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Trends in the Acute Hepatitis B and Acute Hepatitis C in Bulgaria
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Introduction:
Bulgaria joined European Union (EU) on 1 January 2007. Since the accession all regulations, directives, decisions, recommendations, and opinions of the European Parliament, the Council of the European Union, and the European Commission are being implemented.

Aim: The purpose of this study was to present the morbidity of acute hepatitis B virus (HBV) and acute hepatitis C virus (HCV) in Bulgaria before and after accession to the EU.

Materials and methods: A retrospective study was performed. The morbidity of acute HBV and acute HCV infections in Bulgaria was analyzed over a period of sixteen years (2000–2016). The collected data were based on the National Center of Infectious and Parasitic Diseases (NCIPD) and the National Center of Public Health and Analyses (NCPHA).

Results: Between 2000 and 2016, 11038 cases of acute HBV infection and 1681 cases of acute HCV infection were reported in Bulgaria. Before the accession to EU, the morbidity rates of acute HBV and acute HCV infections were 12.77 cases per 100,000 population (95% CI: 11.45–13.97) and 1.52 cases per 100,000 population (95% CI: 1.17–1.96), respectively. After the accession to the EU, the morbidity rates of acute HBV and acute HCV infections were 5.29 cases per 100,000 population (95% CI: 3.86–6.73) and 1.14 cases per 100,000 population, respectively.

Conclusion: Analysis of the data suggests that there is a tendency for lower morbidity rates of acute HBV. The situation with acute HCV is relatively stable over the years regardless of EU membership.

INTRODUCTION
Bulgaria joined European Union (EU) on 1 January 2007. Since the accession, Bulgaria have been implementing all regulations, directives, decisions, recommendations, and opinions of the European Parliament, the Council of the European Union, and the European Commission. Infectious diseases, being part of the healthcare policy, are an important component of this socio-political domain. Acute hepatitis B virus (HBV) infection and acute hepatitis C virus (HCV) infection are socially significant infectious diseases.

The morbidity and mortality rate of acute HBV and acute HCV varied widely before and after Bulgaria’s accession to the EU. The morbidity, mortality and lethality of acute HBV and acute HCV in Bulgaria are presented in Table 1 and Fig. 1 for both time periods we analysed (before and after 2007). In 2014, 24 EU/EEA member states reported 2667 cases of acute HBV infection, a crude rate of 0.6 cases per 100,000 population. In 2014, 458 cases of acute HCV infection were reported in 14 EU/EEA member states, which gives a crude rate of 0.5 cases per 100,000 population. For 2015, 25 EU/EEA member states reported 2505 cases of acute HBV infection, a crude rate of 0.6 cases per 100,000 population. In 2015, 346 cases of acute HCV infection were reported in 12 EU/EEA member states, giving a crude rate of 0.4 cases per 100,000 population. For 2016, 26 EU/EEA member states reported 2529 cases of acute HBV infection, a crude rate of 0.6 cases per 100,000 population. In 2016, 813 cases of acute HCV infection were reported in 19 EU/EEA member states, corresponding to a crude rate of 0.4 cases per 100,000 population. Looking at ECDC’s Annual Epidemiological Reports, it is noteworthy that the incidence of acute HBV is 8.6–11.9% of all cases of HBV-infection in the EU. The number of acute HCV is 1.0–2.4% of all cases of HCV-
infection in EU. Another important fact is that many EU member states do not provide to ECDC information on acute HBV (no data from: Belgium, Croatia, Italy, etc.) and acute HCV (no data from: Belgium, Croatia, France, Germany, Italy, etc.). The facts mentioned above impede a full analysis of the situation with acute HBV and acute HCV in the EU and complicate the work of epidemiologists and public health professionals.

**Acute HBV**
Clinical description - an acute illness with (a) discrete onset of symptoms and (b) jaundice or elevated serum aminotransferase levels. Laboratory criteria for diagnosis: IgM antibody to hepatitis B core antigen (anti-HBc) positive or hepatitis B surface antigen (HBsAg) positive.

**Acute HCV**
Clinical description - an acute illness with (a) discrete onset of symptoms (such as nausea, vomiting, abdominal pain and diarrhea) and (b) jaundice or abnormal serum aminotransferase (ALT) levels. Laboratory criteria for diagnosis – serum ALT levels greater than 7 times the upper limit of normal, and IgM antibody to hepatitis A virus (IgM anti-HAV) negative (if done), and IgM antibody to hepatitis B core antigen (IgM anti-HBc) negative, or if not done, hepatitis B surface antigen (HBsAg) negative, and antibody to hepatitis C virus (anti-HCV) positive, verified by an additional more specific assay.

