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Е гепатитинин серологиялык диагностикасы үчүн тест-системаларын түзүү жана алардын диагностикалык эффективдүүлүгүн эндемикалык жана эндемикалык эмес региондордон алынган клиникалык материалдар боюнча тестирлөө

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МАКАЛА ЖӨНҮНДӨ МААЛЫМАТ

Негизги сөздөр:
Гепатит Е

КОРУТУНДУ

КМШга мүчө-мамлекеттердин 2020-жылга чейинки мезгилге Инновациялык кызматташтыктын мамлекеттер аралык программасынын Е

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Гепатит Е вирусу генотип 1
Гепатит Е вирус генотипы 3
Рекомбинанттык антиген
ORF2
ORF3
Ферментке байланышкан иммуносорбенттик анализ
Сызыктуу иммуно анализ
Иммунохроматография
Сероэпидемиология

гепатитин серодиагностикалоо үчүн тесттик системаларды түзүү боюнча инновациялык пилоттук долбоорду ишке ашыруунун жыйынтыктары сунушталды. Долбоор И.И. Мечников атындагы Федералдык мамлекеттик бюджеттик мекемеси жана Кыргыз Республикасынын Саламаттык сактоо Министрлигинин коомдук саламаттыкты сактоо улуттук институту, Беларусь Республикасынын медициналык жана ветеринария илим-изилдөө профилиндеги илимий-изилдөө мекемелери менен ишке ашырылып жатат.

Изилдөөнүн жыйынтыгында КМШ өлкөлөрүндө басымдуулук кылган 1 жана 3 ВГЕ генотиптеринин, ВГЕге IgG антителолорун санын, ВГЕге IgG антителолорунун активдүүлүгүн, ВГЕге суммардык антителосун, ВГЕге IgM антителолорун, ВГЕнин антигенине детекциясын аныкташ үчүн рекомбинанттуу антигендери иштелип чыккан жана ошондой эле сызыктуу иммундук анализди колдонуу менен ВГЕге антителолорду аныктоо үчүн ырастоочу тест системасы, ВГЕге антителолорду аныктоо үчүн иммунохроматографиялык экспресс-тест жана ПТРдин жардамы менен кан сары суусунда жана кан плазмасында ВГЕге РНКсын аныктоо үчүн жогорку тактыктагы тест системасы иштелип чыкты.

Россия, Кыргызстан жана Беларусия өлкөлөрүндө жүргүзүлгөн сероэпидемиологиялык жана молекулярдык эпидемиологиялык изилдөө өлөрдүн натыйжалары үч өлкөдө тең курч гепатит менен ооругандардын структурасында тастыктоодон жана каттоодон качкан гепатиттин үлүшүнүн ырааттуу көбөйгөнүн көрсөттү.

Создание тест-систем для серологической диагностики гепатита Е и испытание их диагностической эффективности на клиническом материале из эндемичных и неэндемичных регионов

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ИНФОРМАЦИЯ О СТАТЬЕ

Ключевые слова:
Гепатит Е
Вирус гепатита Е 1 генотипа
Вирус гепатита Е 3 генотипа

РЕЗЮМЕ

Представлены результаты выполнения инновационного пилотного проекта по созданию тест-систем для серодиагностики гепатита Е Межгосударственной программы инновационного сотрудничества государств – участников СНГ на период до 2020 года. Проект выпол-

Рекомбинантный антиген
ORF2
ORF3
Иммуноферментный анализ
Линейный иммуноанализ
Иммунохроматография
Сероэпидемиология

