	107.07	90.03	83.12	
Espírito Santo (ES)	82.99	94.01	78.1	77.95	86.4	
Goiás (GO)	69.18	90.65	72.3	84.59	80.19	
Maranhão (MA)	43.49	91.82	56.54	71.69	66.56	
Mato Grosso (MT)	58.67	99.49	78.33	86.00	78.14	
Mato Grosso do Sul (MS)	76.16	112.53	83.15	88.69	82.94	
Minas Gerais (MG)	66.23	100.35	79.07	88.56	87.77	
Pará (PA)	24.11	73.83	55.85	66.97	63.43	
Paraíba (PB)	42.16	83.36	74.95	87.97	79.88	
Paraná (PR)	61.57	105.64	75.43	89.82	87.33	
Pernambuco (PE)	54.97	96.59	76.36	85.68	80.86	
Piauí (PI)	52.87	87.08	60.31	80.24	73.48	
Rio de Janeiro (RJ)	61.25	99.65	77.94	89.35	69.65	
Rio Grande do Norte (RN)	41.17	87.97	63.17	66.77	73.71	
Rio Grande do Sul (RS)	63.89	96.25	72.74	81.59	82.33	
Rondônia (RO)	67.33	116.26	84.04	87.34	80.46	
Roraima (RR)	52.93	98.21	72.93	90.23	79.23	
Santa Catarina (SC)	78.23	103.16	84.03	83.32	82.67	
São Paulo (SP)	67.84	102.42	63.43	80.13	70.19	
Sergipe (SE)	60.08	95.57	68.47	80.8	81.59	
Tocantins (T0)	54.73	94.52	75.63	87.63	78.47	
BRASIL (BR)	60.13	97.07	71.58	82.7	76.72	

^{*}Expressed as a percentage and calculated by the number of doses applied to children aged one year old, in the year and region evaluated, divided by the population of live births from the previous year in the same place. Source¹⁴

and 0.20/100,000 inhabitants, when considering the five Brazilian macro-regions. In 2014 there was a higher incidence in the North Region (17.18/100,000) and lower in the South Region (0.64/100,000). In 2015, once more the highest incidence (8.58/100,000) was in the North and the lowest in the South Region (0.52/100,000). In 2016, there was a higher incidence in the North Region (2.17/100,000) and lower in the Southeast (0.22/100,000). In 2017, the Southeast Region recorded the highest incidence (1.58/100,000) and the Northeast the lowest (0.28/100,000). As for 2018, the situation was repeated, with the Southeast presenting the highest incidence (1.30/100,000) and the Northeast the lowest (0.20/100,000) (Figure 2).

Regarding incidence, when observed according to state, there is a variation over the years analyzed (Table 2). In 2014, higher incidence was found in the states of Amapá (52.74/100,000), followed by Acre (27.46/100,000), Amazonas (26.74), Roraima (25.96/100,000), and Tocantins (18.24/100,000). In 2015 Amapá had an incidence of 26.22/100,000, Tocantins of 18.68/100,000, Acre of 12.07/100,000, Amazonas of 8.61/100,000, and Roraima of 8.50/100,000. In 2016, only three states had an incidence above 3.00/100,000 inhabitants: Acre (8.82/100,000), Amapá (4.86/100,000), and Roraima (3.50/100,000). In 2017, the states of Acre, Amapá, São Paulo, and Roraima recorded the highest incidences: 4.46/100,000, 4.39/100,000, 2.35/100,000 and 1.72/100,000, respectively. In 2018, high incidences were observed in Roraima (3.82/100,000), Rio de Janeiro (2.53/100,000), Acre (1.61/100,000), Amapá (1.45/100,000), and São Paulo (1.31/100,000).



*Cases of hepatitis A confirmed according to laboratory (Anti-HAV IgM reagent) or clinical epidemiological criteria. Source^{16,17}

Figure 2. Incidence rate per 100,000 inhabitants of confirmed cases of hepatitis A*, according to region of residence by year of notification, Brazil, 2014–2018.

Table 2. Confirmed cases and incidence rate of hepatitis A* according to the state of residence and year of notification, Brazil, 2014–2018.

