

Short communication

Impact of the single-dose universal mass vaccination strategy against hepatitis A in Brazil

Francisco José Dutra Souto^{a,*}, Wagner Izidoro de Brito^b, Cor Jésus Fernandes Fontes^a^a Hospital Universitário Júlio Muller, Universidade Federal de Mato Grosso, Faculdade de Medicina, Departamento de Clínica Médica, Cuiabá, Mato Grosso, Brazil^b Núcleo de Vigilância Epidemiológica Hospitalar, Universidade Federal de Mato Grosso, Cuiabá, Mato Grosso, Brazil

ARTICLE INFO

Article history:

Received 18 August 2018

Received in revised form 22 December 2018

Accepted 28 December 2018

Available online 11 January 2019

Keywords:

Hepatitis A virus
Hepatitis A vaccines
Incidence
Epidemiology
Public health
Outbreak

ABSTRACT

Universal vaccination of children against hepatitis A was introduced in 2014 in Brazil as a single-dose schedule. We analyzed the numbers of reported cases of hepatitis A virus infection (HAV) from 2010 to 2017 to evaluate the initial impact of that intervention. Data were assessed and has been freely available on the Brazilian Ministry of Health website. The HAV incidence was steady around 6000 cases per year until 2014. Between 2014 and 2016, there was a 85.5% cumulative drop, independent of gender and geographical macroregions. The fall was especially significant among toddlers (96.8%). In 2017, cases increased due to an outbreak among male adults in São Paulo. Decrease in incidence continued to occur for females and for those under 15 years of age. Data show that there was a significant decrease in HAV cases number in Brazil from 2015 after the introduction of single-dose HAV vaccine program.

© 2019 Elsevier Ltd. All rights reserved.

1. Introduction

Hepatitis A is an enterically transmitted virus-infection that is very common worldwide, particularly in developing countries with poor sanitary conditions [1]. The infection is usually benign and asymptomatic in childhood. However, severe hepatitis and even death can occur in some children and especially at older age [2].

In regions of high endemicity, almost all children get infected early in life. Therefore, vaccination is not recommended in developing countries. In regions of moderate endemicity, the exposure to HAV can take place later in life leading to an increase in the number of symptomatic and severe cases. Children vaccination against HAV has been recommended to countries that experience change in the endemicity of hepatitis A from high to moderate.

Vaccine against HAV is highly immunogenic, and almost all vaccinated healthy subjects develop protecting antibodies. Two doses of the vaccine have been recommended by manufacturers, the second dose being generally administered 6 months following the first dose. On the other hand, this vaccine is quite expensive, preventing its use on a large scale in low-income countries.

It has been shown that the incidence of HAV infection is greatly reduced by the implementation of nationwide HAV vaccination

program of toddlers. It was confirmed by experiences in countries such as Israel [3], USA [4] and Argentina [5]. In this last country, a single-dose vaccination schedule was adopted in 2005 in an attempt to reduce costs. Despite the initial success of the Argentinian single-dose schedule strategy, there remains concern about the duration of the protection afforded by this scheme [6].

In Brazil, hepatitis A mortality rates declined progressively from 1980 to 2002 [7]. These data suggested that there has been a decline in HAV circulation in the last decades with a consequent fall in endemicity from high to intermediate. A multicenter study conducted by Ministry of Health between 2004 and 2005 in two Brazilian macroregions showed that previous HAV exposure prevalence had decreased among individuals aged from five to nine years, ranging from 32% to 41% [8]. A more recent randomized study conducted in public schools of a medium-sized city of other macroregion showed the same trend [9]. The anti-HAV prevalence among 919 subjects aged between one and 19 years was 20.7%. This phenomenon was probably due to the improvement and standards of living and sanitation, especially in big cities.