нялся совместно ФГБНУ НИИВС им. И.И. Мечникова, Национальным институтом общественного здоровья Министерства Здравоохранения Кыргызской Республики и научно-исследовательскими учреждениями медицинского и ветеринарного профилей Республики Беларусь. В результате проведенных исследований были разработаны рекомбинантные антигены доминирующих на территории стран СНГ 1 и 3 генотипов ВГЕ и на их основе создан комплекс иммуноферментных тест-систем: для количественного определения IgG-антител к ВГЕ, для определения авидности IgG-антител к ВГЕ, для определения суммарных антител к ВГЕ, для определения IgM-антител к ВГЕ, для детекции антигена ВГЕ, а также подтверждающая тест-система для определения антител к ВГЕ методом линейного иммуноанализа, иммунохроматографический экспресс-тест для выявления антител к ВГЕ и высокоточная тест-система для выявления РНК ВГЕ в сыворотке и плазме крови методом ПЦР. Результаты серо-эпидемиологических и молекулярно-эпидемиологических исследований, проведенных в регионах России, Кыргызстана и Беларуси, свидетельствовали о последовательном увеличении доли ГЕ в структуре заболеваемости острыми гепатитами на территории всех трех стран с ускользанием большого числа случаев заражения от диагностики и регистрации.

Test kit development for serological diagnostics of hepatitis E and checking of their diagnostic effectiveness on clinical material from endemic and non-endemic regions

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ABSTRACT

The results of the innovative pilot project for kit development for hepatitis E serum-diagnostic assays of the Interstate Program for Innovative Cooperation of the CIS member states for the period up to 2020 are presented. The project was carried out by I.I. Mechnikov Federal State Medical Research Institute for Vaccines and Sera in association with the National Institute of Public Health of the Ministry of Health of the Kyrgyz Republic and Belarusian medical and veterinary research institutions. As a result of research recombinant antigens of the prevalent in the CIS countries HEV genotypes 1 and 3 were developed, and a set of diagnostic assays was made, namely: test for quantification of IgG antibodies to HEV, test for determination the avidity of IgG antibodies to HEV, test for measuring the total antibodies to HEV, test for detection IgM antibodies to HEV, test for detection HEV antigen,

confirmation test for detection antibodies to HEV by linear immune assay, immune-chromatographic rapid test for detection the antibodies to HEV and a high-precision test for detection HEV RNA in sera and plasma by PCR. The results of serum epidemiological and molecular epidemiological studies performed in the regions of Russia, Kyrgyzstan and Belarus indicated a consistent increase proportion of hepatitis E in the structure of acute hepatitis cases in these countries with the avoidance of a large number of the cases from diagnosis and registration.

Introduction

Hepatitis E (HE) is a global health problem, and improving its diagnostics is an urgent task for medical care. The relevance of the chosen topic is also associated with an increase in the frequency of cases of local and imported HE, high serum prevalence of hepatitis E virus (HEV) among animals and workers of pig farms in Russia and Belarus, high endemicity in Central Asia countries. Alongside with the detection of viral RNA by PCR, an important laboratory indicator of HEV infection is the detection the specific antibodies in the patient blood sera. Comparative studies of commercial test systems produced by different manufacturers have demonstrated a wide range of variability in the received results. For example, a meta-analysis of the 73 results of serum prevalence in Europe showed significant differences in the serum positive levels on the surveyed territories, detected by using various commercial test systems, namely: Wantai (WT) - 17%, Mikrogen (MG) - 10%, MP-diagnostics (MP) - 7%, DiaPro - 4%, Abbott - 2% [1].

