CSP CADERNOS DE SAÚDE PÚBLICA
REPORTS IN PUBLIC HEALTH

ARTIGO
ARTICLE

Hepatitis A seroprevalence among special populations in the Rio de Janeiro Metropolitan Area, Brazil

Soroprevalência da hepatite A entre populações especiais na Região Metropolitana do Rio de Janeiro, Brasil

Seroprevalencia de la hepatitis A en poblaciones especiales em el Área Metropolitana de Río de Janeiro, Brasil

Flavio de Carvalho [1]
Luciana Gomes Pedro Brandão [1]
Margaret Catoia Varela [1]
Mari Tuyama [1]
Danusa Ferreira Correa [1]
Ananza Taina da Silva Santos [1]
Alberto dos Santos de Lemos [1,2]
Marcellus Dias da Costa [1]
José Cerbino-Neto [1]
Pedro Emmanuel Alvarenga Americano do Brasil [1]

doi: 10.1590/0102-311XEN075522

Abstract

The objectives were to estimate hepatitis A virus seroprevalence in subjects attending to a travel medicine and immunization clinic in Rio de Janeiro, Brazil, and to develop a prediction model for hepatitis A virus seroprevalence. This retrospective research included individuals sequentially from April 2011 to June 2019 at a travel medicine and special population immunization clinic with an anti-hepatitis A virus IgG chemiluminescence result. Participants' data were verified via electronic medical records. Data were split into development and validation set taking 2018 as the date break. A cross-validated elastic generalized linear model with binomial distribution was performed. In total, 2,944 subjects were analyzed. Hepatitis A virus overall seroprevalence was 67.8%. Health professionals, travelers, and those who had contact with immunocompromised subjects had lower seroprevalence (40%-55%), whereas subjects with chronic conditions (heart, lung, and liver) ranged from 89% to 94%. The retained predictors in the final model were sex, age, year of birth, travelers, HIV/AIDS, spleen dysfunction, transplant candidates, household communicators, cancer-related immunosuppression, health care professionals. Area under the curve was 0.836 and maximum error was 0.051. Users can make predictions with the following calculator: https://pedrobrasil.shinyapps.io/INDWELL/. The groups with lower seroprevalence should be evaluated more carefully regarding need for hepatitis A virus vaccination even when they seek immunization clinics for other purposes.

Hepatitis A; Travel Medicine; Chronic Disease; Health Personnel; Immunization Programs

Correspondence
P. E. A. A. Brasil
Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz.
Av. Brasil 4365, Rio de Janeiro, RJ 21041-900, Brasil.
pedro.brasil@fiocruz.br

[1] Instituto Nacional de Infectologia Evandro Chagas, Fundação Oswaldo Cruz, Rio de Janeiro, Brasil.
[2] Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brasil.

Introduction

Hepatitis A virus is most commonly transmitted via oral-fecal exposure, contaminated food, water, or close physical contact with an infected person [1]. People living in poorly sanitized areas are also more likely to be infected [2].

Hepatitis A virus is one of the most common etiologies of acute hepatitis worldwide [3], infecting 212 million people per year, including 55 million symptomatic cases and 35,245 deaths globally [4]. As the number of asymptomatic infections is unknown, this number may be underestimated [5].

Regions can be characterized by patterns of hepatitis A virus infection into areas of high, intermediate, or low endemicity [6]. According to the World Health Organization (WHO), hepatitis A endemicity classification is related to the seroprevalence among children aged 10-14 years: > 90% – high, 75-89% – high/medium, 60-74% – medium, 40-59% – low/medium, < 20% – low. The WHO susceptibility rate classification in adults aged 35-44 years at risk is as follows: high: > 40%, medium: 20-39%, low/medium: 10-19%, low: 1-9%, and very low: 0%. A high adult susceptibility rate shows an elevated risk of outbreaks [7].

Areas of high endemicity are characterized by widespread hepatitis A virus, such as developing countries with poor sanitary conditions. Most infected individuals are young children, aged under 5 years, who are predominantly asymptomatic or show no specific symptoms. Consequently, apparent disease incidence rates are low and outbreaks are rare. In areas of intermediate endemicity, health conditions vary. In this scenario, many individuals escape hepatitis A virus infection during early childhood. However, viral circulation remains, and infection frequently occurs in adolescents or young adults. In these areas, the number of reported hepatitis A virus cases may be higher than in high endemic regions. Countries with good overall sanitary conditions usually have low endemicity. Thus, infection may occur at a later age and outbreaks are possible among adults and children [8,9].

Brazil can be classified as having a low/medium or intermediate hepatitis A virus burden [10]. Hepatitis A virus incidence rates in Brazil increased until 2005 (14 per 100,000 inhabitants) and since 2006 have been showing a downward trend, reaching 3.2 cases per 100,000 inhabitants in 2014. Cases in children aged up to 9 years correspond to 54.7% of all reported cases in Brazil, and this age group's incidence rate is also higher than in other age groups [11]. In 2021, the incidence rate was estimated to be 0.2 per 100,000 inhabitants, with children accounting for 52.8% of all reported cases and a significant increase in cases in young adults (20-39 years) from 2017 to 2018 [10].

Groups at higher risk for hepatitis A virus infection include: travelers to areas of high endemicity, workers in day care centers and institutions for individuals with disabilities, some categories of health workers, military personnel, sewage system workers, intravenous drug users, and men who have sex with men [12]. Hepatitis A virus seroprevalence can be highly variable according to country or within a country. Evidence shows seroprevalence differences according to age, vaccinated population, and occupation – such as nurses (41.2%), physicians (56.3%), and nursing assistants (73.9%) [13,14] – the number of household contacts, water quality, place of residence, and family size [14]. Subjects with non-A hepatitis are also considered a high-risk group, including those with liver cirrhosis [15,16].

This study aims to estimate the seroprevalence of hepatitis A in subjects attending to a travel medicine and immunization outpatient clinics of the Evandro Chagas National Institute of Infectious Diseases (INI), Oswaldo Cruz Foundation (Fiocruz), Rio de Janeiro, Brazil, and to develop and validate a prediction model to estimate hepatitis A virus seroprevalence among these special groups.

Materials and methods

Settings

This is a retrospective observational study conducted at a Reference Center for Special Immunobiologicals (CRIE), a unit of the INI/Fiocruz. INI is a high-complexity hospital specialized in infectious diseases. CRIE is part of the Brazilian National Immunization Program (PNI), with many CRIE units throughout Brazil. CRIE has special immunizations to attend the special populations who require vaccines that are not usually available for the general public in regular health units and are not

recommended regularly for healthy children or adults by the manual de vacinação (Brazilian vaccination booklet). Thus, CRIE has a list of health conditions or special situations when these vaccines or immunoglobulins are recommended, including adapted schemes and dosages for these cases. Before the COVID-19 pandemic, travel medicine clinics received around 1,000 appointments per year, with four outpatient shifts per week and five travelers scheduled per shift. Similarly, special populations had around 7,200 appointments yearly, and these were performed every weekday during business hours. The outpatient clinic received patients from the Rio de Janeiro Metropolitan Area, including many neighboring cities.