In August 2014, after conducting a cost-effectiveness study, the Brazilian Ministry of Health decided to introduce a universal public immunization program against HAV. Following the Argentinian example, Brazil adopted a single-dose schedule, targeting children aged between one and two years nationwide. The inactivated virus vaccine Vaqta™ Ped/Adol, manufactured by Merck Sharp & Dohme, containing approximately 25 U of HAV antigen was adopted.

* Corresponding author at: Hospital Universitário Júlio Muller, Rua Luiz Philippe Pereira Leite, S/N, Alvorada, Cuiabá, Mato Grosso 78048902, Brazil.

E-mail address: fsouto@terra.com.br (F.J.D. Souto).

The present study analyzes time series of HAV cases reported to the Brazilian National Epidemiologic Surveillance System (SINAN) over the current decade (2010–2017) to assess the impact of vaccination on the incidence of the disease in the early years after the start of the program (2015–2017).

2. Methods

Annual series of HAV cases were assessed and are available on the Brazilian Ministry of Health electronic site (<http://datasus.saude.gov.br/>). These data were also analyzed by sex, age group and macroregions of the country. Data about HAV vaccine coverage and HAV-related mortality were extracted in the following databases respectively (<http://tabnet.datasus.gov.br/cgi/deftohtm.exe?pn/cnv/cpniuf.def>) and (<http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sim/cnv/obt10uf.def>) and are also available on the Brazilian Ministry of Health electronic website. These data are shown as absolute number of cases and incidence rates. Temporal trend across age groups were evaluated by nonparametric test for trend developed by Cuzick [10], an extension of the Wilcoxon rank sum test. The level of statistical significance was set at <0.05.

3. Results

The Brazilian universal mass vaccination program started in August 2014. Initially, the target population was children aged between 15 and 24 months. From 2017, the vaccination was extended to children under five years old in order to catch up children who missed vaccination in the first years of the program. Between August 2014 and the end of 2017, 9,017,706 children were vaccinated. The vaccine coverage has ranged from 60.1% to 97.1%, between 2014 and 2017.

Table 1 shows the absolute number of cases reported to the National Surveillance System between 2010 and 2017. From 2010 to 2014, the number of annual cases orbits around 6000. From 2014 ($n = 6655$ cases) to 2015 ($n = 2984$), there was a fall of 55.2%. Between 2015 and 2016 ($n = 964$), the decline was 67.7%. Between 2014 and 2016, the cumulative reduction was

85.5%. Until 2016, the fall occurred in both sexes (Fig. 1) and in all Brazilian macroregions (Fig. 2). A temporal trend analysis between 2010 and 2017 showed a significant decrease in reported cases ($p = 0.023$; Table 1).

Analysis by age group shows impressive decline of incidence among children ageing under five (Fig. 3). Between 2014 and 2017, cases dropped from 949 to 31 (96.8%). The downward trend was also significant among this age group ($p = 0.017$). The incidence decreasing also occurred in other age groups. The fall between 2014 and 2017 was 97.8% in 5 to 14 years group and 85.1% in 15 to 19 group. There was also a progressive fall among people from 20 to 39 years between 2014 and 2016: 73.5%. Such as among the older group (60 and above): 48.7%. The fall trend was significant in the older group ($p = 0.028$) and borderline in the groups between 5 and 60 years old ($p < 0.010$).

In 2017, the number of cases ($n = 1502$) increased by 55.8% compared to 2016 ($n = 964$). This increase was concentrated in the age group of 20 to 39 years. From 2016 ($n = 261$) to 2017 ($n = 892$), there was an increase of 241.7% in this age group. Most (82.4%) of the cases were male. Cases among males increased by 108%, while female cases continued to decline (−7.1%).

Among 1502 national HAV cases in 2017, 58.4% occurred in the São Paulo State, South-East macroregion. In 2016, only 8.6% of the cases had occurred in this state. The increase of cases in São Paulo State from 2016 ($n = 83$) to 2017 ($n = 877$) was 956%. Technical report from the local health authorities at the end of 2017 described that 87% of the cases of this state occurred in São Paulo, the largest Brazilian city. The most affected group were young (80% aged between 18 and 39) male (87%) adults. According the local health authorities, many (44%) of them were men who had sex with men [11]. There was also a slight increase of male adult cases in other states in the Southeast and in the South macroregion.