I.I. Mechnikov Federal State Medical Research University has become the initiator, coordinator and realizer of the innovative pilot project «Development of test systems for the serological diagnostics of hepatitis E and testing their diagnostic effectiveness on clinical material from endemic and non–endemic regions» of the Interstate Program of Innovative Cooperation of the CIS member states for the period up to 2020, approved by the Decisions of the CIS Heads of Government Councils from 31.05.2013 and 30.10.2015. The project was carried out jointly with the National Institute of Public Health of the Ministry of Health of the Kyrgyz Republic and medical and veterinary research institutions of the Republic of Belarus: RUE «S.N. Vyshelessky Institute of Experimental Veterinary Medicine», Belarusian State Medical University, Vitebsk State Academy of Veterinary Medicine. In Russia, scientific research was carried out within the framework of the Federal Targeted Program «Research and Development in priority areas of progress in the scientific and Technological complex of Russia for 2014-2020» according agreements with the Ministry of Education and Science of the Russian Federation No. 14.613.21.0057 and No. 075-15-2019-1481. In Belarus the project was carried out in accordance with the agreement with the State Committee for Science and Technology of the Republic of Belarus No. 6/2015. In Kyrgyzstan the study was made in accordance with the agreement between the Ministry of Education and Science of the Kyrgyz Republic and the National Institute of Public Health by Order of the Ministry of Health of the Kyrgyz Republic No. 129/1.

Research aims. Development of recombinant antigens dominating on the territory of the CIS countries HEV 1 and 3 genotypes, construction on their basis a set of test kits for the HE diagnostics, carrying out serum epidemiological and molecular epidemiological HE studies in the regions of Russian Federation, Republic of Belarus and Kyrgyz Republic.

Materials and methods

Immune reagents: conjugate of mouse monoclonal antibodies to Fab fragment and Fc fragment of the human IgG (Sorbent-Service, Russia), conjugate of polyclonal rabbit antibodies to human IgG with horseradish peroxidase made by periodate oxidation in the laboratory for viral genomes cloning, I.I. Mechnikov Research Institute for Vaccines and Sera. To work out the conditions for analysis and trial tests of kits following immune reagents were used, namely: International Standard of the World Health Organization (WHO) «Anti-hepatitis E Serum, Human» 95/584 NIBSC; reference panel of sera (n=8) containing and not containing IgG-antibodies to HEV (cat. No. E331, Diagnostic Systems, Russia); blood serum samples of healthy individuals and patients with hepatitis A, B, C, E and other pathological liver infections provided by the Department of Infectious Diseases of the Belarusian State Medical University, National Institute of Public Health of the Ministry of Health of the Kyrgyz Republic, and Clinical and Diagnostic Department of the I.I. Mechnikov Research Institute for Vaccines and Sera. Diagnostic kits «RecomLine HEV IgG/IgM» (RU No. 2012/13543 cat. No. 5072, Mikrogen Diagnostic GmbH, Germany), «DS-ELISA-ANTI-HAV-G» and «DS-ELISA-ANTI-HAV-M» (Cat No. 151, 152, Diagnostic Systems, Russia) were used as comparison tests. Serological markers of infecting with hepatitis A, B, C viruses and infectious liver pathogens were detected using following commercial enzyme immune assays, namely: «DS-ELISA-ANTI-HAV-G-RECOMB» (cat. No. A-151, Diagnostic