Participants (study sample) and data collection

The study population consisted of individuals sequentially attended from April 2011 to June 2019. These subjects were seeking care at the travel medicine clinic and CRIE, and for any reason were requested an hepatitis A virus test (anti-HAV IgG). For CRIE patients, hepatitis A virus tests were requested whenever the patient had a condition and needed vaccination for hepatitis A. For travel medicine appointments, hepatitis A virus tests are requested for all subjects advised to take the hepatitis A virus vaccine. Participants' data were verified via electronic medical records. An inquiry to the electronic medical records was performed, in which they were first filtered by attendance at the travel medicine and immunization clinic and by availability of hepatitis A virus (anti-HAV IgG) test results, then inclusion and exclusion criteria were manually checked for each record. The inclusion criteria were individuals aged ≥ 18 years, attending to a travel medicine outpatient clinic or CRIE, and a hepatitis A test (anti-HAV IgG) request. The exclusion criteria were subjects who did not collect samples for an hepatitis A virus test or did not have a test result in the electronic medical record and subjects that had serology results without the medical request from a travel medicine outpatient clinic or CRIE (INI/Fiocruz).

Outcome

Different hepatitis A virus tests were used during the research period. The anti-HAV antibodies of the collected samples were analyzed at the INI with a chemiluminescence immunoassay (ARCHITECT HAVAb-IgG, Abbott Diagnostics; https://www.abbott.com/for-healthcare-professionals/diagnostics.html) or EIA (EIA Monolysis Total anti-HAV Plus, Bio-RAD; https://www.bio-rad.com/), according to the manufacturer's instructions.

Predictors

The predictors with fewer missing data were sex, gender identity, age, year of birth, outpatient clinic attended, requesting physician, clinical indication, current address, and birthplace. For the research purpose, the clinical indication was considered as the main predictor, retrieved from the CRIE list [17]. The list contained: (1) sexual abuse; (2) accident with biological material; (3) allergy to vaccine or some component; (4) sickle cell anemia and other hemoglobinopathies; (5) functional asplenia; (6) solid organ transplant candidates; (7) heart diseases; (8) coagulopathies; (9) contacts of immunodeficient people; (10) close contacts of viral diseases; (11) hospital contact; (12) severe skin diseases; (13) diabetes mellitus; (14) solid organ donors; (15) bone marrow donor; (16) autoimmune disease; (17) deposit disease; (18) inflammatory bowel disease; (19) neurological disease; (20) previous adverse event; (21) exposure to chickenpox; (22) child of an HIV+ mother; (23) CSF fistula; (24) prison system officers; (25) pregnant; (26) liver disease; (27) chronic arterial hypertension; (28) HIV/AIDS; (29) hospitalized; (30) cochlea implant; (31) primary immunodeficiency; (32) therapeutic immunosuppression; (33) chronic nephropathy; (34) nephropathy in hemodialysis; (35) neoplasm (solid tumor); (36) hematologic neoplasm; (37) lung disease; (38) post-splenectomy; (39) post bone marrow transplant; (40) post solid organ transplantation; (41) pre-splenectomy; (42) pre-immunosuppression by biologicals; (43) pre-transplantation of solid organs; (44) pre-bone marrow transplant; (45) prematurity; (46) prevention of perinatal hepatitis B virus infection; (47) prophylaxis after risky sexual exposure (consensual); (48) health professional; (49) puerperal; (50) genetic syndromes; (51) acetylsalicylic acid allergy.

Analysis plan

The analysis plan consisted of a descriptive analysis with frequencies and dispersion of variables. Prevalence ratio of seropositivity was estimated via a univariate generalized linear model with quasi-Poisson distribution and exponentiating of the regression coefficient. For the continuous variables, the interpretation of prevalence ratio should be an increment in prevalence for each unit of increment of the variable.

The highest missing data within a variable was around 8%. For regression purposes, missing data were imputed with predictive mean matching (multiple imputation). Data were split into development and validation to estimate and eventually correct optimism and generate evidence that the results of the model performance is related to other samples/populations. The development set was defined as all subjects tested for hepatitis A virus from 2011 to 2017 and the validation set was composed of those tested for hepatitis A virus in 2018 and 2019. The regression approach was conducted with a cross-validated, elastic, and generalized linear model with binomial distribution, thus the final model coefficients were converted into odds ratios. This approach allows simultaneous penalization of the model, avoiding overfitting and optimism, using a lasso-type selection and ridge-type penalization. Therefore, the predictors with no contribution for the predictions had their coefficients shrinked to 0. Moreover, this approach does not drop the baseline level for factors, so that the regularization process will shrink the fitted coefficients toward the overall mean rather than toward the estimate for the baseline predictor level. The full model initially tested was year of birth, age, medical indication for immunization, sex, and an interaction of age and year of birth, and the final model was extracted from 100 cross-validated folds from the fold with the least mean squared error. Then, predictions were performed in both the development and the validation sets, and from those the calibration and discrimination measures were estimated: area under the ROC (receiver operating characteristics) curve (AUC – area under the curve), R^2, Brier score, model intercept, model slope, errors (distances) from the predicted probabilities to observed probabilities. The analysis was conducted using the R-project software (http://www.r-project.org) with the following packages: *Hmisc*, *DiagrammeR*, *mice*, *stats*, *MASS*, *glmnet*, and *glmnetUtils*. Moreover, the model was implemented on an online calculator with packages *shiny* and *shinydashboardPlus* to allow users to estimate individual probabilities for hepatitis A virus antibodies (or the prevalence of hepatitis A virus within groups of desired characteristics): https://pedrobrasil.shinyapps.io/INDWELL/.

Ethics

All measures of protection and confidentiality of the patients were followed, based on the good clinical practice and regulatory standards for research with human beings, following the *Resolution n. 466/2012* of the Brazilian National Health Council. The project approval can be accessed on the Brazilian National Ethics System for research with human beings (https://plataformabrasil.saude.gov.br/login.jsf – with the number 85365318.4.0000.5262).