Data on hepatitis A mortality from 2010 to 2017 showed a downward trend in the number of deaths in the period ($p = 0.019$). This trend was already happening before the vaccination program begins (Table 1). The data for 2017 are preliminary. So it can still be revised and increased slightly.

Table 1
Population, number of cases of Hepatitis A, incidence rate per 100,000 inhabitants and lethality rate(%) by year in Brazil (from 2010 to 2017).

	2010			2011			2012			2013			
Age	Cases	Pop.	Inc.	Cases	Pop.	Inc.	Cases	Pop.	Inc.	Cases	Pop.	Inc.	
Unk. age	3	–	–	2	–	–	2	–	–	2	–	–	
<5	1043	15,816,957	6.59	1059	15,587,805	6.79	931	15,363,958	6.06	926	15,147,056	6.11	
5–14	3444	34,117,164	10.09	3676	33,920,142	10.84	3200	33,676,399	9.50	3180	33,384,596	9.53	
15–19	622	17,172,257	3.62	690	17,153,030	4.02	616	17,143,273	3.59	625	17,141,387	3.65	
20–39	930	65,278,048	1.42	1039	65,864,978	1.58	905	66,416,728	1.36	1048	66,921,404	1.57	
40–59	276	43,511,517	0.63	286	44,488,354	0.64	240	45,433,782	0.53	296	46,360,953	0.64	
60–>	106	19,601,854	0.54	124	20,382,709	0.61	115	21,208,322	0.54	117	22,077,318	0.53	
N total	6424	195,497,797	3.29	6876	197,397,018	3.48	6009	199,242,462	3.02	6194	201,032,714	3.08	
Deaths	52	Mort. [#] →	0.026	30	Mort. [#] →	0.015	36	Mort. [#] →	0.018	35	Mort. [#] →	0.017	
	2014			2015			2016			2017			P value [*]
Age	Cases	Pop.	Inc.	Cases	Pop.	Inc.	Cases	Pop.	Inc.	Cases	Pop.	Inc.	
Unk. age	1	–	–	–	–	–	–	–	–	–	–	–	
<5	949	14,938,133	6.35	383	14,737,740	2.60	77	14,545,488	0.53	31	14,360,778	0.22	0.017
5–14	3599	33,046,121	10.89	1355	32,671,352	4.15	310	32,223,917	0.96	116	31,777,888	0.37	0.053
15–19	696	17,144,248	4.06	319	17,140,200	1.86	74	17,166,564	0.43	104	17,150,098	0.61	0.064
20–39	985	67,361,623	1.46	579	67,726,893	0.85	261	68,022,995	0.38	892	68,254,915	1.31	0.097
40–59	302	47,289,819	0.64	240	48,233,579	0.50	155	49,189,007	0.32	257	50,152,631	0.51	0.073
60–>	123	22,988,618	0.54	108	23,940,885	0.45	87	24,933,461	0.35	102	25,964,619	0.39	0.028
Total	6655	202,768,562	3.28	2984	204,450,649	1.46	964	206,081,432	0.47	1502	207,660,929	0.72	0.023
Deaths	29	Mort. [#] →	0.014	24	Mort. [#] →	0.012	29	Mort. [#] →	0.014	20	Mort. [#] →	0.009	0.019

Pop. = Brazilian population estimated by IBGE; Brazilian Institute of Geography and Statistics.

^{*} P value of Cuzick's nonparametric test for trend.

[#] Mortality ratio/100,000.