Systems, Russia), «BLOT HIV ½+0» (RU No. FSR 2009/04019, Bioservice, Russia) and kits manufactured by «Vector-Best, Russia»: «Vectohep B-HBs-antigen» (RU No. RZN 2015/2887,), «HepaBest anti-HBc-IgG» (RU RZN 2017/5606), «Best anti-HCV-auto» (RU No. RZN 2015/2674), «Best anti-HCV-confirmatory test» (RU No. RZN 2015/2895), «VectoCMV-IgG-avidity» (RU No. RZN 2014/2219), «VectoVEB-EA-IgG» (RU No. RZN 2013/1274), «VectoVEB-NA-IgG» (RU No. RZN 2013/1273). Reactions were made in accordance with test kit manuals. For digital accounting, linear immune assay colored strips were scanned, and the staining intensity was measured by the TotalLab program. Swine farm waste water samples were concentrated from the initial volume of 5 liters to 1 ml using a commercial kit «Virosorb-M» (Bioservice, Russia). The concentration method is based on the binding of negatively charged viral particles to the surface of magnetic beads coated by modified silicon dioxide polymer. Nucleic acids were isolated from 1 ml concentrate using the MagNA Pure Compact Nucleic Acid Isolation Large Volume Kit I (Roche Applied Science, Germany). Nucleic acids were purified from clarified fecal extracts using the device «MagNA Pure Compact» (Roche Diagnostics Ltd., Rotkreuz, Switzerland) and the isolation kit «MagNA Pure Compact Nucleic Acid Isolation Kit I». HEV RNA was detected in a polymerase chain reaction combined with reverse transcription (RT-PCR) using degenerate primers to the HEV open reading frame 2 (orf2). HEV nucleotide sequence alignment was made by MEGA 7.0.18 software. Phylogenetic analysis was performed for a fragment of 300 nucleotide residues in length corresponding to HEV orf2 (nucleotide positions 5996 – 6295 according to strain M73218) with reference sequences for known HEV sub-genotypes. Phylogenetic trees were built by HTML 3.0 soft using the GTR model (http://www.atgc-montpellier.fr/html/), the SPR tree correction method (http://www.atgc-montpellier.fr/download/papers/phyml_spr_2005.pdf) and Bayesian test (https://academic.oup.com/sysbio/article/60/5/685/1644562). Tree annotation was performed using TreeAnnotator v.1.8.4, visualization - using Fig Tree v.1.4.3. Statistical analysis of the obtained results was carried out using the standard EXCEL 2010 program and the GraphPadPrism 4 statistical data processing program.

Results and discussion

The project was carried out by participants in conditions of constant and stable co-operation. The cloning of fragments of the viral genome and the preparation of recombinant antigens were carried out by Russian scientists, the development of test systems based on the constructed antigens was carried out by scientists from Russia and Belarus. The approbation of the developed test systems on clinical and biological material, as well as serum epidemiological and molecular epidemiological studies on the territories of the participating countries were carried out by all project partners. Researchers from I.I. Mechnikov Institute for Vaccines and Sera have developed recombinant antigens ORF2 and ORF3 of the HEV 1 and 3 genotypes, as well as a mosaic recombinant polypeptide containing C-terminal fragments of the ORF2 proteins of the HEV 3 and 1 genotypes, a full-sized ORF3 protein of the HEV 3 genotype and a C-terminal fragment of the ORF3 protein of the HEV 1 genotype. Viral genome fragments cloning was carried-out using HEV RNA samples isolated from humans and animals at the various CIS regions. As a result, recombinant plasmids coding unique antigens were constructed, E.coli strains – producers were obtained, methods for biomass getting, isolation and chromatographic purification of recombinant polypeptides were developed. The recombinant polypeptide antigenic properties were studied by immunochemical reactions with the WHO international standard sample «Anti-hepatitis E Serum Human 95/584 NIBSC» and blood serum samples characterized in commercial test systems [2, 3]. The developed antigens were used as the main immune reagents during test kit construction, including the production of polyclonal antibodies (rabbit, mouse), conjugates of antigens and specific antibodies with horseradish peroxidase and colloidal gold nanoparticles. Six complementary diagnostic test systems have been made, namely: enzyme immune assay test kit for the quantification of HEV IgG antibodies by indirect ELISA «Screen-HEV-IgG»; kit for detection of the HEV IgG antibodies avidity levels of by indirect ELISA «Screen-HEV-IgG-avidity»; kit for detection of the HEV total antibodies «Screen-HEV-AB»; kit for detection of HEV IgM antibodies by the ELISA «capture» method «Screen-HEV-IgM»; test kits for the detection of HEV antibodies by linear immunoassay «HEV-Blot»; and kit for quick detection of HEV antibodies by immune chromatographic analysis «HEV-IgG-IChA». Experimental samples of test kits were prepared and their laboratory trials were made. The sensitivity of kits tested in reactions with the WHO international standard sample was 0.62 IU/ml for «HEV-Blot», 0.05 IU/ml for «Screen-HEV-IgG», 0.20 IU/ml for «Screen-HEV–AT», and 0.20 IU/ml for «Screen-HEV-IgM». Parameters of diagnostic sensitivity and diagnostic specificity for the «Screen-HEV-IgG-avidity» and «HEV-IgG-IChA» were measured using the kits «DS-ELISA-ANTI-HEV-M» and «DS-ELISA-ANTI-HEV-G» and exceeded 95%. Experimental kit samples were tested on clinical material from Russia, Belarus and Kyrgyzstan in the I.I. Mechnikov Research Vaccines and Sera Institute and the National Institute of Public Health of the Ministry of Health of the Kyrgyz Republic. It was showed a strong identity of the results getting by developed kits with the results obtained by commercial analogues («recomLine HEVIgG

