12th SAC SEMINAR

COMBATING GLOBAL INFECTIONS

21-24 September 2009

Listvyanka- Irkutsk, Russian Federation

TABLE of CONTENTS

On behalf of the Chairman of the Scientific Advisory Committee (SAC) of the International Science and Technology Center (ISTC), I would like to welcome all of you to participate in the twelfth SAC Seminar on “COMBATING GLOBAL DISEASES”. It is my great pleasure that so many experts and representatives, including young scientist and students, have attended this Seminar from the leading Russian and CIS research institutes, public and international organizations, research centers and universities all the way to Irkutsk. SAC is determined to address the topic of global health issues, since this is becoming more and more important today, mostly due to the fast spread and the impact on humans, and also due to the possible bioterrorism. This has been evidenced by the recent emerging global spread of swine flu.

At the previous SAC Seminar two years ago, SAC selected the subject of nuclear renaissance. This has been evidenced lately, since the number of newly nuclear power introducing countries becomes over fifty this year, whereas the number of already introduced countries is thirty one. Also some years ago, we took up the topic on PET technology, and this has been still stimulating the research on PET in Russia and other countries. For the next year we are thinking to hold the Seminar on risk management as another global issue.
I do hope that this Seminar will provide a good opportunity for the participants to share with us the newest information on the current achievements and challenges that need to be addressed in this area. Also I hope that all the participants will be actively involved at this Seminar for the discussion in order to clearly identify the global health issues for the future.

Finally I would like to express my sincere gratitude to all the colleagues for the preparatory work, conduction and management of this Seminar, especially to the International Science & Technology Center, the Central Research Institute of Epidemiology - Russian Ministry of Healthcare and Social, and Irkutsk State Medical University, for their great help and assistance.
I wish you have a fruitful and successful meeting.

Chairman of Scientific Advisory Committee, International Science and Technology Center
Advisor, Ministry of Education, Culture, Sports, Science and Technology, Japan
Director, Nuclear Technology and Education Center, Japan Atomic Energy Agency
SUGIMOTO, Jun

Dear Colleagues,

On behalf of the Organizing Committee let me welcome all the participants to the International Conference, which is dedicated this time to “Combating Global Diseases”, a topic which has been put on the list of research and applied activities of the Ministry for Public Health and Social Development of the Russian Federation for 2009.

The growth of disease incidence with respect to viral hepatitis, tuberculosis, HIV/AIDS, viral enteric infections, on the one hand, and potential risk of bioterrorism on the other, pose a severe threat to global security today. New infectious diseases (i.e., newly detected), such as avian and pandemic flu are emerging; the need for prophylaxis of “re-emerging” infections (malaria, viral hemorrhagic fever) is becoming more pressing while no steady tendencies to the sickness rate reduction in terms of cholera, anthrax, plague and other highly dangerous infections are observed.

This conference will contribute to the practical implementation of the decisions, made by the G8 member-states during the summit meeting on combating global diseases (Saint Petersburg, 15-17 July, 2006), which suggest a global counterepidemic strategy.
The guidelines, enclosed in the summit decisions, are targeted to global unified modernization of the public health systems:

- Early diagnostics of newly emerging infections and prevention of their proliferation;
- Construction and reinforcement of the relevant infrastructures; implementation of collective approaches to training specialists and to human resource strategy in the public health, especially in the developing countries;
- Enhancement of the prophylactic component in combating global diseases;
- Fund raising to implement global programs on combating infectious diseases;
- Engagement of civilian institutions in counterepidemic activities;
- Build-up of domestic potential in the developing countries to combat infectious diseases;
- Raising the efficiency of population health protection measures in emergency situations.

The above guidelines were taken as the basis to formulate the program and the list of basic topics to be addressed during the conference. The conference will be attended by experts from the leading Russian/CIS research institutions, representatives of public and international organizations in the public health sector; specialists from research centers of the US, Canada, Japan, Germany, France, Hungary, who will make presentations. The program of the conference provides space for many challenging reports, covering topics like global infectious disease surveillance, including the use of molecular, information and communication technologies.

Some topical presentations will be made on treatment of infectious diseases and identification of their resistance to drugs. A special focus of the conference will be on training and competency building of

specialists in the post-graduation phase of education – a separate session will be dedicated to young scientists. Being one of the conference organizers, the Central Research Institute of Epidemiology of Rospotrebnadzor is involved in an active collaboration with the World Health Organization, international centers and organizations, foreign institutes and universities.

CRIE provides a platform for the following centers: center for zoonotic diseases, collaborating with WHO; Federal Research and Methodical Center for AIDS Control; Russian Centers for: nosocomial infections, meningococcosis, purulent meningitis, shigellosis, salmonellosis, viral hepatitis, control of the status of collective immunity to infections, treated by means of specific prophylaxis; Center for Molecular Diagnostics of Infectious Diseases.

The Central Research Institute of Epidemiology of Rospotrebnadzor has a great research potential, employing 6 members of RAMS, 42 doctors of science, 23 professors, 50 PhDs, 7 Honored Workers of RF Science, 6 State Award Laureates, 17 RF Government and Academy Award Laureates. The Institute acts as the Head Organization of the Research Council for Epidemiology, Infectious and Parasitic Diseases, established by a collective order, issued by the Health Ministry of the Russian Federation and RAMS, ensuring coordination and review of research on epidemiology and infection pathology problems, conducted in Russia.

Today the Central Research Institute of Epidemiology under Rospotrebnadzor is one of the largest Russian developers and manufacturers of products, alternative to imported ones, such as test-systems for detecting a wide spectrum of infectious pathogens (HIV, viral hepatitis, avian and highly pandemic flu, tuberculosis etc,) by means of molecular diagnostics. The use of the above-mentioned test-systems ensures epidemiological safety of the Russian Federation. Active involvement of the Institute's staff contributes to successful investigation of outbreaks of infectious diseases in various regions of the Russian Federation. Through basic and applied research and development the Institute creates innovation technologies of infectious disease diagnostics (biochips, nanotechnologies).

I hope, that this Conference on "Combating Global Diseases" will initiate interesting discussions, which would contribute significantly to the global epidemic security.

Dear colleagues, your active involvement in the Conference program will provide an added value to our efforts, focused on combating infectious diseases. Let me wish you further success in your profession.

Co-Chair of the Organizing Committee of the Conference
Director of Federal State Science Institution
"Central Research Institute of Epidemiology"
under Rospotrebnadzor
academician of RAMS

V.I. Pokrovsky

Dear Colleagues,

I would like to cordially welcome you to the twelfth seminar of the Scientific Advisory Committee of the International Science and Technology Centre (ISTC). I am grateful that so many experts involved in health research and promotion have come to Irkutsk to take part in focused discussions on the topic of 'Combating Global Infections'.

I am also pleased to see that special attention has been paid to the active participation of young scientists and students in this seminar program. I thank the Irkutsk State Medical University for arranging the student participation.

The subject of the seminar is highly topical. Health issues affect people in the same way all over the world and, as we are all aware, there are no geographical boundaries to infection.

In October last year a meeting of the State Duma of the Russian Federation discussed ISTC's activities in medicine and healthcare. ISTC presented a report on its work in the field of biomedical science. Of our more than 600 funded projects in the biotechnology and medicinal field, almost half of them (to a value of $100 million) are related to the control of global infections. Projects to date have included: infection surveillance, novel diagnostics and the equipping of diagnostic laboratories with up-to-date devices; drugs and vaccine development, and the introduction of international quality standards into laboratory, production and clinical practices (GLP, GMP, GCP).

Another area of ISTC's work has focused on the integration of Russian and other CIS specialists and scientists into the world research community, whereby travel support to attend international conferences has been just one area of this important program. The principle ISTC beneficiaries in Russia has been scientists from the Institutes of the Ministry of Health, the Russian Academy of Medical Sciences, the Russian Academy of Sciences and the Ministry of Agriculture. Related organizations have been beneficiaries in other countries of the CIS.

ISTC has focused on the following three areas in regard to biotechnology and medicine:

1. Disease surveillance

$25 million for surveillance of MDR/XDR tuberculosis, HIV, hepatitis, zoonotic and water-born infections in Russia and CIS. Of note in this area is ISTC's project on the 'Further Improvement of Influenza Surveillance in Russia - Contribution in Global Influenza Pandemic Preparedness', which started in early 2006. ISTC believes that this project facilitated surveillance and diagnostic capacities at the time when the ability to test for emerging swine influenza was becoming critical.

ISTC runs a special program on 'Central Asian Disease Surveillance' aimed at improving the situation with infectious diseases in a region where there is a clear and present threat.

Also in this field, Information and communication technologies are proving the ad-hoc solution to modern disease surveillance and the work of ISTC in funding surveillance projects will be presented and discussed during the seminar.

2. Diagnostics

More than $3 million has been awarded for the development of microchip technologies for detecting extremely dangerous bacterial and viral pathogens, as well as for technologies to assess the safety of donated blood. Success of projects such as these is measured by the commercialization of their results and the creation of start-up companies producing, for example, microchips at an industrial scale.

3. Drug Discovery

More than one hundred innovative infrastructure projects has been undertaken by ISTC that include as examples the upgrade of laboratories for preclinical trials at Pushino and Chernogolovka, ensuring an animal breeding facility at Pushino accords to international standards and a number of projects related to certification and accreditation, reconstruction and re-equipping, and the training of personal in Russia, Europe, US and Canada.

ISTC will continue to provide solutions to global health issues. A Targeted Initiative on New Drug Development is now operational and projects aimed at countering new infectious threats (such as swine and bird influenza, and MDR/XDR TB) which will correspond to the healthcare priorities of the Russian Federation and other countries of the CIS and, where possible, implemented with co-funding from the Russian/CIS side, are under development.

Diseases that spread across borders and multiply if uncontrolled will obviously be the major topic of the seminar. This is especially the case for infections such as influenza. Equally, tuberculosis is another major global health problem due to multiple drug resistance and serious social impacts. Emerging infectious diseases (HIV, Hepatitis) impact human health dramatically and transmissible infections will prove the major focus of the meeting. Antibiotic resistance makes the threat of infectious diseases even higher and will receive special attention. During the final day of the meeting globalization processes and climate changes in relation to infectious diseases will be the focus of a roundtable discussion.

More information about the work of ISTC can be found in our annual report and on our website at www.istc.ru providing actual case studies of how Russian and CIS researchers provide new solutions to global health challenges.

I expect that this seminar will create an opportunity for participants to learn more about the latest achievements and challenges in the area of combating global infection. ISTC's 12th SAC meeting promises to be both a constructive and interesting gathering for bio- and medical professionals.

I would like to thank all those who have contributed to the organization of this seminar, especially ISTC's co-organizers – the Central Research Institute of Epidemiology (Moscow), Irkutsk Medical University and the various sponsors.

I wish you a fruitful exchange of views.

Adriaan van der Meer
ISTC Executive Director

ИРКУТСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ

Dear participants of the Conference and guests,

On behalf of the Irkutsk State Medical University let me welcome you in Irkutsk. It is a big honor for our University to meet a forum of such a high scientific level.

The history of the Irkutsk State Medical University started 90 years ago, in 1919, when the medical department was attached to the Irkutsk State University. In 1930 independent Medical Institute was established in Irkutsk. Currently the Irkutsk State Medical University is one of the biggest medical higher schools in Siberia. The structure of ISMU includes six basic faculties: medical, pediatric, dentist, medico prophylactic, pharmaceutical, nurse science and medical biochemistry. Also there are preschool faculty, the faculty of rising the level or medical skill and professional preparation of specialists. University campus is located in the central part of Irkutsk and includes teaching buildings, clinics, research laboratory, library, student's hostels and sport complex.

Teaching is conducted by higher professional staff, which includes about 450 teachers, among them there are 98 professors and doctors of sciences, about 300 docents and bachelors of sciences. Today at the University near 4000 students are gave training, among them there are near 100 students from foreign countries. The diploma of the ISMU received international vocation, and many graduates of our Irkutsk Medical University successfully pass tests for working in the countries of Europe and America. The scientific profile of the University is determined by such leading lines as elaborating new methods of diagnostic and treatment of the diseases most common in Siberia, studying of actual problems of surgery, obstetrics and gynecology, pediatrics, stomatology, the investigation of new medicines on basic of plants, which are growing in Easter Siberia, local epidemiology and ecology problems.

I would like to wish you a fruitful collaboration in the field of combating global infections and nice days on the bank of the Lake Baikal.

Rector of Irkutsk State Medical University
Prof. Igor V. Malov

PROGRAM

SEPTEMBER 21, MONDAY, 2009 – LYSTVYANKA *Hotel "Mayak"*	
11:00 -14:00	**MUSEUM OF SIBERIAN WOODEN ARCHITECTURE (optional)**
14:00 – 15:30	**LUNCH**
14:00-18:00	**REGISTRATION**
	SESSION 1. Company's Presentations Co-Chairs**: Acad. Waclaw Gudowski (EU), Tatiana Gremyakova (RF), Alexander Botvinkin (RF), Yulia Plotnikova (RF),**
16:00 – 16:30	Hoffmann-La Rosche Ltd, SWITZERLAND
16:30 - 17:00	Wyeth, USA
17:00 - 17:30	Black & Veatch, USA
17:30 - 18:00	Издательство Elsevier
18:00 – 18:30	Alliance for Rabies Control, USA
18:30 - 19:00	Novartis, SWITZERLAND
19:30	**Welcome RECEPTION**
21:00-22:00	**Meeting of the Sessions Co-Chairs**
SEPTEMBER 22, 2009, TUESDAY - LYSTVYANKA *Hotel "Mayak"*	
	SESSION 2 **Opening Remarks/** **Tracking Emerging Infectious Diseases: Lessons Learnt** Co-Chairs**: Acad. Valentin Pokrovsky (RF), Acad. Sergei Kolesnikov (RF), Acad. Oleg Kisselev (RF), Acad. Waclaw Gudowski (EU), Prof. Igor Malov (RF), Prof. Gaydar Gaydarov (RF), Prof. Andre Syrota (France**)
8:30 – 9:00	WELCOME & OVERVIEW SESSION *MOH, RAMS, State Duma, Irkutsk Governor, ISTC*
9:00 – 9:30	WHAT RESEARCH IS NEEDED TO FACE OCCURING CRISIS DUE TO A NEW EMERGING DISEASE. EXAMPLE OF H1N1? **Andre Syrota**, *Institut National de la Sante et de la Recherche Medicale, France*
9:30 – 10:00	LESSONS LEARNED FROM SARS AND THEIR IMPLICATIONS IN THE H1N1 INFLUENZA OUTBREAK. **Bhagirath Singh**, FRSC, *Institute of Infection and Immunity/Canadian Institutes of Health Research University of Western Ontario, London, Ontario, Canada*
10:00 – 10:20	PREPAREDNESS TO INFLUENZA PANDEMIC IN RUSSIA. **Anna A. Sominina, Oleg Kisselev,** *Research Institute of Influenza, St. Petersburg, Russia*
10:20 – 10:40	DEVELOPMENT OF AN OLIGONUCLEOTIDE MICROCHIP FOR TYPING VARIOUS SUBTYPES OF INFLUENZA VIRUS A. **Alexander Sinyakov,** *Institute of Chemical Biology and Fundamental Medicine, Novosibirsk, Russia*
10:40 - 11:00	PANDEMIC (H1N1) 2009: SITUATION UPDATE IN WHO EUROPEAN REGION AND THE WORLD. **Sergey Eremin**, *World Health Organization, Moscow Office*
11:00 – 11:30	**Coffee-break**

	SESSION 3 **Global Diseases Surveillance** Co-Chairs**: Prof. Nikolai Briko (RF), Evgeny Bochkarev (RF), Prof. Gerry Wright (Canada)**
11:30 – 11:50	GLOBALIZATION AND EPIDEMIC PROCESS. **Nikolai Briko**, *Sechenov Moscow Medical Academy, Russia*
11:50 – 12:10	INFOCOMMUNICATION TECHNOLOGIES IN EPIDEMIOLOGICAL SUFETY. **Evgeny Bochkarev**, *Central Research Institute of Epidemiology, Moscow, Russia*
12:10 – 12:30	NATIONAL SURVEILLANCE STANDARDS AND SERVICES INTEGRATION. **Vladimir Davidyants**, *Department of Epidemiology and Health Informatics, National Institute of Health, Yerevan, Armenia*
12:30 – 12:50	BATS, EMERGING INFECTIONS, AND FUTURE MANAGEMENT INTERVENTIONS. **Charles Rupprecht,** *Centers for Disease Control and Prevention, Atlanta, GA, USA*
12:50 – 13:10	HIV-INFECTION IN IRKUTSK REGION. THE RESULTS OF SURVEILLANCE IN FIRST 10 YEARS AFTER START OF EPIDEMIC (1999-2008). **Alexander Botvinkin**, *Irkutsk State Medical University, Russia*
13:10 – 14:00	Lunch
	SESSION 4 **Understanding Infectious Diseases** Co-Chairs**: Prof. Valery Loktev (RF), Vladimir Poroikov (RF), Bhagirath Singh (Canada), Rakin Alexandr (EU)**
14:00- 14:20	METAGENOMIC DIAGNOSIS OF INFECTIOUS DISEASES. **Iida Tetsuya**, *The Research Institute for Microbial Diseases, Osaka University, Japan*
14:20- 14:40	GENETIC DIVERSITY OF WEST NILE AND TICK BORNE VIRUSES: NEW GENETIC VARIANTS OF FLAVIVIRUSES IN THE ASIAN PART OF RF. **Valery Loktev,** *FSUE SRC VB Vector, Koltsovo, Novosibirsk region, Russia*
14:40- 15:00	COMPUTER-ASSISTED DISCOVERY OF ANTI-INFECTIVE AGENTS. **Vladimir Poroikov**, *Institute of Biomedical Chemistry of Rus. Acad. Med. Sci., Moscow, Russia*
15:00 - 15:20	STRATEGIES FOR IDENTIFICATION OF ANTIVIRAL PREPARATIONS TARGETED AT VARIOLA VIRUS RNA POLYMERASE. **Sergei Shchelkunov**, *FSUE SRC VB Vector, Koltsovo, Novosibirsk region, Russia*
15:20 - 15:40	NOVEL APPROACHES FOR ANTI-PLAGUE THERAPY. **Vladimir Motin,** *University of Texas Medical Branch, Galveston, Texas, USA*
15:40 - 16:00	BETA-LACTAMASES: POLYMORPHISM AND NEW INHIBITORS. **Alexey Egorov**, *M.V. Lomonosov Moscow State University, Moscow, Russia*
16:00 - 16:30	Coffee-break
	SESSION 5 **Emerging & Re-emerging Zoonoses** Co-Chairs**: Profs. Charles Rupprecht (USA), Alexander Botvinkin (RF), Henry Mantsch (Canada)**
16:30 - 16:50	CONNECTING HUMAN AND ANIMAL HEALTH SURVEILLANCE SYSTEMS. **Tracey McNamara, Alexandr Platonov,** *Western University of Health Sciences, College of Veterinary Medicine, san Diego, California USA, Central Research Institute of Epidemiology, Moscow*
16:50 - 17:10	MONITORING AND DIAGNOSTIC OF PRION INFECTIONS IN BELARUS. **Nikolai Poleschuk**, *Research Institute for Epidemiology and Microbiology, Minsk, Belarus*
17:10- 17:30	CARRIERS OF ZOONOTIC INFECTIOUS DISEASES. **Ramazon Murodov**, *Republican Center for Prevention of Quarantine Diseases, Dushanbe, Tajikistan*

17:30- 17:50	YERSINIA – JUST ANOTHER GROUP OF EMERGING PATHOGENS. **A. Rakin,** *Max von Pettenkofer-Institut, LMU, Munich, Germany*
17:50- 18:10	GENETIC DIVERSITY OF SORICID-BORNE HANTAVIRUSES IN SIBERIA, RUSSIA, **Liudmila Yashina**, *FSUE SRC VB Vector, Koltsovo, Russia*
18:15 - 18:30	**Meeting of the Sessions Co-Chairs**
19:30	**DINNER**
SEPTEMBER 23, WEDNESDAY, 2009 - IRKUTSK *Irkutsk State Medical University*	
	SESSION 6. Opening remarks/ Emerging Threats Co-Chairs**: Acads. Sergei Kolesnikov (RF), Acad. Valentin Pokrovsky (RF), Acad. Waclaw Gudowski (EU), Profs. T. Yamomoto (Japan), Vladimir Davydyants (Armenia), Prof. Igor Malov (RF)** *Big conference hall*
9:00 – 9:20	Opening remarks, greetings
9:20 – 9:40	THE END OF ANTIBIOTICS? **Gerry Wright**, *MG DeGroote Institute for Infectious Disease Research, McMaster University, Canada*
9:40 – 10:00	ROLE OF ANTIBIOTIC-RESISTANT OPPORTUNISTIC BACTERIA IN HUMAN DISEASES. **Tatsuo Yamamoto**, *Niigata University Graduate School of Medical and Dental Sciences, Japan*
10:00 – 10:20	EVOLUTION OF EPIDEMIC PROCESS IN MODERN CONDITIONS **Evgeny Savilov,** *Institute of epidemiology and microbiology SCME ESSC SD RAMS, Irkutsk, Russia*
10:20 – 10:40	THE THREAT OF FOODBORNE BIOTERRORISM ON GLOBAL FOOD SUPPLY. **Kingsley Amoako**, *Canadian Food Inspection Agency, Lethbridge Laboratory, Animal Diseases Research Institute, Canada*
10:40 – 11:00	PREPARING EUROPE FOR THE NEXT VIRAL OUTBREAK , **Jean-Louis Romette**, *Université de la Méditerranée, France*
11:00 – 11:30	**Coffee Break**
	SESSION 7. **Continuing Global Threat – MDR-XDR Tuberculosis** Co-Chairs: **Profs. Helmut Hahn (EU), Gail Cassell (USA), Tatiana Gremyakova (RF)** *Big conference hall*
11:30 – 12:00	TUBERCULOSIS AND HISTORY. **Helmut Hahn**, *Koch-Metchnikov-Forum, Germany*
12:00 – 12:20	THE LILLY TB DRUG DISCOVERY INITIATIVE. **Gail Cassell**, *Eli Lilly, USA*
12:20 – 12:40	MOLECULAR EPIDEMIOLOGY OF TUBERCULOSIS IN RUSSIA, **Larissa Chernousova**, *Research Institute of Tuberculosis, RAMS, Moscow, Russia*
12:40 – 13:00	BIOCHIPS AS A TOOL FOR ANALYSIS OF *MYCOBACTERIA* GENOMES. **Danila Zimenkov**, *Engelhardt Institute of Molecular Biology, RAS, Moscow, Russia; Biochip-IMB Ltd., Moscow, Russia*
13:00 – 14:00	**LUNCH**
13:00 – 19:00	**POSTER SESSION**

