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ASSESSMENT OF COLLECTIVE IMMUNITY TO ENTERIC HEPATITIS VIRUSES IN THE KYRGYZ POPULATION

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ОЦЕНКА ПОПУЛЯЦИОННОГО ИММУНИТЕТА К ВИРУСАМ ЭНТЕРАЛЬНЫХ ГЕПАТИТОВ У НАСЕЛЕНИЯ КЫРГЫЗСКОЙ РЕСПУБЛИКИ

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Abstract

The problem of viral hepatitis A (HA) and E (HE), has remained relevant for many decades. According to estimates by the World Health Organization, millions of people are exposed annually to the risk of infection with these hepatitis A (HAV) and E (HEV) viruses. Because HA and HE can be asymptomatic, their true prevalence is very difficult to estimate.

The aim was to assess seroprevalence of HAV and HEV infections in the Kyrgyz Republic, taking into account the infectious and vaccination status and socio-demographic characteristics of volunteers.

Materials and methods. The cohort under examination comprised 6610 apparently healthy individuals (volunteers) aged from 1 to 70+ years residing in the Kyrgyz Republic. The questionnaire included the collection of personal data, information on chronic diseases, blood transfusions, and surgical interventions, as well as specific information on each type of infection considered in the study, including data on past cases of hepatitis A and E, and vaccination against hepatitis A. ELISA analysis for HA and HE marker presence involved anti-HAV IgG, and anti-HEV IgG qualitative determination (test-systems by Vector-Best, and Diagnostic Systems RPC).

Results. During the study, anti-HAV IgG antibodies were detected for 76.8% of cases, and anti-HEV IgG antibodies were detected for 5.6% of cases. The seroprevalence rate for HAV and HEV was higher among women than among men. A direct correlation was shown between the occurrence of anti-HAV IgG and anti-HAV IgG with the age of the volunteers. Anti-HAV IgG was found in 75.4% of individuals denying hepatitis A history, while anti-HEV IgG was detected in 5.6% of those denying hepatitis E history. The share of vaccinated against HAV individuals was 5.9%. During the study, an assessment of the prevalence of markers for HA and HE in the population per 100 thousand inhabitants was conducted, which resulted in 76.030 cases per 100 thousand for HA, and 5.567 cases per 100 thousand for HE.

Conclusion. The need is obvious continuing nationwide vaccination initiatives against hepatitis A, expanding mandatory vaccination coverage for vulnerable groups,

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conducting additional evaluations of existing preventive measures, launching educational campaigns focused on HA and HE prevention strategies.

Keywords: vaccine-preventable infections, collective immunity, viral hepatitis A, viral hepatitis E, hepatitis A virus, hepatitis E virus, seroprevalence, antibodies, Kyrgyz Republic, cohort study.

Резюме

Проблема вирусных гепатитов, в частности гепатитов А (ГА) и Е (ГЕ), остается актуальной на протяжении многих десятилетий. По оценкам Всемирной организации здравоохранения, ежегодно миллионы людей подвергаются риску заражения вирусами гепатита А (ВГА) и Е (ВГЕ). Поскольку ГА и ГЕ могут протекать бессимптомно, их истинную распространенность очень сложно оценить.

Целью данного исследования была оценка серопревалентности инфекций ВГА и ВГЕ в Кыргызской Республике с учетом инфекционного и вакцинального статуса, а также социально-демографических характеристик волонтеров.

Материалы и методы. Обследуемую когорту составили 6610 практически здоровых лиц (волонтеров) в возрасте от 1 до 70+ лет, проживающих в Республике Кыргызстан. Анкетирование включало сбор персональных данных, информации о хронических заболеваниях, переливаниях крови и хирургических вмешательствах, а также конкретной информации по каждому виду инфекции, рассматриваемой в исследовании, включая данные о перенесенных случаях гепатита А и Е, вакцинации против гепатита А. Анализ ИФА на наличие маркеров ГА и ГЕ включал качественное определение анти-HAV IgG и анти-HEV IgG.

Результаты. В ходе исследования анти-ВГА IgG антитела были обнаружены у 5074 человек, а анти-ВГЕ IgG антитела у 368 человек, что составило 76,8% и 5,6% случаев, соответственно. Уровень серопревалентности к ВГА и к ВГЕ среди женщин был выше, чем среди мужчин. Была показана прямая корреляция между частотой анти-ВГА IgG и анти-ВГЕ IgG и возрастом волонтеров. В подгруппе лиц, уверенно отрицавших ГА в анамнезе, анти-ВГА IgG антитела были обнаружены в 75,4% случаев. В подгруппе лиц, уверенно отрицавших ГЕ в анамнезе, анти-ВГЕ IgG антитела были обнаружены у 5,6% участников. Доля вакцинированных против ВГА лиц составила 5,9%. Корреляции между долей вакцинированных лиц и

возрастом не выявлено. При оценке связи между наличием антител класса IgG к ВГА и статусом вакцинации против ВГА статистически значимых различий не выявлено. В ходе исследования была проведена оценка распространенности маркеров ГА и ГЕ в популяции на 100 тыс. жителей, по результатам которой для ГА было получено 76,030 случаев на 100 тыс. населения, для ГЕ – 5,567 случаев на 100 тыс. населения.

Conclusion. Очевидна необходимость продолжения общенациональных инициатив по вакцинации против вируса гепатита А, расширения обязательного охвата вакцинацией уязвимых групп, проведения дополнительных оценок существующих профилактических мер, адаптации их к местным условиям, запуска образовательных кампаний, ориентированных на стратегии профилактики гепатитов А и Е.

Ключевые слова: вакциноуправляемые инфекции, популяционный иммунитет, вирусный гепатит А, вирусный гепатит Е, вирус гепатита А, вирус гепатита Е, серопревалентность, антитела, Кыргызская Республика, когортное исследование.

1 Introduction

The problem of viral hepatitis, particularly A (HA) and E (HE), has remained relevant for many decades and continues to pose a global threat to public health. Hepatitis A (HAV) and E (HEV) viruses represent serious infectious threats worldwide, especially in countries where insufficient levels of hygiene and sanitation prevail [19]. According to estimates by the World Health Organization (WHO), millions of people are exposed annually to the risk of infection with these viruses, which also leads to significant economic losses.

This hepatitis exhibits a wide range of clinical manifestations, ranging from mild forms to severe complications such as liver failure [18, 19, 27]. An additional danger lies in the ability of HEV to cause fulminant hepatitis, characterized by high mortality rates, particularly among pregnant women [1]. Treatment of acute forms requires substantial resources including medical personnel, medications, and infrastructure. Chronic consequences of infection can lead to long-term costs associated with rehabilitation and social support for affected individuals [23].

Currently, vaccines against HAV have been developed, and they have proven effective and safe, providing reliable protection against infection [20, 24, 26, 28]. Additionally, a vaccine against HEV has already been developed, although its use is currently extremely limited [14, 16]. Mass vaccination appears promising as an effective measure to prevent outbreaks. However, the use of enteric hepatitis vaccines is not widespread in all countries, which could undoubtedly pose a significant public health problem.