/IgM», «recomWeel HEV IgG», «DS-IFA-ANTI-HEV-M», «DS-IFA-ANTI-HEV-G») [4]. The reproducibility of the developed kits was corresponded to a coefficient of variation less than 15%. The absence of interference effects on the analysis results was showed for all developed kits. Experiments on accelerated aging of kits showed shelf life levels of kits within at least 1 year.

Belarusian partners have made a high-precision test system for detecting HEV RNA in serum and blood plasma by real-time PCR with reverse transcription [5]. Antigens made in the I.I. Mechnikov Vaccines and Sera Institute were used in developing enzyme immunoassay kits for semi-quantitative detection of HEV IgG and IgM antibodies in humans and HEV IgG antibodies in pigs [6], and in kit developing for HEV antigen detection by ELISA using polyclonal antibodies to polypeptides ORF2 and ORF3 HEV 1 genotype and natural rabbit antibodies to HEV antigens 3 genotype [7]. Prototypes and experimental samples of test systems were made, laboratory regulations and standing order were developed. Due to control testing results taken place at the Belarusian State Medical University minimal detectable HEV RNA concentration measured by test for detecting HEV RNA was around 10 IU/ml. Diagnostic sensitivity of tests for the detection of HEV IgG antibodies in humans and pigs was 94.8%, diagnostic specificity - 100% [8], diagnostic sensitivity of the test for the detection of HEV IgM antibodies in human sera - 99%, diagnostic specificity – 99% [9].

Reviews describing the HE epidemiological situation on in the Russian Federation, the Kyrgyz Republic and the Republic of Belarus have been written, including identification of trends and assessment of the dynamics of morbidity, identification of disadvantaged regions, evaluation of the effectiveness of preventive measures and the development of forecasts related to progression of the HE epidemiological situation. The results of serum epidemiological and molecular epidemiological studies taken place in the regions of Russia, Kyrgyzstan and Belarus indicated a consistent increase the proportion of HE cases around whole number of acute hepatitis, latent circulation of HEV in the territories of the three countries with the escape of a large number of infection cases from diagnosis and registration.

It was shown that in the territory of the Russian Federation, disease was mainly sporadic with the highest registration of HE cases in the Central Federal District among the adults. In Russia, HEV antibodies were detected more frequently among children with acquired immunodeficiency or neurological disorders, and also the elderly, tuberculosis patients, HIV-infected and syphilis patients at the late stages of the disease progression [10]. A study of HEV antibody serum prevalence among a limited contingent of Soviet troops in Afghanistan showed that the level of specific IgG antibodies gradually decreased over 20-30 years. The detection of IgM antibodies in migrant workers from Central Asian countries reflected the possibility of recent or current infection and, therefore, a high probability of HEV spreading into the Russian Federation. Genotyping of HEV isolates from humans, animals and environmental objects confirmed the dominance of genotype 3 in the Russian Federation, with pigs being the main virus reservoir. The HEV widespread extension among pigs led to the formation of an endemic region in the Belgorod region, the center of pig production in Russia [11]. Human exposure to the virus appears to be primarily due to environmental contamination from wastewater from pig-farms. A case of chronic HEV infection associated with a virus genetically related to viral isolates obtained from pigs has been identified and analyzed. The high HEV serum prevalence in the reindeer population in Yakutia was shown, indicating that this animal species is a true natural HEV reservoir [12]. The possibility of importation of uncharacteristic HEV genotypes into the Russian Federation has been proven. Thus, the first imported case of the disease in Russia caused by HEV genotype 4 was described. HEV genotype 4 was also detected in cynomolgus macaques imported from Vietnam; subsequent phylogenetic analysis showed that primates might serve as a natural HEV reservoir.