14:00 – 16:50	**SESSION 8** **International Cooperation, Infrastructure & Training** Co-Chairs**: Aleksey Burdakov (USA), Ezra Barzilay (USA), Yuri Remnev (RF), Mikhail Korotkov (RF)** *Big conference hall*
14:00 – 14:20	EUROPEAN BSL4 INFRASTRUCTURE TO FIGHT EMERGING DESEASES. **Herve Raoul**, *INSERM, France*
14:20 – 14:40	WHO GLOBAL SALM-SVRV: STRENGTHENING FOOD-BORNE DISEASE SURVEILLANCE THROUGH TRAINING. **Ezra Barzilay**, *CDC, USA*
14:40 – 15:00	IMPROVING SURVEILLANCE WITH ELECTRONIC INTEGRATED DISEASE SURVEILLANCE SYSTEM (EIDSS). **Aleksey Burdakov**, *Black & Veatch, USA*
15:00 – 15:20	THE ISTC COMPETENCY BULDING PROGRAM. **Mikhail Korotkov**, *International Science & Technology Centre*
15:20 – 15: 40	ACCESSING NIAID/NIH RESOURCES AND RESEARCH FUNDING". **Paula Strickland**, *Office of International Extramural Activities, DEA/NIAID*, USA
15: 40 – 16: 00	NIAID RESEARCH CENTERS OF EXCELLENCE IN "EMERGING INFECTIOUS DISEASES. **Christopher Beisel,** *NIAID (DMID/NIAID),* USA
16:00 – 16:20	INTERNATIONAL COLLABORATION IN IMPLEMENTATION OF EDUCATIONAL PROGRAM IN BIOSAFETY AND BIOSECURITY. **Yuri Remnev,** *M. Sechenov Moscow Medical Academy, Non Commercial Partnership "Center of Modern Medical Technologies" TEMPO".*
16:20 – 16:50	Coffee Break
	SESSION 9 **Competition of Young Scientists** Co-Chairs**: Acad. Waclaw Gudowski (EU), Acad. Evgeny Avrorin (RF), Prof. Henry Mantsch (Canada), Profs. Andre Syrota (EU), Tatiana Gremyakova (RF), Gitomer Steve (USA)** *Big conference hall*
16:50 – 17:05	INFORMATION SYSTEM "EPIDMONITOR" FOR MORTALITY REGISTRATION ASSOSIATED WITH COMUNICABLE DESEASES. **Vladislav Khromov**, *Irkutsk State Medical University, Russia*
17:05 – 17:20	ANTIBIBIOTIC RESISTANCE OF *E .COLI* AND *S. AUREUS* ISOLATES FROM OUTPATIENTS IN IRKUSK. **Irina Gymninova**, *Laboratory Diagnostics Center, Irkutsk State Medical University, Irkutsk, Russia*
17:20 – 17:35	MULTIDRUG RESISTANT *ACINETOBACTER* NOSOCOMIAL STRAINS COLLECTED FROM RUSSIAN HOSPITALS IN 2003-2008: PHENOTYPES OF THE RESISTANCE. **Ekaterina Kuzhelnaya**, *State Research Center for Applied Microbiology&Biotechnology, Obolensk, Russia*
17:35 – 17: 50	PREDICTORS OF SUSTAINED VIROLOGICAL RESPONSE OF ANTIVIRAL COMBINATION THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C, **Larisa Orlova**, *Irkutsk State Medical University, Russia*
17:50 – 18:05	PROSPECTS FOR THE USE OF HEPATITIS C VIRUS ENVELOPE PROTEIN HIGHLY CONSERVED SITES IN PEPTIDE VACCINES. **Alexandr Moisa**, *Institute of Biomedical Chemistry, RAMS; Moscow, Russia*
18:05 – 18:20	TWO PATHWAYS OF SELF-ASSEMBLY RECOMBINANT BOVINE PRION PROTEIN *IN VITRO*. **Aleksei Pokidishev,** *Ivanovsky Virology Institute, RAMS, Russia*
18:20 – 18:35	MONITORING OF TICK-BORNE INFECTIONS NATURAL FOCI. **Nadezhda Kolyasnikova**, *Central Research Institute of Epidemiology, Moscow, Russia*

18:35 – 18:50	CERTAIN POINT MUTATIONS IN THE ENVELOPE PROTEIN OF TICK-BORNE ENCEPHALITIS VIRUS ENHANCE NON-VIREMIC TRANSMISSION EFFICIENCY IN A TICK VECTOR. **Maksim Khasnatinov,** *Institute of Epidemiology and Microbiology SCME ESSC SD RAMS; Irkutsk, Russia*
18:50 - 19:10	FLU BIOCHIP: A TOOL FOR INFLUENZA A VIRUS SURVEILLANCE. **Evgeny Fesenko**. *Engelhardt Institute of Molecular Biology, RAS, Moscow, Russia*
19:10 – 19:30	**DISCUSSION**
19:30	**DEPARTURE TO LYSTVYANKA**
	SESSION 10 (in parallel with Session 9) New Trends in Education Co-Chairs: **Acad. Valentin Pokrovsky (RU), Prof. Vyacheslav Shkarin (RF), Prof. Nikolai Briko (RF)** *Small conference hall*
16:50 – 17:05	HISTORY OF EPIDEMIOLOGY. **Vladimir Stasenko, Viktor Dalmatov,** *Omsk State Medical University, Omsk, Russia*
17:05 – 17:20	CURRENT CONDITION AND PERSPECTIVES OF TEACHING STAFF IMPROVEMENT ON DEPARTMENTS AND COURSES OF EPIDEMIOLOGY IN RUSSIAN HIGHER MEDICAL EDUCATION. **Valentin Pokrovsky, Nikolai Briko,** *Sechenov Medical Academy, Moscow, Russia*
17:20 – 17:35	TEACHING OF EXPERIMENTAL EPIDEMILIOGICAL STUDIES IN DEPARTMENT OF EPIDEMIOLOGY OF I. M. SECHENOV MEDICAL ACADEMY. **Roman Polibin, Alla Mindlina,** I.M. *Sechenov Medical Academy, Moscow, Russia*
17:35 – 17:50	THE SYSTEM OF PREVENTIVE MEDICINE SPECIALIST'S EDUCATION IN THE ARMES FORSES OF RUSSIAN FEDERATION, **Pavel Ogarkov**, *Military Medical Academy, St-Petersburg, Russia*
17:50 – 18:05	BIOSAFETY QUESTIONS IN TEACHING OF EPIDEMIOLOGY **Alexander Botvinkin,** *Irkutsk State Medical University, Irkutsk, Russia*
18:05 – 18:20	TEACHING OF EPIDEMIOLOGY WITH THE PRINCIPLES OF EVIDENCE-BASED MEDICINE FOR THIRD-YEAR-STUDENTS OF PREVENTIVE MEDICINE FACULTY. **Elena Brusina,** *Kemerovo State Medical Academy, Kemerovo, Russia*
18:20 – 18:35	TEACHING EXPERIENCE OF EPIDEMIOLOGY WITH THE PRINCIPLES OF EVIDENCE-BASED MEDICINE IN DEPARTMENT OF INFECTIOUS DISEASES. **Vera Volodina,** *Russian State Medical University, Russia*
18:35 – 19:30	DISCUSSION
19:30	**DEPARTURE TO LYSTVYANKA**
SEPTEMBER 24, THIRSDAY, 2009 - LYSTVANKA *Hotel "Mayak"*	
09:00 - 11:00	**SESSION 11**. **Emerging & Re-emerging Zoonoses** Co-Chairs**: Charles Rupprecht (US), Dennis Slate (US), Igor Malov (RF)**
09:00- 09:30	RABIES: AN EXPANDING PROBLEM WITH AVAILABLE SOLUTIONS. **Deborah Briggs,** *Global Alliance for Rabies Control, USA*
09:30 - 10:00	GLOBAL SIGNIFICANCE OF BATS AS RESERVOIRS AND VECTORS OF EMERGING ZOONOTIC DISEASES, **Ivan Kuzmin**, *Rabies Program, Centers for Disease Control and Prevention, Atlanta, GA, USA*

10:00 - 10:30	ORAL VACCINATION: A PARADIGM FOR RABIES CONTROL IN MESO-CARNIVORE RESERVOIRS. **Dennis Slate,** *USDA/APHIS/Wildlife Services, Concord, NH, USA*
10:30- 11:00	TICK-BORNE ENCEPHALITIS IN THE LAKE BAIKAL REGION: EPIDEMIOLOGY, CLINIC, PROPHYLAXIS. **Igor Malov**, *Irkutsk State Medical University, Russia*
12.00 – 20.00	**L A K E B A I K A L B O A T T O U R** **Wrap-up and Round Session Discussion: Globalization & Climate Changes Increasing Threat of Infectious Diseases.** ***Awarding of Young Scientists Competition Winners.*** Co-Chairs**: Acads. Sergei Kolesnikov (RF), Valentin Pokrovsky, Acad. Waclaw Gudowski (EU), Acad. Evgeny Avrorin (RF), Prof. Henry Mantsch (Canada), Prof. Igor Malov (RF), Prof. Andre Syrota (France)**

ABSTRACTS
ORAL PESENTATIONS

PATHOGEN ASSET CONTROL SYSTEM (PACS)

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The Pathogen Asset Control System (PACS) is an electronic system for accounting, management and control of biological agent stocks. The application is designed to monitor agents receiving, transfer, movement, destruction and other actions performed with biological materials. PACS tracks samples and strains of any kind. Each item in a repository is marked with a unique barcode label. The barcode technology used with a barcode scanner allows fast and error-free data input and provides an extra level of pathogen asset tracking security.

PACS is implemented at several science research institutes in Former Soviet Union (FSU) Countries and proved to be reliable and accurate method for pathogen tracking. Newer versions of the software were developed with consideration of feedback gained from many actual users of the system.

PACS is a highly customizable tool, which can be configured to meet local needs and regulations, simplify data entry process and organize data in appropriate order. Features such as Repository management, Customizable Fields Editor, Barcode Label Designer and Reference Editor allow system owners to adapt the tool to meet all local requirements.

PACS allows restricting personnel access to a specified set of functions or place in repository, i.e. establish separate data ownership and control. Automatic audit log and event log allow meeting all regulatory requirements for bioagent tracking. Inventory audit and Operations authorization features introduce an additional level of control over pathogens.

Extensive custom search and reporting capabilities allow easily finding and outputting necessary data set under appropriate format.

PACS application is built on the basis of a proved client-server Microsoft .NET and SQL Server technology, and delivers ease of use, multiple language support and security of the processed and stored data.

ELSEVIER – GOING FROM GLOBAL TO LOCAL

Alexei Lutay, Alexander Mzhelsky

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LESSONS LEARNED FROM SARS AND THEIR IMPLICATIONS IN THE H1N1 INFLUENZA OUTBREAK

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Canada has faced two major infectious diseases challenges this decade. In 2003 we were caught by surprise when Severe Acute Respiratory Syndrome (SARS) arrived in Toronto from Hong Kong. In early 2009 H1N1 influenza spread from Mexico to Canada and continues to spread around the world. The 2009 H1N1 influenza pandemic was predictable but its origin, source and timing were not. Although Canadian researchers were first to publish the genome sequence of the SARS coronavirus, a rapid research response to SARS required a national effort to engage the research and stakeholder community. The most important lesson of SARS was that we must be ready for the unseen. Although no one did foresee and perhaps no one could foresee the unique convergence of factors that made SARS a perfect storm. The other major lesson was that there is a need to create a permanent national coordination entity to coordinate response to emerging infectious diseases. As a result a new Public Health Agency of Canada (PHAC) was created in 2004 and Ontario Agency for Health Protection and Promotion (OAHPP) was launched in 2008.

To coordinate health research in Canada, Canadian Institutes of Health Research (CIHR) wascreated in 2000. To address SARS outbreak in 2003, CIHR Institute of Infection and Immunity (III) mobilized the Canadian research community through a rapid research response to SARS. As a lesson learnt from SARS and to prepare for pandemic influenza we created a PandemicPreparedness Strategic Research Initiative (PPSRI) in 2006. A Task Group composed of representatives who carry out relevant research as well as people who use the new researchknowledge in pandemic situation was brought together. They identified strategic research areasincluding: Vaccines and immunization program, better understanding of the biology of theinfluenza virus, rapid diagnostics, strategies to prevent disease spread, optimal use of anti-viraldrugs and effective risk communication, resource allocation and rapid regulatory approval oftherapies. We took the lead to initiate funding opportunities for research in these strategic areasand given the H1N1 outbreak we expedited the review, approval and funding of research that iscritical for an outbreak response. Two special outbreak research teams focus on national network for characterization of influenza virus evolution and antiviral susceptibility and on mathematical modeling of pandemic outbreak were funded within two weeks. In collaboration with PHAC, we created a national influenza research network (IRN) focused on pandemic vaccine evaluation that will link over 80 researchers from 30 academic and public health institutions across Canada. We are also working to ensure that the research results are communicated to those who will use the new information. It is anticipated that pandemic research will: help prevent or mitigate a pandemic; develop better ways to control the spread of influenza; and, provide better treatment to affected individuals. Based upon our experience with SARS, PPRSI will help to develop a strong network of researchers, ensuring Canada has the necessary expertise to respond effectively in the event of a pandemic. This expertise can also be used to assist other countries in crisis.

PREPAREDNESS TO INFLUENZA PANDEMIC IN RUSSIA

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In spite of great achievements in the field of development of large arsenal of influenza vaccines and antiviral drugs influenza continued to be a growing threat to public health for many countries with yearly winter epidemics. Occasionally, an entirely new influenza A virus subtype emerges and spread in human population. Three major pandemics struck the world in the 20th century. By far the most devastating pandemic was that of the “Spanish” flu of 1918-1919. It spread across the globe in three consecutive waves, killing more than 40 million people. Two more pandemics, “Asian flu” in 1957, influenza A(H2N2), and “Hong Kong flu” in 1968, influenza A(H3N2), caused less significant excess in morbidity and mortality.

The recent emergence of swine-origin A(H1N1)v viruses that have been transmitted to and spread among humans, resulting in outbreaks all over the world. Efforts to control these outbreaks which were declared by WHO as a new pandemic on June 11, 2009 and real-time monitoring of the evolution of this virus should provide with invaluable information to direct infectious disease control programmes and to improve understanding of the factors that determine viral pathogenicity and/or transmissibility. Epidemiological data now available indicated that an outbreak of influenza-like respiratory illness started in the Mexican town of La Gloria, Veracruz, in mid-February of 2009. In the United States, the Centers for Disease Control (CDC) identified the first two influenza A(H1N1)v viruses in two specimens independently collected in Southern California in mid-April. Transmissibility of new virus is considered to be substantially higher than for seasonal influenza: basic reproduction number was estimated as 1.4 - 1.6.

Data on the genetic composition of the virus became available soon after viral isolation from the initial cases. These viruses possessed PB2 and PA genes of the North American virus of avian origin, a PB1 gene of influenza H3N2 virus of human origin, HA (H1), NP, and NS genes of classical swine origin virus, and NA (N1) and M genes of Eurasian avian-like swine origin virus. The triple reassortant viruses that emerged in North American pigs in 1997–1998 were the progenitors of the A(H1N1)v viruses.

To July 6 according to WHO information 122 countries had reported 94 512 cases of novel influenza A (H1N1)v infection, 429 of which were fatal. The Southern Hemisphere's regular influenza season has begun and countries there are reporting that the new H1N1 virus is spreading and causing illnesses along with regular seasonal influenza viruses. In the United States, significant novel H1N1 illness has continued into the summer, with localized and in some cases intense outbreaks occurring. The United States continues to report the largest number of novel H1N1 cases of any country worldwide, however, most people who have become ill have recovered without requiring medical treatment but about 9% required hospitalization. In European countries about 36% of patients required hospitalization.

Pandemic preparedness in Russia began before these events. In line with the global concern of emergence of novel influenza strains, further development of national surveillance networks for early recognition of pandemic events, identification of new viruses and prevention of pandemic spread in Russia was an important task of the Project BTEP/ISTC # 107/3070 which was executed by the Research Institute of Institute (RII) and Institute of Virology (IV) in close collaboration with CDC (Atlanta, USA) for the period since 2006 to 2009. As of July 6.2009 three cases of laboratory confirmed influenza A (H1N1)v infection were recognized firstly in Russia by rRT-PCR at the IV, at the Central Institute of Epidemiology (CRIE) and at Base Laboratory of RII in Moscow. The first influenza A (H1N1)v viruses were isolated at the IV from the passengers arrived from affected countries. Both rRT-PCR kits of Russian production (CRIE) and the ones kindly presented by CDC (Atlanta, USA) were used in these investigations. New antigens of influenza A (H1N1)v for serological confirmation of new cases and sera for identification of influenza A(H1N1)v isolates were developed and issued by RII.

At that preparedness to pandemic is conducted in Russia at local, regional and governmental (MoH, "Rospotrebnadzor") levels. New influenza vaccine A (H1N1)v strains developed at CDC and NYMC using classical reassortment and reverse genetic technology were kindly presented by CDC to RII and distributed by the Institute between manufacturers of vaccines to prepare experimental lots of vaccines. Besides, the strain for live attenuated influenza vaccine is under development at the Research Institute of Experimental Medicine in St.-Petersburg. The evaluation of safety and immunogenic properties of new vaccines in preclinical and clinical trials will be conducted at the RII in September-October 2009. In accordance with WHO recommendation three objectives could be adopted as part of pandemic vaccination strategy as soon the vaccines will be prepared and begin to be available: to protect the integrity of the health-care system and the country's critical infrastructure, to reduce morbidity and mortality and transmission of the pandemic virus within communities.

It will be necessary to take into account possibility of further change of antigenic, genetic and biological properties of influenza A(H1N1)v virus during its current circulation in South Hemisphere. The fall 2009 wave could follow the pattern of pandemics of the 20th century by having greater virulence than the initial wave. National authorities need to know how pandemic is evolving, not only in their own country, but also in neighbouring countries and continents.

A well-matched vaccine will not be available for the population until mid-November 2009 at the earliest and will not be effective until two weeks after the final (second) application. Children and young adults will experience the highest attack rates. Community mitigation measures can be effective to slow disease transmission and will be the only tool available for prevention at present time. Emergency medical and hospital planning for an H1N1 pandemic must be conducted beforehand. Mass anti-viral chemoprophylaxis by oseltamivir will not be recommended but early treatment of patients and individual post exposure antiviral chemoprophylaxis among the persons who are at high risk for complications, with neuraminidase inhibitors, oseltamivir and zanamivir, is expected to be the most effective. All investigated new influenza A(H1N1)v viruses appeared to be resistant to rimantadine. Continuing monitoring of

sensitivity of A(H1N1)v to other antivirals will be under surveillance at RII and IV taking into account the first information on appearance of oseltamivir resistant mutants in Denmark, Japan and Hong Kong.

DEVELOPMENT OF AN OLIGONUCLEOTIDE MICROCHIP FOR TYPING VARIOUS SUBTYPES OF INFLUENZA VIRUS A

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Type A influenza virus circulating in the human population as well as domestic and wild animals presents a serious danger as a potential cause of a pandemic resulting from emergence of new influenza virus strains with unusual antigenic properties. An example is emergence of the avian influenza virus H5N1, which is highly pathogenic for fowl and humans. The reference and clinical laboratories must continuously monitor the antigenic shift and drift in the circulating virus strains to determine the vaccine currently necessary for vaccination.

The efficiency of hybridization microarray chips for typing influenza virus essentially depends on the methods for selecting the probes specific for the analyzed DNA. We have developed an original method searching for the typing probes able to determine the subtypes of influenza virus haemagglutinins and neuraminidases.

Eventually, we have designed a microarray chip that is able to type influenza virus A according to haemagglutinin and neuraminidase genes. We have tested the selectivity of the designed probes typing the influenza virus neuraminidase and haemagglutinin genes using the available amplicons of human influenza viruses and, in part, avian influenza viruses. Two parameters were used to ascribe a sample to particular subtype according to the microarray data: (1) mean (normalized) fluorescence of spot (the sum of spot fluorescence intensities of a subtype divided by the number of spots) and (2) the fraction of fluorescing spots (the number of spots of a subtype displaying the fluorescence exceeding the mean fluorescence value for all spots of the microarray). The developed microarray chip correctly determines the analyzed subtypes of type A influenza virus.

The proposed method can be used for screening of the influenza virus reassortants obtained for influenza vaccine production; rapid diagnostics of natural reassortants, including the viruses belonging to different species; and monitoring of the antigenic drift within the same serotype.

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GLOBALIZATION AND EPIDEMIC PROCESS

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Political, economic and social globalization is a characteristic feature of the new millennium. As a result of social and economic shifts and environmental deterioration the rate of evolution and development of infectious diseases has rocketed and can be measured in terms of decades not centures as used to be. In the war between humans and pathogenic microorganisms unfailing vigilance is the matter of life and death. The most challenging problem of the 21-st century is reviving of well-known and spread of new dangerous infectious diseases.

Nowadays, we as mankind have returned to the point when epidemics are getting out of control and spreading througout the world at the rate which has never been seen before. It is a consequence of modern life style: urbanization accompanied with low living standards, high levels of international migration, commerce and commodity circulation, large-scale food production, storing and transportation - all these have led to the emergence of new and spread of well-known pathogens. Modern transport facilities, new ways of transferring huge masses of people and goods by air, sea and land tend to promote the worldwide spread of infections, vectors and carriers.

Globalization is increasingly influencing all spheres of social life challenging the mechanisms of legal regulation. No doubt, WHO plays the main role in international cooperation on combating infectious diseases. A number of WHO resolutions are aimed at prevention and treatment of such scourges as AIDS, tuberculosis, malaria, SARS, avian flu. At the G8 Summit in St. Petersburg the leaders adopted the declaration which outlined the general principles of global strategy on epidemics prevention under global threat of emergence of new infections and permanent dissemination of well-known ones including HIV/AIDS, tuberculosis and malaria.

Unfortunately, epidemiological prognosis for the first decades of the 21-st century is unclear and distressing: any time, any place there may happen a new outbreak or epidemic, caused by infectious pathogens — new, reccurent or invading new geographic areas. In this connection, the most effective approach to combating infectious diseases is

the holistic approach, which implies the consideration of international laws regulating health care, human rights, environmental and commercial policy as well as criminal codes.

