

To the Honorable Members of the Scientific Jury
Appointed by Order No. 182 / 30.06.2026
Of the Director of the NCIPD
Prof. Dr. Iva Christova, MD, PhD

REVIEW

by Assoc. Prof. Dr. Metodi Antonov Kunchev, MD
Head of the Department of Microbiology, Virology, Clinical Laboratory and Immunology at the
Military Medical Academy, Sofia.

regarding the dissertation defense of **Chiydem Baarieva Ismailova**, a full-time PhD student at NCIPD, for the award of the educational and scientific degree Doctor (PhD) on the topic:
“Studies on the Serological and Molecular Genetic Characteristics of the Hepatitis E Virus”
under the doctoral program Virology, field of higher education 4. Natural Sciences, Mathematics and Informatics, professional field 4.3 Biological Sciences

Scientific Supervised: **Assoc. Prof. Lyubomira Nikolaeva-Glomb, MD, PhD.**

I declare that I have no joint publications with the doctoral candidate and no conflict of interest of any other nature within the meaning of §1, item 3 of the Additional Provisions of the Act on the Development of Academic Staff in the Republic of Bulgaria.

Biography

Chiydem Ismailova completed her secondary education in 2013 at the “Apostol Arnaudov” Vocational High School of Electrical Engineering and Electronics in Ruse, specializing in “Computer Engineering and Technologies”. In 2017 she obtained a Bachelor's degree in Molecular Biology from the Faculty of Biology at Sofia University “St. Kliment Ohridski.” At the same institution, she earned a Master's degree in Microbiology and Mycological Control in 2019.

Since 2018, she has been working as a biologist at NCIPD. From October 1, 2020, to October 1, 2023, she was a full-time doctoral student in the Virology program under the scientific supervision of Assoc. Prof. Lyubomira Nikolaeva-Glomb, MD, PhD.

Chiydem Ismailova has completed numerous training courses, both at NCIPD and internationally, including: 2021: Application of Next-Generation Sequencing in Clinical Microbiology and Infectious Disease Diagnostics, organized by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). 2023: Sequencing and Phylogenetic Analysis course at the Luxembourg Institute of Health.

Relevance of the Dissertation Topic

Hepatitis E virus (HEV) is the fifth recognized form of viral hepatitis and was first identified as the cause of an epidemic of unexplained acute hepatitis in the early 1980s. The relevance and

significance of studying this virus stem from the fact that it poses a major public health threat, causing large outbreaks and sporadic cases of acute hepatitis worldwide.

The infection is increasing globally. According to the World Health Organization (WHO), approximately 20 million people become infected with HEV each year, resulting in around 3.3 million symptomatic cases of hepatitis E. In 2015, this led to approximately 44,000 deaths, representing 3.3% of deaths due to viral hepatitis. HEV infection is the most common or second most common cause of acute viral hepatitis among adults in many parts of Asia, the Middle East, and Africa. The European Centre for Disease Prevention and Control (ECDC) reported 21,018 HEV cases from 22 EU countries during the period 2005-2015.

General Characteristics of the Dissertation

The dissertation is structured in accordance with the Regulations for the Implementation of the Academic Staff Development Act at NCIPD. It was prepared in the Department of Virology, National Reference Laboratory for Hepatitis Viruses, NCIPD, Sofia.

The dissertation consists of 13 chapters and comprises 115 pages. It includes 24 tables, 30 figures, and 3 appendices. The distribution of sections meeting the adopted requirements is as follows: title page; acknowledgements (1 page); table of contents (2 pages); list of abbreviations used (1 page); introduction (1 page); literature review (24 pages); aim and objectives (1 page); materials and methods (18 pages); results (25 pages); discussion (10 pages); conclusion (1 page); conclusions (1 page); contributions (2 pages); literature (19 pages), publications related to the topic of the dissertation (1 page); participation in international and national scientific forums in connection with the dissertation (2 pages); scientific projects related to the dissertation (1 page); appendices (4 pages). The bibliography contains 195 references, including 11 in Cyrillic and 184 in Latin script. The dissertation has been approved for public defense before the scientific jury appointed by Order No. 182/30.06.2026 of the Director of NCIPD.

Review and Evaluation of the Dissertation

The dissertation is impressive in scope and in the variety of diagnostic methods used for HEV investigation. A total of 2,467 samples were examined, including:

- 1,823 prospective serum samples from hospitalized individuals with various diagnoses.
- 644 retrospective serum samples from individuals representing a heterogeneous population.

The samples were collected between 2015 and 2023.

