

# Hepatitis E Virus Infection in Bulgaria: A Brief Analysis of the Situation in the Country

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## Abstract

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**BACKGROUND:** Over the past two decades, more thorough investigations for hepatitis E virus (HEV) infection have been done in the world. Reports from Southeast European countries have increased.

**AIM:** The current article presents a critical analysis of all studies for HEV in Bulgaria.

**MATERIAL AND METHODS:** A literature search was done using available medical databases. We analysed the literature in PubMed databases and Bulgarian medical databases for English and Bulgarian languages sources. Preference was given to the sources published within the past 24 years (January 1995 – September 2018).

**RESULTS:** Two thousand two hundred and fifty-seven blood serums were tested for the analysed period (1995 – 2018), and 13.1% of them were positive for acute HEV (Mean  $\pm$  SD: 20.38  $\pm$  25.77%; 95% CI: 1.29 – 39.47%). The following subtypes were established in the country – HEV Subtype 3e, HEV Subtype 3f, HEV Subtype 3c, HEV Subtype 3i, HEV Subtype 3hi and HEV Subtype 1.

**CONCLUSION:** We hope that the National Health Organizations will take adequate and timely measures to increase the knowledge and research for HEV among Bulgarian citizens.

## Introduction

Hepatitis E virus (HEV) infection is an infectious disease which thorough investigation has realised over the past twenty years [1] [2]. First studies of HEV were from the late 1970s and the early 1980s [3], [4]. In Bulgaria, the first human cases were reported by Teoharov et al., in 1995 [5]. The infection has been investigated thoroughly in the country since 2008 [6], [7]. Some Bulgarian authors presented data for HEV infection among Bulgarian patients [8], [9]. However, there are still many unknown questions about this infection in our country.

The aim of this study is a critical analysis of all available articles for HEV infection in Bulgaria.

## Materials and Methods

### Study Design

A literature search was done using available medical databases. We analysed the literature in PubMed databases and Bulgarian medical databases for English and Bulgarian languages sources using the following keywords "Hepatitis E virus" AND "Bulgaria" AND "HEV" AND "Hepatitis E virus infection" AND "HEV infection". No age restriction was observed. All studies were written in the English or Bulgarian language. The critical analysis included original articles, brief reports and case series. The critical analysis excluded articles with missing data for the number of investigated individuals, case reports

and letters to the editor. Preference was given to the sources published within the past 24 years (January 1995 – September 2018).

### Ethics Statement

The study was performed by 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 before the medical examination.

### Statistical Analysis

The results obtained from the majority of studies do not allow detailed statistical analysis. Therefore, basic statistical indicators such as confidence interval (CI), standard deviation (SD), etc. were applied. 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

We found 23 papers (PubMed databases – 5; Bulgarian medical databases – 18). Seven articles fulfilled the inclusion and exclusion criteria and were included in the final data analysis (Table 1) [5], [8], [9], [10], [11], [12], [13]. All articles described hospitalised patients with clinical presentation of acute HEV infection. Two thousand two hundred and fifty-seven blood serums were tested for the analysed period (1995 – 2018), and 13.1% of them were positive for acute HEV (Mean  $\pm$  SD: 20.38  $\pm$  25.77%; 95% CI: 1.29 – 39.47%). Individuals have been tested for anti-HEV IgG and/or anti-HEV IgM. The following subtypes were established in the country – *HEV Subtype 3e* (GenBank accession number 77A 2012-BG, 2588 2011-BG, 2308 2011-BG, et al), *HEV Subtype 3f* (GenBank access. num. 762 2011-BG, 855 2011-BG, 688A 2010-BG, et al.), *HEV Subtype 3c* (GenBank access. num. ISS75 Plov 2014, ISS100 Paz 2014, ISS2 Sof 2013, et al.), *HEV Subtype 3i* (GenBank access. num. 1785 2011-BG, 905 2012-BG), *HEV Subtype 3hi* (GenBank access. num. ISS62 Paz 2014), and *HEV Subtype 1* (GenBank access. num. ISS78 Haskovo – travel Afghanistan 2014) [9], [13]. In Bulgaria HEV infection affected predominantly male gender (male/female – 80.0/20.0%). The mean age of HEV-positive people varied between 50.7  $\pm$  23.0 years (95% CI: 32.26 – 69.06) for Sofia district [8], and 53.6  $\pm$  14.0 years (95% CI: 45.66 – 61.49) for Plovdiv district [10].