INFOCOMMUNICATION TECHNOLOGIES IN PROVISION EPIDEMIC SAFETY

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In development of the document G8 Summit/Saint – Petersburg Russia 2006 «Fight against infectious diseases» they are presented telemedicine projects based on up-to-date digital and info-communication technologies allowing to change drastically the situation in the sphere of medical services to the population, especially to the rural population, people living in remote and hardly accessible regions. The projects allow to achieve the following:

- equal opportunities of access to the modern public health services for the entire country population;
- better quality of medical service for various strata of the country population;
- to save funds allocated by the country budget for public health, and to reduce expenses for medical services by way of a more rational patient treatment;
- to stop unreasonable visits to doctors and patient sending for consultations to the capital or regional medical institutions;
- to raise efficiency of medical services due to reduction of time spent for patient servicing;
- shared use of medical equipment, including for the account of a reduced need in expensive devices;
- use of a remote education and professional retraining network;

Telemedicine network scaesnet (satellite communication antiepidemic screening network). It is a multi-level system solution uniting in a single network various stationary and mobile medical institutions (at the federal, regional and local levels), equipped with special-purpose digital medical diagnostic and telecommunication devices.

System key elements are the *Mobile Telemedicine Complexes (MTC)***,** mounted on cross-country frame (on an aircraft or ship) and equipped with stand-alone crew life support systems. This allows to organize mass examination of the population, including in the remote and hardly accessible regions for tuberculosis, AIDS, malaria, amebiasis and other contagious diseases and transmit the examination results in a digital form via conventional or satellite channels to the central medical institutions, where qualified medical experts analyze the examination results and send their recommendations on the revealed patients' treatment to the laboratory personnel in the off-line or on-line modes. System allows to conduct most various medical examinations in the field of functional, morphological and radiological diagnostics, including fluorography, ultrasonic examination, cardiological measurements, blood analyses and more, providing for general availability and a unified high quality standard of medical services rendered to the population independent of location.

*Anti-Tuberculosis System***.** System principle element are stationary digital low-dose fluorographs with a medical option allowing to transmit the examination results in a digital form via conventional or satellite channels to the central medical institutions, where experts analyze the examination results and issue their recommendations. System may be presented in a mobile variant (fluorograph is mounted on a car, ship, helicopter), allowing to examine population in rural, remote and hardly accessible regions.

System allows to reduce radiation load on the patient 50 to 100 times as compared to classical fluorography or X-ray examination, to avoid using expensive X-ray film and photo materials, that increases economic efficiency of their use.

NATIONAL SURVEILLANCE STANDARDS AND SERVISES INTEGRATION

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Surveillance Standards (SS) – is the regulated by all parameters of the epidemic process, components and levels of epidemiological surveillance system for control of infectious and parasitic diseases. SS include standard case definitions (CD) and number of approaches that are strongly differentiated by each disease that is of high significance for organization of surveillance. For example, what kind of data are necessary, at what levels of surveillance, what kind of analysis and by which methods are required, recording and reporting forms etc.

CD – includes criteria based on which confirmed, probable, suspected or other cases are defined. Clear differentiation between cases is emphasized that is considerably important for public health in whole and

epidemiological investigation particularly. Through use of single CD diseases are detected and recorded based on single criteria. That is why "CD" usually called "Standard CD".

National SS for infection and parasitic diseases in Armenia methodologically based on the following documents: WHO recommended surveillance standards, Case definition for public health surveillance, Consensus meeting on surveillance in Europe, Reporting of Diseases to CDC, Armenian Health Information and State Epidemiological Systems Developmen.

SS development had been done by stages: 1. rationale for surveillance (priority, bioagent, modes of transmission, incubation period); 2. CD clinical description of disease, criteria for laboratory diagnostics, case classification (suspected, probable, confirmed, epidemiologically linked case, etc.); 3. surveillance types (rapid reporting, express reporting of outbreaks, key and others); 4. minimal data required: age, sex, geographic data, beginning of disease, laboratory data, hospitalization, treatment received, consequences, number of contacts, probable source of infection, mode of transmission, number of cases with distribution by age, sex, number of lethal cases, number of hospitalized cases, etc.); 5. description of data analysis (comparative data for the same period in the previous year, data analysis by hospitalization, age, fatality, mode of transmission, source of infection, reporting, etc.); 6. use of data for decision making (plan of measures/actions to prevent and control infection; to define their performance etc.).

This document (450 pages) includes conceptual basis of the Public Health development and the Surveillance System establishment. It includes 60 infectious and parasitic diseases, diseases are grouped into the main sections: enteric infections, vaccine-preventable diseases, zoonotic diseases, STDs, helminthiasis, protozoiasis etc. Each disease has case definition and epidemiological investigation chart and each section has appropriate recording/reporting forms. In conclusion the main principles for the establishment of information system for surveillance and appropriate manuals for software are described.

SS permit to actively integrate laboratory and information systems, human recourses policy, health care and ambulatory-polyclinical services, family medicine etc. Implementation of SS allows increasing effectiveness of the surveillance system and harmonizing it with the international standards. SS – are dynamic. Their development is continued process depended on the developments in science, practice and new technologies according which criteria for diseases, surveillance system, case definitions and surveillance standards are changed. In complex all mentioned parameters will lead to modernization of the surveillance system and its continued enhancing. The first edition of the national surveillance standards was approved by the minister of health in 2001, the second one in 2005. Currently, the third edition is under development.

BATS, EMERGING INFECTIONS, AND FUTURE MANAGEMENT INTERVENTIONS

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Bats have been identified as reservoirs of a number of etiological agents for multiple emerging infectious diseases, such as newly described species of lyssaviruses. Available management options are limited to control such diseases, when bats are implicated under such circumstances. In general, as critical arthropod predators, plant pollinators, and seed dispersers around the globe, population reduction of bats is not recommended for a variety of ecological, ethical, and economical reasons. One historical exception in Latin America is the targeted reduction of vampire bats that prey upon livestock, using specific anti-coagulant techniques. Public education is a key, whenever any mitigative measures are under consideration. When roosts are located in houses, bats should be excluded from human dwellings by appropriate humane methods. As to other possible interventions, rabies serves as the modern paradigm for the development of vaccines for free-ranging wildlife. Such approaches may be extended and tailored to bats, especially exploiting social grooming opportunities, trophic preferences, and the availability of large roosting aggregations. Construction of new rhabdovirus vectors may be feasible by utilization of current reverse genetics techniques. With a combination of modern laboratory techniques on novel vaccine development/delivery, and improved field methods in the applied ecology and social behavior of bat populations, safe, efficacious, humane, economical interventions should be possible in the near future. Such progress would be a considerable step forward in planning for the prevention and control of emerging infectious diseases associated with the *Chiroptera*, especially when combined with an effective global disease detection system that directly monitors selected free-ranging wildlife.

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HIV-INFECTION IN IRKUTSK REGION: THE RESULTS OF SURVAILLANCE IN FIRST TEN YEARS AFTER START OF THE EPIDEMIC (1999-2008)

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HIV infection epidemic started in Irkutsk in 1999, when 3.2 thousands new cases were documented. Earlier, between 1992-1998, only sporadic cases of HIV-infection were reported. The purpose of this publication is the evaluation of consequences of rapid spreading of HIV- infection after introduction into the area.

Currently Irkutsk region belongs to the most HIV-infection affected regions of Russia. After 1999 the infection incidence was changing between 54.9 and 140.9 per 100 thousands of population (2.5 thousands cases in average for 10 years). In total 26.4 thousands cases were officially reported. At the end of 2008, the infection prevalence in the total population was 723.6 per 100 thousands (0.7%); 1.3% - among pregnant women; 5.8% - among drug users. During the observation period, 3.7 thousand children were born by HIV-positive mothers, and HIV- infection was confirmed in 7.4% of these. As a result of selective study during 2006-2007, 0.4% of the hospital patients in Irkutsk were HIV infected. At the beginning of the epidemic, the main risk groups were males (79.7%) and drug users (95.4%). This pattern was changed significantly by the end of 2008: only 59.2% of HIV-positive patients were males and 41.9% were drug users. The impotence of heterosexual transmission was increased, especially among females. The most vulnerable age group was 20-29 years; the infection incidence in this group was 3-4 times higher, compared to the total population. Within the10 years period, 2.9 thousands of HIV-positive patients died (11.0% of all reported cases). Mortality in the group of HIV-infected people was progressively increased: 28 cases in 1999, and 1184 cases in 2008. According to archive data, 24.2% of patients, whom were confirmed as HIV-positive in 1999, died the following 10 years. However the official records include only 84 patients who died of AIDS. Pneumonia and different forms of TB-infection predominated among the secondary pathology in HIV-positive patients in Irkutsk. Severe forms of pneumocystosis, brain toxoplasmosis, cryptococcosis and other opportunistic infections have been more and more frequently reported in clinics last years only.

The HIV infection, together with other risk factors (alcohol, drugs), had exerted negatively on the population health and demography. This includes the increasing rates of total infectious morbidity, increasing of TB morbidity and mortality, the rise of total mortality in age cohort born during 1970-1980 (especially males).

METAGENOMIC DIAGNOSIS OF INFECTIOUS DISEASES

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Infectious diseases are caused by various pathogens including microorganisms that remain unidentified to date. Once an outbreak of infectious diseases occurs, it is necessary to identify the pathogens promptly and take appropriate measures to be able to control, and thus limit, the spread of the disease.

Newly developed “next generation” DNA sequencers have the full capability to determine more than 100 Mb of DNA sequences in several hours. Tapping this potential, we are developing a new system to detect and identify various pathogens, including unknown ones, using a simplified protocol of high-throughput DNA sequencing. In this talk, I will further elaborate on this system that we are developing.

We are establishing a protocol to rapidly obtain the whole genome information of bacterial and viral pathogens, that is expected to significantly accelerate the speed of pathogen identification. Also, by using metagenomic approach, we could successfully demonstrate the presence of pathogenic microbes in clinical (diarrheal) human samples without using conventional selective procedures for specific pathogens.

Emerging infectious pathogens to humans are often of animal origin, and in many cases, they are already known microorganisms. The approach that we are developing in this project, the detection and identification of pathogens based on high-throughput DNA sequencing, should be quite promising, especially now when a tremendous amount of genome information of various microorganisms is continually being accumulated in databases.

GENETIC DIVERSITY OF WEST NILE AND TICK-BORNE ENCEPHALITIS VIRUSES: NEW GENETIC VARIANTS OF FLAVIVIRUSES IN THE ASIAN PART OF RUSSIA

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Emergence of over 35 new infectious diseases caused by various pathogens have been recently recorded. The flaviviruses (family *Flaviviridae, Flaviviruses*) are not an exclusion from this rule. Currently, this virus group comprises about 80 members, the majority of which are transmitted from arthropods to warm-blooded animals. Many flaviviruses are able to cause human diseases. The most significant flavivirus infections for humans are caused by dengue, yellow fever, Japanese encephalitis, West Nile, and tick-borne encephalitis viruses.

Tick-borne encephalitis virus (TBEV) is the prototype of the similarly named virus serogroup. Three main TBEV variants are known: Far Eastern, European (Western), and Siberian. The homology of nucleotide sequences of TBEV genotypes is 80–85%. The main TBEV vector is the ticks *Ixodes persulcatus* and *I. ricinus*. The tick-borne encephalitis morbidity is recorded in more than 25 European and seven Asian countries. One of the hypotheses on TBEV spreading postulates that TBEV went westward over Eurasia for approximately last 2000 years. However, currently we know many facts that strains of Far Eastern TBEV subtype have circulated on the territories of Europe and Siberia. In 1999, unusual Far Eastern TBEV variants were recorded in the Novosibirsk oblast; they caused lethal hemorrhagic forms of the disease. In 2004, a new highly pathogenic TBEV isolate, Glubinnoe/2004, was recovered. Phylogenetic analysis demonstrated that the strain Glubinnoe/2004 forms a separate new branch within the Far Eastern TBEV genotype. The complete genomic sequence was determined, and 53 (57) amino acid substitutions relative to strain 205 (Sofjin-HO) were found. The estimation of the divergence time by molecular clock method demonstrated that the strain Glubinnoe/2004 separated from TBEV Chinese isolates (strain Senzhang) 300–470 years ago and from the TBEV Oshima–Sofjin group about 320–490 years ago. It was found that the strain Glubinnoe/2004 more efficiently replicated in the PEK cells as compared with strain 205, the difference at early replication stages reaching 250-fold.

The TBEV monitoring in Tomsk and its suburbs provided for forming the collection of virus RNA isolated from individual *I. persulcatus* and *I. Pavlovskyi* ticks. The nucleotide sequence of the 5'-untranslated region (5'-UTR) was determined for over 50 specimens of the TBEV RNA. All original sequences of TBEV 5'-UTR were deposited with the GenBank. The genotyping of TBEV based on the analysis of a fragment of nucleotide sequence of the TBEV genome 5'-end demonstrated the circulation of Far Eastern (27.8%) and Siberian (72.2%) TBEV genotypes; note that the Siberian genotype was predominant in the suburb foci, while in the urban biotopes, the fraction of Siberian genotype increased to almost 50%. The Siberian genotype was genetically diverse and formed at least three different genetic groups. One of these groups was genetically similar to the TBEV strain Zausaev, known for its ability to cause lethal chronic tick-borne encephalitis. Genetic diversity of the detected Far Eastern TBEV variants is considerably lower, being limited by two genetic groups. One of these groups is new, and the degree of divergence of its members suggests a rather long evolutionary history within the studied Tomsk biotopes. The other TBEV genetic group is similar to TBEV strain 205, isolated earlier in the Khabarovsk krai. These results suggest that the Far Eastern TBEV genotype was twice imported to the territory of Tomsk and Tomsk oblast and that it is connected with human economic activities.

The average homology level of TBEV 5'-UTR was 95% for the TBEV variants with Far Eastern genotype and 89% for the Siberian genotype. The conserved and hypervariable 5'-UTR regions were detected. When studying the TBEV adaptation to new host type, 20 RT-PCR positive specimens from individual *I. persulcatus* and *I. Pavlovskyi* ticks were analyzed. They were passaged in pig embryo kidney cells, and the TBEV RNA was detected in three cases at the third passage; for them, the sequence of 5'-UTR was determined. The adapted variants (Prot1, Prot2, and Prot3) contained 14, 21, and 28 nucleotide substitutions as compared with the initial RNA sequence in the tick.

The nucleotide substitutions in the adapted variants, their initial variants in individual ticks, and in the collection of viral RNA isolated from individual *I. persulcatus* and *I. Pavlovskyi* ticks were mainly localized to the Y-structure of the 5'-UTR, which could cause considerable changes in the secondary structure of this RNA region. We assumed that such variation could be connected with the selection of more efficiently replicating TBEV variants in the virus population when changing the host cell types (ticks and mammals). The most likely molecular basis of these genetic changes is the remodeling of the secondary structure of the virus RNA 5'-UTR leading to spatial

modifications of the binding sites for viral specific RNA-dependent RNA polymerase and the IRES element of the 5'-UTR, which provides for the interaction of virus RNA with the ribosomes of tick and mammalian cells. Computer modeling of the 5'-UTR secondary structure of the obtained variants confirms this hypothesis.

West Nile virus (WNV) is a member of the antigenic complex of Japanese encephalitis virus (JEV) and the etiologic agent of West Nile fever. In 1999, WNV was first detected in the United States and then spread over practically all countries of Central America and was detected in Argentina in 2006. A large outbreak of West Nile fever was also detected in 1999 in southern regions of Russia. Later we for the first time demonstrated that WNV circulated among both migratory and nonmigratory West Siberian avian species [12–14]. Study of small mammals in the Novosibirsk oblast also detected WNV markers. This suggested that the local focus of West Nile fever had formed in the forest–steppe and steppe regions in the south of West Siberia. Three human cases of West Nile fever were for the first time practically simultaneously recorded in the Novosibirsk oblast. Analysis of field specimens has demonstrated that WNV is not confined to Siberian region and colonized the south of Primorsky krai. WNV genotyping demonstrates that this rapid spreading of the virus is connected with the WNV genotype Ia. Most likely, WNV genotype Ia quickly spread from the region of the Caspian Sea to the south part of Asian Russia and even to the Pacific coast.

The WNV monitoring in Tomsk and its suburbs provided for the pioneering discovery of West Nile fever markers. RT-PCR and the enzyme immunoassay with monoclonal antibodies to WNV E protein detected the virus RNA and the virus antigen in *I. persulcatus* and *I. pavlovskyi* ticks in both urban and suburban biotopes. The average rate of WNV-infected ticks varied from 0 to 11.7%. The nucleotide sequence of a fragment of the gene encoding WNV E protein suggests that the isolated cDNA fragments belong to the WNV genotype Ia, namely, to the strains similar to the Volgograd strain LEIV-Vlg99-27889-human.

The above described changes in the distribution area of the RNA viruses pathogenic for humans and emergence of their new genetic variants have become an important factor influencing the organization of the control of infectious diseases in Russia. New genetic variants of flaviviruses enter natural ecosystems of new regions and form new natural foci of infectious diseases. Several achievements of the modern civilization changing natural ecosystems due to man's activities enhance the "success" of RNA viruses in spreading over new geographical territories. The possibility of transmission of these viruses with migratory birds; their ability to replicate in new species of mammals, birds, and insects; and their high genetic variation and easy adaptation to new environmental conditions provide for formation of new natural foci of infectious diseases, which also involve the local population.

COMPUTER-ASSISTED DISCOVERY OF ANTI-INFECTIVE AGENTS

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The most prospective macromolecular targets (separate or in combinations) associated with certain pathologies can be identified by comparative analysis of biomedical data including genomics, postgenomics and others. Three-dimensional structure of the target protein, either obtained from the Protein Data Bank (PDB) or computed with molecular modeling methods, can be used for target-based design of potential ligands or for their virtual screening among the commercially available samples. Drug-candidates may be obtained by ligand-based (Q)SAR approach applied for optimization of pharmacodynamics' and pharmacokinetics' characteristics of lead compounds. Examining the amino acid sequences of proteins relatively conservative antigenic determinants are revealed and used for further design of recombinant vaccines.

The whole computational platform "From genomes to drugs *in silico*" has been developed in the Institute of Biomedical Chemistry of Rus. Acad. Med. Sci. These computer-assisted methods are widely used in applied projects directed to detection of the targets and their ligands for the treatment of infectious diseases, including HIV/AIDS, tuberculosis, influenza, and hepatitis C (HCV). Examples of new antimycobacterial targets identification, virtual screening and design of HIV-1 protease, reverse transcriptase and integrase, flu neuraminidase, HCV protease inhibitors will be presented. New joint projects could be initiated in cooperation with Russian scientists (organic chemists and biologists) and foreign collaborators and partners, to find out and develop new pharmaceutical agents and vaccines for the treatment and prevention of widespread and emerging infectious diseases.

Acknowledgement

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STRATEGIES FOR IDENTIFICATION OF ANTIVIRAL PREPARATIONS TARGETED AT VARIOLA VIRUS RNA POLYMERASE

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The first goal of the ISTC project # 3516p is to produce purified preparations of vaccinia virus RNA polymerase from virions in order to determine its structure and facilitate the design of new drugs that inhibit vaccinia virus and related variola virus and other orthopoxviruses. Furthermore, purified RNA polymerase will be used to set up a miniaturized test for the enzymatic activity that can be employed in screening for inhibitors. The second goal of the project is to produce variola virus RNA polymerase subunits in insect cells using baculoviral expression system with the purpose of obtaining a reassembled enzymatically active RNA polymerase of variola virus.

The situation on the methods for vaccinia virus production and purification based in the experience and data of the project participants and the published data has been comprehensively analyzed. The performed experiments allowed to choice the most optimal method of the virus purification. The system vaccinia virus strain WR/BHK-F cells for isolation of vaccinia virus was used as it is sufficiently efficient, convenient for laboratory conditions, and least inexpensive from the standpoint of supplies and reagents.

The strategy for cloning nine genes of variola virus (VARV) strain Ind-3a RNA polymerase subunits was developed. At this moment the nucleotide sequences of genes encoding the subunits of variola virus RNA polymerase RPO7, RPO18, RPO19, RPO22(His), RPO30, RPO35, RPO132, RPO147, and RAP94 were cloned into plasmids of *E. coli*, and the correctness of these structures was confirmed by sequencing. The bacterial producers of proteins RPO18, RPO19, RPO22(His), and RPO30 were constructed. The preparations of proteins RPO18, RPO19, and RPO30 were isolated from *E. coli* lysates and used for rabbits immunization. The plasmid pFBDM-RPO30-RPO35 for integration into baculovirus genome was constructed. The recombinant plasmids, containing the sequences of the natural VARV ORF F7R (gene RPO18) and the ORF F7R optimized for the frequencies of codons necessary for an efficient expression in insect cells were constructed. Selections of recombinant baculoviruses producing variola virus proteins into insect cells are in progress.

NOVEL APPROACHES FOR ANTI-PLAGUE THERAPY

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The growing resistance of bacterial populations to the traditional drugs that kill the microorganism has promoted an interest in developing antibacterial agents that target the virulence mechanism of the particular pathogen, or a group of pathogens, that employ a similar strategy to exhibit their virulence. Such chemical attenuation will enable a host to clear the infection, and inhibitors of virulence could be useful as prophylactic and therapeutic agents in combination with traditional drugs and vaccines.

Yersinia pestis, the agent of plague, contains a surface-located protease Pla which acts in a manner similar to that of mammalian plasminogen activators, namely by converting plasminogen to plasmin by limited proteolysis. This protease, called plague plasminogen activator, is unique to *Y. pestis* and essential for the development of both the bubonic and pneumonic form of plague. For that reason, the inhibitors of Pla could potentially be used as prophylactic and therapeutic treatments against plague infection. Using a positional scan approach, we have identified substrates for Pla enzyme through the parallel synthesis of small fluorogenic peptides which could be used as leads for the development of inhibitors of the protease Pla. Moreover, the fluorogenic substrate has been utilized to perform a high-throughput screen for small molecule inhibitors of Pla. A total of 54,100 compounds from 19 libraries were subjected to the assay protocol. This analysis produced 124 commercial compounds as hits. The hits have been further ranked according to the determined percentage of inhibition, followed by subsequent testing for the ability to block plasminogen activation by Pla in the fluorimetric and fibrinolytic assays.

BETA-LACTAMASES: POLYMORPHIZM AND NEW INHIBITORS

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The aim of present study was to develop DNA microarray for the identification of single nucleotide polymorphisms (SNPs) of CTX-M extended spectrum beta-lactamases and to apply it for characterization of clinical enterobacterial isolates.

The method of DNA microarray consisted of several steps involving DNA extraction from clinical samples, amplification and labeling of target DNA with different labels (Cy3 or biotin) by PCR and the subsequent hybridization of PCR product with oligonucleotide probes immobilized on epoxy-glass slides. After hybridization biotin in duplexes was developed with conjugate streptavidin-horseradish peroxidase (HRP) followed by the detection of HRP with chromogenic substrates which oxidation is accompanied by the formation of colored insoluble product. The results of microarrays were validated using control strains from Russian and europian collections with CTX-M-2, -3, -4, -5,-8, -9, -14, -15, - 42.