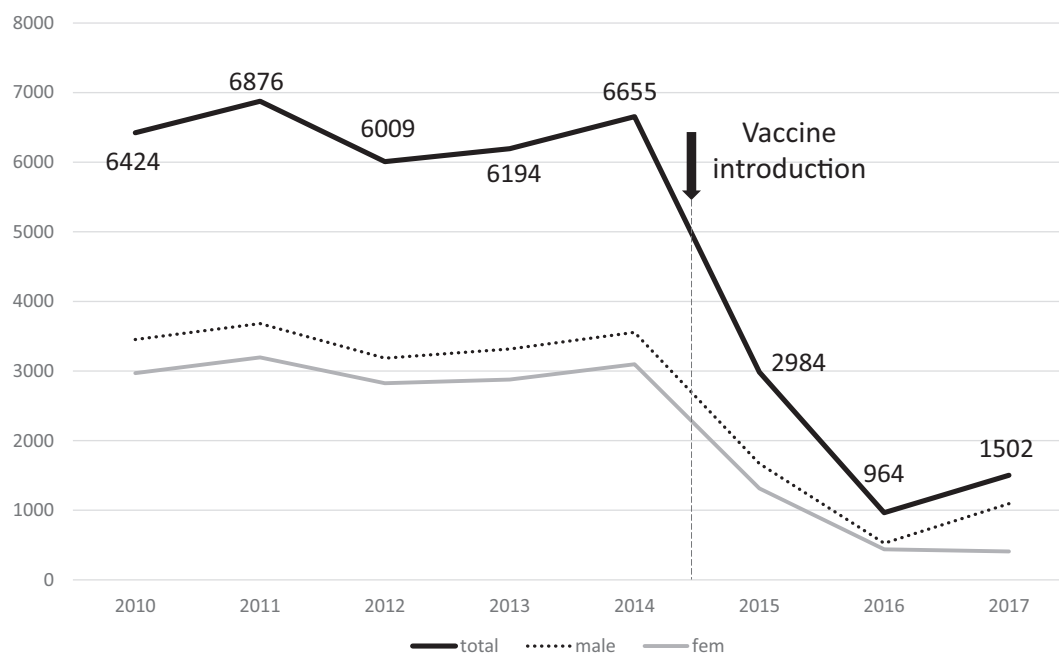


Fig. 1. Cases of hepatitis A in Brazil, from 2010 to 2017 (total number and by gender). Search: National Surveillance System, Ministry of Health. The arrow points out the start of vaccination program.