Belarusian partners have investigated the manifestations of HEV epidemic process in the Republic of Belarus. The HEV circulation among humans and animals (rabbits, hares, pigs, wild boars, and deer) has been proven. The analysis of the epidemiological and epizootic situation of HE in the Republic was carried out, the sources of infection, transmission routes, risk groups were identified, and set of measures for HEV prevention was developed [13]. The HE pathogenetic mechanisms development, the mechanisms of infection transmission, and the dynamics of laboratory parameters were studied in detail using a model of experimentally infected laboratory rabbits [14]. A study on 1126 blood sera of domestic pigs from 90 farms was carried out in 4 regions of Belarus. The detection rate of HEV IgG antibodies was in average 33.7% (26.1% in the Mogilev region, 28.3% in the Vitebsk region, 36.9% in the Minsk region, 67.2% in Grodno region). It has been established that in pigs from private farms this rate was significantly higher compared to pigs raised at state plants. The most pronounced differences were found in the Minsk region, where the HEV serum prevalence in pigs on private farms exceeded this indicator in pigs on state plants by more than 2 times (59.8 ± 4.4 and 28.8 ± 3.3 per 100 studies, respectively) [15]. On the other hand, testing of serum samples from workers associated with pork production for antibodies to HEV showed that the relative risk of infection on pig farms was up to 80% higher in comparison with pigs breeding in domestic conditions. [16]. The integration of methods for HEV serum diagnostics and HEV RNA detection for patients with

viral hepatitis of unknown etiology at the Minsk City Clinical Infectious Diseases Hospital made possible to improve the diagnostics for cases of infectious hepatitis and to make better the medical care quality. 6.4% of identified acute HE cases were associated with the consumption of meat infected with HEV genotype 3. HEV serum markers were found in 44.9% of examined patients with chronic viral hepatitis B and C, in 10% of patients after liver transplantation, and in 4.6% of HIV-infected patients [17]. The detection level of HEV IgG antibodies in the general population of residents was 7.3%. In the group of patients with liver damage, this indicator was significantly higher – 11.2%. The detection level of antibodies was gradually increased, reaching an average of 15.9% in the age group over 64 years. The actual spread of HEV infection among the population of the Republic of Belarus was many times higher than the number of diagnosed cases [18]. The study of the genetic polymorphism of HEV strains isolated from HE patients in the Republic of Belarus showed that they mainly belong to the 3rd genotype of HEV and phylogenetically are similar to viruses isolated from domestic pigs. This fact explains zoonotic origin of the majority of HE autochthonous cases in the Republic of Belarus [19]. HE cases caused by HEV of other genotypes were imported from abroad. For example, one case of the importation of other genotype from the Asia had been verified: the RNA sequence of HEV isolate from patient being on a trip in Pakistan belonged to the HEV genotype 1 and was clustered in phylogenetic branch the same with strains isolated in Pakistan, India, Nepal and Mongolia [20].

Based on the results of epidemiological studies taken place in Russia and Belarus, we can conclude that for controlling HEV infection, first of all, it is necessary to organize measures directed to reduction the circulation of HEV among pigs and disinfection of wastewaters from pig farms.