We developed two types of DNA microarrays with fluorescent and colorimetric detection for rapid identification of mutations in CTX-M β-lactamase genes. Careful design of oligonucleotide probes and optimization of hybridisation conditions ensured specific identification of all control CTX-M-type ESBLs. The sensitivity of SNP detection with colorimetric microarray was comparable with that of fluorescent microarray, the discrimination power for selected SNPs was higher for the colorimetric microarray. The developed methods were applied for analysis of 90 clinical isolates of *Enterobacteriaceae* determined as carrying *bla* $_{CTX-M}$ gene with real-time PCR. The genes for CTX-M-1-related β-lactamases (CTX-M-3 and CTX-M-15) were found in the majority of the isolates. The genes for CTX-M-2 and CTX-M-9-related β-lactamases (CTX-M-5 and CTX-M-14) were also found in selected isolates.

The oligonucleotide microarrays with fluorescent and colorimetric detection can identify SNPs of all tested CTX-M beta-lactamases. The concordance of CTX-M subtype identification with DNA microarray and DNA sequencing was 100%. DNA microarray technique offers the identification of a pathogen and its antibiotic resistance at the molecular level and is proposed as a useful tool for epidemiological investigation of ESBL-producing organisms.

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CONNECTING HUMAN AND ANIMAL HEALTH SURVEILLANCE SYSTEMS

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Spread of zoonoses presents a number of challenges to national and regional health systems that require complex multidisciplinary and multisectoral approach. The need to improve interface between human and animal sectors has become essential for the international health community in recent years with an increased threat of pandemic influenza and other emerging and re-emerging infectious diseases. This collaborative study will identify points of intersectoral human and animal health collaboration that will strengthen early disease detection and response. We will draw from experience of the national surveillance systems in Russia, Central Asia, United States, United Kingdom in their efforts to improve interface between the human and animal health systems.

The group will explore the following areas of the interface of the human and animal health systems:

1. Collaboration between Ministries / Agencies of Health, Veterinary and Agriculture
2. Information sharing between H-A ministries / departments/ agencies
3. Joint investigations involving human and animal health experts
4. Community based surveillance of zoonoses

The group will convene for a workshop in July of 2009 In Moscow. The outcome of the group’s discussion will be reported at the conference. The results of the study will be submitted as a manuscript for publication at the end of 2009.

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MONITORING AND DIAGNOSTIC OF PRION INFECTIONS IN BELARUS

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This project is devoted to implement epidemiological surveillance of transmissible spongiform encephalopathies (TSE)/prion diseases in Belarus, to study a role of astrocytes in TSE pathogenesis, and to develop new diagnostic approach for early detection of animal and human TSEs using the proteome- and nanotechnology-based methods (Prion Diseases #B-1440). Prion diseases like Creutzfeldt-Jacob desease (CJD), included the new variant – nvCJD, amyotrophic leucospongiosis (AL) and bovine spongiform encephalopathy (BSE) are a group of neurodegenerative disorders with extended incubation times, slowly-progressive disease course and an invariably fatal outcome. Currently, routine laboratory diagnosis of the majority of TSE in Belarus is based on postmortem clinic-morphological investigations, immunohistochemical detection (IHC) of disease-specific proteinase-resistant prion protein (PrP^d) and Western blot analysis in autopsies brain of affected individuals.

In 1984-2007, 22 cases sporadic CJD and 29 cases AL (12 – familial and 17 – sporadic) in Belarus are revealed. In 2008, more than 50 autopsies of human brain and 350 cattle brain samples from the risk population (human with neurodegenerative disorders unknown origin and animals in poor condition more than 30 months old) were analyzed by histopathology and/or western blotting, with negative results.

Moreover, in the past few years, we were developed atomic force microscopy (AFM) approaches for study the PrP^d aggregated forms in brain, which are responsible for prion diseases in human and animals. AFM techniques aimed at increasing the sensitivity and specificity of PrP^d detection in body tissues and fluids and at identifying novel surrogate markers are under development. We believe, that the received technology will be allowed a diagnosis to be made prior to the development of clinical signs.

Thus, although epidemiological monitoring both nvCJD and BSE showed, that the state is safe in regard to their infections, however, more extensive active surveillance programs for TSE in Belarus are needed, because theoretical possibility of their presence exists.

CARRIERS OF ZOONOTIC INFECTIOUS DISEASES

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Currently in the territory of Tajikistan has been found 29 species of rodents, and among them 4 types tamariskovaya gerbil (*Meriones tamariscus*). In the south-west (up to 1600 meters above sea level) and north (up to 2200 meters above sea level) in Tajikistan the midday gerbil (*Meriones meridianus*) has been found in the sandy desert in the lower parts of rivers Kofarnigan, Vakhsh and in Ferghana valley also. The large gerbil (*Rhombomus opimus*) lives in Golodnaya steppes, the Ferghana Valley and partly in the foothills of Nurkestan ridge; red-tail gerbil (*Meriones erythrourus*) is widespread. These types can be regarded as the main carriers, and their ectoparasites main carriers of pestilential microbe. The major carriers are *X. conformis* and *X. gerbili*. On the territory of the survey the majority of fleas were collected fleas of red-tails 85%. Tajikistan antiplague activities focused on the epizootic survey on plague in the mountain range of Gissar range and an array of sandy Kumsangir area. During the survey it has been captured 1444 rodents, and 1550 ectoparasites were removed.

In Kumsangir area (southern Tajikistan) in October 1975 it has been revealed the midday gerbil with antibodies to the causative agent of plague, and in September 1983 specific antibodies were detected in red-tail gerbil. Over the last three years (2006 - 2008) surveyed the area on three occasions. Totally it has been catched 251 red-tails. In spring 2006 (April - May) was found red-tail gerbil with antibodies to the plague. The latter may indicate the presence of this pest during epizootics. This requires a further thorough epizootological survey of the territory in order to identify the existence here of natural focal plague.

In order to highlight the causative agent of plague, confirming the phenomenon of natural focal, epizootic survey these sites, as well as in the valley Gulomov conducted in 2006 Lyahshskim mountain summer epidroup. In a survey of the territory identified rodents (vole juniper) with antibodies to the plague.

In the surveyed area has been found beam and diffuse type of settlement of the red marmot. The densest settlement noted in the subalpine and alpine zones. Wood mouse typical denizen of green belt and other belts catch extremely rare. Silver vole catches in both zones. Reproduction of the red marmot came under the rule. Of all adult females marked 82.6% of nursing. Pregnant and lactating females silver vole occurred throughout the period of the order (July - August). The peak of females participating in reproduction was in July - 85.1%. The number of red

marmot relatively stable from year to year and an average of 44 copies at 1 sq. km. he number of silver vole is quite high and amounts to an average of 6.0 to 6.2% hit.

The number of forest mouse close to the high values of 5.5 - 6.0% hit. It should be noted that the survey area used for grazing, the cultivation of grain, in the vicinity of its major towns are located Lyahsh -1, Lyahsh -2 and other locations. All of the above determines the necessity for careful epizootological survey of the territory. In autumn 2008 (September - October) was examined Havatagskim (northern Tajikistan) by the epidgroup of the piedmont area around Sanatoriums Havatag of the Istaravshan area. It revealed a large gerbil with antibodies to the plague. In the mountain forest area the most numerous and widely distributed juniper vole (*Microtus carruthersi*) has been found in three zones of vegetation - trees and shrubs, sub-alpine meadows and upland kserofit, lower alpine meadows. On the territory of Gissar range juniper vole habitat in the heights from 2200 to 3700 meters above sea level. From the individual studies fleas collected from rodents and their nests was allocated 56 strains of plague microbe. Of the fleas from *A. phaiomudis, C. caspius, F. elata vara, P. nemorosus, L. nana*, shot with juniper polevok, isolated 40 strains, 4 strains from fleas *F. elata* and *A. phaiomudis*, collected in a nest of juniper vole, from O. silvantieni with marmot. The number of juniper vole low, the percentage falling to 100 trap-days, on average, 7 - 8 persons. Period of the reproduction of juniper vole quite large - from February to October. At Gissar range of embryos ranged from 2 to 6. Totally during the period were 258 captured animal. Among them 76 pregnant, 72 barren females, 35 young females and 73 male specimens. In the period from 2006 to 2008 at enzootic to plague the territory Gissar range produced 66 adult females, among them 23 participated in the reproduction. At enzootic to plague the territory of spatial location and size of marmots have their own characteristics. In all areas dominated by girder type settlements with considerable variation in the number of landscape zones. At the top of the green belt (the lower part of Dehkondara million), the number of marmot is 25 - 30 copies at 1 sq. km In the subalpine zone (Zambar sai), the number is 45 - 50 copies. one square kilometers, in the alpine zone (the central part of Dehkondara million), 60 copies 1 sq.km.

YERSINIA – JUST ANOTHER GROUP OF EMERGING PATHOGENS

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Yersiniosis is a zoonotic disease of wild and domestic animals with humans usually as incidental hosts. Human pathogenic *Yersinia* include *Yersinia pestis*, the agent of plague, and two enteropathogens, *Y. pseudotuberculosis* and *Y. enterocolitica*. Worldwide *Y. enterocolitica* is associated with 1-3% of acute enteritis followed by erythema nodosum and reactive arthritis as most common post-infectious sequels. *Y. enterocolitca* biotypes (BT) 1B, 2, 3, and 4 are pathogenic for humans, while biotype 1A strains are supposed to be non-pathogenic. However, there is growing evidence that “non-pathogenic” 1A strains, devoid of the established virulence determinants might cause human disease as well.

To uncover mechanisms behind the emergence of new pathogens and to predict their possible routes of evolution we have sequenced three genomes of closely related Y. enterocolitica, an environmental non-pathogenic strain of biogroup 1A, a “non-pathogenic” 1A isolate that caused a hospital outbreak in Australia, and a moderate pathogenic BT2 human isolate, and compared them with a highly virulent BT1B strain. Although some known *Y. enterocolitica* virulence markers are missing from the moderate-pathogenic isolate (like the high pathogenicity island) and “apathogenic” strains (e.g. the virulence plasmid), the latter two still possess T1SS, T2/4SS, T5SS, T6SS as well as other virulence-associated determinants. Moreover, both BT1A isolates have acquired novel potential virulence markers like autotransporters, hemolysins, and toxins. Such a new combination of various virulence and fitness-associated determinants in normally “apathogenic” *Y. enterocolitica* 1A strains supply them with ability for rapid pathoadaptation to both environmental and host challenges. Thus bacteria are able to realize their virulence potential through alternative strategies using different “patchworks” of pathogenic features.

GENETIC DIVERSITY OF SORICID-BORNE HANTAVIRUSES IN SIBERIA, RUSSIA

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Hantaviral antigens were reported more than 20 years ago in tissues of the Eurasian common shrew (*Sorex araneus*), medium shrew (*S. caecutiens*) and pygmy shrew (*S. minutus*), captured in European and Siberian Russia. Recently, a phylogenetically distinct hantavirus, named Seewis virus (SWSV), has been identified in *Sorex araneus* captured in Switzerland, Hungary and Finland. The Eurasian common shrew is among the most widely dispersed small mammals species in Eurasia, spanning from Europe to Siberia.

To further clarify the geographic distribution and genetic diversity of SWSV and other hantaviruses harbored by shrews, lung tissues from 44 *Sorex araneus*, 13 *Sorex tundrensis*, 13 *S. minutus* and 27 *Sorex sp.*, captured throughout Western and Eastern Siberia (Altai, Kemerovo, Omsk, Krasnoyarsk, Irkutsk and Novosibirsk regions) in 2007-2008, were analyzed by RT-PCR. To verify the taxonomic identity of the hantavirus-infected shrews, the cytochrome *b* gene of mtDNA was amplified by PCR.

Hantavirus L- and S-segment sequences were detected in eleven *S. araneus,* two *S. tundrensis,* and two *S. daphaenodon*. Overall, the sequences appeared to be genetic variants of SWSV, differing from the prototype mp70 strain from Switzerland by 16-20% at the nucleotide level and 0-2% at the amino acid level. Alignment and comparison of nucleotide and amino acid sequences showed an intra-strain difference of 1-9% and 0-2% for the L-segment and 0-8% and 2% for the S-segment, respectively. Phylogenetic analysis, based on 353- and 837-nucleotides of the L and S segments, showed geographic-specific clustering of SWSV strains. At the same time, at a third site SWSV strains from *S. araneus* showed two separate lineages within the SWSV group.

The detection of SWSV in *S. araneus, S. tundrensis* and *S. daphaenodon* in widely separated geographic localities in Siberia demonstrates the vast distribution of SWSV among different but closely related *Sorex* species. Whether this is a consequence of cross-species virus transmission or co-divergence is unclear. Also, to what extent other sympatric shrews are infected with SWSV warrants further investigation.

EVOLUTION OF EPIDEMIC PROCESS IN MODERN CONDITIONS

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At present time, the evolution of epidemic process is under active influence of a new adjusting risk factor - technogenic environmental contamination. Negative influence of ecological pressure on manifestations of infectious diseases is realized in destabilization of epidemic process: significantly higher level of incidence, greater amplitude of its fluctuations around a trendline and shortening cyclic componenta. Besides this, the more heavy clinical manifestations of infectious process and its longer duration with simultaneous development of the complications, accompanying diseases and synchronization of process takes place. Decrease of immunological and epidemiological effectiveness of vaccination is also registered.

It is established, that the minimal period of infection incidence is the most vulnerable part in a uniform circuit of epidemic process. Technogenic environmental contamination determinate an annual (seasonal) morbidity during this period. It is shown in epidemiological experiment that the complex of preventive actions at management of infection incidence is necessary for making active during a minimum level of development of epidemic process in its intraannual dynamics.

FOOD SAFETY REGARDING POTENTIAL BIOTHREAT ON GLOBAL FOOD SUPPLY IN THE CONTEXT OF FOODBORNE BIOTERRORISM RESPONSE PREPAREDNESS

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Recent natural and accidental incidents involving botulism from carrot juice and chili sauce, *Listeria* contamination of processed meat, and an *E. coli* O157:H7 outbreak linked to spinach, demonstrate the vulnerability of the food supply to contamination. The magnitude of unintentional food outbreaks suggests that a concerted, deliberate attack could be more devastating, especially if a dangerous biological agent such as *Bacillus anthracis* or *Clostridium botulinum* neurotoxin was used. The release of anthrax spores through the postal system in the US in October 2001, resulting in 22 cases of anthrax and 5 deaths indicates that the threat of bioterrorism involving this agent is real. The intentional contamination of a salad bar in Oregon by the Rajneeshee cult, that caused 751 cases of salmonellosis and a recent National Academy of Science paper highlighting the vulnerability of the milk supply chain underline the vulnerability of food to a potential bioterrorist attack. Food is considered a vulnerable target for bioterrorist attack, and events related to the deliberate contamination of food using conventional foodborne pathogens such as Salmonella make foodborne bioterrorism involving biothreat agents such as botulinum neurotoxin, *Bacillus anthracis and Yersinia pestis* a possibility.
Foodborne bioterrorism response preparedness is required to deal with any potential threat involving the food supply. The threat of foodborne bioterrorism on global food supply and mitigation strategies are discussed.

PREPARING EUROPE FOR THE NEXT VIRAL OUTBREAK

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Viral infections represent a major threat for the public health. The last of them the A flue, for the second time in the recent history, comes from West (Mexico, USA, Canada) and is touching Europe and Asia. The first similar pandemic was the Spanish flue in 1918. We all remember what happened.

All kind of neglected viral diseases may develop in fatal pandemics: Dengue fever is one them. Today, 100 millions persons suffer from the disease, which has a major impact on the economy of the countries, and 25000 persons are dying every year due to a lack of appropriate treatments.

We should be prepared to the next viral pandemic through the development of efficient antivirals.

Industrial companies are focusing on the major infection like HIV, and hepatitis where there is a commercial market. Very few is done on other viral diseases. The European community has decided to fund consortium to facilitate new drug development against neglected viral diseases.

We report in the following the last results obtained by the VIZIER consortium on *Flavivirus* and *Norovirus* antivirals drug design.

The access to high quality viral clinical isolates represents an important bottleneck to drug development. The European Viral archive will answer to the users demand for the supply of fully characterized and fully sequenced virus. This consortium will represent the largest viral collection worldwide. To increase and diversify its offer, this network is expanding to non European countries: South Africa, China, Australia, (Russia?). We present its organization, its user interface and we report in the following the latest developments.

TUBERCULOSIS AND HISTORY

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Tuberculosis accompanies mankind during thousands of years. Analyses of ancient Egyptian mummies of the Middle Kingdom revealed that M. tuberculosis and M. tuberculosis caused various forms of pulmonry and extrapulmonary tuberculosis among upper class members. This indicates that the working class suffered even more from tuberculosis. As old as clinical findings and descrptions of the disease are attempts for therapy. Ancient Egyptian papyri, recipes of the ancient Greeks and Romans and pragmatic measures have come to ur knowledge. In order to maintain the health of slaves, many Romans sent them to specialized sanatoria (valetudinaria) to treat tuberculosis by good air and environment. In the Middle Ages, kings were known to heal tuberculosis by their hands. In addition, many magic formulas were applied. In later centuries, healing tuberculosis by good air led to the travel of

many patients, mainly from the United Kingdom, to Mediterrean regions, especially to Naples. Later, the sanatorium movement tried to formalize this way of treatment.

The presentation has two aims:

1) It gives a short overview of the development of diagnostics and treatment of tuberculosis through the centuries in the pre-microbiological and pre-chemotherpeutical era.

2) It also highlights the influence, tuberculosis had on history, e.g. affecting kings, politicians, painters, poets etc, but also inspiring them sometimes in their works.

MOLECULAR EPIDEMIOLOGY OF TB IN RUSSIA

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TB spread in Russia remains at high level. Based on surveillance and survey data, WHO estimates that 157 000 new cases of TB occurred in 2007 (110 per 100 000 population). Of these 157 000 new cases, an estimated 43% or 68 000 (48 per 100 000 population) were new smear-positive cases. There were an estimated 164000 prevalent cases in 2007 (115 per 100 000 population) in Russian Federation. An estimated 20 000 HIV-negative people (14 per 100 000 population) died from TB in 2007, and there were an additional 5100 TB deaths among HIV-positive people (WHO report 2009. Global Tuberculosis Control. Epidemiology, Strategy, Financing).

Implementation of molecular techniques has considerably benefited the classical epidemiology of *Mycobacterium tuberculosis*. In particular, repetitive and insertion sequences have proven useful for studying the epidemiology, evolution and phylogeography of *M. tuberculosis*.

It was investigated 1227 *M. tuberculosis* strains obtained from patients from various regions of Russia (Ivanovo, Vladimir, Nizhnii Novgorod, Samara, Tomsk, Kemerovo, Khabarovsk oblasts, Republics MariiEl and Tuva). We used the following methods of genotyping: RFLP IS6110; spoligotyping; VNTR typing. Drug susceptibility was determined by methods of absolute concentrations and microarray technology ("TB-Biochip MDR") revealing mutations in genes *rpoB, katG, ahpC, inhA*.

RFLP IS6110 typing of 1227 *M. tuberculosis* strains (from 9 regions of Russia) revealed more than 42 clusters. Data showed that strains of W family (40%) and AI family (18.2%) were predominated. 19.7% of strains had nonclusterized genotypes. Spoligotyping of 167 *M.tuberculosis* strains revealed 11 cluster groups and 13% of strains with nonclusterized spoligotypes. The most quantity of strains belonged to Beijing spoligotype (65%). VNTR typing of 136 *M.tuberculosis* strains revealed large diversity of groups. 42435 cluster was predominated. Analysis of genotyping of each strain by three methods (RFLP IS6110, spoligotyping, VNTR) showed that 97% of 60 W family strains had Beijing spoligotype; 95% of 73 42435 VNTR strains had Beijing spoligotype; 77% of 91 Beijing spoligotype strains had 42435 VNTR type. Thus investigation showed that *M.tuberculosis* strains with the same genetic characteristic prevalented in Russia: belonged to Beijing spoligotype, had 42435 VNTR type and belonged to W family.

To determine the difference on the molecular epidemiological markers between MDR TB strains and sensitive strains it was studied TB strains of patients from the Middle Volga region. According to results of detection of drug susceptibility of TB strains was selected 97 MDR TB strains and 58 sensitive *M.tuberculosis* strains. Genotyping (RFLP IS6110, spoligotyping, VNTR) showed that strains belonged to the same cluster groups were found as among MDR so as among sensitive strains. However MDR strains were more clusterized than sensitive strains. Sensitive strains were more various. 81.8% of MDR strains belonged to W family. In contrast among sensitive strains only 44.4% belonged to W family. 85% of MDR strains had Beijing spoligotype. Among sensitive strains 41.3% belonged to Beijing spoligotype. 76% of MDR strains belonged to 42435 VNTR cluster but among sensitive strains only 30% belonged to 42435 VNTR cluster. Complex analysis of *M.tuberculosis* strains of patients from Middle Volga region showed that about 70% of MDR strains had the same genetic characteristics: belonged to W family, had Beijing spoligotype and had 42435 VNTR type. The same results were obtained by analysis of 164 MDR strains and 180 sensitive strains of *M.tuberculosis* from other regions of Russia. 49% of 164 MDR strains belonged to W family. In contrast only 24% of 180 sensitive strains belonged to W family. Sensitive strains were more various than MDR strains.

Molecular epidemiology investigation showed: predominance of *M.tuberculosis* strains belonging to the same genetic group (W- Beijing family). Our results testify about the threat of possible spread of MDR tuberculosis in Russia.

BIOCHIPS AS A TOOL FOR ANALYSIS OF *MYCOBACTERIA* GENOMES.

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The gel-based biochips developed in the Engelhardt Institute of Molecular Biology, RAS contain hemispherical (150 μm in diameter) hydrogel elements which are arranged on a hydrophobic surface at the density of 10 units per square mm. The gel elements could bear immobilized nucleic acids, proteins, other biomolecules and even live bacterial cells. The biochip is a powerful tool for simultaneous analysis of a number of genomic loci to identify mutations including single nucleotide polymorphisms. Oligonucleotide probes interact specifically with complementary sequences of analyzed DNA target. To perform biochip-based analysis, the amplified and fluorescently labeled DNA/RNA specimen is injected into a biochip microchamber where hybridization takes place. Specific fluorescence signals are captured and processed by a special biochip reader which is used to analyze all types of biochips produced by EIMB.