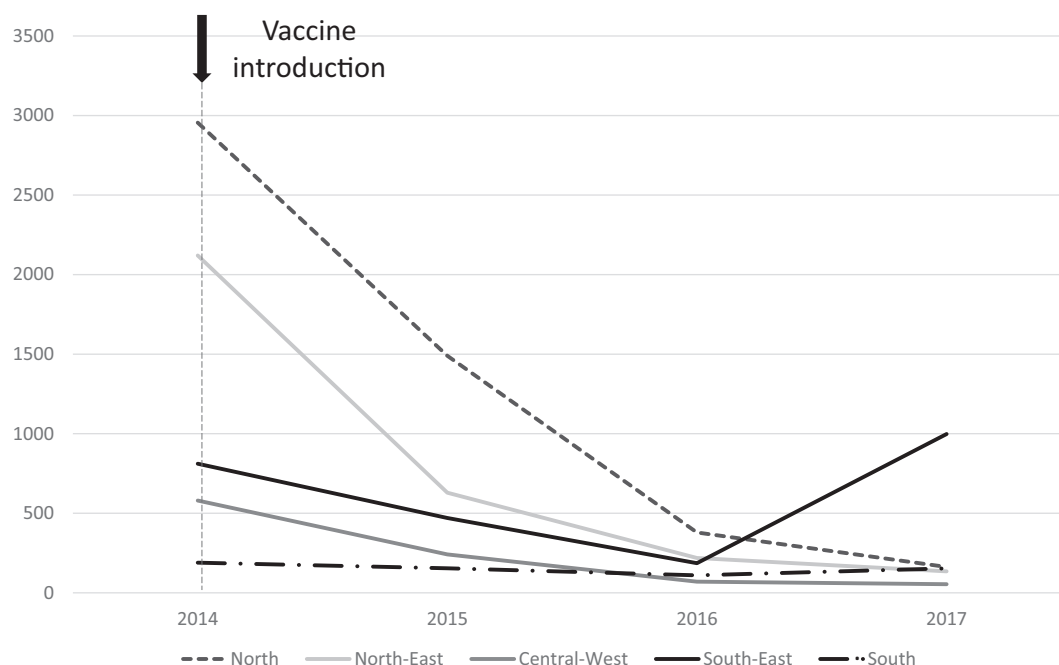


Fig. 2. Cases of hepatitis A by Brazilian macroregions, from 2014 to 2017. The arrow points out the start of vaccination program.

4. Discussion

In recent decades, the high endemic status for HAV infection in Brazil has changed to intermediate endemicity. The number of cases has fallen as a result of improving of living conditions and sanitation facilities in large urban centers, where most of the population lives [7,12]. Furthermore, HAV vaccine has already been available for purchase since the previous decade. About 25% of Brazilian population has access to private health insurance.

The incidence of HAV infection has remained steady at the beginning of the decade until 2014. However, there was a progressive and significant decrease in number of cases from 2015, soon after the beginning of vaccination program.

The dramatic accumulated decrease of new cases especially among children under 5 years old, just after 2014, reinforces the idea that it was due to the vaccine effect. The sharp decline in HAV infection rates in older children and teenagers may indicate the phenomenon of herd immunity, as verified in other HAV vaccination programs worldwide [3–5].

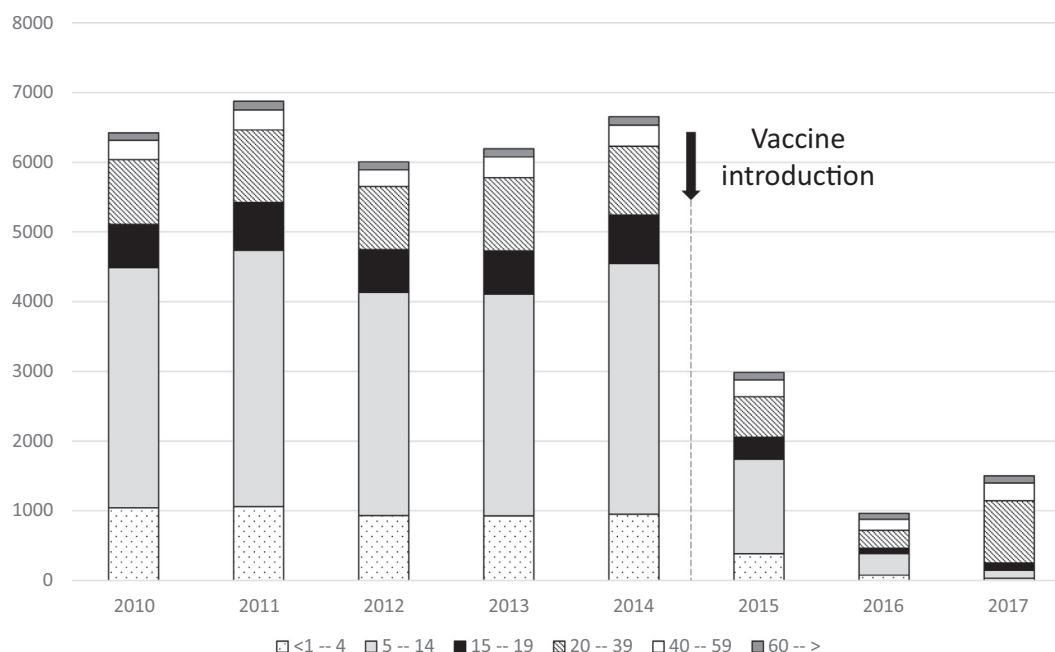


Fig. 3. Cases of hepatitis A in Brazil by age groups, from 2010 to 2017. The arrow points out the start of vaccination program.