The analysis of the HE epidemiological situation in Kyrgyzstan and the results of large-scale serum epidemiological studies taken place in republic regions jointly by scientists from the National Institute of Public Health of the Ministry of Health of the Kyrgyz Republic and the I. Mechnikov Research Institute for Vaccines and Sera indicated the high endemicity of the surveyed territories. The highest HEV antibody levels were detected in the population of regions bordering Uzbekistan and Tajikistan: Jalal-Abad, Batken and Osh regions [21]. Most often, HEV IgG antibodies were found in age groups of 40 years and older, that is typical for many countries of Central Asia. Conversely, HEV IgM antibodies were detected more often (up to 40.8%) in children and adolescents. It is noteworthy that the data on quite intense HEV circulation among the children's population partially do not coincide with the generally accepted ideas about the epidemiology of HEV, namely, about the predominant infection of the adult male population in working ages. Assessment the risk for infecting pregnant women by HEV was carried out in Osh and the Osh region [22]. The HEV antibody serum prevalence among pregnant women was 9.9%, which is consistent with a meta-analysis data about prevalence of IgG antibodies to HEV in pregnant women in high endemic Middle East regions: in Pakistan - 8.9%, in Iran - 6.2% [23]. The increase of HEV IgG antibody detection level correlates with increase of patient age, and almost identical levels of detected IgM antibodies in all age groups indicate about high degree of vulnerability of pregnant women in all ages to HEV infection. In 2016-2017, HEV was in second place among the etiological agents causing acute viral hepatitis (AVH), proportionally 32.4% after hepatitis A virus (39.4%). A significant proportion (47.9%) of IgM positive patients was revealed among those with clinically and laboratory-confirmed diagnosis of AVH, which corresponds to the indicators predicted for high endemic regions, and may indicates an increase the morbidity during studied time period (2018-2019). [24]. The high level of detected HEV IgG antibodies is alarming: the antibodies had been detected among 15.7% of all examined patients with AVH and 53% of HEV serum positive persons, since the presence of HEV IgG antibodies may indicate not only previous disease, but also recent infection. The wide prevalence (up to 15%) of mixed infection with HEV and hepatitis A, B and C viruses indicates the need for mandatory testing of all patients with AVH for specific IgG and IgM antibodies to HEV.

Data on study the spread of HEV serological markers among patients with hepatitis and clinically healthy individuals in Kyrgyzstan indicate the continuous circulation of HEV during the inter-epidemic period. The refore, it is necessary to develop an effective strategy for carrying out sanitary, hygienic and preventive measures to control and prevent the spread of HEV in general and especially among pregnant women from high endemic regions of Central Asia.

Final remarks

Thanks to the coordinated work of the project co-executors, all the aims were achieved. More than 40 scientific articles have been published, 3 patents for inventions have been obtained [2, 3, 7], the results of the work were reported at 35 scientific conferences with international participation. In accordance with the plan of commercialization of the project results, license agreements with biotech companies on the rights to use the intellectual activity results under patents No.2754791 and No.2711907 were concluded. The manufacturing of recombinant antigens and diagnostic kits were started. Based on the project results, the Institute of Bioorganic Chemistry of the National Academy of Sciences of Belarus performs research and development work on the

project «To develop a technology for the industrial manufacture of test systems for the detection of IgG and IgM-class antibodies to HEV in humans and animals using enzyme immunoassay and organize their production» within the framework of the State Program «High-tech technologies and equipment» for 2021-2025, approved by Council of Ministers of the Republic of Belarus No. 245.

Stable cooperative ties between the project co-executors have been formed. The interaction of scientific organizations of Russia, Belarus and Kyrgyzstan will continues after the project completion in an expanded format under agreements on scientific cooperation in the epidemiology, immunology, pathogenesis of viral and bacterial infections, as well as the development of diagnostic, preventive and therapeutic drugs and methods of their control.

Жазуучулар ар кандай кызыкчылыктардын чыр жоктугун жарыялайт.
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The authors declare no conflicts of interest.

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