One of the most important clinical applications of biochips is genomic analysis of the TB causative agent. It is extremely important to obtain results of antimycobacterial drug resistance in short time due to growing number of MDR (multidrug resistant) and XDR (extremely drug resistant) tuberculosis cases.

The TB-biochip is used to identify genomic mutations responsible for rifampin (RIF) and isoniazid (INH) resistance in *Mycobacterium tuberculosis* strains. These mutations are located in the *rpoB*, *katG*, *inhA* genes and in the intergenic regulatory region of the *ahpC-oxyR* genes. The developed technique allows detection of more than 95% of RIF-resistant and about 80% of INH-resistant MTB strains in clinical samples within twenty four hours.

Another microarray (TB-biochip-2) was developed to reveal fluoroquinolone (FQ)-resistance in *M. tuberculosis* isolates and clinical samples. The method allows to identify 8 mutant variants of DNA in FQ-resistant strains (about 85% of all resistant forms). The sensitivity and specificity of the developed approach upon testing clinical samples were 93% and 100%, correspondingly.

Both TB diagnostic systems were approved by the Russian Ministry of Health and certified to be applied in clinical practice. TB-Biochip and TB-Biochip-2 kits are already used in seventeen antituberculosis institutions in Russia, as well as in a number of USA and Kyrgyzstan laboratories.

We are also developing biochips to genotype MTB strains by spoligo patterns and identify species of other *Mycobacteria*. The biochip for spoligotyping (SPOLIGO-Biochip) contains probes specific for 43 known unique spacers in the direct repeat region of mycobacterial DNA. The spoligotyping allows identification of the genotypes belonging to the Beijing family as well as differentiation of *M.tuberculosis* from *M.bovis*. The results of genotyping could be also used for epidemiological surveillance.

The increasing number of non-TB mycobacterial infections makes identification of *Mycobacteria* at the species level clinically important. Rapid and accurate analysis is directed to prescribing the effective antimycobacterial treatment, particularly for HIV and TB co-infected patients. The biochip (IMS-Biochip) bears probes to the specific region of the *gyrB* gene. More than two hundred clinical samples and isolates have been tested. The specificity of the method was found to be at least 80%.

WHO GLOBAL SALM-SURV: STRENGTHENING FOODBORNE DISEASE SURVEILLANCE THROUGH TRAINING

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WHO Global Salm-Surv is a capacity-building network consisting of institutions and individuals working in veterinary, food and public health disciplines. The mission of the network is enhancing the capacity of countries to detect, control, and prevent foodborne and other enteric infections. The program promotes integrated, laboratory-based surveillance, promotes outbreak detection and response, and fosters intersectoral collaboration and communication among microbiologists and epidemiologists in human health, veterinary, and food-related disciplines. WHO Global Salm-Surv has six main program components: International Training Activities, External Quality Assurance System (EQAS), Global *Salmonella* Country Databank (CDB), Focused Regional and National Projects, Reference Services and Communication. Since its inception in 2000, WHO Global Salm-Surv has conducted training

courses in 17 sites around the world. Typically, 30-40 participants from 10-12 countries attend a weeklong training course.

Courses are offered at the basic, intermediate, or advanced level to enhance epidemiologic and laboratory capacity. The course content covers a wide range of foodborne disease topics and can be modified to match the needs of individual regions. To date, 63 courses have been conducted, training >1000 participants in over 120 countries. Six courses have been held in the Commonwealth of Independent States (CIS) (four in St. Petersburg and two in Moscow); more than 100 participants have attended these courses.

In addition to the courses, EQAS, the CDB, and the Focused Regional and National Projects enhance laboratory capacity. From 2003-2007, three CIS institutions contributed to the Country Databank; two training sites participate in the EQAS. An enhanced surveillance project was launched in 2006 in the Russian Federation to strengthen laboratory-based surveillance for *Salmonella*.

Foodborne and other infectious enteric diseases are a common cause of illness, disability, and death worldwide. Although preventable, diseases caused by unsafe food are a constant threat to public health security as well as socioeconomic development throughout the world. WHO Global Salm-Surv strives to build capacity for laboratory-based surveillance for foodborne diseases as well as national and international outbreak detection and response through training and communication between human, veterinary, and food sectors.

IMPROVING SURVEILLANCE WITH ELECTRONIC INTEGRATED DISEASE SURVEILLANCE SYSTEM (EIDSS)

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EIDSS version 2.0 strengthens and supports monitoring and prevention of human and animal diseases, including especially dangerous infections. EIDSS integrates human and veterinary data, case plus disease specific investigation, aggregate disease data collection for non-cased based diseases, sample and laboratory data into an integrated data set enhancing decision making, and information analysis capabilities.

The development of EIDSS is based on cutting edge expertise from institutes such as the Centers for Disease Control and Prevention (CDC), Walter Reed Army Institute of Research (WRAIR), and others (more than 75,000 man-hours of expertise has been incorporated into EIDSS design).

EIDSS is a distributed database system with a hierarchical architecture consisting of three primary levels including from the top down the Central Data Repository at a national level, Zonal or Regional Level Epidemiological Offices and Diagnostic Laboratories, District Level public health offices, and other mobile installations. The cohesive information set is continuously synchronized amongst all EIDSS sites within a country providing near-real time information flow to the appropriate organizations.

Human case-based disease data includes demographic data, disease specific clinical data based on standardized case definitions, epidemiological investigation data, sample tracking linked to a specific case, and laboratory tests including results linked to a specific sample. Standardized case definitions and suspected-probable-confirmed case classification along with embedded data checks and rules allow improving disease surveillance accuracy, data quality and hence analysis through surveillance system standardization.

Veterinary (avian and livestock) case based disease data including household details, clinical signs, epidemiological investigation data, laboratory and penside tests, and samples are captured through logically displayed tabs that match paper veterinary investigation forms.

The geographical information subsystem provides real-time mapping of case events as these unfold on vector maps showing settlement, demographic, hydrographic, topographic and other layers.

The laboratory module was designed to mimic the workflow in a laboratory from sample processing and management to test assignment and results tracking. Features such as selecting multiple samples across numerous records to perform common tasks like batch tests enhance the usability of tracking test data in a laboratory. Aliquots and their derivatives are also conveniently accessioned into a laboratory. Tracking of all intermediate diagnostic steps allows the supervisor to easily control test result interpretation correctness thus ensuring better test results quality.

EIDSS includes a tool for Analysis, Reporting and Visualization (along with embedded EPI INFO instrument with 15 years of success in the epidemiology field) that provides features ranging from standard reports to configurable and even ad-hoc reports, data analysis, and more in-depth statistical analysis.

EIDSS is designed with flexibility and scalability in mind, allowing for easy expansion of diseases to include new reportable diseases, customization of clinical signs according to case-definitions, case-investigation forms and reports to meet national and international requirements. Administrators can adjust a wide range of system lookups

and apply customization without intervention of programmers; all modifications are automatically propagated to the sites. The electronic forms can be designed to match the paper forms, making data entry accurate and user friendly.

EIDSS is fully localized including the user interface, database, help, reports, and user manuals. Current languages include Russian, English, Azeri and Georgian; and new languages can be easily added.

The communications and computer infrastructure supporting EIDSS is designed on widely available and supported off-the-shelf components, which makes the system's maintenance and support costs effective. EIDSS incorporates a high level of security that includes reliable data synchronization across multiple administrative levels. Data transferred through the channels is encrypted, while low bandwidth requirements allow the use of inexpensive land or radio links from existing service providers.

A complete training program tailored for EIDSS allows preparing specialists from scratch starting with the introduction to the computers, office packages, Internet and electronic mail, to advanced training on EIDSS and epidemiological analysis. Trainers and trainees are provided with a set of localized training materials. More than 500 trainees have been trained in four FSU countries under this program.

EIDSS assists countries with the IHR 2005 compliance requirements by providing national level authorities with near-real time information on disease cases, and allowing to send data electronically on select diseases from EIDSS via a data transfer module to the Computerized Information System on Infectious Diseases (CISID) operated by the WHO Regional Office for Europe. A similar export module is planned for electronic data export into WAHIS (to be implemented by OIE in 2010).

EIDSS is currently deployed and sustained at numerous sites in the Republics of Kazakhstan, Uzbekistan, Georgia and Azerbaijan as a part of the Threat Agent Detection and Response (TADR) network created by the Defense Threat Reduction Agency (DTRA). At present, Azerbaijan, for example, has more than 100 sites with 200 plus health professionals trained and using EIDSS (complete coverage of health surveillance network).

EIDSS development plans budgeted for the next five years include versions 3, 4 and 5 accommodating new requirements and deployment in the US, FSU countries and globally.

THE ISTC COMPETENCY BUILDING PROGRAM

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Brief assess and summary of the main impacts and results of the ISTC's Competency Building Programs (CBP) are presented. CBP was established in 2004, and has been a fundamental building block of the support ISTC provides to former Soviet WMD experts to support their long-term sustainability.

The main features of the CBP program are described, including its activities and major achievements. Data on achievements was collected from beneficiaries over a period of several months. Market research and statistic analysis are also carried out and included.

The main CBP activities include:

- organization and implementation of business consultations, lectures, seminars and workshops for ISTC beneficiaries;
- development and publication of books, pamphlets, and other reference and study materials for former WMD experts;
- development, publication and implementation of multimedia courses to provide a "mini-MBA" on major business topics for former WMD experts;
- development and creation of ISTC training and resource centers at "hubs" of former WMD knowledge;
- provision of long term training on business disciplines in a cost-effective and flexible distance learning format.

The main results of CBP's training activities to date are detailed. Although it typically takes time for scientists to obtain significant business results following their training, near-term results which have been obtained and can be measured include the development of business plans, submission of Records of Invention or Patent Support Requests. Over time, longer-term outcomes include beneficiary success in obtaining investments (e.g. grants, loans, venture capital) from both government and private sources, conclusion of business contracts, and establishment of revenue-generating businesses.

Specific examples of success are presented.

INTERNATIONAL COLLABORATION IN IMPLEMENTATION OF EDUCATIONAL PROGRAM IN BIOSAFETY AND BIOSECURITY

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In view of the current evolving globalization and the latest advances in life sciences, biosafety and biosecurity or in general biorisk issues are approaching the front line and becoming more significant. Biorisk management comprises issues involving political, economic, medical, engineering, organizational, and training/educational actions targeted at providing as much as possible protection to individuals, society, environment and state against potential or real threats associated with the use of biological agents. Human factors are very important elements. Also, it should be noted that biorisk management is a dynamically evolving scientific and practical discipline, and applied biorisk science is generating new advances almost every year. To ensure employee performance at a high safety level and to provide personnel training for conducting new functions (transfer to a new position or tackling new tasks in the area of biosafety and biosecurity), it is necessary to have initial and periodic training of biosafety and biosecurity specialists in the framework of additional professional education. Therefore, the educational (training) program "Biosafety and Biosecurity Management" has been developed. Basically the program includes main modules of program curriculum that was developed by the Global Partnership Program of Canada. The curriculum and the program are based on the internationally recognized documents. The program's objective is to provide participants with an up-to-date knowledge required for establishing biosafety and biosecurity management systems and guidelines in their areas of activity, as well as for designing new laboratories working with dangerous biological agents. The program's aims are a) to advance professional competency of biological safety specialists in accordance with the international guidelines; b) to provide principles and foundations of building biosafety and biosecurity management systems, procedures and international best practices for working in research laboratories handling agents requiring biosafety levels BSL 1-4 and biotech/microbiology manufacturing facilities and clinical laboratories; and c) to introduce methods and tools for safe pathogen handling based on the international biosafety guidelines for microbiological laboratories and manufacture facilities. The program was developed and implemented in the frame of the international scientific-educational project "Development of an Outline for Biosafety and Biosecurity Program in Russia According to the International Standards". NP TEMPO, a Project Recipient from the Russian side, is responsible for the project organization and implementation with the support of the Global Partnership Program of Canada and the International Science and Technology Center. The program was developed by the specialists from NP TEMPO institutes: I.M. Sechenov Moscow Medical Academy, Research Center for Toxicology and Hygienic Regulation of Biopreparations, State Scientific Center for Applied Microbiology and Biotechnology, N.F. Gamaleya Institute of Epidemiology and Microbiology, State Research Center of Highly Pure Biopreparations in collaboration with the international experts from Global Partnership Program of Canada, and the Swedish Institute of Infectious Diseases. First pilot training course "Train the Trainer in Biosafety & Biosecurity" was conducted from 17-19 November, 2008, at the Institute of Pharmacy of the I.M. Sechenov Moscow Medical Academy. 70 specialists were trained in the frame of the ISTC Workshop "Pilot Stage "Competence building in biosafety and biosecurity by training" during May-July 2009 with the support of the Global Partnership Program of Canada.

RABIES: AN EXPANDING PROBLEM WITH AVAILABLE SOLUTIONS

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Rabies has the highest case fatality rate of any disease known to infect man and yet it is totally preventable. More than 95% of all human deaths occur as a result of exposure to infected dogs and most if not all of the 55,000 estimated human deaths that occur annually could have been prevented. Most of the human rabies victims belong to the poorest segment of the population. They lack the educational awareness necessary to prevent exposures and often do not have the financial resources required to buy the anti-rabies biologicals required to save their lives. Canine rabies continues to spread to new regions, for example the recent introduction of canine rabies into Bali,

previously considered to be 'rabies free', is an indication of how this deadly disease can spread to new areas. In other countries for instance Angola, the re-introduction of canine rabies into a population unaware of the dangers of the disease has caused numerous human casualties. Most of the victims of rabies are children, partly due to their lack of awareness about infected dogs and proper treatment after a wound does occur. The implemetation of a 'One Medicine' approach could reduce the ongoing tragedy of human rabies by eliminating the disease in the canine population. Additionally, educational initiatives that promote responsible pet ownership, dog vaccination programs, and pre-exposure vaccination for indigenous populations living in high risk canine endemic regions would save the lives of many people that need not die of rabies.

GLOBAL SIGNIFICANCE OF BATS AS RESERVOIRS AND VECTORS OF EMERGING ZOONOTIC DISEASES

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Among mammals, bats (order *Chiroptera*) are second only to rodents in their number of species (approximately 1,000). They are particularly numerous in subtropical and tropical areas. The ecology and life history of bats make them particularly likely to serve as reservoirs, and vectors of infectious agents. These characteristics include: 1) long life spans that facilitate long incubation periods and persistence of the infection; 2) flight and the migratory behavior that promote long-distance dispersal of infectious agents; 3) dense aggregations and multiple species within roosts that enhance contact and disease transmission among large numbers of susceptible individuals; 4) use of torpor which may prolong incubation periods and further promote spread of an infectious agent over space and time; 5) bats are often commensal with humans in buildings and on trees in human settlements; indirect contact with humans via common food can occur when bats feed on fruits in plantations.

The best studied infection, associated with bats, is rabies. This fatal encephalitis is caused by viruses from the *Lyssavirus* genus. Bats are primary hosts of 10 out of 11 described lyssavirus species and tentative species (while for the 11th the primary host has to be established yet). In the CIS territory, several lyssaviruses have been identified in bats, including European bat lyssavirus, type 1, Aravan, Khujand, Irkut and West Caucasian bat viruses. Three cases of human rabies, caused by bat bites, have been described in Russia and the Ukraine, although this number may be inadequate due to insufficient surveillance.

Among other viruses, detected in bats and their ectoparasites in the territory of CIS, are flaviviruses (such as tick-born encephalitis and Sokuluk viruses), and presumable bunyaviruses (such as Issyk-Kul, Tahyna and Uzun-Agach viruses). Outbreaks of Issyk-Kul fever among humans have been repeatedly reported from the Central Asia, where they were attributed to the exposure to bats and their ectoparasites.

In other continents bats are reservoirs of various pathogens, which can be potentially translocated to CIS and other areas not only by migratory bats, but also via the bat importation, as had been described for Lagos bat virus, or with other imported animals and travelling humans, initially exposed to bats abroad. As number of emerging pathogens discovered in bats is increasing, public health and veterinary awareness should be put in place for the preparedness, prevention and control of such infections.

ORAL VACCINATION: A PARADIGM FOR RABIES CONTROL IN MESO-CARNIVORE RESERVOIRS

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Access to safe and effective oral rabies vaccines, palatable baits attractive to target species, and efficient bait delivery systems has facilitated a paradigm whereby rabies control is possible in diverse meso-carnivore reservoir species. Examples of oral rabies vaccination (ORV) successes include elimination of rabies in red foxes (*Vulpes vulpes*) in several European countries. In North America, ORV has been applied toward elimination of red fox rabies in southern Ontario, Canada and canine rabies in coyotes (*Canis latrans*) in south Texas, leading to the

declaration of canine rabies free status in the U.S. ORV is also being applied to control rabies in gray foxes (*Urocyon cinereoargenteus*) in the southwestern U.S. and in raccoons (*Procyon lotor*) in the eastern U.S. and the Canadian Provinces of New Brunswick, Ontario and Quebec. In spite of documented successes, ORV in wild carnivores presents many challenges, and the lessons learned can be applied to other diverse geographical locations. Chief among them are needs for: adequate interjurisdictional coordination across political boundaries; adequate surveillance to increase certainty of strategic placement of ORV zones; an understanding of meso-carnivore population structure, dynamics and abundance; and low cost oral vaccine-bait combinations that perform well in all meso-carnivore reservoir species. The recent signing of the North American Rabies Management Plan in 2008 acknowledges that effective rabies control can be best achieved through a continental framework given the geographic distribution of diverse rabies virus variants that are adapted to unique meso-carnivore species or geographic areas in North America. A similar framework could serve as a model for other regions. Application of a direct rapid immunohistochemistry test in several states to complement public health rabies surveillance has led to an increase in rabies suspect animal sampling intensity and geographic scope that has facilitated improved real-time rabies management decisions. Training has been provided by CDC so that use of this rapid diagnostic test may be expanded to other areas in North America, and abroad. Density indexing of raccoon populations demonstrates that raccoons often occur at ~30/km^2 in suburban habitats, an approximately 2 to 3 fold greater abundance than has been observed in most rural habitats. ORV baiting densities are adjusted to target varying raccoon densities in these habitats. Mean post-ORV seroconversion rates for coyotes (63%) and gray foxes (61%) are relatively high compared with raccoons (~30%). The lower rate for the raccoons along with frequent spillover of raccoon rabies into the striped skunk (*Mephitis mephitis*), a species more difficult to orally vaccinate against rabies, points to the need for improvements to the single oral vaccine-bait available (Raboral V-RG®) in the U.S. and the need for continued efforts toward licensing new vaccines and baits. Recent testing of a new oral adenovirus recombinant rabies vaccine in Ontario shows promise for higher seroconversion in raccoons and skunks.

ORV successes and challenges are used to illustrate environmental, ecological, technical, and logistical complexities of rabies management in target meso-carnivore reservoir species in North America, and have relevance for other countries affected by wildlife rabies.

TICK-BORNE ENCEPHALITIS IN THE LAKE BAIKAL REGION: EPIDEMIOLOGY, CLINIC, PROPHYLAXIS

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Tick- borne encephalitis (TBE) is one of the most widespread wildlife zoonoses in the Lake Baikal region. This disease has been registered in all taiga areas of Irkutsk oblast, Republic of Buryatia and Transbaikal territory. TBE was an example of emerging infection 70 years ago. The first 59 TBE cases in Irkutsk oblast were described within 1938-1952. During the later years morbidity rate was growing and had the cycle character. Pronounced increasing of TBE case number was reported in 1960s and 1990s. After 1999 the tendency to diminish the reported case number occurred. Within the recent 10 years 3.0 – 17.0 cases per 100000 of population were registered. The high density of ticks *Ixodes persulcatus (main TBE virus vector)* was observed in many forest areas of the region, especially on the southern Baikal coast (up to 900 ticks on 1 km of linear route). Annually up to 3000-6000 people asked for medical aid after they had been bitten by the ticks in Irkutsk. About 1.0 – 18.6% of the ticks were infected with TBE virus by ELISA. Lethality rate after TBE varied significantly on different territories and in different years. For example, only sporadic lethal TBE cases were reported in Irkutsk oblast during last 10 years. At the same time, in Transbaikal region lethality rate reached 10-15%. Probably it is associated with the spread of different TBE virus variants. The fever-form of TBE was everywhere predominating. For 70 years on the discovery of TBE essential changes have occurred in epidemiology and clinic of the disease. It has resulted from anthropogenic landscape transformation, social processes, an improvement of laboratory diagnosis and prophylaxis.

YOUNG SCIENTIST'S PRESENTATIONS

INFORMATION SYSTEM "EPIDMONITOR" FOR MORTALITY REGISTRATION ASSOCIATED WITH COMMUNICABLE DESEASES

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In biological security systems, the rapid collection of data on mortality from infectious diseases implements an importance role. Under the current system of statistical records of mortality in Russia is not possible, especially if the death certificate of a patient with infectious disease as the main causes of these non-communicable diseases (pneumonia + HIV-infection, acute cardiac insufficiency + flu, etc.). The use of information systems for the registration of causes of death showed a high efficiency. The aim of this work is improving the operational analysis of mortality on the basis of modern information technologies.

We have developed electronic information system (IS) for collecting and processing data on deaths «Epidmonitor». The system is a unique software, which includes a data input interface of a standard death certificate (form 106/u-08, order MH RF from 26.12.2008 № 782n), as well as graphical tools and statistical analysis. Statistical information can be found in the form of interactive reports via web-interface for all registered users with the appropriate access level. Web-oriented system allows to work with the database from any PC with Internet connection. IS Epidmonitor contains a mechanism to automatically alert users by telecommunication channels (e-mail, sms, etc.) on the registration of death certificates for any particular pathology. For example, in the case of registration of the death certificate with HIV infection, the information is automatically been sending to the message controlling organization and/or experts.

To date, IS Epidmonitor is passing test operation in a large city with a population of more than 600 thousands people (Irkutsk). To illustrate the capabilities of IS give the results of 191 death certificates that were selected without randomization for an arbitrary period of time. The proportion of deaths from infectious diseases was 33,5% ± 3,4 (64 out of 191 abs.). The proportion of deaths from tuberculosis - 23,5% ± 3,1, from HIV-infection - 9,4% ± 2,1. For associated causes of deaths: tuberculosis + HIV-infection - 2,1% ± 1,0, tuberculosis + hepatitis C - 1,0% ± 0,7, HIV-infection + tuberculosis - 4,2% ± 1,5. There is a possibility distribution of diagnoses by sex, age, date of death, place of residence and other epidemiological characteristics in different combinations for any period of time. IS Epidmonitor significantly increases the speed and accuracy of statistical information on mortality from infectious diseases and other causes.

