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Epidemiological Study of Hepatitis A Infection in Eastern Bulgaria

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Background: Hepatitis A virus (HAV) infection is an acute, self-limited liver disease transmitted usually through the faecal-oral route via person-to-person contact. Bulgaria has intermediate HAV endemicity with higher susceptibility among adults and recurrent outbreaks.

Aim: As HAV infection is strongly related to human movements and represents a significant risk to travelers and migrants, as well as to local population receiving these groups, we set out to analyze the epidemiological data on hepatitis A in five of the largest tourist border regions of Bulgaria located in its eastern part: Varna, Shumen, Dobrich, Burgas and Yambol.

Materials and methods: We reviewed retrospectively all reported cases of acute hepatitis A in the eastern regions of Bulgaria over a 7-year period between 2008 and 2014.

Results: A total of 2879 newly infected patients were registered during the study period, the number varying widely: from 190 cases in 2014 to 923 in 2012. The average incidence of HAV was higher in the south-eastern regions than in the north-eastern regions (55.30‰ vs 15.04‰ respectively, $p < 0.0001$). The most affected age group in all regions was the 5-9-year olds ($p < 0.0001$) and males were significantly more susceptible to HAV ($p = 0.02$).

Conclusion: Hepatitis A is still a major public health problem in Bulgaria; there is a significant difference in the incidence of the disease between the regions in the south-east and those in the north-east and between the different age groups and sexes.

BACKGROUND

Hepatitis A virus (HAV) infection is an acute, self-limited disease of the liver with world-wide distribution.¹ Generally, it is transmitted through the faecal-oral route via person to person contact. Alimentary and water routes are also possible. In rare cases HAV can be transmitted via infected blood of asymptomatic donors and people in incubation period.² Despite the clinical form of the disease (asymptomatic, subclinical, symptomatic or fulminant), the sick person with acute infection is the reservoir for spreading of the infection. In the late incubation period (1-2 weeks before the onset of prodromal symptoms) and during the first week after the onset of jaundice, the virus is released with the feces in concentrations higher than 10^8 particles in 1 ml.³ Following the ingestion by the new host, HAV particles reach the liver and infect hepatocytes. After replication in the liver, the vi-

rus is released into bile and, eventually, shed in the feces.⁴ The infection is asymptomatic among children up to 6 years whereas in more than 70% of the cases among adolescents and adults it leads to clinical disease.¹

According to World Health Organization, clinical cases with HAV account for 1.5 million each year with the highest number registered in Africa, Asia, Central and South America.⁵ The spread of hepatitis A strongly correlates with low socioeconomic and cultural development of a country.³ The majority of cases occur in developing countries with unsafe water and poor sanitation infrastructure.⁶ Serological prevalence profiles vary widely among countries.^{2,6} In highly endemic areas (e.g. Sub-Saharan Africa and parts of South-East Asia) at least 90% of the population becomes immune by the age of 10. In communities with intermediate endemicity (Southern and Eastern Europe, China, Latin America, Northern

Africa, the Middle East and Russia) at least 50% of the population is immune by the age of 15. Higher susceptibility among adults and recurrent outbreaks are observed in these areas. In regions with low endemicity (prevalence of anti-HAV antibody exceeds 50% by age of 30 but is less than 50% by age of 15) and very low endemicity (less than 50% seroprevalence by age 30 years) such as Western and Northern Europe, Australia, Canada, Japan, and the United States disease may occur among specific-risk groups.^{1,2}

Despite the improved sanitary hygienic conditions, the morbidity of HAV in Bulgaria is still an important problem and the country is currently placed in the list of intermediate endemicity areas. From 1984 to 2005, the average incidence has varied between 27 – 80 cases per 100 000 population during non-epidemic periods and has reached 234 cases/100 000 during epidemic periods.⁷ No recent published data are available regarding the HAV incidence rates in Bulgaria and the burden of the disease cannot be easily defined. HAV infection is highly related to human movements and represents a significant risk to travelers and migrants, as well as to local population receiving these groups.⁸ Over the last decade, Bulgaria has experienced an increase in international transport and human connections and in this context it is important to know the actual burden of HAV and other infectious diseases.

AIM

The aim of this study was to analyze the epidemiological data on hepatitis A transmission in five of the largest regions of Bulgaria – Varna, Shumen, Dobrich, Burgas and Yambol – which represent the eastern part of the country.