Abbreviation	າ 2014		2015		2016		2017		2018	
State	n	IR	n	IR	n	IR	n	IR	n	IR
AC	217	27.46	97	12.07	72	8.82	37	4.46	14	1.61
AL	157	4.73	115	3.44	37	1.10	18	0.53	4	0.12
AP	396	52.74	201	26.22	38	4.86	35	4.39	12	1.45
AM	1,036	26.74	339	8.61	66	1.65	48	1.18	15	0.37
BA	490	3.24	124	0.82	44	0.29	37	0.24	26	0.18
CE	117	1.32	48	0.54	15	0.17	18	0.20	19	0.21
DF	61	2.14	32	1.10	14	0.47	13	0.43	6	0.20
ES	14	0.36	3	0.08	8	0.20	5	0.12	6	0.15
GO	72	1.10	28	0.42	13	0.19	21	0.31	14	0.20
MA	283	4.13	160	2.32	43	0.62	28	0.40	14	0.20
MT	335	10.39	149	4.56	36	1.09	16	0.48	33	0.96
MS	115	4.39	32	1.21	8	0.30	8	0.29	6	0.22
MG	132	0.64	132	0.63	79	0.38	108	0.51	103	0.49
PA	787	9.71	474	5.78	146	1.76	50	0.60	53	0.62
PB	304	7.71	59	1.49	7	0.18	15	0.37	8	0.20
PR	38	0.34	83	0.74	42	0.37	75	0.66	42	0.37
PE	559	6.03	73	0.78	37	0.39	17	0.18	15	0.16
PI	91	2.85	29	0.91	20	0.62	8	0.25	12	0.37
RJ	420	2.55	170	1.03	22	0.13	205	1.23	434	2.53
RN	54	1.58	9	0.26	7	0.20	10	0.29	15	0.43
RS	100	0.89	40	0.36	52	0.46	62	0.55	139	1.23
RO	122	6.98	63	3.56	20	1.12	6	0.33	23	1.31
RR	129	25.96	43	8.50	18	3.50	9	1.72	22	3.82
SC	48	0.71	30	0.44	16	0.23	47	0.67	39	0.55
SP	245	0.56	170	0.38	84	0.19	1,060	2.35	596	1.31
SE	72	3.24	15	0.67	6	0.26	7	0.31	2	0.09
ТО	273	18.24	283	18.68	24	1.57	9	0.58	6	0.39
BR	6,667	3.29	3,001	1.47	974	0.47	1,972	0.95	1,678	0.80

IR: incidence rate per 100,000 inhabitants Source^{16,17}

DISCUSSION

Until 2014, vaccination against hepatitis A in Brazil, by the Unified Health System (*Sistema Único de Saúde* – SUS), was only available to individuals at greater risk of developing severe forms of the disease, such as: people with chronic liver disease, carriers of hepatitis B or C virus, individuals with coagulopathies, children under 13 years of age with HIV/AIDS, people with immunosuppression, among others¹⁸.

In the year of universal children vaccination implementation, VC was found to be low across the country (60.13%). No state had a VC above that recommended by the MS, possibly because the vaccination started in the second half of 2014 and aimed to reach children born between 2012 and 2013, according to the vaccination schedule at the time. Therefore, the low coverage can be explained by the lack of time to vaccinate the target population. To compensate this coverage gap in 2014, it was decided to extend vaccination in 2017 to children under five, in an attempt to recover (catch-up) the unvaccinated cohorts from 2013¹⁰.

In 2015, Brazil presented an expressive VC, exceeding the established target of \geq 95%. The vaccination of part of the eligible ones not reached in the previous year should explain this good performance. In subsequent years, the VC decreased in all regions and in most states. The drop in VC was not an exclusive phenomenon of the inactivated hepatitis A vaccine, extending to practically all vaccines in the childhood vaccination schedule (MMR, poliomyelitis, hepatitis B, rotavirus, and others)^{15,19}, a fact that reinforces the need to intensify health education strategies, providing adequate information to the population, especially regarding the benefits of vaccination.

According to the MS, the success of the immunization actions caused a false feeling that there is no longer a need for vaccination¹⁵. In addition, the drop in vaccination may be related to the period of operation of primary health care facilities, incompatible with the routines of mothers or those responsible for taking children to vaccinate, thus making access to the immunization service rather difficult¹⁵.

Studies also explain that the drop in children's VC may be related to vaccination hesitation. Hesitating individuals are located between two extremes and are heterogeneous groups: some accept only some vaccines and others deliberately delay them, not accepting the recommended vaccination schedule. To a lesser extent, there are those who refuse only a few vaccines and those who still have doubts about the benefits and risks of the vaccine. Vaccination hesitation has been consolidated as one of the main concerns of Brazilian health authorities^{20,21}.