Introduction

In the introduction, Ch. Ismailova discusses the history of Hepatitis E, its discovery, transmission routes, cloning and sequencing, and its recognition as the fifth hepatotropic virus

alongside hepatitis A, B, C, and D viruses. She addresses its significance for human pathology, the relationship between viral genetic characteristics and epidemiology, and the clinical course and severity of infection. Special emphasis is placed on expanding HEV research in Bulgaria and developing prevention programs.

Literature Review

The literature review is quite extensive, detailed and well-structured on 24 pages. The historical data on HEV, its classification, morphology, structure, genetic diversity, physico-chemical properties and the viral genome are comprehensively and in detail described. The epidemiology, transmission mechanism, spread, pathogenesis and clinical manifestations are examined in great detail. An important part of the review is the presentation of various serological and molecular methods, including sequencing for diagnosis and phylogenetic analysis of the virus. Attention is paid to the risk groups, modern treatment, prophylaxis and prevention of HEV infection.

Aim and Objectives

The aim of the dissertation is highly relevant and clearly formulated. The **five objectives** are logically connected to the conclusions and scientific contributions presented in the dissertation.

Materials and Methods

The materials and methods occupy 18 pages, which describe in detail the patient groups, the anamnestic and clinical data used, clinical and laboratory examinations, molecular biological diagnostic methods (Nested PCR, RT-PCR, Sequencing), statistical methods and subtyping and phylogenetic analyses.

Results

The results obtained, presented on 25 pages, are correctly described, analyzed and well-illustrated, which reveals the good theoretical and practical preparation of the doctoral student. The detected serological markers of infection with HEV in serum samples from different populations, distributed by gender, age, diagnosis, type of antibodies detected and risk groups, are described. Seropositive individuals are distributed by gender (men predominate) and age (the largest group is > 50 years). The studied seropositive samples for the presence of HEV RNA show a relationship between the viral load and the value of anti-HEV IgM. In the prospective group, the largest relative share of anti-HEV IgM positive samples is found in individuals with acute hepatitis 58%, and in the retrospective group in children with hematological diseases 56%. The results of the dissertation are of great value, as they establish, through sequencing and phylogenetic analysis of samples with positive HEV RNA, not only their belonging to genotype 3, but also five different subtypes: HEV-3e, HEV-3f, HEV-3c, HEV-3m and HEV-3a.

Discussion

The discussion section comprises 10 pages and presents a precise and professional comparison between the candidate's findings and those of authors cited in the literature review. At the end of the dissertation, **8 logical conclusions** are outlined, which reflect the most significant results of the dissertation work.

I accept the **4 scientific contributions** presented by the candidate.

Bibliography

The literature review contains 195 sources, of which 11 are in Cyrillic and 184 in Latin. Of these, 112 (58%) are from the last 10 years 2015-2025.

Evaluation of the Dissertation Summary

The abstract covers 69 pages, in which the doctoral student has very well succeeded in concisely containing and presenting the entire structure of his dissertation.

Publication Activity

Ch. Ismailova has presented a total of 5 scientific publications related to the topic of the dissertation, 3 of which are referenced and indexed in the world-renowned databases of scientific information (Web of Science and Scopus), which fully covers and exceeds the criteria of the indicators from group G specified in accordance with the Regulations for the Implementation of the Act on the Development of the Academic Staff in the Republic of Bulgaria. During the period of her doctoral studies, she participated in three projects on the topic and 13 scientific forums, two of which were abroad.

CONCLUSION

HEV infection remains a global cause of morbidity and mortality. Its diagnosis is challenging because of its nonspecific clinical presentation. Over the last decade, substantial progress has been made in understanding the virus's pathobiology. Through her dissertation, Chiydem Ismailova has made an important contribution to the understanding of the epidemiology and genetic characteristics of HEV in Bulgaria, as well as the significance of risk groups for improving prevention and public health control measures.

The dissertation fully complies with the mandatory requirements and scientometric criteria of the Act on the Development of the Academic Staff in the Republic of Bulgaria and the Regulations

for its Implementation (last amended, State Gazette No. 16/10 February 2026). Based on the scientific merits of the dissertation, I give it a positive evaluation and strongly recommend that the esteemed Scientific Jury award Chiydem Baarieva Ismailova the educational and scientific degree of Doctor in the scientific specialty Virology, Professional Field 4.3 Biological Sciences, Field of Higher Education 4. Natural Sciences, Mathematics, and Informatics, professional field 4.3. Biological sciences; scientific specialty: Virology.

07.08.2026
Sofia

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