Results

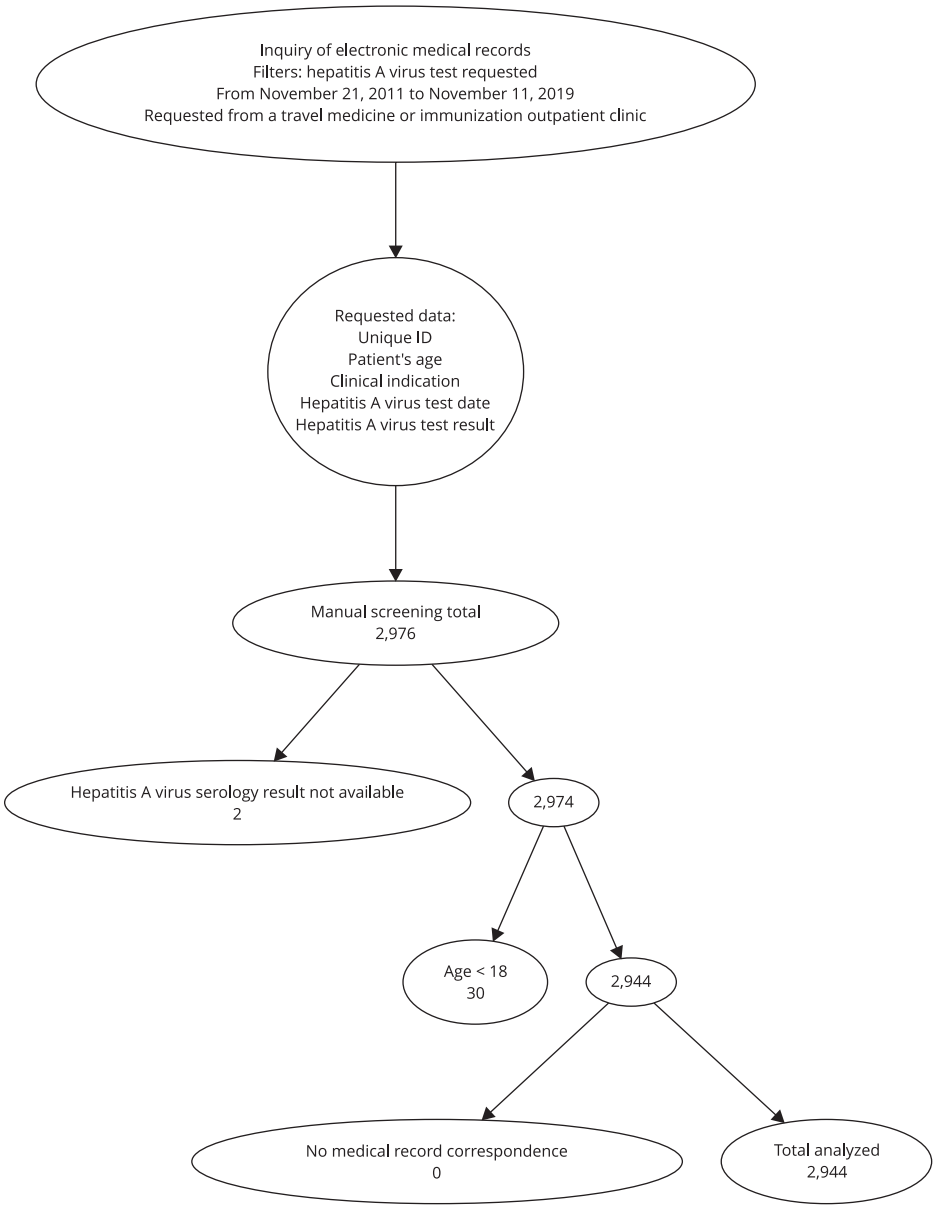
Participants and seroprevalence

In total, 2,976 electronic medical records were verified. After applying the inclusion and exclusion criteria, we analyzed 2,944 records (Figure 1).

From the 2,944 attended participants, hepatitis A virus's overall seroprevalence was 67.8% from November 21, 2011 to November 11, 2019 (Table 1). The median age was 42 years, and it was higher among hepatitis A virus reagent subjects. As age increased, seroprevalence also increased. Likewise, as year of birth increased, seroprevalence decreased (Table 1). The seroprevalence among travelers (pre-travel) was much lower than among subjects with chronic conditions seeking vaccinations at the CRIE. Moreover, subjects attended up to 2017 (development set) had slightly higher seroprevalence than subjects attended in 2018 and 2019 (validation set) (Table 1).

Figure 1

Inclusion and exclusion flow diagram.



The travelers group was the biggest group analyzed, making up 39.9% of the sample. From the CRIE list of special populations, four major groups made up 42.1% of the sample: candidates for solid organ transplantation, HIV/AIDS, spleen dysfunction, and therapeutic or cancer-related immunosuppression.

The different groups attending to CRIE for vaccination had a substantial difference in seroprevalence. Some groups had a substantially lower seroprevalence than the overall seroprevalence, namely: health professionals, travelers, and those who had contact with immunocompromised subjects (Table 2). A group characterized as "others", which is an aggregate of indications, had a low attendance frequency at the CRIE.

Table 1

Participants' characteristics – subjects seeking outpatient clinic immunization tested for hepatitis A virus from 2011 to 2019.

Characteristics	Reagent n (%)	Non-reagent n (%)	Total n (%)	Prevalence ratio (95%CI)
Total	1,995	949	2,944	
Sex				
Female	990 (68.32)	459 (31.68)	1,449 (100.00)	1.00 (NA-NA)
Male	890 (66.67)	445 (33.33)	1,335 (100.00)	0.98 (0.93-1.03)
Age (years)				
Median (IQR)	49.00 (38.00-59.00)	31.00 (25.00-39.00)	42.00 (31.00-55.00)	1.02 (1.02-1.02)
18-30	213 (33.81)	417 (66.19)	630 (100.00)	1.00 (NA-NA)
30-40	374 (54.12)	317 (45.88)	691 (100.00)	1.60 (1.46-1.76)
40-50	451 (76.31)	140 (23.69)	591 (100.00)	2.26 (2.06-2.48)
50-60	489 (90.22)	53 (9.78)	542 (100.00)	2.67 (2.44-2.93)
60-70	363 (94.78)	20 (5.22)	383 (100.00)	2.80 (2.55-3.09)
70-80	88 (98.88)	1 (1.12)	89 (100.00)	2.92 (2.54-3.36)
80-90	16 (100.00)	0 (0.00)	16 (100.00)	2.96 (2.19-3.90)
110-120	1 (50.00)	1 (50.00)	2 (100.00)	1.48 (0.38-3.80)
Year of birth				
Median (IQR)	1,966.00 (1,956.00-1,976.00)	1,984.00 (1,977.00-1,990.00)	1,972.00 (1,960.00-1,984.00)	0.98 (0.98-0.98)
1900-1960	680 (95.10)	35 (4.90)	715 (100.00)	1.00 (NA-NA)
1960-1970	492 (83.96)	94 (16.04)	586 (100.00)	0.88 (0.83-0.94)
1970-1980	444 (72.55)	168 (27.45)	612 (100.00)	0.76 (0.71-0.82)
1980-1990	283 (40.90)	409 (59.10)	692 (100.00)	0.43 (0.40-0.47)
1990-2000	95 (28.36)	240 (71.64)	335 (100.00)	0.30 (0.26-0.34)
2000-2010	1 (25.00)	3 (75.00)	4 (100.00)	0.26 (0.07-0.67)
Clinic that requested the exam				
CRIE	1,395 (74.96)	466 (25.04)	1,861 (100.00)	1.00 (NA-NA)
Travel medicine clinic	600 (55.40)	483 (44.60)	1,083 (100.00)	0.74 (0.70-0.78)
Data fraction				
Development (2011-2017)	1,524 (68.99)	685 (31.01)	2,209 (100.00)	1.00 (NA-NA)
Validation (2018-2019)	471 (64.08)	264 (35.92)	735 (100.00)	0.93 (0.88-0.98)

95%CI: 95% confidence interval; CRIE: Reference Center for Special Immunobiologicals; IQR: interquartile range; NA: not aplicable.
Note: the prevalence ratio shows the prevalence of being hepatitis A virus-reactive over the prevalence of not being hepatitis A virus-reactive.