**AIM**
The aim of this study was to present the morbidity of acute HBV and acute HCV infections in Bulgaria in two different periods of time: before and after the accession of Bulgaria to the EU.

**MATERIALS AND METHODS**

**Study Design**
A retrospective study of the morbidity of acute HBV and acute HCV infections in the Republic of Bulgaria for the period 2000 to 2016 was carried out. Data were collected from the annual reports of National Center of Infectious and Parasitic Diseases (NCIPD) and National Center of Public Health and Analyses (NCPHA). Epidemiological reports contain information from all 28 districts and 265 municipalities of the country.

**Ethics Statement**
The study was performed in accordance with the principles of the Declaration of Helsinki. Participation in the study was fully voluntary and anonymous, and written informed consent was obtained from each person prior to the medical examination.

**Statistical Analysis**
Data for the morbidity were compared by Chi-square and unpaired F (Kruskal-Wallis) tests. Statistical analysis was performed by Excel 2007 (Microsoft, Redmond, Washington, USA) and SPSS Statistics 19.0 (IBM Corp., Armonk, New York, USA). A p value < 0.05 was considered statistically significant.

**RESULTS**
A total of 11038 cases of acute HBV infection and 1681 cases of acute HCV infection were reported between 2000 and 2016. The morbidity of acute hepatitis B for that period was 8.37 cases per 100 000 population (95% CI: 6.34–10.39), and 1.29 cases per 100 000 population for acute hepatitis C (95% CI: 1.14–1.43). For the analyzed period the lethality rates associated with acute HBV and acute HCV infection were 2.14% (95% CI: 1.14–1.43) and 0.72% (95% CI: 0.30–1.14), respectively. The national attributable mortality from acute hepatitis B was 0.14 cases per 100 000 population (95% CI: 0.11–0.17), and from acute hepatitis C – 0.007 cases per 100 000 population (95% CI: 0.0021–0.012). Epidemiological parameters of acute HBV and acute HCV infections are shown in Tables 1, 2, and Figs 1, 2. The results are separated in two groups according to the Bulgarian accession to the EU. First period: before the accession to EU (2000–2006) and second one as EU member (2007–2016). The analysis of morbidity of acute hepatitis B and acute hepatitis C in the country during 2000–2016 is shown in Table 3.

The analysis shows that the incidence of acute HBV infection decreased by 55.7% after the Bulgarian accession to the EU. The morbidity per 100 000 population declined by 58.6%, and the mortality per 100 000 population dropped by 40%. After the admission to the EU the lethality associated with acute hepatitis B was almost twice as large. The morbidity of acute HCV infection decreased by 25% per 100 000 population during the second analyzed period (2007–2016). The lethality related to acute hepatitis C declined by 35.8% in the period of EU membership.

**DISCUSSION**
The prevalence of acute HBV and acute HCV infections differs in some Southeast European countries. Leblebicioglu et al. reported that 46.8% of patients...
Table 1. Morbidity, mortality and lethality from acute HBV and acute HCV in Bulgaria (2000–2016)