ANTIBIBIOTIC RESISTANCE OF *E .COLI* AND *S. AUREUS* ISOLATES FROM OUTPATIENTS IN IRKUSK

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Antimicrobial resistance is a global pandemic. The screening pilot study in Siberian city with population of 600000 was performed. The purpose of study is to evaluate the prevalence of antimicrobial resistance of *E. coli* and *S. aureus* isolated from outpatients. In 2008-2009 1029 samples from 882 patients with various pathologies were received. 58 *E. coli* isolates (98% from urinary tract) and 104 *S. aureus* isolates (69% from respiratory tract) were tasted. For microorganisms' isolation Endo, 6% salt egg yolk and blood agar were used. The semiautomatic analyzer «AutoScan4 System», Siemens (USA) was used for bacteria identification and susceptibility testing. The 95% CIs for the percentage of resistant isolates were calculated.

Of the *E.col* isolates, 38% (31.6-44.4) were resistant to penicillins; 14% (18.6-9.4) to quinolones, 12% (16.3-7.77) to aminoglycozides, and 5% (7.7-2.3) to 3rd generation cephalosporines; all isolates were susceptible to imipinem. 29% (24,6-33,4) were resistant to two or more first-line antimicrobials: 19% (13,9-24,1) were resistant to ampicillin and trimethoprim–sulfamethoxazole and 10% (6,1-13,9) to ampicillin, trimethoprim–sulfamethoxazole and ciprofloxacin. In comparison with EARSS data, the prevalence aminopenicillins resistant *E. coli* isolates in Irkutsk is on the same level with Scandinavian and Baltic countries, but significantly lower than in majority of Central and West Europe countries. The situation with third generation cephalosporines resistance in Irkutsk is better, than in majority European countries.

Of *S. aureus* isolates, 58% (53.2-62.8) were resistant to penicillines; 32% (36.6-47.4) to tetraciclines, 22% (17.6-26.4) to macrolides, 16% (12.4-19.6) to chloramphenicol,. 8% (5.3-10.7) were meticillin-resistant (MRSA). All isolates were susceptible to β-lactamase inhibitor combinations, glycopeptides, nitrofurans and carbapenems. 26%

(21,7-30,3) of isolates were multidrug-resistant, 61.5% (65.3-57.7) β-lactamase positive, 15% (11,5-18,5) resistant to two first-line antimicrobials in ampicillin and eritromycin or ampicillin and ciprofloxacin combinations. In comparison with ERASS data, the MRSA prevalance in Irkutsk is lower than in majority West and Central Europe countries.

Thus the rough data of antimicrobal resistance of *E. coli* and *S. aureus* isolates from outpatients in Irkutsk, necessary for comparing control study planning, were received. According to preliminary data, the antimicrobials resistant isolates prevalence in Irkusk is lower, than in majority European countries.

MULTIDRUG RESISTANT *ACINETOBACTER* NOSOCOMIAL STRAINS COLLECTED FROM RUSSIAN HOSPITALS IN 2003-2008: PHENOTYPES OF THE RESISTANCE

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High level and wide spectrum of the antibacterial resistance among nosocomial strains is world-wide problem. Nonfermenters are very important in this case because they are 35-40% of gram-negative hospital-associated bacterial pathogens. General clinically significant characteristics of Nonfermenters are their natural resistance to many antibacterials, high level of the resistance to disinfectants, and ability for transmission from one patient to another.

Objective of current study is comparative phenotypic analysis of three *Acinetobacter* spp. nosocomial strain collections: collected from Russian hospitals in 2003-2007 (n=73); collected from Moscow Medical Academy (MMA) in 2005-2007 (n=39); and collected from the separate burn center of Chelyabinsk city in 2008 (n=75). *Acinetobacter* spp. strains were 23, 29, and 96 % of total Nonfermenters isolated from named hospitals on the named period correspondingly.

Resistant phenotypes have been estimated using measuring of antibacterial Minimal Inhibitory Concentrations (MICs) by microdilution in broth, accordingly Clinical and Laboratory Standards Institute recommendations.

MICs of antibacterials belong to different functional classes (beta-lactams, aminoglicosides, fluoroquinolons, chloramphenicol, sulfonamides) have been determined. It was shown that *Acinetobacter* spp. strains under study characterized in high levels of resistance to Cefotaxime (93-94% of the strains); to Ceftazidime (65-75%); to Cefepime (40-60%); to Gentamicin (55-78%); to Amikacin (18-50%); to Ciprofloxacin (67-98%); to Chloramphenicol (70-97%); to Sulfonamides (42-93%). Only Meropenem has kept his activity against *Acinetobacter* spp. strain: less than 1% of the strains collected from different Russian hospitals are resistant; excepting MMA hospitals where such characteristic is 30%.

So, dramatically high level of the resistance to common using antibacterials has been determined among *Acinetobacter* spp. agents of nosocomial infections collected from Russian hospitals in 2003-2008.

Further objectives of current study is molecular mechanisms of observed resistance (most effective genes, plasmids, and clones), that will be useful for the understanding of going processes, prediction of future situation, and development of the recommendations for possibly correction of antibacterial therapy.

PREDICTORS OF SUSTAINED VIROLOGICAL RESPONSE OF ANTIVIRAL COMBINATION THERAPY IN PATIENTS WITH CHRONIC HEPATITIS C

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The population of Irkutsk region has a high prevalence of HCV-infection. On the whole the prevalence of anti-HCV is 4,4±0,04%. Among HCV-infected people prevail those who are able to work (65,5%). Chronic liver diseases inflict social and economic damage on people's health. Chronic liver diseases, including viral hepatitis, take the sixth place among the main reasons of death in Irkutsk region. Due to this reason every year the population of our region loose 31232,5 years (years of potential life lost method). Health-related quality of life (psychical, physical, emotional) in patients with chronic hepatitis C is decreasing.

According to the modern recommendation one hundred and fifty patients with chronic hepatitis C have been treated with combination of α-interferon (standard or pegylated) and ribavirin. Sustained virological response (SVR) to the antiviral combination therapy of the patients with chronic hepatitis C is 67,3%. Among the patients with HCV genotype non-1b sustained virological response at the end of follow-up is 84,4±0,03%; among the

patients with HCV genotype 1b sustained virological response is 54,2±0.41%. According to mathematic statistics (Kolmogorova-Smirnova method) these factors significantly are associated with the achieving of a sustained virologic response: genotype other than 1, pretreatment viral load less than 3,3 10^6 copies/ml, small duration of disease (10 years or less), a body weight of 70 kg or less and second blood group. These factors have not been associated with the achieving of a sustained virologic response: gender, body mass index, ALT level, bilirubin, race, stage of fibrosis, Rh-factors, smoking during treatment, consumption of alcoholic drinks and drug abuse before treatment, marital status, place of residence (p>0,05).

PROSPECTS FOR THE USE OF HEPATITIS C VIRUS ENVELOPE PROTEIN HIGHLY CONSERVED SITES IN PEPTIDE VACCINES

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Hepatitis C virus (HCV) is know as a dangerous infectious disease. About 170 million people all over the world are chronically infected by hepatitis C virus, and 3-4 million new cases of infections are registered annually. In most cases the immune system cannot eliminate the virus. Despite of a considerable improvement of hepatitis C treatment, there is still no therapy for general use. That's why the development of vaccines against HCV is needed.

The use of a classical approach of the vaccine design based on the preparation of attenuated or inactivated virus strain is ineffective in case of HCV. Therefore new generation vaccines development is actual. A synthetic peptide-based vaccine is one of the promising variants. Synthetic peptide-based vaccines do not contain bacteria and viruses, products of their functioning, cause strictly specific immune responses and are highly standardized. Difficulties of virus cultivation, storage as well as possibilities of viral replication in a vaccinated organism that exist while using live vaccines are excluded. Several different peptides can be attached to the same carrier, more immunogenic among them can be chosen for the complex formation with a carrier while creating this vaccine type.

In the course of this work two constructs were synthesized, that represented 30-mer and 31-mer peptides containing predicted B- and T-helper epitopes - fragments of HCV E2 protein conserved sites connetcted with a linker. Immunogenicity of the prepared constructions was studied in mice and rats. Both constructs were shown to possess their own immunogenicity and were able to raise antibodies without the conjugation to a carrier protein both against themselves and envelope E2 protein fragments, which form these constructs, and against HCV full-size E2 protein and E1E2 heterodimer. One construct demonstrated the immunogenicity upon administration to mice even in the absence of an adjuvant. One of the reasons of the high immunogenicity of these constructs can be associated with their ability to the oligomerization, which may increase the stability of the constructs to the degradation in tissues of immunized animals. The prepared synthetic peptide constructs can be included into a candidate vaccine against hepatitis C

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TWO PATHWAYS OF SELF-ASSEMBLY RECOMBINANT BOVINE PRION PROTEIN *IN VITRO*

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The existence of prion strains and their capacity of overcoming species barriers seems to point out high conformational adaptability of prion protein. Amyloid fibrils formed by the same prion protein show structural polymorphism which appears to underlie prion strain diversity. It is important to determine how structural polymorphism develops during the process of amyloid fibrils formation by the prion protein.

The goal of the present study is to characterize the fibrilization pathways of the truncated bovine recombinant prion protein (rPrP) at different concentrations of urea, GndHCl , pH and compare formed fibrils with those of other rPrP.

Bovine rPrP protein (102-240 a.a.), produced in Escherihia coli expression system, was purified, using metal-affinity chromatography. Solutions of bovine rPrP at concentration 200 μg⁄ml were incubated in sodium acetate buffer, pH 3,7- 4.5, containing 2-4 M urea or GndHCl in conical plastic tubes, at 37ºC from 1 hour to 7 days. The kinetics of fibrils formation was monitored by electron and atomic force microscopy. Resistance to PK-digestion of developed fibrils was controlled by PAGE and WB.

Bovine rPrP protein (102-240 a.a.) spontaneously assembled in 7 types of fibrils under acid conditions (pH 3,7- 4.5) in presence of 2-4 M of denaturing agents (urea or GndHCl). After one hour of incubation, numerous flexible

worm-like (WL) fibrils (width ~ 12 nm) with no obvious periodic sub- structure along their axis appeared. After 5 hours of incubation, rigid polimorphic fibrils (RP) start to form on the background of WL fibrils. RP fibrils presented: a) straight and flexible ribbon-like twisting structures (length 150-300 nm, cross-over spacing 130-160 nm); b) side-by side associated two filaments (length 120-250nm, width 25-34nm), c) straight, non-periodic fibrils (length 240nm, width 16nm); d) short rod-like(RL) structures (length 25-80nm, width 7.5-24 nm).WL persisted in the solution until the end of incubation. Partial resistance to standard PK-digestion was demonstrated for all types of named fibrils.

The assumption is that the observed aggregation mechanism is concurrent self-assembly of recombinant mammalian prion protein into WL and RP fibrils under above mentioned conditions. We propose two routes of forming WL and RP fibrils. One pathway represents non-nucleated growth of WL fibrils. In contrast to WL structures, the second pathway occurs by nucleation - dependent growth, characterized by lag-phase, resulting in the formation of RP fibrils. Structural polymorphism of fibrils, generated by bovine rec-PrP in vitro, may correlate with the unusual expanded multi-species tropism of infectious BSE-prion protein variants and partially may explain the overcoming of interspecies molecular barriers in vivo.

MONITORING OF TICK-BORNE INFECTION NATURAL FOCI

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This study represents the results of monitoring of *Ixodes persulcatus* ticks picked up in the European part of Russia (Vologda region), the Middle Urals (Sverdlovsk region) and the Western Siberia (Kemerovo region) for detecting the following pathogens: tick-borne encephalitis virus (TBEV), *B. burgdorferi sensu lato,* A. *phagocytophillum*, *E. muris*, *E. chaffeensis*. The ticks have been picked in the 2003-2008 epidemic seasons. We have used the Real-time PCR with fluorescent hybridization probes for detecting the pathogens.

In the natural foci of Vologda region the TBEV prevalence in ticks was established at 2% in 2006-2008. The ticks infected with borrelia were close to numbers that are average for the European part of the Russian Federation – 26%, 21%, 17% (2006, 2007 and 2008 respectively). *E. muris* was detected in 4% of specimens (that test was introduced in 2007), *A. phagocytophillum* – 1%. The results of study have shown that in the natural foci of Sverdlovsk region the prevalence of TBEV in ticks reached in average 4% in the epidemic seasons 2003, 2004 and 2006, and 9% in 2007. The ticks infected with borrelia were recorded in average at 44% of specimens, *E. muris* – at 4%, A. *phagocytophillum* – at 3%. In the natural foci of Kemerovo region the prevalence of TBEV in 2005 and 2008 was 3% and 5% respectively. The ticks infected with borrelia were recorded in 2005 at 60% of specimens, in 2008 – at 30%. We examined the collected specimens for the presence of *E. muris* in 2008 only, the ehrlichia prevalence was 3%, *A. phagocytophillum* was 9% in 2005, and 3% in 2008.

All samples of RNA TBEV we have revealed in the studied regions were attributed to the Siberian genotype. The two major borrelia genospecies detected mainly by PDRF were *B. afzelii* and *B. garinii*. *E. chaffeensis* is an etiological agent of granulocyte disease was not revealed throughout the years. Of great importance is the fact that in the natural foci of studied regions all four agents were detected in ticks *I. persulcatus* and some ticks contained more than one pathogen and therefore each case of disease developing after tick bite shall be considered as a potential mixed infection.

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CERTAIN POINT MUTATIONS IN THE ENVELOPE PROTEIN OF TICK-BORNE ENCEPHALITIS VIRUS ENHANCE NON-VIREMIC TRANSMISSION EFFICIENCY IN A TICK VECTOR

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Tick-borne encephalitis (TBE) is severe infectious disease widely spread in forest regions of Eurasia. The agent of TBE, tick-borne encephalitis virus (TBEV), is transmitted to humans during bite of Ixodid ticks causing about 10 000 cases of disease worldwide annually. The risk of human infection depends on the ability of natural populations of virus to circulate between infected and uninfected ticks.

In present work we studied how particular mutations in envelope protein affect the ability of TBEV to transmit between vector ticks. Methodological approach was based on the genome analysis of nature-derived TBEV isolates with atypical phenotype of envelope followed by site-directed mutagenesis and extensive biological testing of mutants in various models.

We analysed the genome sequences of several TBEV isolates with abolished haemagglutinating activity and identified three unique amino acid substitutions in the envelope glycoprotein, D67G, E122G or D277A, each resulting in an increase of net charge and hydrophobicity on the virion surface. When introduced individually into an infectious clone of TBEV, each substitution inhibited HA activity and reduced mouse neuroinvasiveness. E122G and D277A, but not D67G, reduced virus growth in mammal cell culture whereas in adult unfed ticks virus growth was reduced by D67G but not by E122G or D277A. Each of the 3 mutations increased TBEV reproduction in feeding females of *Ixodes ricinus* ticks. Transmission efficiency from infected to uninfected ticks co-feeding on laboratory mice (non-viraemic transmission) was increased by each individual substitution. Thus, it appeared that certain mutations at envelope protein residues 122 and 277 considerably enhance the viral reproduction in ticks and viral transmission between co-feeding ticks, whereas reproduction of those mutant viruses in mammal models is significantly reduced. In contrast, mutation at residue 67 less affected the reproduction in mammal model systems but decreased virus reproduction in adult ticks.

These results provide valuable information to understand the mechanisms of maintenance of TBEV populations in nature as well as the emergence of pathogenic varians of TBEV.

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FLU BIOCHIP: A TOOL FOR INFLUENZA A VIRUS SURVEILLANCE

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The emergence of novel flu viruses with pandemic potential calls for rapid improvement of virus subtype identification methods to institute influenza monitoring and pandemic preparedness measures. The most common methodologies for identification of influenza virus strains require virus isolation, culture, and characterization by immunoassay. This "gold standard" method for virus identification requires 3 to 7 days to culture virus prior to antigenic testing. Current molecular methods based on reverse transcription and amplification of hemagglutinin (HA) and neuraminidase (NA) genes offer higher sensitivity and speed for virus identification, so the results can be obtained in a few hours. However, certain limitations in the number of simultaneously amplified genomic targets in one amplification reaction limit the number of flu subtypes detectable in a single assay.

We propose a rapid and efficient method for molecular subtyping of influenza A virus based on hybridization with low-density oligonucleotide biochip. The method employs a gel-based biochip technology, developed in the Engelhardt Institute of Molecular Biology. The whole procedure takes about 10 hours, and it enables one to identify 15 molecular variants of HA and 2 variants of NA. We used the developed biochip to identify the causative agent of local epizooties in the Novosibirsk region (2005), Astrakhan region (2005), republic of Tuva (2006) and the Primorye Territory (2008). RNA samples were isolated from suspensions of internal organs of dead birds. For all outbreaks, the "bird" flu H5N1 was identified as the causative agent of epizooties and the produced results were in full agreement with those obtained by the traditional immunological methods. Investigations of epizooty in the Primorye Territory, led us to conclude that the A/Primorye/H5N1/2008 strain differs markedly from the H5N1 strains, which were identified in earlier epizooties. It belongs to a more virulent phylogenetic branch. To assess the potential of the developed method for analysis of clinical samples isolated directly from humans, we studied 15 samples of viral RNA isolated from nasopharyngeal swabs. These specimens were obtained from patients hospitalized with acute symptoms, of respiratory viral infection. In 7 cases, influenza virus subtype H3N2 was identified, our results being in full concordance with the diagnostic amplification test for influenza A virus. As the epidemiological *situation with the «swine» flu* **is** *worsening steadily with the spread of* A/California/H1N1/2009 in human population, we performed a biochip analysis of RNA samples isolated from different strains of H1N1 subtype provided by the D.I.Ivanovskiy Institute of Virology. The viruses were previously cultivated in chicken embryos. Analysis showed that the developed biochip allows to distinguish the strains of H1N1 subtype of different origin on the basis of their hybridisation pattern. The distinct differences in hemagglutinin and neuraminidase patterns of human H1N1 and novel H1N1 enables one to unambiguously differentiate these strains.

Introduction of the developed method for influenza subtyping in laboratory practice may substantially improve influenza A epidemiological surveillance. The ability to rapidly identify new, potentially pandemic strains of influenza virus will allow public health service to more rapidly respond and, potentially, reduce the spread of the disease.

POSTER PRESENTATIONS

EPIDEMIOLOGICAL AND CLINICAL FEATURES OF THE INTRODUCED MALARIA IN IRKUTSK AND THE IRKUTSK REGION

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One of the major problems of the public health service of Irkutsk and the Irkutsk region is prevention of reintroduction and spreading of malaria. Arrival of foreign citizens (workers), returning of our experts and tourists from endemic in malaria countries as well as the population shift from the former Union's southern republics have always contributed to the delivery of malaria into the city and demanded taking certain preventive measures. In the present message we submit some data about malaria introduction into the Irkutsk region during the last 11 years.

During the period from 1997 to 2008 57 cases of the introduced malaria have been registered in the city and the region. According to the presented data, there are marked specificities of introduction during different periods. The greatest incidence of malaria was in 1998-2001 due to its introduction by migrants from Tajikistan and Azerbaijan. Since 2002 the incidence of the cases has been steadily decreasing. And during the last 2.5 years no cases of malaria were registered. In 70 cases malaria was introduced from Tajikistan, in 14 - from Azerbaijan, in 1.7 - from Uzbekistan and Northern Korea, in 12.3 - from the African countries. In the patients' age structure the group aged 21-30 years prevails. During the period of 1997 - 2006 the delivered cases were distributed by the specific structure ofactivators as follows: P.vivax 93%, P. falciparum - 5%, and P. ovale - 2%. From 57 delivered cases registered in thecity during the period from 1997 to 2006 there were 91 cases of a middle weight, 5 - of a severe one and 4 - of a mild one.

The clinical characteristics of tertian malaria. In non-immune persons subjected for the first time the illness begins with prodrome malaise, weakness, headache, backache, pain in the extremities. In most cases typical malaria attacks follow an atypical 2-3-day rise of the body temperature to 38-39 degrees Celsius. Later on malaria attacks are clinically precisely expressed, come with equal intervals and more often at the same day time (between 11 and 15). In the severecourse of the disease the chill is accompanied by expressed weakness, sharp headache, rheumatic pains, accelerated respiration and repeated vomiting. Patients have heavy chill. They turn pale. The body temperature quickly reaches 38-40degrees Celsius. Chill is followed by fever. The face reddens, the skin becomes hot. Patients complain of a headache, thirst, nausea, tachycardia. The arterial pressure decreases up to 105/50-90/40 mm of mercury. Dry ralcs indicating the development of bronchitis are heard over the lungs. Almost all patients have moderate swelling of the stomach and watery stools. Duration of chill is 20-60 minutes, that of fever - 2-4 hours. Then the body temperature decreases and becomes normal after 3-4 hours. During this period there is hyperhidrosis. Feverish attacks last 5-8 hours. Intermission lasts about 40-43 hours. The liver and spleen enlargement is revealed during the first week of the disease. Anemia develops gradually. In the natural course of the self-limited disease feverish attacks last 4-5 weeks.

The clinical characteristics of tropical malaria. In people subjected lor the first time such prodromal phenomena as a general malaise, hypcrhidrosis, loss of appetite, nausea, loose stool, 2-3-day rise of the body temperature to 38 degrees are marked. In the majority of non-immune persons the onset of the disease is sudden and is characterized by a moderate chill, high fever, excitation, bad headache. pains in the muscles and joints. During the first 3-8 days fever is constant, then becomes remittent. At the height of the disease the attacks of fever have some specific features. There is no strict periodicity in the onset of fever attacks. They can begin at any time but more often arise during the first half of the day. Decrease of the body temperature is not accompanied by hyperhidrosis. feverish attacks last longer than a day (about 30 h), the apyrexia periods are short (less than a day). During the chill and fever periods the skin is dry. There arc tachycardia and significant decrease of the arterial pressure to 90/50-80/40 mm of mercury.Respiratory rate increases, there is a dry cough, dry and moist rales, showing the development of bronchitis or bronchopneumonia. Dyspeptic phenomena such as anorexia, nausea, vomiting, epigastric pains, enteritis and enterocolitis often develop. The spleen enlargement is observed from the first days which is shown by pains in the left hypochondrium growing on deep breath. By the 8-10th day it is easily palpated, its edge is dense, smooth and painful. In the blood serum a direct and indirect bilirubin content increases, aminotransferases activity increases moderately by 2-3 times. Normocytosis anemia is revealed from the first days of the disease. On the 10-14th day hemoglobin content usually decreases to 70-90 g/f the erythrocyte number decreases to 2.5-3.5 per 10*12/l. leucopenia and neutropenia, relative lymphocytosis and nuclear shift towards the young forms of neutrophils are marked, reticulocytosis and the ESR increase. In the peripheral blood

plasmodia in a ring-stage are revealed from the first days. According to the clinical manifestations malaria ovale is similar to tertian malaria. The distinctivefeature is the onset of attacks in the evening and night hours, 'the treatment was performed by the standard scheme (chloroquinc within 3-5 days and primaquinc within 14 days). Feverish reaction was stopped on the 2nd, less often on the 3d day of the treatment. Recurrence was observed only in two persons and was connected with primaquine. Considering the epidemiological situation on malaria delivery supervision of the carrier (An. maculipennis) is conducted, and measures against it are taken. Under the conditions of financial crisis the increase of population shifts and malaria delivery from endemic countries is possible.