Three groups had very high seroprevalence: chronic lung disease, chronic liver disease, and chronic heart disease (Table 2). The lowest seroprevalence was found in healthcare professionals and travelers (Table 2).

Model development

As progressively fewer participants were born before 1960, the year of birth was truncated at 1960, that is, participants born in 1960 or before were considered to have the same effect on predictions. In the adjusted analysis, all initial predictors were retained: year of birth, age, sex, PNI special population list (indication for vaccination), including the interaction of age and year of birth (Table 3). The interaction term had a very small effect, but it is highly significant. The retained interaction term means that there is a cohort effect (typical on hepatitis A virus seroprevalence studies) and a generation effect. For example, a participant aged 20 years, born in 1991 had a different probability of having hepatitis A virus antibodies of an identical participant aged 20 years born in 1999 beyond the usual decrease of seroprevalence due to year of birth alone.

Table 2

Prevalence of indications for special immunobiological immunization among subjects who were tested for hepatitis A virus from 2011 to 2019.

	Reagent n (%)	Non-reagent n (%)	Total n (%)	Prevalence ratio (95%CI)
Total	1,995	949	2,944	
Reason for appointment (PNI list)				
Traveler	645 (54.85)	531 (45.15)	1176 (100.00)	1.00 (NA-NA)
Other	56 (61.54)	35 (38.46)	91 (100.00)	1.12 (0.96-1.31)
HIV/AIDS	456 (81.14)	106 (18.86)	562 (100.00)	1.48 (1.38-1.58)
Anatomical or functional asplenia and related diseases (sickle cell anemia, greater thalassemia)	145 (72.14)	56 (27.86)	201 (100.00)	1.32 (1.19-1.46)
Chronic lung diseases (COPD, bronchiectasis, asthma, etc.)	48 (88.89)	6 (11.11)	54 (100.00)	1.62 (1.37-1.91)
Candidates for solid organ transplantation	209 (82.28)	45 (17.72)	254 (100.00)	1.50 (1.37-1.64)
Chronic heart diseases	20 (90.91)	2 (9.09)	22 (100.00)	1.66 (1.27-2.11)
Chronic liver diseases, cirrhosis, and hepatitis C virus carriers	29 (93.55)	2 (6.45)	31 (100.00)	1.71 (1.37-2.09)
Household communicators of immunocompromised	37 (57.81)	27 (42.19)	64 (100.00)	1.05 (0.87-1.27)
Immunodeficiency/Immunodepression other (acquired or congenital)	14 (70.00)	6 (30.00)	20 (100.00)	1.28 (0.93-1.70)
Therapeutic or cancer-related immunosuppression	182 (81.98)	40 (18.02)	222 (100.00)	1.49 (1.36-1.64)
Not informed	32 (52.46)	29 (47.54)	61 (100.00)	0.96 (0.78-1.16)
Chronic nephropathies/Hemodialysis/Nephrotic syndrome	55 (87.30)	8 (12.70)	63 (100.00)	1.59 (1.36-1.86)
Healthcare professional	32 (40.00)	48 (60.00)	80 (100.00)	0.73 (0.59-0.89)
Solid organ transplant	35 (81.40)	8 (18.60)	43 (100.00)	1.48 (1.22-1.79)

95%CI: 95% confidence interval; COPD: chronic obstructive pulmonary disease; NA: not aplicable; PNI: Brazilian National Immunization Program.
Note: the other category includes the following categories for having less than 20 observations: sexual abuse; accident with positive biological material or strongly suspected of hepatitis B virus infection; stroke; severe or moderate asthma; coagulopathies; sexual communicators of hepatitis B virus carriers; diabetes mellitus; solid organ or bone marrow donors; deposit disease; disabling chronic neurological diseases; previous adverse event; pregnancy; chronic arterial hypertension with comorbidity; cochlear implant; immunocompetent > 1 year, hospital contact; acute lymphocytic leukemia and solid tumors; no seroconversion; prophylaxis after risk exposure; Down's syndrome; susceptibility to the disease and immunocompetent people living with immunocompromised individuals; transplanted; bone marrow transplant; private service user. The prevalence ratio indicates the prevalence of reagent for hepatitis A virus over the prevalence of non-reactive for hepatitis A virus. Prevalence ratio = 1 identifies the reference group.

Due to the nature of the modeling, one can see that some categories of the vaccination indication (PNI special group list) were removed (Table 3). This means that these categories had their effect reduced to 0. The retained categories representing the vaccination indications were travelers, HIV/AIDS, spleen dysfunction, transplant candidates, household communicators, cancer-related immunosuppression, health care professionals, others, and not informed (Table 3). Additionally, one must pay attention that, regardless of the presence of odds ratios for many categories, there are mutually exclusive categories (e.g., one cannot be in the female and male categories simultaneously) and the effect is an increase or decrease related to the overall mean.

Model validation

Based on the equation provided by this regression, it is possible to estimate the seroprevalence of a particular group or subject with defined characteristics in the model. The performance measures showed that the calibration and discrimination are good to very good, for both development and validation sets. The calibration is represented by the positive relationship between the actual (observed) probability and the predicted (expected) probability, the small values of errors, the slope close to 1, intercept close to 0, and the non-significant Spigelhalter test; and the discrimination is represented by high values of the R^2 and AUC and small Brier score values (Figure 2). Moreover, the performance measures are very similar in both sets, meaning that performance travels and gives the user confidence that the model will behave similarly for new predictions.

Table 3

Coefficients and odds ratio of the final generalized linear model penalized model.