MATERIALS AND METHODS

We analyzed HAV epidemiological patterns in Dobrich, Shumen, Varna (located in the northeast) and in Burgas and Yambol (in the southeast). The information for the number of HAV cases was received from the Regional Health Inspections in Varna, Dobrich, Shumen, Burgas and Yambol. In Bulgaria, hepatitis A infection is a nationally notifiable infectious disease which must be reported from all medical specialists when detected. The European Union case definition and case classification of probable and confirmed cases (European Commission Decision 2012/506/EU on 8 August 2012) is used as the basis of clinical and laboratory criteria. In our study, all confirmed reported cases of hepatitis

A in the chosen regions were investigated over a 7 year-period (2008-2014).

The incidence rates for each region were calculated on the basis of officially reported confirmed cases of HAV divided by the population estimates of each region for the corresponding year (<http://www.nsi.bg/>). Sociodemographic data were also obtained by the official statistics of the National Statistical Institute and estimates from the last census (2011) were used for correlation analysis.

Statistical analyses were performed with EpiInfo7 software (contingency table analysis, chi-square) or “R” software (correlation coefficient tests); $p < 0.05$ was considered statistically significant.

RESULTS

Between 2008 and 2014, a total of 2879 newly infected individuals were registered in the five studied regions (**Table 1**). The total incidence varied widely – from 190 cases in 2014 to 923 in 2012. Burgas showed the highest average incidence of HAV infection in 2012 (144.63‰) with 599 infected individuals, while the lowest was reported for Varna in 2010 (0.94‰) (**Fig. 1**). Statistically significant trend of increase or decrease during the investigated period was not observed for any of the regions.

Southeastern regions (Burgas and Yambol) showed higher average incidence of HAV (with a total of 1943 infected persons per population of 539908, according to the national 2011 census)

Figure 1. HAV incidence between 2008 and 2014 (blue line - Burgas; purple - Yambol; green - Varna; black - Dobrich and red - Shumen).

compared with the regions in the north – Varna, Dobrich and Shumen which had a total of 936 registered cases per 833537 inhabitants. The aver-

age incidence for the whole period in the southern regions was 55.30‰ while the average incidence in the north was 15.04‰ ($p < 0.0001$).

The Spearman's rank correlation coefficients were calculated to assess the association between

the incidence rates in the studied regions and sociodemographic variables. HAV incidence did not correlate with the following factors: total number of the population of the corresponding region, population density, Roma ethnic origin, proportion

Table 1. Distribution of HAV

	Dobrich		Shumen		Varna		Yambol		Burgas		Total
	n	Inc.*	n	Inc.*	n	Inc.*	n	Inc.*	n	Inc.*	n
2008	95	46.77	49	25.06	41	8.85	78	55.45	27	6.41	290
2009	62	30.5	18	9.27	24	5.15	160	115.58	40	9.47	304
2010	17	8.5	23	11.96	9	0.94	75	55.22	71	16.85	195
2011	8	4.05	17	9.46	50	10.54	155	119.18	220	53.02	450
2012	18	9.57	3	1.67	276	58.29	27	21.00	599	144.63	923
2013	8	4.29	10	5.61	116	24.47	50	39.31	343	82.75	527
2014	63	34.11	2	1.13	27	5.70	57	45.33	41	9.89	190
Total	271		122		543		602		1341		2879
Aver. Inc.		19.68		9.17		16.28		64.44		46.15	

*Incidence rates (Inc.) were calculated using the official data of the Regional Health Inspections for the number of HAV cases and National Statistical Institute for total population number. The resulting number was multiplied by 100000 and incidence rates were presented as cases per 100000 inhabitants.

Table 2. Spearman's rank correlation coefficients between 7-year average HAV annual incidence and sociodemographic variables in regions Varna, Burgas, Shumen, Dobrich and Yambol

Potential risk factors	Correlation coefficient
Total population number	0.1
Population density (per km ²)	0.1
Proportion of population of Roma ethnic origin (%)	0.3
Proportion of population aged <10 years (%)	0.3
Enrollment rate of children in day-care units (%)	-0.7
Useful floor area per person (m ² per person)	-0.6
Poverty rate (%)	0.1

of population aged under 10 years and poverty rate (correlation coefficients lower than 0.4 and $p > 0.05$) (**Table 2**). It showed a relatively strong negative correlation with the available useful living space per person (-0.6) and with the number of children enrolled in daycare units (-0.7). However, the last two coefficients were not statistically significant ($p > 0.05$) (**Table 2**).