Thus, the relevance of hepatitis A and E issues is due to their widespread prevalence, severe course of disease, and economic and social costs arising from mass outbreaks. Therefore, identification and prevention of enteric hepatitis are critically important tasks within modern healthcare programs.

In the Kyrgyz Republic, there was consistently high incidence of acute hepatitis A (AHA) until 2019. Following that year, anti-epidemic measures were introduced regarding COVID-19, which also impacted the occurrence of HA (Figure 1) [3]. Over the last 25 years, three waves of increased HA cases have been observed,

with the most recent wave clearly beginning in 2024. This serves as irrefutable evidence of the urgency of early detection and timely implementation of preventive measures against acute viral hepatitis in this region.

According to data from the «Report on Infectious and Parasitic Diseases» in the Kyrgyz Republic: in 2021, there were 1920 registered cases of AHA (children under 14 years old – 1652 cases, aged 14-17 years – 63 cases); in 2022, there were 2935 cases (children under 14 years old – 2625 cases, aged 14-17 years – 94 cases); in 2023, there were 8973 cases (children under 14 years old – 8301 cases, aged 14-17 years – 275 cases); and in 2024, there were 20996 cases (children under 14 years old – 19350 cases, aged 14-17 years – 775 cases). During these same four years, according to reports, only one case of acute hepatitis E (AHE) was recorded in 2023 [2].

Based on the presented data, particular attention should be paid to prevention efforts among children and adolescents whose bodies are at a stage of growth and immune system development.

Despite the successes achieved in developing vaccines and implementing preventive measures, unresolved challenges remain concerning early diagnosis, adequate treatment of chronic and latent forms, and effective communication with the general public. Continuous efforts are needed to overcome existing threats and increase the level of protection and awareness among the population regarding enteric hepatitis.

Thus, the aim of this study was to assess seroprevalence of HAV and HEV infections in the Kyrgyz Republic, taking into account the infectious and vaccination status and socio-demographic characteristics of volunteers.

2 **Materials and Methods**

A cross-sectional, randomized study was conducted as part of Rospotrebnadzor's program 'Assessment of Collective Immunity to Vaccine-Controllable and Other Significant Infections'. The program was approved by the local ethics committee of the Saint Petersburg Pasteur Institute (protocol No. 166 dated August 01, 2023). Participants, or their legal representatives, were informed

about the objectives and methods of the research and provided written consent. Volunteers for participation in the study were selected through questionnaires. The questionnaire included the collection of personal data (full name, gender, date of birth, place of residence, occupation, information on attendance at kindergartens, schools, universities by children, contact details, medical organization with which the volunteer is associated), information on chronic diseases, blood transfusions, and surgical interventions (with dates), as well as specific information on each type of infection considered in the study, including data on past cases of hepatitis A and E (dates of illness, vaccination against hepatitis A and revaccination, vaccine names, and dates) [8, 9]. Vaccination data were obtained from vaccination certificates or other medical documentation.

After processing the questionnaires, individuals who met the established requirements were invited to the medical center for subsequent laboratory tests. Exclusion criteria included:

- refusal to undergo laboratory testing involving venipuncture and subsequent peripheral blood sampling;
- active form of an infectious disease of any etiology.

The study material consisted of plasma samples taken with the use of EDTA anticoagulant in November-December 2024. The size of the representative sample was calculated using a formula based on the Moivre-Laplace theorem, following the previously described methodology, utilizing an online calculator. The cohort under examination comprised 6,610 apparently healthy individuals (volunteers) residing within the Kyrgyz Republic.

Volunteers were divided into nine age groups: 1-5 years (n=909), 6-11 years (n=1021), 12-17 years (n=876), 18-29 years (n=668), 30-39 years (n=685), 40-49 years (n=698), 50-59 years (n=692), 60-69 years (n=654), and 70 years and older (n=407). The proportion of child age groups in the overall sample of volunteers was approximately equal and varied in number by 1-2%. Adult groups were comparable in volume, except for the group aged 70 and over (Figure 2).

It should be noted that the male portion of the surveyed volunteer cohort accounted for 26.4% (n=1904), while the female portion made up 73.6% (n=4706).

ELISA analysis for HA and HE marker presence involved anti-HAV IgG, and anti-HEV IgG qualitative determination (test-systems by Vector-Best, and Diagnostic Systems RPC), in compliance with manufacturer instructions.

Data analysis was performed using MS Excel software and GraphPad Prism 9.3 (GraphPad Software Inc., https://www.graphpad.com/support/prism-5-updates/). To assess statistical error, the exact Cloepper-Pearson interval was applied. Results are presented with a 95% confidence interval (CI). For assessing the significance of differences in quantitative data during paired comparisons, either Fisher's exact test or the Chi-square test with Yates' correction was used depending on the characteristics of the samples. A probability value of $p<0.05$ was set as the threshold for statistical significance. Correlation analysis was conducted taking into account compliance with parametric distribution, with calculation of Spearman rank correlation coefficients (rs), whose values were evaluated using Chaddock's scale. Differences were considered statistically significant when $p<0.05$.

3 **Results**

During the study, out of 6610 volunteers, anti-HAV IgG antibodies were detected in 5074 individuals, and anti-HEV IgG antibodies were detected in 368 individuals, accounting for 76.8% (95% CI: 75.7-77.8%) and 5.6% (95% CI: 5.0-6.2%) of cases, respectively.

Within the scope of this study, differences in the frequencies of antibodies to HAV and HEV between men and women were identified. The seroprevalence rate for HAV was higher among women (n=3850 out of 4706; 81.8%; 95% CI: 80.7-82.9%) than among men (n=1224 out of 1904; 64.3%; 95% CI: 62.1-66.4%) — χ^2 = 232.41 at $p < 0.0001$, df=1, OR= 2.499 (95% CI: 2.2-2.8). Similarly, the frequency of anti-HEV IgG antibodies was also higher among women (n=293 out of 4706; 6.2%; 95% CI: 5.6-7.0%) than among men (n=75 out of 1904; 3.9%; 95% CI: 3.1-4.9%) — χ^2 = 13.055 at $p = 0.0003$, df=1, OR= 1.619 (95% CI: 1.2-2.1).

Also, seroprevalence to HAV and HEV was assessed in different age groups (Table 1).