Characteristics/Category	Coefficients	OR
Intercept	105.6153	-
Year of birth (truncated in 1960)	-0.0274	0.973
Age	0.0166	1.0167
Reason for appointment (PNI special group list)		
Traveler	-0.8345	0.4341
Other	-0.4633	0.6292
HIV/AIDS	0.4927	1.6368
Anatomical or functional asplenia and related diseases (sickle cell anemia, greater thalassemia)	-	-
Chronic lung disease (COPD, bronchiectasis, asthma, etc.)	-	-
Candidates for solid organ transplantation	0.1359	1.1455
Chronic heart disease	-	-
Chronic liver disease, cirrhosis, and hepatitis C virus carriers	-	-
Household communicators of immunocompromised people	-0.2077	0.8125
Immunodeficiency/Immunodepression (acquired or congenital)	-	-
Therapeutic or cancer-related immunosuppression	0.1433	1.1541
Not informed	-0.1616	0.8508
Chronic nephropathies/Hemodialysis/Nephrotic syndrome	-	-
Healthcare professional	-0.4942	0.6101
Solid organ transplant	-	-
Sex		
Female	0.0302	1.0307
Male	-0.0161	0.9840
Year of birth (truncated in 1960)	-0.0265	0.9738
Age	0.0160	1.0162
year_birth_trunc60: age	0	1

COPD: chronic obstructive pulmonary disease; OR: odds ratio; PNI: Brazilian National Immunization Program.

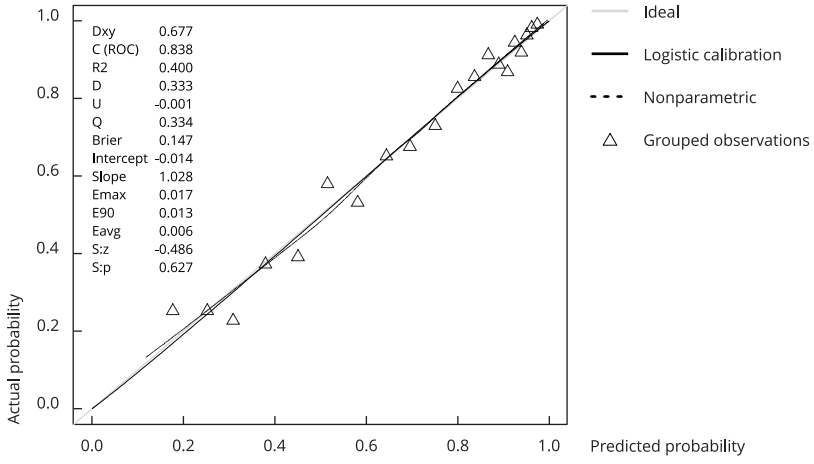
Note: the other category includes the following categories for having less than 20 observations: sexual abuse; accident with positive biological material or strongly suspected of hepatitis B virus infection; stroke; severe or moderate asthma; coagulopathies; sexual communicators of hepatitis B virus carriers; diabetes mellitus; solid organ or bone marrow donors; deposit disease; disabling chronic neurological diseases; previous adverse event; gestation; chronic arterial hypertension with comorbidity; cochlear implant; immunocompetent > 1 year, hospital contact; acute lymphocytic leukemia and solid tumors; no seroconversion; prophylaxis after risk exposure; down's syndrome; susceptibility to the disease and immunocompetent people living with immunocompromised individuals; bone marrow transplant; private service user. Some categories in the penalty process had the coefficient reduced to 0 and are not represented.

To estimate the expected prevalence/probability within groups or for individuals with different characteristics, the formula is 105.615255884114 + -0.0273661927529627*Birth year (shortened in 1960) + 0.0165676033302336*Age + -0.834531343441931*Traveler + -0.463282721011027*Other + 0.492723472942024*HIV/AIDS + 0.135859483485275*Candidates for solid organ transplantation + -0.207684574265356*Household communicators of immunocompromised + 0.143294468976904*Therapeutic or cancer-related immunosuppression + -0.161607935383998*Not informed + -0.494205392220694*Healthcare professional + 0.030248899690747*Female + -0.0161122283830219*Male + -0.0265110489291436*Birth year (shortened in 1960) + 0.0160300303022014*Age + 7.51220177808591e-06*Birth year (shortened in 1960)*Age. In categorical predictors, you must enter 1 when present or 0 when absent. For continuous predictors, you enter the value of the predictor. Then use the logistic function to transform the linear predictor into probability: probability = 1/(1 + 2.718282 ^ -Y).

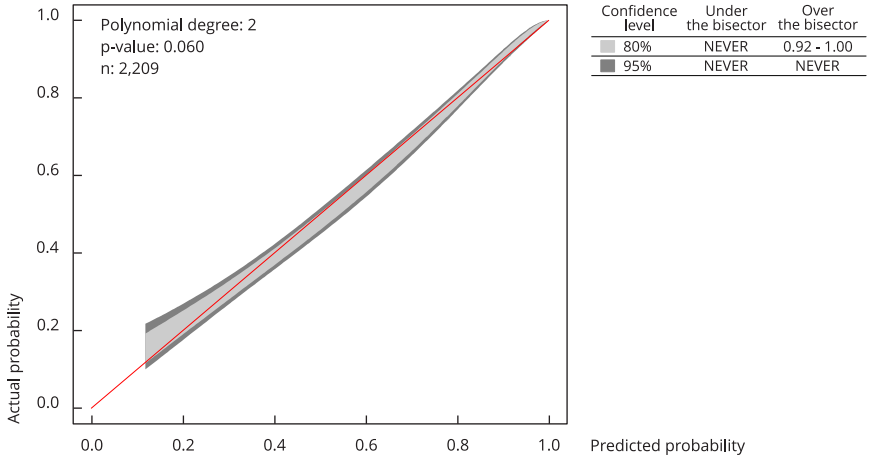
Figure 2

Final model calibration belt and performance measures for development and validation sets.