**Table 1: Studies on acute hepatitis E virus infection in Bulgaria**

First author and reference	Year of Publication	Methodology	Target group	Diagnostics	Investigated, (n)	HEV positive, (n)
Teoharov et al. [5]	1995	Retrospective	Hospitalized	ELISA	53	4
Dikov et al. [8]	2012	Retrospective	Hospitalized	ELISA	117	6
Teoharov et al. [9]	2014	Retrospective	Hospitalized	ELISA HEV RNA	741	67
Petrov et al. [10]	2015	Retrospective	Hospitalized	ELISA	112	12
Baymakova et al. [11]	2016	Retrospective	Hospitalized	ELISA	806	20
Stoykova et al. [12]	2017	Retrospective	Hospitalized	ELISA	325	111
Bruni et al. [13]	2018	Retrospective	Hospitalized	ELISA HEV RNA	103	76

## Discussion

HEV infection more frequently affects male than female (61-69%) [14]. Similar data were found in Bulgarian studies for HEV gender distribution (male/female – 80.0/20.0%). But opposite data were reported from Romania (male/female – 40/60%) [15], and Turkey (21.4/78.6%) [16].

The highest incidence of HEV infection is observed in people over fifty years [14]. Similar data are reported from Romania (28% HEV-positive in the age group of 45-65 years) [15], Turkey (50.9  $\pm$  16.8 years) [16], and Albania (35% HEV-positive in the age group over 50 years) [17]. In Bulgaria, HEV infection occurs mainly in people over 50 years of age.

Up to now, there are only two Bulgarian studies for HEV phylogenetic analysis of human samples [9], [13]. The studies established *HEV Subtype 3e*, *HEV Subtype 3f*, *HEV Subtype 3c*, *HEV Subtype 3i*, *HEV Subtype 3hi* and *HEV Subtype 1* [9], [13]. It is known that *HEV Subtype 3e* occurs mainly in swine, *HEV Subtype 3f* is human subtype, and *HEV Subtype 3i* is mainly wild boar subtype. The established *HEV Subtype 3e* in Bulgaria is close to the reference sequence AB248520 Japan 3e. The established *HEV Subtype 3f* showed high similarity with reference sequence EU495148 France Hu 3f. The third found *HEV Subtype 3i* in Bulgaria is familiar to reference sequence FJ705359 Germany wild boar 3i. These results indicate that the virus might have an autochthonous character in Bulgaria with zoonotic potential and main reservoirs as domestic pigs and wild boars.

In Bulgaria, HEV infection is poorly known and diagnosed. The realised human studies are focused on the clinical manifestations and characteristics of acute clinical form. There are many uncertain things about HEV infection in Bulgaria. First, a basic problem has no established HEV case definition in Bulgaria. Second, has not enough investigations on HEV RNA among Bulgarian patients. Third, there is no licensed diagnostic laboratory for hepatitis E sequencing (HEV RNA analysis). Fourthly, there are no morbidity registers for HEV in Bulgaria.

Therefore, in some areas of the country, it is not known what is the real prevalence of HEV among the population. Fifth, the mortality of HEV is unknown among Bulgarian citizens. Sixthly, HEV seroprevalence is unknown for risk groups (HIV-positive patients, immunocompromised persons, transplanted patients and pregnant women). Seventh, animals' investigations are limited in the country. There is one study for HEV seropositivity among pigs in industrial farms in Bulgaria [18]. The results from this project found 40% HEV-positive pigs [18].

There are some reasons for those missing information and knowledge for HEV in Bulgaria. First, there is a lack of coordination and collaboration between scientific societies of infectious diseases specialists, microbiologists, virologists and gastroenterologists. Second, the researches in the country are poorly financed. Third, the Ministry of Health does not record the incidence and mortality of HEV infection in Bulgaria. Fourthly, National Health Authorities do not conduct a screening programme for blood and blood products for hepatitis E virus. Fifth, the veterinary services in the country do not search for HEV infection routinely in animals (domestic pigs, wild boars, bears, dogs, cats, etc.). Sixthly, lack of efficiency of some hospitals. Seventh, poor diagnostic capacity of some hospital laboratories. Eighth, poorly trained medical staff is seeking, recognising and investigating HEV infection.

In conclusion, the combination of these facts leads to the national position of insufficient evidence of HEV infection in our country. The notified weaknesses could be revised, and the local situations could be improved. We hope that the National Health Organizations will take adequate and timely measures to increase the knowledge and research for HEV among Bulgarian citizens.

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