In the analysis of antibody prevalence depending on age, a significant increase in the occurrence of IgG antibodies to HAV was observed with increasing age in groups up to 50 years old. Between the groups aged 40-49, 50-59, 60-69, and 70 years or older, no significant differences were found. Among the three children's groups, anti-HAV IgG antibodies were significantly more common in the 12-17-year-old group than in the 6-11-year-old group ($\chi^2 = 77.196$ at $p < 0.0001$, df = 1, OR = 2.345 (95% CI: 1.9-2.8)) and the 1-5-year-old group ($\chi^2 = 173.01$ at $p < 0.0001$, df = 1, OR = 3.687 (95% CI: 3.0-4.5)), while they were also more frequent in the 6-11-year-old group compared to the 1-5-year-old group ($\chi^2 = 23.754$ at $p < 0.0001$, df = 1, OR = 1.572 (95% CI: 1.3-1.9)). In the 18-29-year-old group, seroprevalence for HAV was higher than in the 12-17-year-old group — $\chi^2 = 37.04$ at $p < 0.0001$, df = 1, OR = 2.202 (95% CI: 1.7-2.8). In the 30-39-year-old group, IgG antibodies to HAV were detected more frequently than in the 18-29-year-old group — $\chi^2 = 26.002$ at $p < 0.0001$, df = 1, OR = 2.562 (95% CI: 1.8-4.0), but less often than in the 40-49-year-old group — $\chi^2 = 4.471$ at $p = 0.0345$, df = 1, OR = 1.723 (95% CI: 1.1-2.8).

In the sequential comparative analysis of the seroprevalence of anti-HEV IgG antibodies by age, significant differences were only revealed between the groups aged 50-59 years and 40-49 years — $\chi^2 = 8.912$ at $p = 0.0028$, df = 1, OR = 1.8 (95% CI: 1.2-2.5). Between the groups aged 50-59, 60-69, and 70 years or older, no significant differences were found ($p > 0.05$). When comparing the groups aged 50-59 with the highest frequency of anti-HEV IgG antibodies, and those aged 1-5 with the lowest frequency of anti-HEV IgG antibodies, χ^2 was 7.715 at $p = 0.0055$, df = 1, OR = 2.186 (95% CI: 1.3-3.8).

During the study, an assessment of correlations between the presence of anti-HAV IgG and anti-HEV IgG antibodies and the age of the examined individuals was conducted (Figure 3).

As part of the correlation analysis of the prevalence level of hepatitis virus antibodies with age, trend lines were constructed. To assess the correlation of HAV seroprevalence relative to age, a linear regression line was built with the following characteristics: the coefficient of determination R^2 was 0.785, the multiple correlation coefficient R = 0.89. The Spearman rank correlation coefficient rs = 0.85, df = 7, critical value of the Spearman criterion = 0.7, p=0.0061, the strength of association according to Chaddock's scale is high.

Similarly, within the framework of evaluating the linear regression of HEV seroprevalence relative to age, a straight line was obtained with the following parameters: the coefficient of determination R^2 was 0.8887; the multiple correlation coefficient R = 0.95. The Spearman rank correlation coefficient rs = 0.9333, df=7, critical value of the Spearman criterion = 0.7, p=0.0007, the strength of association according to Chaddock's scale is very high.

A total of 263 volunteers reported having had HA, which accounted for 4.0% (95% CI: 3.5-4.5%), of whom 251 were anti-HAV IgG-positive (95.4%, 95% CI: 92.2-97.6%). Only 4 volunteers reported having had HE, accounting for 0.1% (95% CI: 0.02-0.2%), none of whom tested positive for anti-HEV IgG antibodies. In the subgroup of individuals who confidently denied having had HA (n=6055, representing 91.6% of the entire sample, 95% CI: 90.9-92.3%), anti-HAV IgG antibodies were detected in 4567 people (75.4%, 95% CI: 74.3-76.5%). In the subgroup of individuals who confidently denied having had HE (n=6557, making up 99.2% of the whole sample, 95% CI: 99.0-99.4%), anti-HEV IgG antibodies were found in 365 participants (5.6%, 95% CI: 5.0-6.2%). There were 292 individuals uncertain about their infectious status regarding HA, comprising 4.4% (95% CI: 3.9-5.0%), of whom 256 were seropositive (87.7%; 95% CI: 83.3-91.2%). Similarly, there were 49 individuals unsure about their infectious status concerning HE, amounting to 0.7% (95% CI: 0.6-1.0%), of whom 3 had anti-HEV IgG antibodies (6.1%; 95% CI: 1.3-16.9%).

The seroprevalence of anti-HAV IgG and anti-HEV IgG antibodies across different age groups based on infection status is presented in Figures 4 and 5.

When assessing the correlation, it was shown that the prevalence of anti-HAV IgG among individuals who had HA may depend on age, revealing a linear relationship with the following characteristics: the coefficient of determination R^2 was 0.6091; the multiple correlation coefficient R = 0.78. The Spearman's rank correlation coefficient rs = 0.801, df=7, the critical value of the Spearman criterion = 0.7, p=0.0341, the strength of association according to Chaddock's scale is high.

Among volunteers who denied having had HA but had detectable anti-HAV IgG antibodies, a linear dependence of HAV seroprevalence on age was also revealed: the coefficient of determination R^2 was 0.6496; the multiple correlation coefficient R = 0.81. The Spearman's rank correlation coefficient rs = 0.850, df=7, the critical value of the Spearman criterion = 0.7, p=0.0061, the strength of association according to Chaddock's scale is very high.

A significant predominance of anti-HAV IgG occurrence was demonstrated in each age group compared to the previous one in groups up to 50 years old (Table 2). In the group aged 40–49 years, the seroprevalence of HAV among volunteers who were confident that they had never suffered from hepatitis A was higher than in the group aged 30–39 years ($\chi2 = 4.758$ with $p = 0.0292$, df = 1, OR = 1.773 (95% CI: 1.1–2.9)). In the group aged 30–39 years, it was higher compared to the group aged 18–29 years ($\chi2 = 26.911$ with $p < 0.0001$, df = 1, OR = 2.67 (95% CI: 1.8–3.9)). In the group aged 18–29 years, it was higher compared to the pediatric group aged 12–17 years ($\chi2 = 27.867$ with $p < 0.0001$, df = 1, OR = 2.037 (95% CI: 1.6–2.7)). Among children, antibodies against HAV were more common in the age group 6–11 years compared to those aged 1–5 years ($\chi2 = 19.427$ with $p < 0.0001$, df = 1, OR = 1.521 (95% CI: 1.3–1.8)) and even more frequent in the age group 12–17 years compared to those aged 6–11 years ($\chi2 = 72.048$ with $p < 0.0001$, df = 1, OR = 2.352 (95% CI: 1.9–2.9)).

It should be noted that in the group with an undetermined infectious status, a correlation between the occurrence of anti-HAV IgG antibodies and age was also observed: a linear dependency with the following characteristics: the coefficient of determination R^2 was 0.7688; the multiple correlation coefficient R = 0.88. The

Spearman's rank correlation coefficient rs = 0.942, df=7, the critical value of the Spearman criterion = 0.7, p=0.0019, the strength of association according to Chaddock's scale is very high.

The analysis of the occurrence of anti-HEV IgG antibodies based on infectious status was performed only in relation to the group that confidently denied HE in their history. It is not difficult to trace how the results of the analysis turned out to be similar to the overall sample since the groups with unknown infectious status and those who had contracted HE together included only 53 people.