1a) Performance measures: development set

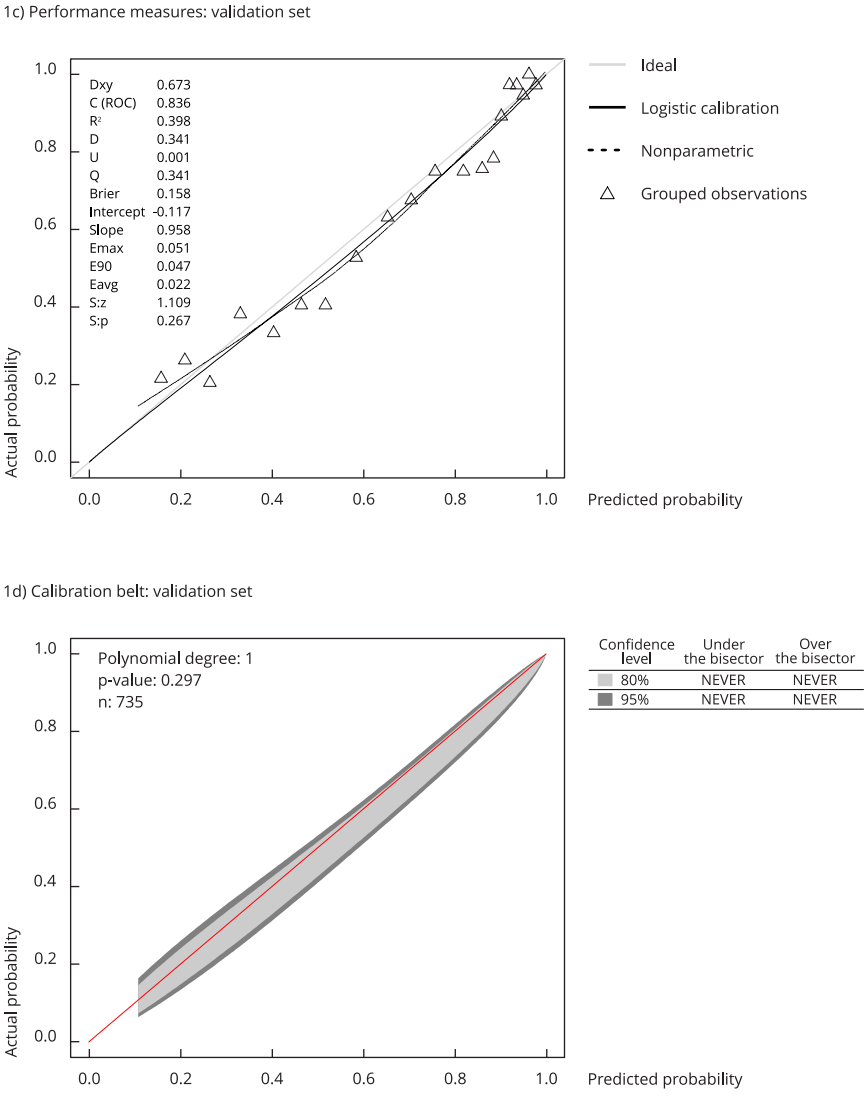


1b) Calibration belt: development set



(continues)

Figure 2 (continued)



Brier: Brier score; C (ROC): curve (receiver operating characteristics); D: discrimination index D; DXY: Somers' Dxy rank correlation; E90: the 0.9 quantile of absolute difference in predicted and loess-calibrated probabilities; Eavg: the average in absolute difference in predicted and loess-calibrated probabilities; Emax: maximum absolute difference in predicted and loess-calibrated probabilities; Intercept: model intercept; Q: quality index Q; R^2: Nagelkerke-Cox-Snell-Maddala-Magee R-squared index; Slope: model slope; S:z: the Spiegelhalter Z-test for calibration accuracy; S:p: Spiegelhalter Z-test two-tailed P-value; U: unreliability index U.

Discussion

The main results are: (a) hepatitis A virus seroprevalence among the special population was high, with relevant differences across different subgroups; (b) the lowest hepatitis A virus seroprevalence was in the health professionals and travelers groups, and the highest hepatitis A virus seroprevalence were in the chronic conditions group (liver, heart, and lungs) and HIV infected subjects; (c) an instrument to predict the presence of hepatitis A virus antibodies was developed with good discrimination and calibration in both development and validation sets allowing to identify the subjects more likely to be susceptable to hepatitis A virus infection.

Age is an important indicator of the amount of exposure and is present in many studies, even in studies with special populations. The age effect is related to the idea that as one becomes older, they are more exposed over time and the seroprevalence in older subjects is higher. The year of birth effect is related to the idea that modern generations have more access to preventive measures, such as better quality water and food, sanitary conditions, and immunization, thus decreasing seroprevalence in modern generations. Differences in hepatitis A virus seroprevalence exist in health professionals according to age, similarly to the general population [13,18].

Moreover, data reported here showed that subjects with chronic conditions had higher hepatitis A virus seroprevalence when compared with other special groups and the general population even when adjusted to age effect. Other independent determinants may rise even when age is adjusted, bringing more evidence to Brazil's seroprevalence heterogeneity [19]. Hepatitis A virus infection determinants possibly have interactions with characteristics of special groups, such as schooling level, housing conditions, and socioeconomic levels.

Hepatitis A virus seroprevalence among health professionals is highly variable depending on known seroprevalence determinants such as age and endemic status of an area [16]. In Northern Iran, hepatitis A virus seroprevalence was estimated to be 57.8-86.3% [20]. Meanwhile, in Turkey, hepatitis A virus seroprevalence was estimated to be 34.9% among first-year students in the health field [21]. The results presented here follow the interpretation that the overall seroprevalence among health professionals was around 40%, and it also increased as age increased and decreased as year of birth year.

The burden of hepatitis A virus is greater among people living with HIV, and the hepatitis A virus viral load is higher and viremia is longer in HIV-infected people than in non-HIV patients [22]. Hepatitis A virus seroprevalence is higher among HIV infected patients and among men who have sex with men than in the general population. Evidence also suggests that the age effect is also present in this group even when adjusted for other determinants, such as regionality and concomitant hepatitis B infection [12,23]. Hepatitis A virus seroprevalence among people living with HIV is also variable, being estimated from 15% to 97%, as described in several studies [23,24,25].

Acute hepatitis A in patients with chronic hepatitis B is clinically more severe and has a higher risk of death [26]. Case fatality rates for acute hepatitis A in hepatitis B antigen carriers are 5.6 times higher when compared with HBsAg-negative patients [27]. Hepatitis A virus seroprevalence is also variable among this group (with liver disease hepatitis B virus, hepatitis C virus, or liver cirrhosis) being estimated from 55% to 100% [16,28].

Globalization is changing hepatitis A virus epidemiology. Developments arising from the globalization have allowed diseases to spread more easily and more quickly across international borders [29]. Hepatitis A virus is one of the most common vaccine-preventable diseases among international travelers [30]. Susceptible travelers can contract the virus and often become ill after returning to their country of origin [31].

Hepatitis A virus seroprevalence among travelers is also variable, and besides the place and age determinants, vaccination status and the visiting places may also play a role. Hepatitis A virus seroprevalence among European travelers ranged from 57.6% to 78.9% [32].

The literature has few models to predict hepatitis A outbreaks and hepatitis A-related mortality in special populations, such as liver transplant. We found few multivariable analyses stating hepatitis A virus antibodies as the outcome, however we could not find any published development or validation of a model to predict hepatitis A virus infection or prevalence. The model presented here can be recommended to estimate hepatitis A virus seroprevalence in similar settings, or to estimate the individual probability of hepatitis A virus antibodies. This estimate may help decide if subjects should be further tested/investigated for hepatitis A virus or should be vaccinated.

Some restrictions must be considered. Firstly, this is a retrospective study and some relevant epidemiological data were not available, such as socioeconomic characteristics, schooling level, income, number of households, etc., and were not explored as potential predictors. Moreover, hapatitis A virus seroprevalence may change over time, possibly determining the need for a model update. One may are not be sure if the results observed at an immunization clinic, where subjects seek care on their own, can be inferred to other clinics or special populations that would never seek vaccination.