Another outstanding aspect was that the decline occurred in all regions of the country, including the less developed North and Northeast macroregions, where the highest Brazilian incidence rates have taken place so far.

The numbers are not better because there has been a significant outbreak in young adult men in 2017, especially in the city of São Paulo, the largest and most cosmopolitan in the country. A similar phenomenon has recently been described in Europe and Americas [13–15]. This outbreak reinforces the necessity to implement prevention and vaccination strategies to reach and protect this vulnerable population.

Anyway, when the cases in the female sex and in the age groups below the age of 15 years are analyzed separately, the fall in incidence of HAV cases continued in 2017, even in the presence of an outbreak in young adult men.

As described in Argentina, the first country to implement vaccination with a single dose schedule, there was also an important decrease in hepatitis A numbers in Brazil. A recent study has shown that in children vaccinated under the Brazilian immunization program, more than 93% of the vaccinated children developed anti-HAV antibodies [16]. It is still necessary to follow the cohorts of vaccinated children to observe the persistence of anti-HAV antibodies, but these data are encouraging and indicate a progressive control of hepatitis A in children in the country.

The trend of decreasing HAV mortality in Brazil in the recent years should be carefully considered, since the data for 2017 are not yet definitive and can still be recalculated. On other hand, this trend was already occurring before vaccination started, probably because of recent improvements in sanitary conditions.

The adult men's outbreak in São Paulo likely arises as a consequence of the progressive fall in HAV circulation in the last decades in Brazil, that generated cohorts of susceptible teenagers and young adults. In this regard, it is a matter of concern that the number of serious and fatal cases has decreased less than would be expected with the fall in the number of cases. This may be happening because the infection is affecting more adult individuals, age group in which the disease shows higher morbidity and mortality rates. Awareness of the risk of exposure in older cohorts, which have not been vaccinated and remained susceptible, is a task of

the Brazilian health authorities to try to prevent the spread of outbreaks such as that in São Paulo.

For younger cohorts, it will be important to assess whether the protection conferred by single-dose strategy will last and if the trend detected in the first years after the program beginning will consolidate in the next years.

Conflict of interest

There is no conflict of interest to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2018.12.054>.

References

- [1] World Health Organization. Hepatitis A. Available at: <<http://www.who.int/news-room/fact-sheets/detail/hepatitis-a>> July 5, 2017 update. [Accessed: July 31, 2018].
- [2] Aggarwal R, Goel A. Hepatitis A: epidemiology in resource-poor countries. *Curr Opin Infect Dis* 2015;28(5):488–96. <https://doi.org/10.1097/QCO.0000000000000188> [Accessed: August 13, 2018].
- [3] Dagan R, Leventhal A, Anis E, et al. Incidence of hepatitis A in Israel following universal immunization of toddlers. *J Am Med Assoc* 2005;294(2):202–10 [Accessed: August 14, 2018].
- [4] Wasley A, Miller JT, Finelli L, et al. Surveillance for acute viral hepatitis – United States, 2005. *MMWR Surveill Summ* 2007;56(3):1–2 [Accessed: August 13, 2018] <https://www.cdc.gov/mmwr/preview/mmwrhtml/ss5603a1.htm>.
- [5] Vizzotti C, Gonzalez J, Gentile A, Rearte A, Ramonet M, Canero-Velasco MC, Pérez Carrega ME, et al. Impact of the single-dose immunization strategy against hepatitis A in Argentina. *Pediatr Infect Dis J* 2014;33(1):84–8 [Accessed: August 14, 2018] <https://insights.ovid.com/pubmed?pmid=24352191>.
- [6] Curran D, de Ridder M, Van Effelterre T. The impact of assumptions regarding vaccine-induced immunity on the public health and cost-effectiveness of hepatitis A vaccination: Is one dose sufficient? *Hum Vacc Immunother* 2016;12(11):2765–71 [Accessed: August 14, 2018] <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5137541>.
- [7] Vitral CL, Gaspar AM, Souto FJ. Epidemiological pattern and mortality rates for hepatitis A in Brazil, 1980–2002: a review. *Mem Inst Oswaldo Cruz* 2006;101(2):119–22 [Accessed: August 14, 2018] <https://doi.org/10.1590/S0074-02762006000200001>.