| Years            | Acute HBV |                  |                  | Acute HCV |                  |                  |
|------------------|-----------|------------------|------------------|-----------|------------------|------------------|
|                  | Morbidity (per 100 000) | Mortality (per 100 000) | Lethality (%) | Morbidity (per 100 000) | Mortality (per 100 000) | Lethality (%) |
| Before accession to EU |
| 2000             | 15.02     | NDA              | NDA             | 1.07      | NDA              | NDA             |
| 2001             | 13.92     | NDA              | NDA             | 1.26      | NDA              | NDA             |
| 2002             | 13.61     | 0.14             | 1.02            | 1.66      | 0.03             | 1.53            |
| 2003             | 12.30     | 0.23             | 1.02            | 1.85      | 0.01             | 1.53            |
| 2004             | 12.42     | 0.23             | 1.90            | 1.87      | 0.01             | 1.70            |
| 2005             | 12.11     | 0.22             | 1.32            | 1.37      | 0.00             | 0.00            |
| 2006             | 10.01     | 0.17             | 1.68            | 1.57      | 0.00             | 0.00            |
| After accession to the EU |
| 2007             | 9.81      | 0.10             | 1.06            | 1.28      | 0.03             | 2.04            |
| 2008             | 8.17      | 0.12             | 1.44            | 1.16      | 0.00             | 0.00            |
| 2009             | 6.63      | 0.12             | 1.79            | 1.22      | 0.01             | 1.08            |
| 2010             | 5.12      | 0.19             | 3.62            | 0.77      | 0.01             | 1.72            |
| 2011             | 4.67      | 0.12             | 2.62            | 0.81      | 0.00             | 0.00            |
| 2012             | 4.39      | 0.15             | 3.42            | 1.26      | 0.00             | 0.00            |
| 2013             | 4.15      | 0.10             | 2.32            | 1.30      | 0.00             | 0.00            |
| 2014             | 3.24      | 0.04             | 1.28            | 1.24      | 0.00             | 0.00            |
| 2015             | 3.65      | 0.11             | 3.04            | 1.18      | 0.00             | 0.00            |
| 2016             | 3.06      | 0.14             | 4.57            | 1.13      | 0.01             | 1.23            |

NDA: no data available.

Table 2. Acute HBV and acute HCV infections in Bulgaria – before and after accession to the EU (2000–2016)

| Variable     | Number (n) | Morbidity (per 100 000) | Mortality (per 100 000) | Lethality (%) |
|--------------|------------|-------------------------|-------------------------|---------------|
|              |            |                         |                         |               |
| Acute HBV    | 7085       | 12.77                   | 0.20                    | 1.39          |
| Acute HCV    | 840        | 1.52                    | 0.01                    | 0.95          |

| Variable     | Number (n) | Morbidity (per 100 000) | Mortality (per 100 000) | Lethality (%) |
|--------------|------------|-------------------------|-------------------------|---------------|
|              |            |                         |                         |               |
| Acute HBV    | 3953       | 5.29                    | 0.12                    | 2.52          |
| Acute HCV    | 841        | 1.14                    | 0.006                   | 0.61          |

Table 3. Analysis on the morbidity of acute HBV and acute HCV infections in Bulgaria

| Variable     | Mean±SD   | Range   | 95% CI       |
|--------------|-----------|---------|--------------|
| Acute HBV (2000–2006) | 12.71±1.70 | 10–15   | 11.45–13.97  |
| Acute HCV (2000–2006) | 1.57±0.53  | 1–2     | 1.17–1.96    |
| Acute HBV (2007–2016) | 5.30±2.31  | 3–10    | 3.86–6.73    |
| Acute HCV (2007–2016) | NA        | NA      | NA           |

SD: standard deviation; CI: confidence interval; NA: not applicable.
with acute HBV infection (158 cases) had positive HbeAg and 37.9% were positive for anti-HbeAg. Another study by Ozer et al. found 22.5% HbsAg positive spouses in a couple with acute HBV and 21.7% HbsAg positive parents, consequently determined that having an HbsAg positive spouse and living with HbsAg positive parents are significant risk factors for acquiring HBV infection. In Greece, from 2014 to 2016, 65 cases of acute hepatitis B (0.20 cases per 100,000 population) and 6 cases of acute hepatitis C (<0.10 cases per 100,000 population) were reported. In Romania over the same period (2014-2016), 661 cases of acute HBV infection (1.10 cases per 100,000 population) and
214 cases of acute HCV infection (0.37 cases per 100,000 population) were reported. 3-8 In Slovenia, 42 cases of acute HBV infection were reported between 2014 and 2016 (0.70 cases per 100,000 population) and 17 cases of acute HCV infection (0.23 cases per 100,000 population). 3-8 In Bulgaria from 2014 to 2016, the data for acute hepatitis B morbidity was 3.32 cases per 100,000 population and morbidity of acute HCV infection - 1.18 cases per 100,000 population. 1,2 The presented data show the morbidity rate of acute HBV infection in Bulgaria was higher than those in other Southeastern European countries. Possibly it could be associated with lack of vaccination among some ethnic groups (gypsies, low-income social groups, etc.) and anti-vaccination movements. The morbidity rate of acute HCV is the highest in Bulgaria compared with the countries of Southeastern Europe. This most likely is due to unresolved problems with intravenous drug users and the lack of effective control over tattoos and piercing services.