Thus the following is necessary: duly revealing patients with malaria and parasite carries; carrying out laboratory study of people arriving from endemic areas if they have temperature, chill, malaise, anemia, liver and spleen enlargement, herpes irrespective of the initial diagnosis within 3 years after arrival, as well as those leaving their regions and having fever for more than 3 days with the unstated diagnosis.; on delivery of tertian malaria (vivax) during the transmission season taking antimalaria measures in the focus is necessary during the following epidemic season as well due to the presence of the disease after a long incubation; timeliness of treating the revealed patients; carrying out entomological supervision over a carrier in every administrative unit and actions to decrease its number; treatmcnt-and-consullation work on prevention of malaria among the population.

STUDYING TRENDS OF ACTIVITY OF PLAGUE NATURAL FOCI IN GEORGIA

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In Georgia two natural foci of plague are currently recognized: the foothills of the plains and the high mountainous areas. Though endemic foci of plague have existed in Georgia for several centuries (possibly since the 1st pandemic), no human plague cases from the FSU were reported to WHO until the late 1989 (i.e., before "glasnost"). The National Center for Disease Control and Public Health of Georgia (formerly the Georgian Antiplague Station) had a rigorous and very active plague surveillance program during the communist regime. The break-up of the USSR and the resulting poor economic conditions caused the surveillance for plague epizootics in Georgia to be drastically reduced. Only recently surveillance on plague natural foci became possible.

It is very important to understand possible threat from natural focus, its activity, as having uncontrolled, major endemic foci of plague in regions close to main urban areas (e.g., the many plague foci in the Georgia) creates the risk of major outbreaks or an epidemic of human plague suddenly emerging in those regions.

The goal of current investigation is to study the fluctuation of *Y. pestis* genetic populations in the endemic foci, and the emergence/prevalence of major types or clusters of *Y. pestis*. Developing epizootics in Georgia had cyclic character with rises and falls, and happened, especially in high mountainous plague focus on average every 5 - 7 years.

Based on results of field works in plague foci during last 60 years we tried to draw plague epizootics algorithm. General trends in epizootics rising were followed; attempts of mathematical modeling were carried out.

BENEFITS OF THE NEW ORAL RABIES VACCINE RABIVAC-O/33 FOR RABIES CONTROL IN WILDLIFE

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As many other countries, Russia is enzootic on rabies. The main virus hosts are wild carnivorous: red foxes (*Vulpes vulpes*), raccoon dogs (*Nyctereutes procyonoides*), arctic foxes (*Vulpes lagopus*), jackals (*Canis aureus*) and corsac foxes (*Vulpes corsac*). Most of the countries in the Western Europe eliminated rabies by means of oral vaccination. Two oral rabies vaccines have been used for wildlife vaccination in Russia. These vaccines were manufactured using Russian vaccine rabies virus strains which were quite pathogenic in laboratory experiments for different mammalian species, but there is no information whether these strains caused rabies in wildlife or not.

The new oral rabies vaccine "Rabivac-O/333" was developed at the Pokrov Plant of Biologics in Russia during the implementation of ISTC #2090/BTEP #50 Project. The vaccine is the fishmeal bait contained plastic blister filled with 2.0 ml of ERA G333 rabies virus strain. The ERA G333 virus was created at CDC by Dr. Wu and Dr. Rupprecht and kindly provided us within collaborative project. This is ERA strain but arginine at position 333 of glycoprotein ectodomain is replaced with glutamic acid (all three nucleotides were replaced to minimize a possibility of reversion).

Our study showed that this strain is avirulent for 11 species of target and laboratory species even if inoculated intracerebrally and caused rabies only in suckling mice. ERA G333 rabies virus strain showed high immunogenicity for 35 red foxes inoculated orally in laboratory experiment. All animals developed rabies virus-neutralizing antibodies (VNA) with titers ≥0.5 IU on the 30th day after vaccination and survived challenge with lethal dose of street rabies virus conducted on the 180th day.

Field trial of baits acceptance by wild animals and immunogenicity of oral rabies vaccine "Rabivac-O/333" was carried out in Krasnodar region situated in the South of European part of Russia. 2,800 baits were distributed at the area of about 100 sq.km where 10 control points were arranged for evaluation of vaccine acceptance. The consumption of baits was registered at control points every day by the presence of baits, blisters, and traces of animals. About 30% of baits were consumed at the first day after baiting and by the 4th day 99.3% were eaten. Five wild raccoon dogs were captured at the territory of vaccination before baiting for immunogenicity study. Animals were kept in cages near hunting lodge and were immunized by feeding 1 bait of "Rabivac-O/333" per animal. Raccoon dogs were negative for rabies virus-neutralizing antibodies before vaccination. All animals developed rabies VNA with titers ≥0.5 IU on the 30th day after vaccination.

Considering the vaccine safety and appropriate immunogenicity for wild carnivorous as well as the results of study of baits consumption by wild animals received in our experiments it can be concluded that oral rabies vaccine "Rabivac-O/333" is safe, immunogenic, and attractive for target species and suitable for wildlife oral immunization.

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THE FORECAST OF OCCURRENCE PANDEMIC INFLUENZA VIRUSES: PERIODIC REEMERGING OF NEW/OLD VIRULENT STRAINS H1N1. THREAT OF EMERGING NEW RECOMBINANT INFLUENZA VIRUSES, CAPABLE TO OVERCOME INTERSPECIFIC BARRIERS IN PREPANDEMIC PERIOD. DEVELOPMENT OF NEW APPROACHES FOR CREATION OF GEOGRAPHICAL AND POLYVALENT VACCINES OF NEW GENERATION

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Recent years were marked by growing anticipation and fear of a flu pandemic caused by one of high pathogenic avian influenza (HPAI) viruses. Unexpected recent emergence in Mexico and the United Sates of swine-origin influenza A H1N1 virus capable of effective human-to-human transmission and its rapid worldwide spread caught health officials and epidemiologists off guard. Detailed genetic analysis indicated that the new virus was derived from several viruses circulating in swine and that its genomic segments have been circulating undetected for an extended period suggesting that the reassortment of swine lineages may have occurred years before emergence in humans . This provides additional evidence that mixing, reassortment and, possibly, recombination of influenza genetic elements in swine can lead to emergence of viruses with pandemic potential in humans.

Several of past pandemics, in particular in 1957, 1968 and 1977, have been caused new influenza viruses originated in Southeast Asia, in particular in China. Recent isolation of avian-like H1N1 virus from pigs in China that appears to have originated from European swine H1N1 viruses and new H1N2 reassortant viruses carrying gene segments from classical swine, human and avian lineages supports long standing hypothesis that swine can serve as "mixing vessels" for generation of pandemic influenza viruses. While the emerged pandemic swine flu virus appears to cause generally mild infection, further adaptation to humans and increase in its pathogenicity is anticipated and widely feared due to its lready acquired efficient human-to-human transmission. On the other hand, reverse transmission from humans to pigs has been already detected in several countries.

The already highly contagious virus possesses two segments that originated from avian lineage, thus its return back into "the mixing vessel" may lead to further reassortment with HPAI and to better adaptation to mammalian hosts. These findings underscore the urgent need for systematic worldwide surveillance of influenza in swine, especially along natural bird migration routes from Southeast Asia to Europe.

This project is designed to establish systematic sampling and characterization of influenza viruses from migrating waterfowl , from pigs in pig farms and from reported human cases. The following Specific Aims are defined for this study:

1. To organize systematic collection of samples in Novosibirsk city area, in the southern part of the Novosibirsk oblast bordering the north-eastern part of Kazakhstan, in Almaty city area, in the Almaty region, and in eastern Kazakhstan along routes of bird migration from China to Eurasia through the Jungar gates involving lakes Alakol, Sasykkol, long the Black Irtysh river leading to lakes Zaisan, Markakkol, along the Ili river, and lakes Kapchagai and Balkhash.
2. To detect and amplify influenza virus isolates in chick embryos, primary chick fibroblasts or in MDCK cell lines.

3. To characterize and serotype virus isolates using hemagglutination inhibition, ELISA and neutralization assays with type-specific control reference sera.
4. To characterize virus isolates by sequencing of genome segments amplified by RT-PCR to identify new reassortants and new genetic variants with predicted increase in mammalian virulence and transmissibility.
5. To characterize virulence and transmission of selected influenza virus isolates with predicted increased virulence and transmissibility in the ferret model of influenza developed at the Southern Research Institute (Birmingham, AL, USA) under contract with NIAID.
6. To develop predictive algorithm for timely design of influenza vaccines effective against emerging viruses with epidemic and pandemic potential.

NOVEL CONJUGATE OF MOXIFLOXACIN AND CARBOXYMETHYLATED GLUCAN WITH ENHANCED ACTIVITY AGAINST MYCOBACTERIUM TUBERCULOSIS

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Mycobacterium tuberculosis is an intracellular pathogen that persists within macrophages of the human host. One approach to improving the treatment of tuberculosis (TB) is the targeted delivery of antibiotics to macrophages using ligands to macrophage receptors. The moxifloxacin-conjugated dansylated carboxymethylglucan (M-DCMG) conjugate was prepared by chemically linking dansylcadaverine (D) and moxifloxacin (M) to carboxymethylglucan (CMG), a known ligand of macrophage scavenger receptors. The targeted delivery to macrophages and the antituberculosis activity of the conjugate M-DCMG were studied in vitro and in vivo. Using fluorescence microscopy, fluorimetry, and the J774 macrophage cell line, M-DCMG was shown to accumulate in macrophages through scavenger receptors in a dose-dependent (1 to 50 μg/ml) manner. After intravenous administration of M-DCMG into C57BL/6 mice, the fluorescent conjugate was concentrated in the macrophages of the lungs and spleen. Analyses of the pharmacokinetics of the conjugate demonstrated that M-DCMG was more rapidly accumulated and more persistent in tissues than free moxifloxacin. Importantly, therapeutic studies of mycobacterial growth in C57BL/6 mice showed that the M-DCMG conjugate was significantly more potent than free moxifloxacin.

Tuberculosis (TB) still remains a leading cause of death among bacterial infections worldwide. The causative agent of TB, Mycobacterium tuberculosis, is a facultative intracellular pathogen that primarily persists within macrophages in the human host, the cells that are involved in dissemination of the infection. Intracellular bacilli are generally more difficult to treat because of the limited access of drugs to bacteria within macrophages, necessitating chronic treatment with high therapeutic doses for effective control and treatment of the disease. Moreover, TB treatment problems are exacerbated in AIDS patients undergoing chronic, combined therapies for human immunodeficiency virus infection and attendant opportunistic diseases. The increased prevalence of single- and multiple-drug-resistant forms of TB has further limited treatment options.

Many of these drug therapy problems could be attenuated or potentially eliminated through selective delivery of anti-TB drugs into infected macrophages, the primary site of infection. Unlike many other cell types, macrophages are known to express high levels of specific receptors on their plasma membrane that bind and internalize their specific target ligands through a variety of uptake mechanisms. For example, specific polysaccharide receptors (e.g., mannan receptors, glucan receptors, and galactan receptors) generally bind neutral polysaccharides of bacterial origin and internalize these ligands via specific receptor-mediated phagocytosis. Additionally, macrophage scavenger receptors bind anionic macromolecules and use phagocytosis for ligand uptake. These receptors have a high affinity for a wide spectrum of polyanionic molecules including negatively charged polysaccharides (e.g., dextran sulfate, heparin, bacterial lipopolysaccharides, and others), modified lipoproteins, and proteins. Chemical labeling of glucans with carboxy or sulfate groups can lead to their selective accumulation by tissue macrophages via scavenger receptor-mediated uptake. The affinity and selectivity of these macrophage receptors may offer a unique opportunity for the selective delivery of anti-TB agents conjugated to macrophage receptor ligands. Such an approach might allow the high levels of anti-TB drugs to be concentrated in the main cellular reservoir of the tubercular bacilli, the macrophage, while minimizing exposure of other host tissues to high levels of potentially nonselective and/or toxic agents. In fact, it has been demonstrated recently in a murine TB model that a mannosyl-dextran conjugate of norfloxacin exerted a higher anti-TB effect than norfloxacin alone. Also, a p-aminosalicylic acid-bovine serum albumin

antibiotic conjugate had superior efficacy compared to the free drug when tested in murine macrophages as well as a guinea pig TB infection model.

Previously, we demonstrated that chemical modification of glucans with carboxymethyl groups leads to their selective uptake by tissue macrophage scavenger receptors of the A type (ScR-A). In this study, we prepared a conjugate of the antibiotic moxifloxacin with carboxymethylglucan (CMG), investigated the targeted delivery of this conjugate to infected macrophages, and evaluated its antituberculosis activity. Here we show that the moxifloxacin-CMG conjugate has enhanced uptake into macrophages and increased antimycobacterial activity relative to the free drug.

CHARACTERISTIC OF STREPTOCOCCUS (GROUP A) ISOLATED FROM PATIENTS WITH GENERALIZED FORMS OF INFECTION

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The spreading of generalized forms of group A streptococcal (GAS) infections in hospital inpatient settings in Moscow (2002-2003; 2008-2009) was studied. Findings suggest that these forms are widely spread: 1064 cases were diagnosed with mortality rate 92.6 % (986 cases). We performed the genomic molecular analyses of GAS strains isolated from patients with severe infection. Such analyses imply two objectives:

- to identify *emm*-types of GAS strains**;**
- to see whether and which erythrogenic toxins (*speA, speB, speC*) are present.

To identify microorganisms as GAS we applied the method of latex-agglutination with the help of Slidex Strepto-Kit ABCDFG (bio Merieux, France). The methods of DNA isolation, *emm*-typing and *speA-, speB-, speC-* detecting are given in. We used those methods in accordance with international protocols.

Since the only gene always present in the strains was *spe B* there were four combinations of erythrogenic toxins possible: *speA, speB, speC; speA, speC; speB, speC; speB.* Our study revealed all of them. *emm*-typing showed the GAS strains (16 cultures, isolated in 2009) could be divided into two groups – those found before in the sick and carriers and those revealed for the first time. The GAS strains of the first group contain *emm 59, emm 41, emm 74, emm 60* and some others as markers; strains of the second – *emm 17, emm 66 (90)*, the latter being revealed in strains of four epidemiologically unrelated cultures.

Wide spreading of generalized forms of GAS infections in Moscow inpatient settings necessitates permanent monitoring of typical and molecular-genetic characteristic features of Streptococcal cultures isolated from patients. It will enable us to improve clinical-laboratory diagnostics of invasive forms of the infection and to better predict the further developments in epidemiological situation.

BURDEN OF GASTROINTESTINAL ILLNESS IN GEORGIA

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The Republic of Georgia suffered a catastrophic decline in standards of living since 1991. A substantial proportion of adults are believed to be infected with *Helicobacter pylori*, an organism causing peptic ulcers and epigastric pain. Since no published data exist on the burden of epigastric pain or other gastrointestinal illness in Georgia, or other countries in the Caucasus mountains region of Eurasia, we conducted a national household survey to determine their prevalence.

Households were selected using a two-step cluster sampling methodology. Administrative units were randomly selected from a variable number of strata in ten regions according to probability proportionate to size methodology; villages or census units were then randomly selected. Within each village or census unit, a randomly generated start address was specified and subsequent households identified based on a specified “random walk” sampling algorithm.

Data were collected on 11,188 individuals from 2,742 households. At least one episode of diarrhea in the previous month was reported for 2% of all household members, a rate of 0.3 episodes per person per year. The prevalence of diarrhea was highest among children <5 years of age (8%), followed by persons ≥65 years of age (4%) and those 5-14 years of age (3%). Of those with diarrhea, 8% reported bloody diarrhea. Recurrent gnawing or

burning epigastric pain was reported for 7% of household members; rates were higher in males (8%) and those 45 to 64 years of age (13%).

These data provide useful baseline information on the burden of gastrointestinal illness in the Republic of Georgia. The overall prevalence of diarrhea is within the range reported for developed countries. Diarrhea is and was an important cause of illness in children. Epigastric pain suggestive of peptic ulcer disease was reported mostly among males over 45 years of age.

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SOFTWARES AND EPIDEMIOLOGICAL DATA BASED IN SURVEILLANCE

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Epidemiological intelligence (EI) is the most important methodological principle of epidemiology. EI serves as the main component in the epidemiological investigation and epidemiological diagnosis. Depending on goals, objectives, situation in the development of military actions, strategy and tactics, EI has to be divided into the following characteristics: tactical EI (routine), operative EI (in case of epidemiological actions), strategic EI (area's characteristics, including bordering ones, strategic epidemiological register, epidemiological and medicogeographic atlases).

Adequately and comprehensively constructed epidemiological data base permits considerably increase surveillance effectiveness. Both these direction have to include the following main components: social characteristics; demographic characteristics; natural conditions (climate and landscape); sanitary characteristics; epidemiological situation; characteristics of health facilities; health network and its reserves; vehicles and communication, etc.

Epidemiological database was created with appliance of the EpiInfo and GIS software. Computer based data were successsfully applied in the practice.

Example 1. In 2003 Tularemia water born outbreak was registered in Fantan village in Armenia; of 232 cases, 59 were children under 14 years of age. All patients were detected through door-to-door visits and appropriate treatment of those infected along with preventive antibiotic treatment of village population was organized. Taking into consideration a persisting Tularemia threat in this village the population vaccination was carried out. Case based data were entered into computer for daily analysis (in EpiInfo for Windows). Anti-epidemic measures were carried out based on permanent (annual) and daily computer data analysis. It created an opportunity for appropriate planning of actions for the next day and operative decision-making.

Example 2. Choice of indicators for assessment of high morbidity and outbreaks of enteric infections requires very serious and comprehensive data base concerning epidemiological features of this group of infection. The ecology-geographical features in Gyumri (disaster zone after the earthquake of 1988) promote outbreaks of enteric infections. On the basis of defined epidemiological parameters during investigations of data within 20 years by appliance of GIS technologies became possible (probable) to predict years of biological activity for various enteric infections, that has enabled to divine a probable place, time, high morbidity and to undertake preventive anti-epidemiological measures against particularly expected infections.

Data bases and applied softwares are interconnected with epidemiological surveillance standards.

PREVALENT MECHANISMS OF MULTIDRUG RESISTANCE IN ENTEROBACTERIACEAE NOSOCOMIAL STRAINS: GENES, CASSETTES, PLASMIDS

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Enterobacteriaceae agents are responsible for approximately 20% of nosocomial infections in Russian hospitals during the period 2003-2007. In this study, 670 nosocomial isolates of *Escherichia coli* (n=264), *Klebsiella pneumoniae* (n=258), and *Enterobacter* spp. (n=148) from 14 Russian cities were analyzed using molecular methods. All strains under study were resistant to one-three Cephalosporin III-IV (cefotaxime, ceftazidime, cefepime),

and to some of antibacterials belonged to other (non-beta-lactam) functional groups (aminoglycosides, quinolones, sulfonamides, chloramphenicol). Multidrug resistant (MDR) phenotype (resistance to three and more classes of antibacterials) has been detected for 14% of *E. coli* (n=36), 8% *K. pneumoniae* (n=41), and 28% *Enterobacter* spp. (n=41). This data may be compared with the data published in USA, namely 2.0%, 13.3%, and 5.9% accordingly[4]. Moreover, remarkable part of the strains under study have been estimated as extreme drug resistant (XDR) bacteria (resistant to five classes of antibacterials simultaneously): 9% of *E. coli* (n=24), 14% of *K. pneumoniae* (n=35), and 24% of *Enterobacter* spp. (n=353).

Resistance to beta-lactams has been shown mainly coding by *bla*CTX-M genes (n=537, 80% of the strains). So, CTX-M-producing strains have greatly increased in Russian hospitals since 1997-1998 when such index was ~35% (Edelstein M., et al., 2003). This data is in accordance with all-Europe pandemic dissemination of the named genes. Moving forces that provide such successful dissemination among nosocomial strains are both: genetic environments surrounding *bla*CTX-M genes, and successful conjugative plasmids.

Study of *Inc* groups for conjugative plasmids has shown that *bla*CTX-M genes have been located mainly on the plasmids belonged to *IncF, IncL/M*, *IncA/C, IncN*, and *IncI1.* Interestingly, that some of conjugative plasmids either have been in cooperation for transfer, or has been hybrid in their nature.

Genetic determinants of the resistance to other antibacterial classes have been located mainly as cassettes consisting of class 1 and class 2 integrons. Seven variants of integron insertions have been identified for CTX-M-producing strains: *aadB* (0.7 Kb); *aadA* (1 Kb); *aadA1* (1 Kb); *aadA2* (1 Kb); *aac(6')Ib Ib11* (1.2 Kb); *dfr-aadA5* (1.7 Kb); *dhfrXII-aadA2* (1.9 Kb); *dfrA12-aadA2* (2 Kb); *dfrA5-ereA2* (2 Kb); *oxa1-aad(3')* (2 Kb); *cmlA1- aacA4* (2.3 Kb); *aac(6)Ib-cmlA1-aac(6)Ib* (2.3 Kb).

Variability found in the genetic environments surrounding *bla*CTX-M genes subdivided into rearrangements of *ISEcp1* mobile element upstream of *bla*CTX-M (deletions; and insertions of *IS26, IS10, IS1*, or *resolvase Tn3*); length of the short specific nucleotide sequences between *ISEcp1* and *bla*CTX-M (19 bp; 42 bp; 45 bp; 48 bp; and 127 bp), and variations in the downstream flanking region (*ORF477* and *mucA* sequences; IS903 element, intact or partially truncated).

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ESTABLISHMENT OF A DATA ANALYSIS AND MODELING CENTER TO ASSESS THE ASSOCIATIONS BETWEEN WEATHER AND WATERBORNE INFECTIONS AND THE PROBABLE IMPACTS OF FORECAST CLIMATE CHANGES ON THESE INFECTIONS IN RUSSIA (ISTC-3796)

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The main objectives of this project are to: (1) establish a center for data analysis and modeling of weather, drinking water quality and infectious disease data to assess associations between extreme weather events and waterborne infections; (2) using existing models of global climate change, forecast the effects of predicted increases in ambient air temperature and extreme weather events on the burden of waterborne gastrointestinal infections in Russia; (3) using waterborne infections as an example, develop methodologies to forecast climate-related changes in other infectious diseases.