The significance of various occupations for the frequency of occurrence of anti-HAV IgG and anti-HEV IgG antibodies was assessed. Preschoolers (n=648 individuals; IgG antibodies to HAV detected in 40.3% (n=261), 95% CI: 36.5-44.2%; IgG antibodies to HEV detected in 1.9% (n=12), 95% CI: 1.0-3.2%), schoolchildren (n=1627 individuals; IgG antibodies to HAV detected in 60.1% (n=978), 95% CI: 57.7-62.5%; IgG antibodies to HEV detected in 1.9% (n=34), 95% CI: 1.5-2.9%), students (n=164 individuals; IgG antibodies to HAV detected in 72.0% (n=118), 95% CI: 64.4-78.7%; IgG antibodies to HEV detected in 1.8% (n=3), 95% CI: 0.4-5.3%) and retirees (n=611 individuals; IgG antibodies to HAV detected in 96.9% (n=592), 95% CI: 95.2-98.1%; IgG antibodies to HEV detected in 13.58% (n=83), 95% CI: 11.0-16.6%) were considered separately as these groups are likely more dependent on volunteer age.

In these groups, a significant predominance of anti-HAV IgG occurrence was also demonstrated in each subsequent age group compared to the previous one. Regarding the occurrence of anti-HEV IgG antibodies, no significant differences were found between preschoolers, schoolchildren, and students ($p>0.05$). In the retiree group, seroprevalence for HEV was significantly higher than in the other three groups: preschoolers ($\chi^2 = 60.38$ at $p < 0.0001$, df = 1, OR = 8.331 (95% CI: 4.5-15.4)), schoolchildren ($\chi^2 = 116.14$ at $p < 0.0001$, df = 1, OR = 7.365 (95% CI: 4.9-11.1)) and students ($\chi^2 = 16.94$ at $p < 0.0001$, df = 1. OR = 8.436 (95% CI: 2.6-27.1)).

Among the adult population, the smallest groups were from the tourism sector (n=6 individuals; IgG antibodies to HAV detected in 100% (n=6), 95% CI: 54.1-100.0%; IgG antibodies to HEV detected in 0% (n=0), 95% CI: 0.0-45.9%), the arts/creativity sector (n=13 individuals; IgG antibodies to HAV detected in 92.3% (n=12), 95% CI: 64.0-99.8%; IgG antibodies to HEV detected in 15.4% (n=2), 95% CI: 1.9-45.5%), as well as the military personnel group (n=10 individuals; IgG antibodies to HAV detected in 90.0% (n=9), 95% CI: 55.5-99.8%; IgG antibodies to HEV detected in 10.0% (n=1), 95% CI: 0.3-44.5%).

Among the remaining groups (Figure 6), the lowest prevalence of anti-HAV IgG antibodies was found among workers in the IT sector (n=28 out of 66 individuals; 42.4%, 95% CI: 30.3-55.2%), office workers (n=61 out of 81 individuals; 75.3%, 95% CI: 64.5-84.2%), and the education sector (n=168 out of 198 individuals; 84.9%, 95% CI: 79.1-89.5%). At the same time, the seroprevalence in the IT worker group was significantly lower than in the office worker group — χ^2 = 15.115 at p = 0.0001, df = 1, OR = 4.139 (95% CI: 2.1-8.4); lower than in the education sector group — χ^2 = 44.396 at p < 0.0001, df = 1, OR = 7.600 (95% CI: 4.1-14.2), as well as when compared to all other groups. No significant differences were found between the education sector and office worker groups (p>0.05).

The highest frequency of anti-HAV IgG antibodies was observed in the public service worker group (n=167 out of 174; 96.0%, 95% CI: 91.9-98.4%), where the rate was significantly higher than among volunteers from the IT sector — χ^2 = 11.593 at p = 0.0007, df = 1, OR =4.260 (95% CI: 1.8-10.0), office workers — χ^2=22.804 at p < 0.0001, df = 1, OR = 7.822 (95% CI: 3.2-19.4), and the education sector — χ^2=86.598 at p < 0.0001, df = 1, OR = 32.378 (95% CI: 13.2-79.7). No significant differences were found with other groups (p>0.05).

High seroprevalence for HAV was also noted in the medical worker group (n=1197 out of 1276; 93.8%, 95% CI: 92.3-95.1%), where the rate was significantly higher than among volunteers from the IT sector — χ^2 = 201.8 at p < 0.0001, df = 1, OR = 20.563 (95% CI: 12.0-35.2), office workers — χ^2=35.857 at p < 0.0001, df = 1, OR = 4.968 (95% CI: 2.9-8.6), and the education sector — χ^2=18.808 at p <

0.0001, df = 1, OR = 2.706 (95% CI: 1.7-4.2). No significant differences were found with other groups (p>0.05).

The occurrence of anti-HEV IgG antibodies was zero in both the IT sector group (n=0 out of 66; 0%; 95% CI: 0.0-54.4%) and the production worker group (n=0 out of 24; 0%; 95% CI: 0.0-14.3%). In other groups, the maximum seroprevalence was observed among healthcare workers (n=99 out of 1276 individuals, 7.8%; 95% CI: 6.4-9.4%). Low occurrence of anti-HEV IgG antibodies was found in the government employee group (n=7 out of 174 individuals, 4.0%, 95% CI: 1.6-8.1%) and the education sector group (n=9 out of 198 individuals, 4.5% CI: 2.1-8.5%). However, no statistically significant differences were found between these groups (p< 0.05).

During the study, the proportion of vaccinated individuals was analyzed. Calculations were made only with respect to volunteers who were certain of their vaccination status, as evidenced by an appropriate entry in their medical documents. The share of vaccinated individuals was 5.9% (n=373 out of 6280 volunteers) as shown in Table 3. When comparing vaccination rates between men and women across different age groups, significant differences were only observed in the category of 70 years and older, where men (n=0 of 104) were vaccinated less frequently than women (n=25 of 303) – $\chi^2 = 7.767$, p = 0.0053, df = 1. In all other age groups, no significant differences were found between genders (p > 0.05).

Among volunteers, no differences were found in the proportion of vaccinated individuals between groups of children under 18 years old (groups: 1-5 years, 6-11 years, 12-17 years). Therefore, a combined group of 1-17 years was considered further. A significant difference was observed exclusively between the group with the highest prevalence of vaccinated individuals, those aged 30-39, in comparison to groups with low vaccination rates: those aged 60-69 years (χ^2=7.534 at p=0.0061, df = 1, OR = 2.021 (95% CI: 1.2-3.3)) and those aged 40-49 years (χ^2=6.354 at p=0.0117, df = 1, OR = 1.163 (95% CI: 1.2-2.9)). There was also no correlation detected between the proportion of vaccinated individuals and age (p > 0.05). Consequently, the level of vaccination remained stable with minimal fluctuations.

When assessing the association between the presence of anti-HAV IgG antibodies and HAV vaccination status, no statistically significant differences were found ($p > 0.05$) (Table 4).