Data from the present study showed that there is a tendency for the cases of acute HBV infection to decrease in Bulgaria. After the admission to the EU, the Bulgarian national statistics reported a decreasing trend in this respect. The reasons for this tendency can be accounted for by the following factors. First, the accession of the country to the EU has considerably increased the investments in health promotion and health education. 11,12 Second, different programs were funded with aim to inform people at risk (gypsies, men who have sex with men, heterosexual persons with multiple sex partners or contact with sex workers, drug users and others) about the disability that could cause HBV. 13,14 Third, the diagnostic capabilities of transfusion hematology centers have been improved. 15,16 Fourth, measures have been taken to improve sanitary and hygienic conditions in medical practices for dental care. 17,18 Fifth, improved control and implementation of hepatitis B virus vaccine. 19-23 Sixth, the results from the study could be influenced by disorders in medical statistics.

Data from the present study do not suggest that there are dramatic changes in the morbidity rates of acute HCV infection in Bulgaria. The reasons for this finding could be explained by the following considerations. First, the National Health Organizations should pay more attention to drug users. 24 Second, the prisons are place for getting serious infectious diseases, especially viral hepatitis. 25-27 Third, low health education among some communities (gypsies, low-income social groups, etc.). 28 Fourth, lack of effective control on unregulated tattoos and piercing services. 29

The clinical relevance of our study increases the physicians’ awareness of acute HBV and acute HCV. The important message to General Practitioners and Hospital Physicians is to guide their thinking on acute HCV. The key point to the National Health Organizations is to enhance the programs and policies on prevention of acute HCV.

Limitations of the Study: It was a retrospective study, so we could not make a detailed analysis. The study presented morbidity of acute HBV and acute HCV by years. No data were available for sex, age and districts. Information on transmission of acute HBV and acute HCV was missing.

CONCLUSION
The analysis of acute HBV and acute HCV shows that the incidence of acute HBV has a tendency to decrease, and the morbidity of acute HCV is relatively stable over the years. This is a reason to believe that our country’s membership to the European Union has a positive impact on health policies in the healthcare sector, particularly in the field of infectious diseases (acute HBV).

CONFLICT OF INTERESTS
All authors declare there is no support from any organization for the submitted work, or financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, and no other relationships or activities that could appear to have influenced the submitted work.

ABBREVIATIONS USED IN THIS ARTICLE
HBV: hepatitis B virus; HCV: hepatitis C virus; EU: European Union; NCIPD: National Center of Infectious and Parasitic Diseases; NCPHA: National Center of Public Health and Analyses; EEA: European Economic Area; ECDC: European Centre for Disease Prevention and Control; SPSS: Statistical Package for the Social Sciences; IBM: International Business Machines.

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Введение: Болгария вступила в Европейский Союз (ЕС) 1 января 2007 года. С момента нашего присоединения применяются все положения, директивы, рекомендации и мнения Европейского парламента, Совета Европейского союза и Европейской комиссии.

Цель: Целью данного исследования было представить информацию о заболеваемости вирусами гепатита B (HBV) и гепатита C (HCV) в Болгарии до и после вступления в ЕС.

Материалы и методы: Проведено ретроспективное исследование. Заболеваемость инфекциями остrego гепатита HBV и остrego гепатита HCV в Болгарии были анализированы в течение 16 лет (2000-2016 гг.). Собранные данные были основаны на базе данных Национального центра инфекционных и паразитарных заболеваний (НЦЗПБ) и Национального центра общественного здравоохранения и анализов (НЦОЗА).

Результаты: В период с 2000 по 2016 год в Болгарии было зарегистрировано 11038 случаев острых инфекций HBV и 1681 случай острых инфекций HCV. До вступления показатель заболеваемости острыми инфекциями HBV составлял 12.77 случаев на 100 000 жителей (95% CI: 11.45-13.97) и острого гепатита HCV составляла 1.52 случая на 100 000 жителей (95% CI: 1.17-1.96). После нашего вступления в ЕС частота острых инфекций HBV и острых инфекций HCV составляла 5.29 случаев на 100 000 жителей (95% CI: 3.86-6.73) и 1.14 случаев на 100 000 жителей.

Заключение: Анализ данных показал, что существует тенденция к снижению заболеваемости острым гепатитом HBV. Ситуация с острым HCV была относительно стабильной на протяжении многих лет, несмотря на наше членство в ЕС.