The incidence rate in Shumen, Varna, Burgas and Yambol regions was the highest in the 5-9 year age group (609 cases), followed by individuals of 10-14 years (383 cases in total) (**Table 3**). The highest number of reported cases among children in the age group 5-9 is observed also in Dobrich region with 59 reported cases in this age group and incidence rate of 164.78‰ (data not shown). In all regions, the incidence rate in the most affected age group (5-9 years) had a very high statistical significance when compared to the incidence rates in the other groups ($p < 0.001$).

During the examined period, male cases (1578) predominated over female cases (1287) (**Table 4**).

Table 3. Distribution of HAV by age*

Age (years)	Shumen		Varna		Burgas		Yambol		Total
	n	Inc.&	n	Inc.&	n	Inc.&	n	Inc.&	n
0-04	8	94.75	32	126.62	133	595.00	85	1392.53	258
05-09	23	273.91	113	527.62	369	1885.64	104	1754.09	609
10-14	35	414.54	67	325.65	205	1069.60	76	1255.78	383
15-19	11	105.17	44	186.75	117	545.07	65	975.54	237
20-24	7	58.72	27	79.39	53	202.68	38	536.57	125
25-29	8	68.92	37	101.23	74	252.94	47	630.96	166
30-34	10	80.76	42	106.30	86	265.31	31	378.79	169
35-39	4	29.84	48	121.85	73	219.27	36	425.38	161
40-44	4	31.10	41	122.60	56	191.36	35	417.26	136
45-49	4	32.08	34	111.17	53	189.27	39	420.85	130
50-54	4	31.18	25	81.54	48	162.65	27	281.57	104
55-59	2	16.25	19	59.42	40	136.39	12	115.74	73
>60	2	4.44	14	12.95	15	15.62	7	18.47	38

*Age distribution of HAV in Dobrich region is not included due to incomplete data.

&Incidence rates were calculated by dividing the number of reported HAV cases in each age group by the total population in the same age group (as reported in the last national census 2011).

The observed male predominance was significant in four of the studied regions (Dobrich, Burgas, Varna and Yambol) with $p < 0.05$, while in Shumen region HAV infection affected equally males and females ($p = 0.89$). However, the overall trend shows that males in Eastern Bulgaria are significantly more susceptible to HAV (chi-square for trend 5.5, p -value = 0.02). The risk ratio (male to female) is 1.27 and after accounting for possible variability, the male sex could be considered to increase the risk of HAV infection from 1.04 to 1.55 times when compared to female sex.

DISCUSSION

In the present study we discuss the epidemiological patterns of hepatitis A infection in some of the most vulnerable regions in Bulgaria – Burgas, Dobrich and Varna cover the Bulgarian coastline of the Black sea and receive most of the tourists visiting the country. In addition, Burgas and Yambol bound on the south Turkey and experience the outcome of enlarged migrant's flow during the last years. The current work shows that HAV infection does not

Table 4. Distribution of HAV by gender (number of cases for 2008-2014)

Region	Males	Females	Chi-square	p
Dobrich	157	114	8.48	0.004
Shumen	59	63	0.02	0.90
Varna	294	249	5.89	0.02
Yambol	329	273	7.50	0.01
Burgas	739	588	24.16	< 0.001
Total	1578	1287	5.5	0.02

demonstrate a distinct trend of decrease or increase during the 2008-2014 period in all regions of interest. In addition, for one and the same year, the incidence rates varied widely even in neighboring regions. The highest incidence in our study was reported for Burgas region in 2012 when there was an outbreak in two of the high schools in the town. This result is expected as HAV is highly contagious

and is usually presented under the form of recurrent local outbreaks in countries of intermediate endemicity such as Bulgaria.²

A statistically significant difference was found in the cumulative incidence between regions in the south and regions in North. South regions have more than 3-fold higher incidence rates (for the period of study) than north regions. These data provoked us to hypothesize that the national pattern of HAV epidemiology largely reflects the European distribution with the highest rate in southeastern areas. The same pattern is widely observed for other viral hepatitis on both national⁹ and European level¹⁰.

HAV infection correlates with low hygienic living conditions and in Plovdiv region of Bulgaria people with bad hygienic habits were found to be 9 times more affected by HAV.¹¹ Other studies correlates HAV seropositivity with the ethnic origin.¹² This prompted us to investigate some important sociodemographic variables (**Table 2**) and their relation to the HAV incidence in the investigated regions. The population number, its density, age or ethnic structure cannot be related to the number of reported HAV cases in Eastern Bulgaria. HAV incidence is also independent of the poverty rate of population – another social factor broadly accepted to influence disease occurrence. The only factors that showed a negative correlation (although not statistically significant) with HAV rates were the available living space and the attendance of children in day-care centers. Their influence is not surprising as overcrowded living conditions facilitate the close contact for HAV transmission. The negative correlation between HAV cases and the rate of daycare attendance of children can be explained by the fact that higher attendance is usually related to economically active population in high-income social groups while unemployed parents of lower social level prefer to keep children at home facilitating the virus transmission between them.