As mentioned above, when analyzing data on the prevalence of anti-HAV IgG antibodies depending on vaccination status, we included only those volunteers whose HAV vaccination was documented in their vaccination certificate along with the specified date, excluding individuals without such documentation. Since antibodies detected in unvaccinated individuals are obviously associated with past hepatitis A infection, further analysis focused on the prevalence of anti-HAV IgG among volunteer groups with various combinations of infectious and vaccination status (Table 5).

Upon comparative analysis of unvaccinated individuals, statistically significant differences were shown in the frequency of anti-HAV IgG occurrence between those who had experienced hepatitis A (95.8%, 95% CI: 92.4-97.7%) and those who did not have hepatitis A (75.2%, 95% CI: 74.1-76.4%) – $\chi^2 = 51.269$, $p < 0.0001$, df=1, OR=7.440 (95% CI: 3.9-14.1). In the group of subjects who had been infected with HA, statistically significant differences in the prevalence of anti-HAV IgG antibodies were not found between sub-groups unvaccinated and vaccinated against HAV ($p > 0.05$). It is important to note that among unvaccinated volunteers, 75.2% had indeed contracted the illness, however, they were completely unaware of this fact and were certain they had never had HA.

It was not possible to analyze the representation of different vaccines in the sample because, in most cases, vaccination against HAV was recorded in the vaccination certificate only by indicating the date of vaccination without specifying the vaccine's name.

During the study, an assessment of the prevalence of markers for HA and HE in the population per 100 thousand inhabitants was conducted, which resulted in 76.030 cases per 100 thousand for HA, and 5.567 cases per 100 thousand for HE. This indicates exposure of participants to HAV or HEV, respectively, as well as potential asymptomatic episodes or histories of acute hepatitis A/E infections.

4 Discussion

The obtained results confirmed that in Kyrgyzstan there is a high prevalence of antibodies to HAV and HEV among the population. During the current study, anti-HAV IgG antibodies were detected in 76.8% of participants, and anti-HEV IgG antibodies were found in 5.6%. By comparison, in a similar study conducted in 2018 in Bishkek, the capital city of Kyrgyzstan, involving 1075 conditionally healthy individuals, anti-HAV antibodies were detected in 75.3% and anti-HEV antibodies in 3.3% [12]. According to WHO criteria, low, medium, and high levels of endemicity for Hepatitis A virus have been defined. High endemicity is characterized by a prevalence of anti-HAV antibodies exceeding 50% in individuals under the age of 10 years. Medium endemicity assumes similar antibody prevalence up to the age of 25 years, while low endemicity corresponds to less than 50% antibody prevalence until the age of 50 years. Based on our study results, Kyrgyz Republic can be classified as a country with high endemicity for Hepatitis A [17]. All countries in Asia and Central Asia are considered highly endemic for HEV [8, 11]. Nevertheless, the epidemiological situations regarding HE in these countries, including Kyrgyzstan, largely remain unknown. Outbreaks of HE were recorded in Kyrgyzstan in the 1990s, but there is no available data concerning its seroprevalence during that period [4, 6, 10].

In the course of the research, correlations were identified between the share of persons seropositive for HAV and HEV and their age. However, in the case of HA, antibodies remain throughout life, making the accumulation of antibodies over time a natural process. For HEV, antibodies persist for about 20–30 years [5, 13], suggesting either random coincidence of increased seropositivity with age or other reasons, such as historical, social, and environmental factors influencing the dynamics of HE incidence. Individuals born and raised in regions with elevated risks of infection (for example, rural areas with limited access to sanitary standards) face multiple sources of infection throughout their lives, gradually increasing the percentage of seropositive individuals with age. Moreover, earlier periods saw poorly organized water supply and sewage disposal systems, raising the risk of

widespread outbreaks of HA and HE. Consequently, younger individuals less often encounter acute infections since current sanitary conditions have improved. Partially, this also explains the lack of reliable differences in the occurrence of antibodies to these viruses after the age of 50.

In a 2020 study conducted in northeastern Argentina among children under 18 years old, the prevalence of anti-HEV antibodies was only 1.7%, despite less than 15% having access to piped water; the authors considered this observed prevalence unexpectedly low given sanitary conditions. Low occurrence of anti-HEV antibodies was also found in Colombia among children aged 5–18 years, amounting to just 1.1% [15]. In our current study, the seroprevalence of HEV among children was 1.9%, which again does not qualify as high prevalence, yet it is not equal to zero, thus confirming the relevance of enteral hepatitis problems not only in the Kyrgyz Republic but also in other countries [21].

Traditional Kyrgyz cuisine is rich in meat dishes, cheese, homemade dairy products, fresh vegetables, and fruits directly from gardens. The use of inadequately processed animal-derived foods (meat, milk, eggs), or consumption of fresh produce grown near polluted areas, could increase the risk of introducing pathogenic microorganisms, including hepatitis viruses. Women traditionally take greater responsibility for preparing meals in families, especially in Central Asian cultures, which may explain why higher frequencies of anti-HAV IgG and anti-HEV IgG antibodies were found among women compared to men in our study.

Of those surveyed, 4.0% reported having had HA, and among them, 95.4% tested positive for anti-HAV IgG antibodies. Interestingly, out of 12 individuals who did not show any anti-HAV antibodies, 11 were under 18 years old. It's important to note that children with weakened immune systems or underlying diseases might struggle to develop a robust immune response, increasing their risk of either missing or rapidly losing protective antibodies. On the other hand, initial tests for detecting antibodies sometimes yield false-positive results. Four volunteers reported experiencing HE; none of them tested positive for anti-HEV IgG antibodies, yet they were all seropositive for HAV. However, we cannot claim that errors occurred

during data collection because we know that protective antibodies to hepatitis E typically last around 20–30 years, while the average age of these four volunteers was 44 years old [4, 5].

From the perspective of volunteer activity domains, the lowest prevalence of anti-HAV IgG and anti-HEV IgG antibodies was observed in groups whose members predominantly work indoors where direct contact with natural sources of infection is minimized. In fields like IT, office work, education, and manufacturing, most job processes involve sitting at computers or desks without interacting with contaminated soil, bodies of water, or animals, which serve as primary reservoirs of viruses transmitted enterally.

The highest frequency of antibodies to enteral hepatitis viruses was detected among state employees and healthcare workers. For comparison: in 2020, a screening study was conducted among medical workers in Turkey (n = 1722 people), according to the results of which anti-HAV antibodies were detected in 71.3% of those examined [22]. Some representatives of government service, particularly law enforcement officers, firefighters, and rescuers, frequently interact with places of mass gatherings, participate in emergency response operations, and work in areas affected by ecological disasters and natural calamities. All these factors increase the likelihood of contracting various infections, including enteral hepatitis viruses. Among rural-based civil servants, a large portion reside in homes lacking basic amenities such as centralized water supply and proper sanitation systems. Consumption of untreated water, purchase of questionable food products, and poor adherence to hygiene practices further elevate the risk of viral infections. Additionally, the average age within the group of state employees was 45.5 years old, which partly explains the high prevalence of anti-HAV IgG antibodies.