Another important aspect that may have influenced the reduction of VC in Brazil was the change of the PNI information system in 2014. The system that was previously fed according to the doses applied, was from then on based on nominal register, being fed in the vaccination rooms of the municipalities. The new system, called SI-PNI, in addition to equipment and logistics, depends on trained personnel to be fed. Information such as full name, address, telephone number, type of vaccine applied, etc. is required, which makes the process more complex and requires more organization¹⁹. It is possible that difficulties in

implementing the new system have resulted in less registration of the doses applied, making the VC data inaccurate.

The lack of inactivated hepatitis A vaccine, which occurred from the beginning of 2016 to the end of 2017, also contributed to the reduction of VC in the country. It is important to mention that the hepatitis A vaccine applied in Brazil is imported. Consequently, the use of this vaccine depends on the release of the National Institute for Quality Control in Health (*Instituto Nacional de Controle de Qualidade em Saúde* – INCQS)^{22,23}.

As for homogeneity, data for Brazil and its respective states show that VC is much lower than the expected target set by the MS. Vaccination campaigns should be promoted by municipalities with inadequate numbers taking advantage of vaccination for other diseases, such as influenza or measles, which have more appeal to the population, carried out preferably on weekends, as a strategy to improve VC more uniformly.

Despite VC's being below the established target, the incidence of notifications of hepatitis A dropped significantly in the country, after the adoption of universal vaccination in children. The incidence rate dropped from 3.29 to 0.80/100,000 between 2014 and 2018. There was a reduction in cases in all age groups, suggesting herd immunity effect^{24,25}. However, the fall was particularly significant among children under five years of age, with a 96.8% decrease in incidence between 2014 (949 cases) and 2017 (31 cases)²⁵. The gross number of cases increased again in 2017, compared to the previous year, as a result of an outbreak that occurred mainly in male adults in the state of São Paulo²⁶. A phenomenon already described in other metropolitan areas of the world^{27,28}.

Currently, there is a stabilization of incidence rates in the country, but in numbers lower than those registered before the beginning of the vaccination program. This decreased drop in the incidence rate may be related to the epidemic in adults that occurred in 2017, among men aged 20 to 39 years, mainly in the Southeast Region and possibly related to sexual practice²⁶, but it may also have occurred because the vaccination strategy achieved the peak of positive effects, drastically reducing the incidence of cases among young people in the country. However, as the HAV VC only reached the intended goal (95%) in one of the five years of the program (2015), ranging from 60 to 82% in the other years, it is possible that this is the cause the fall in incidence rates has stopped. In populations where universal vaccination was introduced in childhood, a significant reduction in the incidence of the disease was observed, even with moderate VC (50–70%). Countries such as Australia, Israel, Italy (in the region of Puglia), Spain (in Catalonia), and the United States, after the implementation of universal childhood vaccination in their vaccination schedules, have substantially reduced the incidence, outbreaks, mortality rates and hospitalizations caused by HAV²⁹.

Estimates of trends in the incidence of hepatitis A through case reports to the Epidemiological Surveillance System are underestimated by underreporting and the fact that the infection is often asymptomatic, however underreporting has been a constant factor, having decreased over the decade spent in the country with the creation of policies that reinforced health surveillance and the importance of disease notification. Therefore, there is no reason to suppose that the drop in notifications is due to an abrupt increase in the proportion of underreporting.

CONCLUSION

The public program of universal childhood vaccination against HAV can be considered successful, due to the significant drop in the incidence of the disease, although the goals set for VC have not been achieved. Even disregarding the years 2014 (only one semester of vaccination) and 2015 (high rates for the recovery of eligible 2014) and the shortage that occurred in 2016 and 2017, the inadequate VC observed and the low homogeneity verified prove the current trend of carelessness in immunization actions in the country. It is worth remembering that with just one dose, VC against HAV is not difficult to achieve. It is important to note that the states with the worst coverage rates are mainly in the North and Northeast regions, those with the highest rates of hepatitis A incidence. Not by chance, these are not only the poorest states but also the ones with worst conditions of access to health services for part of their populations. Strategies to better understand this situation should be put in place, such as, for example, through VC household surveys³⁰. At this moment, an effort to improve the VC indexes seems justified, in order to further reduce the incidence of the disease.

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