In the present study we also confirm that children play an important role in the spread of HAV as the most affected age group was of 5-9 year-old individuals. Similar results were obtained in other Bulgarian towns – Ichtiman and Plovdiv. During the hepatitis A outbreak in Ichtiman-Iztok, Sofia region in 2012 the most affected was the age group of 5-9-year-old children while in older age groups only single cases were registered.¹³ During another hepatitis A outbreak in Plovdiv-Stolipinovo (in 2006), 75% of all 701 cases were in children aged 1-9 years.⁷ Again, in Plovdiv region (2005-2008), the age group

5-9-year-olds was found to be the most affected by HAV infection followed by the group 1-4 years.¹¹ We also have found that morbidity decreased with age and reaches its lowest level in 60-65-year-old individuals. In epidemiological study conducted in New South Wales during 2000-2009, morbidity level was found to be the lowest in individuals above 55, which according to the authors was due to the individual's exposure to HAV in their earlier age.¹⁴ Here, we should clearly state one of the limitations of the present work – cases with asymptomatic infection were not included because investigation of anti-HAV Ig M of individuals, which were in contact with HAV infection, was not performed.

In addition, male sex was found to be a possible predisposing factor for HAV infection (risk ratio of 1.27). In total, 1578 men (from a population of 679414 men in the investigated regions according to the 2011 census data) were infected with HAV during the period of study in comparison with 1287 women out of 707689. These numbers yield incidence rates of 232 and 182 per 100000 for men and women, respectively. In absolute terms, the increase in risk for males was 50 cases per 100000. In both developed and developing countries frequency rates of acute HAV among males are higher than among females^{15,16}, although the seroprevalence is equal in both sexes¹⁷.

CONCLUSION

We have demonstrated that over the seven years of study a clearly defined decrease or increase trend in the incidence rate of HAV cannot be determined. HAV is an infectious disease usually present as recurrent outbreaks in different regions in our country which shows a significant time and geographic fluctuations. However, we present evidence that south geographic location, male sex and age under 9 years are statistically significant risk factors for hepatitis A infection.

In the context of the results obtained, it is necessary to raise the health knowledge of children and adolescent about hepatitis A and to improve the essential hygienic habits (washing hands), as well as to consider inclusion of the HAV vaccine in the National Immunization Calendar of Bulgaria to decrease HAV circulation in general population.

CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

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Эпидемиологическое исследование инфекции гепатита А в восточной Болгарии

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Введение: Вирусная инфекция гепатита А (HAV) является острым самолимитирующим заболеванием печени, с фекально-оральным механизмом передачи возбудителя при контакте человек-человек. В Болгарии встречается средняя степень HAV эпидемичности с большей распространенностью среди взрослых и рецидивирующими очагами.

Цель: В силу того, что HAV инфекция непосредственно связана с передвижением людей и представляет собой значительный риск для как для мигрантов, так и для местного населения, принимающего данные группы, нами был предпринят анализ эпидемиологических данных о гепатите А в наиболее крупных туристических приграничных районах Болгарии, расположенных в восточной части страны: Варна, Шумен, Добрич, Бургас и Ямбол.

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гепатовирус, инфекционный гепатит, воспаление печени, эпидемиология

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Материал и методы: Мы рассмотрели в ретроспективном порядке все зарегистрированные случаи острого гепатита А в восточных районах Болгарии в рамках 7-летнего периода между 2008 и 2014 годами.

Результаты: Новые случаи заражения общим количеством 2879 были зарегистрированы за время периода исследования, количество которых колеблется в широких границах: от 190 случаев в 2014 г. до 923 в 2012 г. Средняя заболеваемость HAV была более высокой в юго-восточных областях (55.30‰ и соответственно 15.04‰, $p < 0.0001$). Наиболее подверженной заболеванию возрастной группой во всех областях являются 5-9 летние ($p < 0.0001$), а мужчины значительно более податливы заражению HAV ($p = 0.02$).

Заключение: Гепатит А все еще остается основной проблемой общественного здравоохранения в Болгарии: существуют значительные различия в масштабах заболевания как между областями на юго-востоке и на северо-востоке, так и между различными возрастными и гендерными группами.