The high prevalence of antibodies to enteric viral hepatitis among healthcare workers can be explained by their professional activities, work intensity, lack of opportunities to maintain personal health, and difficulties in ensuring optimal sanitary conditions in daily practice. A study from 2017 to 2020 among newly employed healthcare workers is particularly interesting as it demonstrated that anti-

HAV IgG antibodies are more frequently detected among physicians than nurses (74 and 52%, respectively) [25]. To address this issue, healthcare professionals have been included in the risk groups recommended for vaccination against HAV. However, the low vaccination rates against HAV and high frequency of both anti-HAV and anti-HEV antibodies in this group suggests insufficient measures have been taken so far. A survey conducted among healthcare workers in 2020 revealed the following most common reasons for not receiving recommended vaccines: they were busy (77%), the vaccination process was complicated (68%), and they simply forgot about vaccination (55%) [25]. It is important to develop specific recommendations and preventive measures tailored for these categories of citizens.

Hepatitis A vaccination is conducted selectively, regardless of age. In the absence of mandatory requirements for both adult and pediatric populations, the vaccination rate remains lower than expected among older age groups. As a result, only 5.9% of the population was vaccinated.

To prevent outbreaks of HA, the following measures may be necessary: raising public awareness through mass media and social networks; and regularly updating vaccination recommendations, including mandatory inclusion of adult populations at risk into national immunization schedules. Given that Kyrgyzstan has diverse climatic zones and varying levels of infrastructure development, improving coordination between local authorities and healthcare institutions will also be needed. Training medical personnel on modern methods of information dissemination, and patient counseling, are also essential. These steps would help increase vaccination rates across all age groups and create an adequate foundation for preventing future HA outbreaks. However, at present, no significant differences have been found when evaluating the correlation between anti-HAV IgG antibody prevalence and presence/absence of HAV vaccination.

It is noteworthy that among individuals who have never contracted HA and were not vaccinated against it, the proportion of seropositive individuals reached 75.2%. This indicates that three out of every four people were likely infected but unaware of this fact due to minimal, or nonexistent, clinical symptoms. This finding

points to a high level of hidden infection with HAV. However, it should be noted that many older residents had encountered this infection in the past, leading to the formation of long-lasting immunity which persists for years. Nevertheless, residents of rural areas and individuals working in unsanitary environments still have a higher chance of contracting HA and HE. Therefore, stricter control over water quality must be implemented, possibly complemented by improvements in living conditions in rural areas.

5 **Conclusion**

The study identified a significant prevalence of antibodies to HAV and HEV among the population of Kyrgyzstan. The obtained data confirm the hypothesis that unfavorable sanitary-hygienic conditions, and occupational hazards, play a key role in shaping collective immunity. Improving vaccination programs, and enhancing public awareness campaigns, emerge as critical tasks aimed at reducing the risk of hepatitis epidemics in the country.

This research underscores the necessity of continuing nationwide vaccination initiatives against hepatitis A, expanding mandatory vaccination coverage for vulnerable groups, conducting additional evaluations of existing preventive measures, adapting them to local circumstances, launching educational campaigns focused on hepatitis prevention strategies and individual responsibility, and supporting efforts to upgrade residential-commercial infrastructure and environmental conditions in cities and villages.

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ТАБЛИЦЫ

Table 1. Seroprevalence of anti-HAV IgG and anti-HEV IgG antibodies among individuals of different age groups.

Age group, years	**Number of volunteers, N**	**Presence of anti-HAV IgG**		**Presence of anti-HEV IgG**	
		abs, (n)	**%, 95% CI**	**abs, (n)**	**%, 95% CI**
1-17 years	2806	1510	53.8% (52.0-55.7)	52	1.9% (1.4-2.4)
1-5 years	909	364	40% (36.8-43.3)	15	1.7% (0.9-2.7)
6-11 years	1021	523	51.2% (48.1-54.3)	19	1.9% (1.1-2.9)
12-17 years	876	623	71.1% (68.0-74.1)	18	2.1% (1.2-3.2)
18-29 years	668	564	84.4% (81.5-87.1)	21	3.1% (2.0-4.8)
30-39 years	685	639	93.3% (91.1-95.0)	33	4.8% (3.3-6.7)
40-49 years	698	670	96.0% (94.3-97.3)	51	7.3% (5.5-9.5)
50-59 years	692	670	96.8% (95.2-98.0)	85	12.3% (9.9-15.0)
60-69 years	654	634	96.9% (95.3-98.1)	78	11.9% (9.5-14.7)
70+ years	407	387	95.1%	48	11.8%

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			(92.5-97.0)		(8.8-15.3)
Total:	6610	5074	76.8% (75.7-77.8)	368	5.6% (5.0-6.2)

Table 2. Seroprevalence of anti-HAV IgG antibodies among individuals who denied having had HA in different age groups.

Age group, years	**Number of volunteers, N**	**Presence of anti-HAV IgG**	
		abs, (n)	**%, 95% CI**
1-17 years	2635	1380	52.4% (50.4%)
1-5 years	892	352	39.5% (36.5-42.8%)
6-11 years	950	473	49.8% (46.6-53.0%)
12-17 years	793	555	70.0% (66.7-73.2%)
18-29 years	575	475	82.6% (79.3-85.6%)
30-39 years	602	558	92.7% (90.3-94.6%)
40-49 years	634	607	95.7% (93.9-97.2%)
50-59 years	627	605	96.5% (94.7-97.8%)
60-69 years	602	582	96.7% (94.9-98.0%)
70+ years	380	360	94.7% (92.0-96.8%)
Total:	6055	4567	75.4% (74.3-76.5%)

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Table 3. Volunteers vaccinated against HAV by age group (among those confident of their vaccination status).

Age group, years	**Number of volunteers, N**	**Vaccinated against HAV**	
		Abs, n	**%, 95% CI**
1-17 years	2665	167	6.3% (5.4-7.3%)
1-5 years	886	62	7.0% (5.4-8.9%)
6-11 years	974	49	5.0% (3.7-6.6%)
12-17 years	805	56	7.0% (5.3-8.9%)
18-29 years	638	36	5.6% (4.0-7.7%)
30-39 years	656	52	7.9% (6.0-10.3%)
40-49 years	674	30	4.5% (3.0-6.3%)
50-59 years	656	38	5.8% (4.1-7.9%)
60-69 years	612	25	4.1% (2.7-6.0%)
70+ years	379	25	6.6% (4.3-10.0%)
Total:	6280	373	5.9% (5.4-6.6%)

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Table 4. Seroprevalence of anti-HAV IgG among vaccinated and non-vaccinated volunteers.