Conclusions

We conclude that hepatitis A virus seroprevalence was 67.8% in this adult population, but this special group was heterogeneous and seroprevalence may range from 40% to 95.6%. Moreover, hepatitis A virus seroprevalence was slightly decreasing over time, and, as expected, we observed an evident age, year of birth effect, and an interaction between them. The groups with the lowest hapatitis A virus seroprevalence were health professionals and travelers. These groups should be evaluated more carefully regarding their need for vaccination when seeking immunization clinics for other purposes.

The developed model allows for an accurate estimation of the seroprevalence of a particular special group or estimate the probability of a particular subject to have hepatitis A virus antibodies and further consider the need of vaccination or further testing, adjusted for age and birth year.

Contributors

F. Carvalho contributed to the study design, data collection, and writing; and approved the final version. L. G. P. Brandão contributed to the study design, data collection, writing, and review; and approved the final version. M. C. Varela contributed to the study design, data collection, and review; and approved the final version. M. Tuyama contributed to the data collection, and reviewed; and approved the final version. D. F. Correa contributed to the data collection, and review; and approved the final version. A. T. S. Santos contributed to the data collection, and review; and approved the final version. A. S. Lemos contributed to the data collection, and review; and approved the final version. M. D. Costa contributed to the study design, data collection, and review; and approved the final version. J. Cerbino-Neto contributed to the study design, and review; and approved the final version. P. E. A. A. Brasil contributed to the study design, data analysis, and writing; and approved the final version.

Additional information

ORCID: Flavio de Carvalho (0000-0002-0020-0331); Luciana Gomes Pedro Brandão (0000-0002-5271-422X); Margaret Catoia Varela (0000-0002-8161-1158); Mari Tuyama (0000-0002-0082-5155); Danusa Ferreira Correa (0000-0002-6121-6919); Ananza Taina da Silva Santos (0000-0002-3826-5528); Alberto dos Santos de Lemos (0000-0003-0138-6577); Marcellus Dias da Costa (0000-0003-2493-5583); José Cerbino-Neto (0000-0001-9254-917X); Pedro Emmanuel Alvarenga Americano do Brasil (0000-0002-6700-2268).

Acknowledgments

This study was partly supported by the General Coordination of Education, Vice Presidency of Education, Information and Communication (CGE/VPEIC), via a Grant from the Rio de Janeiro State Research Foundation (FAPERJ; grant E-26/210.246/2021) and the Brazilian Coordination for the Improvement of Higher Education Personnel (CAPES; finance code 001).

References

1. Prasoppokakorn T, Vanichanan J, Chaiteerakij R, Jutivorakool K, Udomkarnjananun S, Pongpirul K, et al. A randomized controlled trial of comparative effectiveness between the 2 dose and 3 dose regimens of hepatitis a vaccine in kidney transplant recipients. Sci Rep 2021; 11:50.
2. Organización Mundial de la Salud. Hepatitis A. https://www.who.int/es/news-room/fact-sheets/detail/hepatitis-a (accessed on 27/Aug/2021).
3. Iorio N, John S. Hepatitis A. Treasure Island: StatPearls Publishing; 2021.
4. Mirzaei J, Ziaee M, Farsad SA, Fereydooni M, Anani Sarab G, Rezvani Khorashad MR. Vaccination against hepatitis A for hemophilic patients: is it necessary? Hepat Mon 2016; 16:e37447.
5. World Health Organization. The immunological basis for immunization series: module 18: hepatitis A. https://apps.who.int/iris/handle/10665/44570 (accessed on 22/Oct/2021).
6. Nunes HM, Soares MCP, Silva HMR. Infecção pelo vírus da hepatite A em área indígena da Amazônia oriental brasileira. Rev Soc Bras Med Trop 2004; 37:52-6.
7. Department of Immunization, Vaccines and Biologicals, World Health Organization. The global prevalence of hepatitis A virus infection and susceptibility: a systematic review. https://apps.who.int/iris/bitstream/handle/10665/70180/WHO_IVB_10.01_eng.pdf (accessed on 17/May/2021).
8. WHO position paper on hepatitis A vaccines – June 2012. Wkly Epidemiol Rec 2012; 87:261-76.
9. Aggarwal R, Goel A. Hepatitis A: epidemiology in resource-poor countries. Curr Opin Infect Dis 2015; 28:488-96.
10. Secretaria de Vigilância em Saúde, Ministério da Saúde. Hepatites virais 2021. Boletim Epidemiológico de Hepatites Virais 2021; número especial.
11. Secretaria de Vigilância em Saúde, Ministério da Saúde. Hepatites virais 2017. Boletim Epidemiológico de Hepatites Virais 2017; 48(24).
12. Santos MV, Lopes MH. Vacina inativada contra a hepatite A: revisão da literatura e considerações sobre seu uso. Rev Soc Bras Med Trop 1997; 30:145-57.
13. Ji SK, Jang SH, Park MH, Lee JE, Jeong HS, Park J, et al. A study on seroprevalence of hepatitis A virus among healthcare workers at a University-affiliated Hospital in Deajeon, Korea. Korean J Healthc Assoc Infect Control Prev 2020; 25:54-9.
14. Saneian H, Rahimi H, Shoaei P. Hepatitis A seropositivity among first-year students of the medical university in Isfahan, Iran. Int J Prev Med 2014; 5 Suppl 3:S208-12.
15. Özden HT. Hepatitis A seroprevalence in patients with chronic viral hepatitis in Konya, Turkey. Eur J Gastroenterol Hepatol 2016; 28:333-7.
16. Cho HC, Paik SW, Kim YJ, Choi MS, Lee JH, Koh KC, et al. Seroprevalence of anti-HAV among patients with chronic viral liver disease. World J Gastroenterol 2011; 17:236-41.
17. Departamento de Imunização e Doenças Transmissíveis, Secretaria de Vigilância em Saúde, Ministério da Saúde. Manual dos centros de referência para imunobiológicos especiais. https://bvsms.saude.gov.br/bvs/publicacoes/manual_centros_imunobiologicos_especiais_5ed.pdf (accessed on 26/Sep/2021).
18. González-Praetorius A, Rodríguez-Avial C, Fernández C, Pérez-Pomata MT, Gimeno C, Bisquert J. Prevalencia de hepatitis A en la provincia de Guadalajara. ¿Es España un país de baja endemia? Enferm Infecc Microbiol Clín 2001; 19:428-31.
19. Kury CM, Pinto MA, Silva JP, Cruz OG, Vitral CL. 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 Saúde Pública 2016; 32:e00175614.
20. Bayani M, Sadeghi M, Kalantari N, Sayadmanesh A. Hepatitis A virus seropositivity in nurses and paramedical personnel at a University Hospital in North Iran. Iran Red Crescent Med J 2013; 15:409-13.
21. Acikgoz A, Cimrin D, Kizildag S, Esen N, Balci P, Sayiner AA. Hepatitis A, B and C seropositivity among first-year healthcare students in western Turkey: a seroprevalence study. BMC Infect Dis 2020; 20:529.
22. Gallego M, Robles M, Palacios R, Ruiz J, Nuño E, Márquez M, et al. Impact of acute hepatitis A virus (HAV) infection on HIV viral load in HIV-infected patients and influence of HIV infection on acute HAV infection. J Int Assoc Physicians AIDS Care (Chic) 2011; 10:40-2.
23. Lee YL, Lin KY, Cheng CY, Li CW, Yang CJ, Tsai MS, et al. Evolution of hepatitis A virus seroprevalence among HIV-positive adults in Taiwan. PLoS One 2017; 12:e0186338.
24. Aloise R, De Almeida AJ, Sion FS, Morais-De-Sá CA, Gaspar AMC, De Paula VS. Changes in hepatitis A virus Seroepidemiology in HIV-Infected Brazilian patients. Int J STD AIDS 2008; 19:321-6.
25. Tseng YT, Sun HY, Chang SY, Wu CH, Liu WC, Wu PY, et al. Seroprevalence of hepatitis virus infection in men who have sex with men aged 18-40 years in Taiwan. J Formos Med Assoc 2012; 111:431-8.
26. Reiss G, Keeffe EB. Hepatitis vaccination in patients with chronic liver disease. Aliment Pharmacol Ther 2004; 19:715-27.
27. Ahmad F, Hamzah NAC, Mustaffa N, Gan SH. Anti-hepatitis A seroprevalence among chronic viral hepatitis patients in Kelantan, Malaysia. World J Gastroenterol 2011; 17:4130-4.