- [8] Ximenes RA, Martelli Cm, Merchán-Hamann E, et al. Multilevel analysis of hepatitis A infection in children and adolescents: a household survey in the Northeast and Central-west regions of Brazil. *Int J Epidemiol* 2008;37(4):852–61 [Accessed: August 14, 2018] <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2483311>.
- [9] Cury CM, Pinto MA, da Silva JP, et al. Hepatitis A seroprevalence in public school children in Campos dos Goytacazes, Rio de Janeiro State, Brazil, prior to the introduction of the hepatitis A universal childhood vaccination. *Cad Saude Publica* 2016;32(11):e00175614. <https://doi.org/10.1590/0102-311X00175614> [Accessed: August 14, 2018].
- [10] Cuzick J. A Wilcoxon-type test for trend. *Stat Med* 1985;4(1):87–90 [Accessed: August 14, 2018] <https://www.ncbi.nlm.nih.gov/pubmed/3992076>.
- [11] Secretaria de Estado de Saúde de São Paulo. Surto de Hepatite A. Informe técnico. Centro de vigilância epidemiológica. Divisão de doenças de transmissão hídrica e alimentar. Available at: <http://www.saude.sp.gov.br/resources/cve-centro-de-vigilancia-epidemiologica/areas-de-vigilancia/doencas-transmitidas-por-agua-e-alimentos/doc/2017/hepatitea17_iftecnico.pdf>. [Accessed June 1, 2018].
- [12] Vitral CL, Ospina FL, Artimos S, et al. Declining prevalence of hepatitis A virus antibodies among children from low socioeconomic groups reinforces the need for the implementation of hepatitis A vaccination in Brazil. *Mem Inst Oswaldo Cruz* 2012;107(5):652–8. <https://doi.org/10.1590/S0074-02762012000500012> [Accessed: August 14, 2018].
- [13] Bordi L, Rozera G, Scognamiglio, et al. Monophyletic outbreak of hepatitis A involving HIV-infected men who have sex with men, Rome, Italy 2008–2009. *J Clin Virol* 2012;54(1):26–9. <https://doi.org/10.1016/j.jcv.2012.01.009> [Accessed: August 14, 2018].
- [14] Werber D, Michaelis K, Hausner M, et al. Ongoing outbreaks of hepatitis A among men who have sex with men (MSM), Berlin, November 2016 to January 2017 – linked to other German cities and European countries. *Euro Surveill* 2017;22(5):30457 [Accessed: August 14, 2018] <https://www.ncbi.nlm.nih.gov/pubmed/28183391>.
- [15] Rivas V, Barrera A, Pino K, et al. Hepatitis A outbreak since November 2016 affecting men who have sex with men (MSM) in Chile connected to the current outbreak in MSM in Europe, situation up to October 2017. *Euro Surveill* 2018;23(9):18-00060 [Accessed: August 14, 2018] <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5840922>.
- [16] de Brito WI, Alves-Jr ER, Oliveira RM, et al. Initial evaluation of universal immunization with a single-dose against hepatitis A virus in Central Brazil. *Braz J Infec Dis* 2018;22(3):166–70. <https://doi.org/10.1016/j.bjid.2018.04.001> [Accessed: August 14, 2018].