Vaccination against HAV	**Number of volunteers, N**	**Presence of anti-HAV IgG**		
		abs, (n)	**%**	**95% CI**
Received vaccination Вакцинированы	373	283	75.9%	71.3 - 79.9
No vaccination received Не вакцинированы	5907	4527	76.6%	75.5 - 77.7
Information unavailable Не известно	330	264	80%	75.4 - 84.0
Total: Всего:	6610	5074	76.8%	75.7 - 77.8

Table 5. Seroprevalence of anti-HAV IgG among volunteers with known infectious-vaccination status.

Infectious-Vaccination Status for HA	**Number of volunteers, N**	**Presence of anti-HAV IgG**		
		abs, (n)	**%**	**95% CI**
Had HA infection, not vaccinated against HAV	236	226	95.8	92.4 - 97.7
Had HA infection, vaccinated against HAV	18	17	94.4	74.2 - 99.0
Did not have HA infection, not vaccinated against HAV	5447	4098	75.2	74.1 - 76.4
Did not have HA infection, vaccinated against HAV	333	252	75.7	70.8 - 80.0
Total:	6034	4593	76.1	75.0 - 77.2

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РИСУНКИ

Figure 1. Prevalence of acute hepatitis A in the Kyrgyz Republic over the past 25 years.

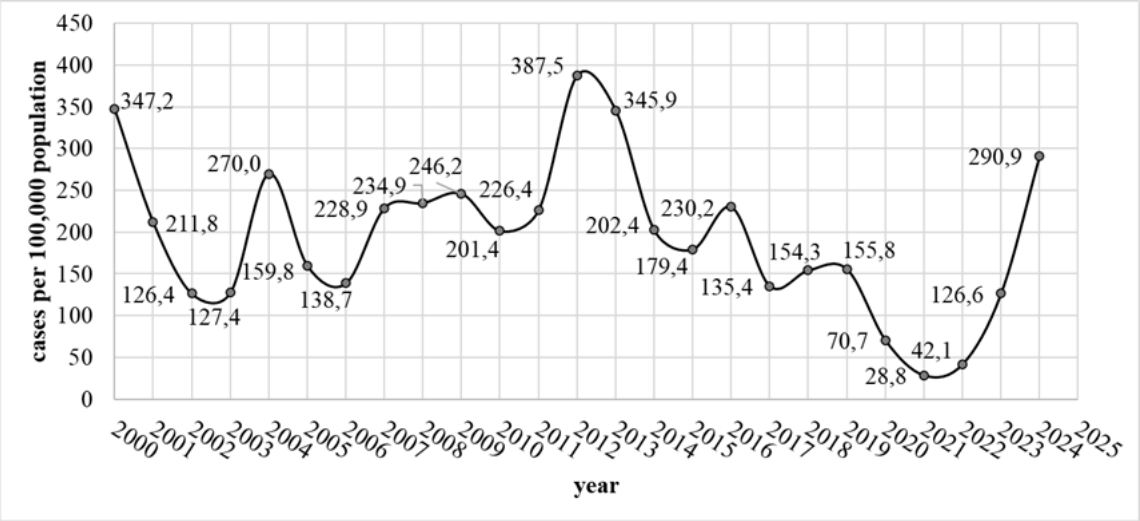

Figure 2. Distribution of Kyrgyz volunteers by age group .

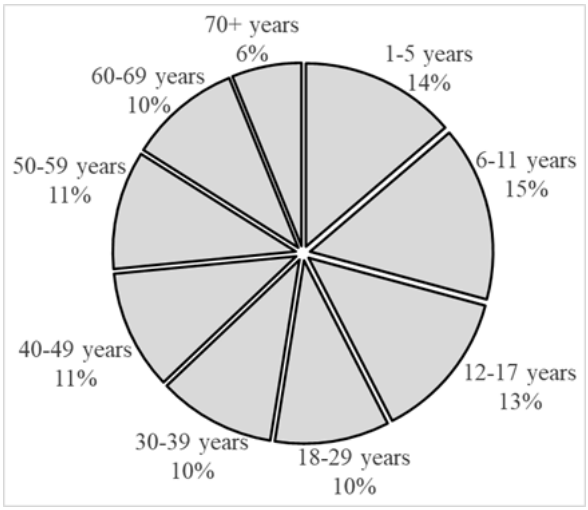

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Figure 3. Correlation assessment of the frequency of anti-HAV IgG and anti-HEV IgG antibody occurrence with volunteer age.

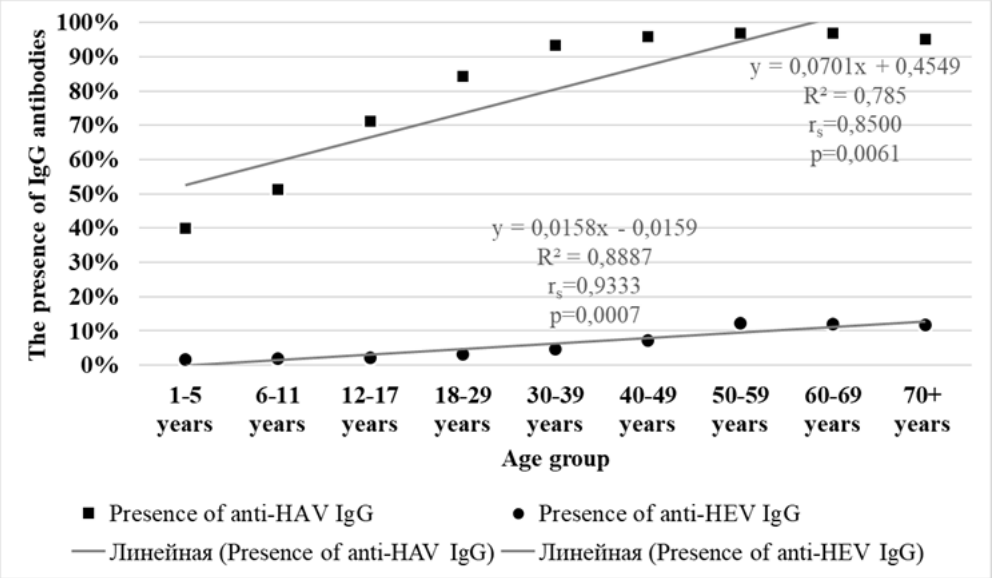


Figure 4. Seroprevalence of anti-HAV IgG antibodies by age according to the infectious status of hepatitis A in volunteers.