28. Shoaei P, Zeidabadinejad L, Hassannejad R, Ataei B, Yaran M, Kassaian N, et al. Seroprevalence of hepatitis A in patients with chronic hepatitis C in Isfahan Province. Int J Prev Med 2012; 3 Suppl 1:S102-6.
29. Gushulak BD, MacPherson DW. Population mobility and infectious diseases: the diminishing impact of classical infectious diseases and new approaches for the 21st century. Clin Infect Dis Off Publ Infect Dis Soc Am 2000; 31:776-80.
30. Boggild AK, Castelli F, Gautret P, Torresi J, von Sonnenburg F, Barnett ED, et al. Vaccine preventable diseases in returned international travelers: results from the GeoSentinel Surveillance Network. Vaccine 2010; 28:7389-95.
31. Jacobsen KH. Globalization and the changing epidemiology of hepatitis A virus. Cold Spring Harb Perspect Med 2018; 8:a031716.
32. Rocha S, Tejo S, Ferreira E, Trindade L, Rabadão E, Marques N, et al. Prevalence of hepatitis A virus antibody in Portuguese travelers: a new paradigm. Acta Med Port 2017; 30:534-40.

Resumo

Este estudo teve como objetivo estimar a soroprevalência do vírus da hepatite A, em indivíduos atendidos em uma clínica de medicina de viagem e imunização no Rio de Janeiro, Brasil, e desenvolver um modelo de predição para a soroprevalência do vírus da hepatite A. Esta pesquisa retrospectiva incluiu indivíduos sequencialmente de abril de 2011 a junho de 2019, em uma clínica de medicina de viagem e uma clínica de vacinação de população especial, que, por qualquer motivo, tem um resultado de quimioluminescência IgG antivírus da hepatite A . Os dados dos participantes foram verificados em prontuário eletrônico. Os dados foram divididos em desenvolvimento e validação, tomando 2018 como data limite da divisão. Um modelo linear generalizado elástico com distribuição binomial submetido a validação cruzada foi aplicado. Foram analisados 2.944 indivíduos atendidos. A soroprevalência geral do vírus da hepatite A foi de 67,8%. Profissionais de saúde, viajantes e contatantes de indivíduos imunocomprometidos apresentaram menor soroprevalência, variando de 40% a 55%, enquanto indivíduos com condições crônicas (coração, pulmão e fígado) tiveram soroprevalência variando de 89% a 94%. Os preditores retidos no modelo final foram sexo, idade, ano de nascimento, viajantes, HIV/aids, asplenia funcional, candidatos a transplante, comunicante domiciliar, imunossupressão relacionada ao câncer e profissionais de saúde. A área sob a curva foi de 0,836 e o erro máximo foi de 0,051. Os usuários podem fazer previsões com uma calculadora (https://pedrobrasil.shinyapps.io/INDWELL/). Os grupos com menor soroprevalência devem ser avaliados com mais cuidado quanto à necessidade de vacinação contra o vírus da hepatite A, mesmo quando procuram clínicas de vacinação para outros fins.

Hepatite A; Medicina de Viagem; Doença Crônica; Pessoal de Saúde; Programas de Imunização

Resumen

Los objetivos del estudio son estimar la seroprevalencia de hepatitis A en sujetos que asisten a una clínica de medicina para viajeros e inmunización en Río de Janeiro, Brasil, y desarrollar un modelo de predicción de la seroprevalencia de hepatitis A. Esta investigación de seguimiento retrospectivo incluyó a individuos de forma secuencial desde abril de 2011 hasta junio de 2019 en una clínica de medicina para viajeros y de vacunación de poblaciones especiales que por cualquier motivo tienen un resultado de quimioluminiscencia IgG anti-hepatitis A. Los datos de los participantes se verificaron en los registros médicos electrónicos. Los datos se dividieron en conjunto de desarrollo y validación tomando 2018 como fecha de corte. Se realizó un modelo lineal generalizado validado cruzado elástico con distribución binomial. Se analizaron un total de 2.944 sujetos atendidos. La seroprevalencia global del hepatitis A fue del 67,8%. Los profesionales sanitarios, los viajeros y las personas en contacto con sujetos inmunodeprimidos presentaron una seroprevalencia más baja, que osciló entre el 40% y el 55%, mientras que los sujetos con afecciones crónicas (cardíacas, pulmonares y hepáticas) presentaron una seroprevalencia que varió entre el 89% y el 94%. Los predictores retenidos en el modelo final fueron el sexo, la edad, el año de nacimiento, los viajeros, el VIH/SIDA, la disfunción del bazo, los candidatos a trasplante, los comunicadores domésticos, la inmunosupresión relacionada con el cáncer y los profesionales sanitarios. Su área bajo la curva fue de 0,836 y el error máximo de 0,051. Los usuarios pueden hacer predicciones con una calculadora (https://pedrobrasil.shinyapps.io/INDWELL/). Los grupos con menor seroprevalencia deben ser evaluados más cuidadosamente en cuanto a la necesidad de vacunación contra hepatitis A, incluso cuando acudan a las clínicas de vacunación con otros fines.

Hepatitis A; Medicina del Viajero; Enfermedad Crónica; Personal de Salud; Programas de Inmunización

Submitted on 25/Apr/2022
Final version resubmitted on 28/Jun/2022
Approved on 12/Dec/2022