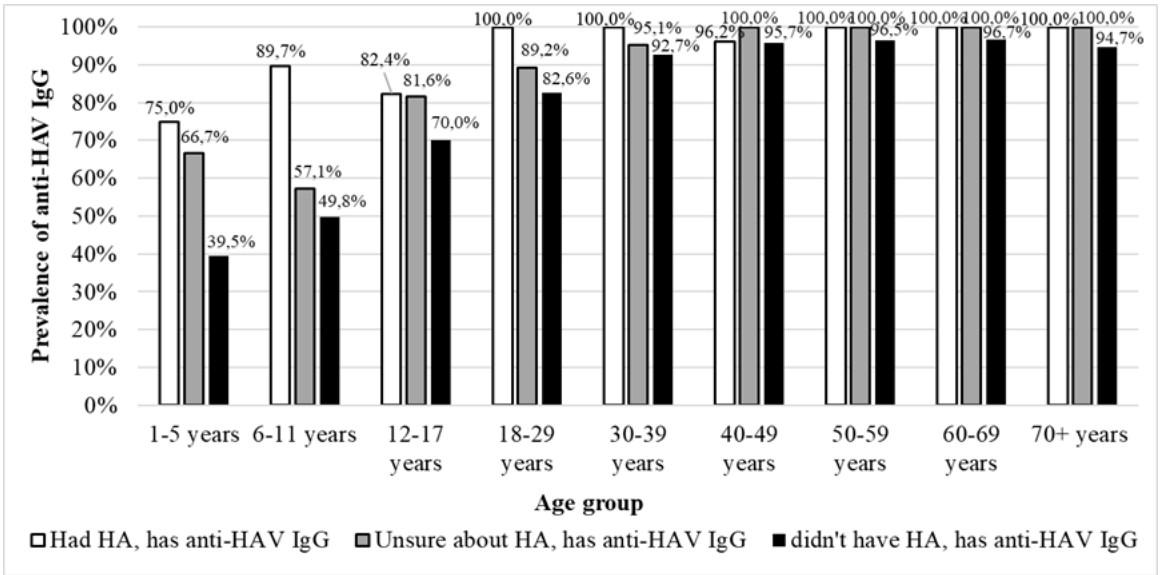


Figure 5. Seroprevalence of anti-HEV IgG antibodies by age according to the infectious status of hepatitis E in volunteers.

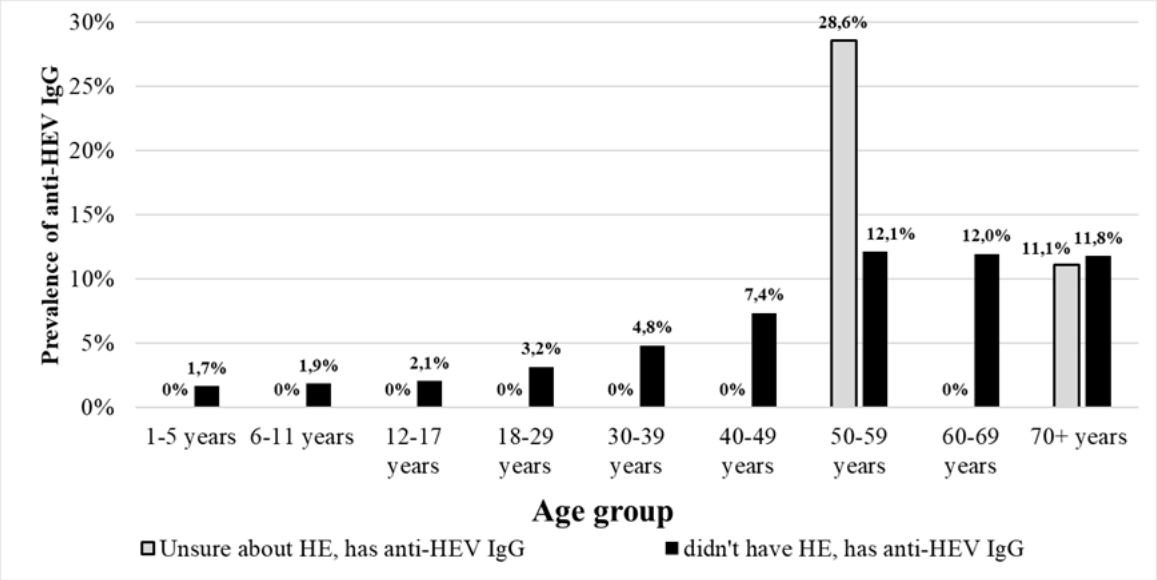
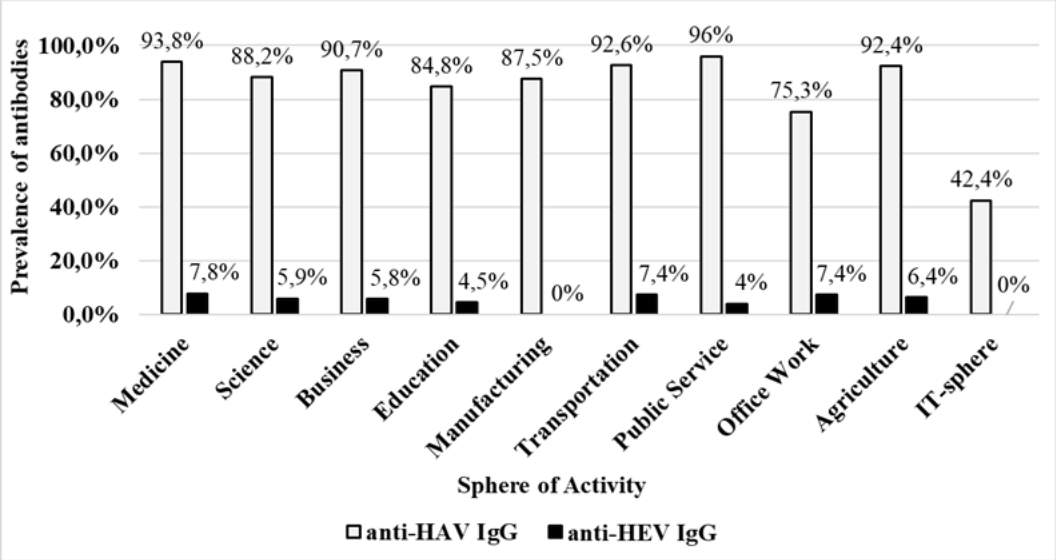


Figure 6. Prevalence of anti-HAV IgG and anti-HEV IgG antibodies based on occupation.



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Блок 3. Метаданные статьи

ОЦЕНКА ПОПУЛЯЦИОННОГО ИММУНИТЕТА К ВИРУСАМ ЭНТЕРАЛЬНЫХ ГЕПАТИТОВ У НАСЕЛЕНИЯ КЫРГЫЗСКОЙ РЕСПУБЛИКИ

ASSESSMENT OF COLLECTIVE IMMUNITY TO ENTERIC HEPATITIS VIRUSES IN THE KYRGYZ POPULATION

Сокращенное название статьи для верхнего колонтитула:

ПОПУЛЯЦИОННЫЙ ИММУНИТЕТ К ВГА И ВГЕ В КР

HERD IMMUNITY TO HAV&HEV IN KYRGYZSTAN

Ключевые слова: вакциноуправляемые инфекции, популяционный иммунитет, вирусный гепатит А, вирусный гепатит Е, вирус гепатита А, вирус гепатита Е, серопревалентность, антитела, Кыргызская Республика, когортное исследование.

Keywords: vaccine-preventable infections, collective immunity, viral hepatitis A, viral hepatitis E, hepatitis A virus, hepatitis E virus, seroprevalence, antibodies, Kyrgyz Republic, cohort study.

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