To achieve these objectives, the project has four specific aims: (1) prepare databases of hydrometeorological, water quality and health data from several selected Russian cities, which represent different geographic regions of Russia and use surface water sources for their water supplies; (2) analyze short-term, seasonal and mid-term patterns in environmental and health data to determine associations between various hydro-meteorological parameters and specific illnesses; develop multi-level spatio-temporal models incorporating data on these cities; (3) develop pilot population dynamic models of the infectious process for selected infections; (4) using the associations between extreme weather events and illness derived from historical data and the existing scenarios of climate warming and its effects on weather variability and frequency of extreme weather events, estimate the expected increase in waterborne illnesses. The following cities have been selected to participate in this project: Novosibirsk, Barnaul, Vladivostok, Chelyabinsk, Yekaterinburg, and Krasnoyarsk.

Meteorological data have been acquired for all of these cities from the Russian Weather Archive for the period January 01, 2000–December 31, 2007 and from the US National Climatic Data Center for the period January 01, 1948–February 01, 2009.
Data on water quality for Chelyabinsk have been collected for the period January 01, 2002 – June 30, 2008; for Yekaterinburg, for January 01, 2001 – November 30, 2008; for Krasnoyarsk for January 01, 2006 – June 30, 2008; for Barnaul for January 01, 2008 – December 31, 2008, and for Novosibirsk for March 07, 2002–January 31, 2009.
Data on potential waterborne infections for Barnaul were collected for 2006 - 2009 (13,023 cases of illness); Novosibirsk, for 2008–2009 (8,400 cases); additional data on norovirus infection for June 2003–May 2004 (662 cases) have also been acquired; this databases will be expanded to cover a 4-year period; Yekaterinburg: January 2005–October 2008 (58,278 cases); Vladivostok: October–December 2008 (820 cases); Chelyabinsk: 2008-2009; Krasnoyarsk: 2008-2009 (2,216 cases).
The database has been developed using MS SQL Server Studio 2005. The following work is ongoing: preprocessing of climatic data from Novosibirsk, Barnaul, and Yekaterinburg for 2005–2007; preliminary time-series data analysis; preliminary qualitative and quantitative analysis of the infectious diseases and water quality data for Novosibirsk, Barnaul, and Yekaterinburg. New data are being acquired, entered into the database, and checked for quality and consistency. Infections data are being re-coded using ICD-10 codes.
The database under development is unique in that it incorporates data for six large cities in the Asian part of Russia over many years. Weather, water quality and health (waterborne infections) data are being collected and processed. Preliminary analyses of these data are ongoing.

FUNCTIONAL ACTIVITY OF DENDRITIC CELLS FROM PATIENTS WITH PULMONARY TUBERCULOSIS

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Dendritic cells (DC) are professional antigenpresenting cells that act as a first line of defense against microbial agents. Defects of protective mechanisms of the DC in response to multidrug-resistant (MDR) tuberculosis (TB) are still poorly understood. DC pulsed with antigens of either microorganisms or cancer cells can be used in immunotherapy. Therefore the objective of the current study was to characterize the phenotype and cytokine production of monocyte-derived dendritic cells (mdDC) in patients with TB to assess their possible use in immunotherapy of TB.

Patients with TB were divided into 2 groups: Group I — patients with MDR (n=12) and Group II — patients without MDR (n=8). Control group (C) consisted of 23 donors. PBMC were separated from whole blood by density centrifugation. Monocytes were isolated from PBMC using adhesion to plastic flasks and were cultured for 6 days in RPMI-1640 with 10% FCS and rhGM-CSF and rhIL4 to obtain immature DC (iDC)[2]. iDC were treated with rhTNF-alpha for 24 hours to produce mature DC (mDC). Cell phenotyping was performed using antibodies to CD1a, CD14, CD80, CD83, CD86 and HLA-DR antigens[3]. Production of IL10 and IL12p40 by mDC was measured in cell-culture supernatants by ELISA. Mann-Whitney's U-test was used for statistical analysis.

Expression of CD14 was increased on iDC and at the same time expression of CD1a was reduced in TB patients compared to C ($P<0.05$), indicative of insufficient differentiation in response to GM-CSF. Expression of CD80 on both iDC and mDC from patients with TB was reduced ($P<0.05$), indicative of impaired co-stimulatory functions of DC. Expression of CD86 was decreased only on DC from Group I. Maturation of mdDC by TNF-alpha was impaired, with significantly decreased expression of CD83 ($14.36\pm1.37\%$ in Group I and $5.61\pm1.70\%$ in Group II versus $64.68\pm2.02\%$ in C, $P<0.001$). Production of IL12p70 by mDC was not impaired, although production of IL10 was reduced significantly in Group I ($P<0.05$).

Abnormal phenotype and impairment of mdDC function was found in TB patients. Impairments of both phenotype and cytokine production were more severe in patients with MDR. Correction of mdDC function *in vitro*, especially in MDR patients, may be necessary before DC-based immunotherapy.

To pulse mdDC derived from patients with TB with the lysate of autologous mycobacteria, co-culture DC with autologous T-cells to evaluate T-cell proliferation and cytokine production in response to DC stimulation.

EVALUATION OF BACTERICIDAL ACTIVITY OF MULTI-FUNCTIONAL BIOACTIVE NANO-STRUCTURED FILMS FOR LOAD-BEARING IMPLANTS

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Samples with multi-functional bioactive nano-structured films (MuBiNaFs) have been prepared for analysis of bactericidal activity. MuBiNaFs were deposited by DC magnetron sputtering of composite targets in an atmosphere of Ar or in a gaseous mixture of $Ar+N_2$.

Bacterial strains *Escherichia coli X-blue*, *Escherichia coli 09, Salmonella typhimurium* and *Pseudomonas aeruginose* (gram negative) and gram positive strains *Bacillus brevis* and *Bacillus subtilis* have been cultivated with 6 samples on solid medium LB with 2% agar during 1 night. No difference has been obtained to compare with cultivation of these strains without samples.

Bacterial strains *Escherichia coli X-blue* and *Pseudomonas aeruginose* (gram negative) and gram positive strains *Bacillus brevis* and *Bacillus subtilis* have been cultivated in liquid medium LB. Total number of bacteria was 10^6 cells per ml. The bacterial growth has been analyzed by optical density at 625 nm. During 4 hours of cultivation with samples no difference has been obtained to compare with cultivation of these strains without samples.

Tested samples have not showed any statistical significant bactericidal activity during cultivation on solid and liquid medium.

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AVIAN INFLUENZA VIRUSES FROM WILD BIRDS THAT NESTING IN EASTERN SIBERIA

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The continuous monitoring of Avian Influenza virus (AIV) in Eastern Siberia is necessary due to its geographical location. This place is used by various species of birds during their annual migrations both from East to West (linking the Europe and Asia) and from South to North (linking South-Eastern and Northern Asia). Besides this, The Eastern Siberia itself is a popular nesting place for numerous species of birds.

The results of the study of genetic diversity of AIV among birds that are nesting in Eastern and Northern Siberia are present in this work. In 2005-2008 we were monitoring 4 locations of Easten Siberia: an estuary of Selenga river and Tunka valley in Buryat Republic, Baikal lake near Small Sea in Irkutsk Region and Angara river near Boguchan hydropoverstation in Krasnoyarsk region. The cloacal swabs have been collected from 784 wild birds. The viruses were isolated in embryonated chicken eggs and allantoic fluids after third blind passage were used for further research. All allantoic fluids were tested for Haemagglutinating (HA) activity. Positive samples were characterized antigenically in haemagglutination inhibition (HI) test with the panel of reference antisera (from “PPDP Ltd.”, Moscow) to subtypes A(N1H1), A(N2H2), A(N3H2), A(N0H1), A(Nsw1H1), A(N5H1). Viral RNA was extracted from HA-positive allantoic fluids and used as template for RT-PCR with universal M-gene specific primers to confirm the presence of AIV. Identification of HA-subtype was done using PCR with the set of 15 pairs of subtype-specific primers (Tsukamoto K et al., 2008).

Total of 85 AIV isolates were characterized during this work. More than 46% of isolates were identified as H3 influenza viruses and this subtype appeared to be the most widespread during all period of study. The proportion of H0 viruses was 6%, H1 - 13%, Hsw1 – 6%, H2 - в 4%, H5 - 9%, H7 - 7% and H6 - 13%. The nucleotide sequences of 320bp haemagglutinin gene fragments of 5 H3 isolates were determined to analyze the phylogenetic relationships, origin and natural pathways of Eastern Siberian viruses. These HA gene fragments were most similar to AIV that infected birds in China and Korea in 1999-2006. The closest relatives appeared to be the isolates A/aquatic bird/Hong Kong/399/99(H3N8) and A/aquatic bird/Korea/KN-5/2006(H3N6). Surprisingly, the Eastern Siberian viruses isolated in 2008 had a unique nucleotide substitution in comparison with viruses isolated in 2007 that indicate the active genetic drift among AIV in Eastern Siberia.

Simultaneous circulation of several AIV subtypes at nesting places of wild birds combined with active evolutionary processes may be of definite interest in relation with the possibility of genome reassortation followed by emergence of new viruses with unpredictable epidemic potential.

CANDIDATE VACCINE CAPABLE OF ELICITING BROADLY REACTING ANTIBODY RESPONSE TO STRUCTURALLY CONSERVED AREAS ON THE HIV-1 V3 REGION

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The main challenge to the development of anti-HIV vaccines arises from the extremely high genetic variability of the virus. Our approach is aimed at eliciting a response to the certain areas on the V3 region that are "structurally conserved" across HIV strains. We have developed a *chimeric peptide library* (CPL) mimicking the antigenic variety of existing and potential variants of the HIV-1 subtype B third variable region. The library was created with using original antigenic similarity matrix to select amino acids that mimic the heterogeneity of variable positions. CPL-based candidate vaccine induced marked humoral immune response to broad range of both existing and potential variants of V3 region in mice and rabbits. To study the breadth of reactivity, we designed a representative peptide panel (RPP), containing 35 peptides, which represent the least probable variants of the antigenic diversity of existing and potential variants of the HIV-1 V3 region, for all subtypes. The results of cross-reactivity of anti-CPL sera with RPP peptides demonstrate that most rabbit sera react strongly with almost all peptides of the RPP. Thus, immune response to the candidate vaccine was characterized by broad specificity, covering almost all subtypes and main virus variants. This indicates that immune responses to the conserved higher order motifs of V3 region were elicited in several models.

The data suggest that CPL-based candidate vaccine elicits pronounced potentially protective and therapeutic humoral immune response to a broad range of HIV-1 variants. It may be a valid approach for vaccine development, providing desirable cross-reactivity, especially for therapeutic HIV/AIDS vaccine development, because of being capable to prevent virus mutated in V3 region.

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IXODOIDEA TICKS- THE TRANSMITTERS OF INFECTIOUS AND INVASIVE DISEASES IN TAJIKISTAN

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In the various natural-landscape zones of the south and central part of Tajikistan have been determined distribution, number and the host ranges of 10 species of *Ixodidae* and 3 species of *Argasidae* ticks. These species have been recognized as the main transmitter of Crimean-Congo hemorrhagic fever (CCHF), arbovirus infections, tick-borne relapsing fever, mycobacterium of tuberculosis, brucellosis, etc.

Currently, there are known 34 species and subspecies of *Ixodoidea* ticks in Tajikistan, including 26 species and subspecies of *Ixodidae* and 8 species of Argasidae. During 2004-2008 years we conducted ticks collection from the domestic animals and rodents of the livestock farmers located in the plain, foothill, low-mountain as well as the middle-mountain zones (350-2200 above sea level). There have been examined 2309 domestic animals, including 1107 cattle, 1024 sheep, 142 goats, 12 horses, 9 donkeys and 15 dogs. In total, have been collected 9362 *Ixodidae* and 368 *Argasidae* ticks. The collected ticks belong to 10 species of Ixodidae and 3 species of Argasidae (subfamily of Ornithodorinae).

In most cases on domestic animals were found the ticks of *Hyalomma anatolicum* - the main transmitter of CCHF virus in Tajikistan (51.5% of gathered *Ixodidae* ticks). The number of others Ixodidae ticks appeared much less and included mainly *Rhipicephalus turanicus* - 21.3%, *Hl.detritum* – 11.4%, *Haemaphysalis sulcata* – 7.5%, *Boophilus annulatus* – 4.5% and *Dermacentor marginatus* -2.3%. Ticks of *Hl.plumbeum turanicum*, *Hl.asiaticum*, *Hl.scupense*, *H.punctata* met in 0.1-0.5% cases. Among *Ornithodorinae* ticks the dominating species had been observed *Alveonasus lahorensis* (61.1% from the general gathering *Ornithodorinae*). The number of other species of *Argasidae*, particularly *Ornithodoros papillipes* and *O.tartakovskyi*, which are the main transmitter of spirochaetes of relapsing fever in Tajikistan, was less and made 8.6 and 3.1% , respectively.

In the plain and foothill zones have been observed 7 species of *Ixodidae* ticks and 3 species of *Ornithodorinae*. The number *Ixodidae* in these zones made 13.9 and 62.5% respectively, and the ticks of *Ornithodorinae* 5.2 and 6.3%, respectively. In the low- and middle mountain zones have been observed 4 species of *Ixodidae* ticks with the number of 15.1 and 7.1 %, respectively. The number *Ornithodorinae* in low mountain zone

made 2.4 %, and in the middle mountain zone no observed. It has to be mentioned that *A. lahorensis* has a focal distribution in the all surveyed zones.

There are known 30 species of rodents in Tajikistan among which the greatest species diversity have *Crisetidae, Muridae, Scuiridae*, making 82.8 % of total rodents fauna of the country. In the rodents (*Rhombomus opiomus*, *Meriones libycus, Rattus turkestanicus, Mus musculus, Ellobius tancrei*) have been observed to parasitize *Hl. anatolicum, Hl. asiaticum*, *Rh. turanicus, O. papillipes, O. tartakovskyi.* During the examination of *Mus musculus* and *Rattus turkestanicus*, 4.6 % of animals have been found to be infected with spirochaetes.

Thereby, the widespread and high number of ticks (the main carrier of transmissible diseases in Tajikistan), requires further epidemic-epizootic control over the certain regions of country with the aim of revealing their natural focus of diseases.

DETECTION OF GMOs IN FOODSTUFFS AND SEEDS IN TAJIKISTAN

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Food safety is an increasingly important public health issue. Tajikistan imported more than 70% food staffs. The composition of imported food staff varies from seeds, cereal crops, forage, wheat and its products, rice, soybean and soybean products, grouts, the tonics and other beverages. A lot of above mentioned food products has unknown origin. The increasing of allergies and cancer can be related to such foods.

A GMO (genetically modified organisms) is usually defined as living organisms whose genetic composition has been altered by means of gene technology. This involves DNA isolation, defined DNA modification, and transfer of DNA into genome of target organism that successively becomes a GMO. This process is referred to as transformation event. Normally, new gene functions are inserted into the GMO, but new techniques have been developed that make targeted knock-out of existing genes possible, among others in higher organisms, such as food plants. A lot of meat products like sausages, pates are contents 80% of soybean protein. Some of the milky products such as cheese, yogurts are contented soybean milk. It's well known that these soybean products are prepared from genetically modified plant (GMO). Genetically modified (GM) crops are increasingly being introduced into the worlds food supply. Concerns raised by consumers and regulatory agencies in various countries have highlighted the need for reliable and accurate testing for the presence and the amount of GM-components. The detection and identification of GMOs represents a relatively new area of diagnostics in which much progress has already been achieved with DNA- and protein-based methods.

The special point of view should take to safety assessment of food derived from GM crops. The safety assessment focuses on the new gene products and of whole foods derived from the GM crops. Both intended and potential unintended effects from the genetic modification should take into account. The assessment involves the following steps: (i) characterization of the donor organism from which any recombinant DNA sequences are derived, the transformation process, and the introduce recombinant DNA sequences; (iii) safety assessment of the introduced gene products (proteins and metabolities); and (iv) food safety assessment of whole food derived from, or edible part of, the GM crop. The assessment should focus on those nutrients, toxins, anti-nutrients, allergens, and bioactive constituents in the host plant or in its close relatives; changes in the levels of consumptions of which might affect human health and nutrition. Nutrients are components in a particular food that may have a substantial nutritional impact on the consumer or animal. These may be macro-nutrients (fats, proteins, carbohydrates) or micro-nutrients (mineral and vitamins). A majority of imported food hasn't proper labels, so it's necessary to provide expertise on harmful carries in food for health protection.

Tajikistan hasn't modern control system for food safety and protection of consumers from negative impacts of unknown matters. We are highly needed in organization of special analytical laboratory for food chemistry, food microbiology and agricultural industries, which should be well-equipped both modern technology and qualified staff. The Research Institute of Plant Physiology and Genetics, Academy of Sciences of Republic of Tajikistan is equipped with scientists with vast experience in molecular biology, biochemistry, analytical chemistry, who are able to operate a full range-testing laboratory. On the basis of the Institute laboratories it's possible to organize the Specialized Analytical Laboratory for Food, Feed and Crop's Expertise. This laboratory can provide a full range complex biological and genetic assessment of crops, food, feed, pharmaceuticals, etc.

Such laboratory can be created, certified and accredited on the basis of the Institute of Plant Physiology and Genetics of Republic of Tajikistan collaboration with ISTC.

DESIGN OF A NOVEL TECHNOLOGY FOR BORRELIA DBPA PROTEIN CONSTRUCTION USING RECOMBINANT *E.COLI* STRAINS-PRODUCERS FOR SEROLOGICAL DIAGNOSTICS OF TICK-BORN BORRELIOSIS

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Decorin-binding Borrelia protein DbpA represents a lipoprotein, which may play an important role in spirochete adhesion. High titer of persistent antibodies to DbpA suggests that the protein can be used for serological diagnostics of tick-born borreliosis (tick-born borreliosis, Lyme disease).

Genes encoding DbpA synthesis from *Borrelia afzelii*, *garinii*, *sensu stricta* are structurally highly heterogeneous that makes the study of immunobiological properties of DbpA from all Borrelia subspecies very important. In the experiments performed structural parts of genes encoding mature forms of DbpA *Borrelia* Afzelia, Gorinia, Sensu stricta have been obtained by PCR and cloned in *E.coli* cells by standard genetic-engineering techniques. As a result, three strains producers of DbpA *Borrelia afzelii*, *garinii*, *sensu stricta* were constructed. 18-20-kDa hybrid DbpA proteins were found to be synthesized in the cells of E.coli strains-producers. Recombinant proteins DbpA-af, DbpA-gar, DbpA-ss were purified by affinity chromatography with a metal-chelate sorbent. The purified proteins were tested on the sera from Lyme disease patients, syphilis patients and on the sera from healthy persons by western-blot and ELISA.The testing performed showed that recombinant proteins DbpA-af, DbpA-gar, DbpA-ss are capable of identifying specific antibodies in the sera of Lyme disease patients and have no cross-reactions with the sera from healthy persons and syphilis patients. Thus, the obtained recombinant proteins can be applied for serological diagnostics of tick-born borreliosis.

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CONSTRUCTION OF RECOMBINANT *E.COLI* STRAINS-PRODUCERS OF *M.TUBERCULOSIS* PROTEINS PROSPECTIVE FOR SEROLOGICAL DIAGNOSTICS OF TB.

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Current increase of TB incidents observed all over the world demands improvement of methods for diagnostics and treatment of the disease. Up-to-date immunochemical diagnostics providing methodical simplicity and high level diagnostic efficacy should enlarge the armory of traditional methods, such as XR-study, bacteriological testing and tuberculin skin testing. Currently, there is a lack of mycobacterium antigens optimum for TB serological diagnostics, therefore a search for new antigens and design of technologically effective ways of their production are of special importance. Strains-producers of the following *M.tuberculosis* antigens, namely MTSA10, MTB12, MTC28, MTB48, MPB64, Rv1636, Rv2430, Ag85 have been recently constructed in our Laboratory.

In the performed experiments *M.tuberculosis* genes encoding antigens Rv3616, Rv1833, Rv3873, Rv3878, Rv3803, Rv0934, Rv0222, Rv2031 were cloned. Structural parts of the genes coding mature proteins were put under the control of a strong promoter in recombinant plasmid DNA, which provides high yield of recombinant proteins. C-terminus of each of the recombinant antigens was fused with polyhistidine domain to optimize chromatographic purification procedure.

As a result, eight strains-producers of *M.tuberculosis* antigens were constructed; conditions of their cultivation were developed. The produced proteins were purified by affinity chromatography to a high degree.

Immunochemical studies on the interaction of the constructed proteins with the serum from TB patients are currently performed to select a combination of the proteins optimum for serological test development.

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CLINICAL AND IMMUNOLOGICAL FEATURES OF PERINATAL HIV-INFECTION

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There was performed a prospective analysis of clinical immunological data on 194 children with perinatal HIV-infection at the age of 1.5 months – 9.5 years during lifetime. It was stated that the disease is characterised by early clinical symptoms (in 87.6% of infancy), prevalance of stage 4 at diagnosing from 1 to 3 years (60.8 – 71.4%) and diverse range of opportunistic and non-opportunistic diseases. Among organ lesions there were remarked high incidence of blood diseases (100%), respiratory apparatus diseases (77.4%), gastrointestinal tract diseases (50.4%), urinary (23.1%) and cardiovascular system diseases (20.0%); and relatively lower prevalence of oncopathology (2.0%).

In the structure of HIV-associated diseases in children the first place (100%) is occupied by infectious pathology: candidiasis (61.3%), herpes virus infection (79.4%), bacterial infections (100%), and tuberculosis (7.7%). The main part (78.5%) of AIDS-indicator pathology is also constituted by diseases of infectious nature which contribute much (88.2%) into the patients' deathrate – generalised forms of cytomegalovirus infection (23.5%), tuberculosis (17.6%), candidiasis (11.8%), severe bacterial infections (17.6%), pneumocystic pneumonia (11.8%), along with oncological lymphoproliterative diseases (17.6%). The earliest superinfection in age asopect is pneumocystosis (0.3 – 0.5 years) before 2 year old there is remarked first episode of bacterial infection and candidiasis; cytomegalovirus infection occurs relatively early (1-2.2 years), later – infections of Herpes Simplex (2.1-3.5 years) and Epstein-Barr (2.3-4.5 years); tuberculosis is registered at 0.7-2.0 years.

Sings of immune system lesions include clinical - infectious and lymphoproliterative syndromes and laboratory – combined immunodeficiency with the deviation towards Th2 response. The most evident $CD4^+$ count deficit in children is remarked under pneumocystosis, tuberculosis, generalised form of cytomegalovirus infection and candidiasis. Multisystem involvement and rapid progression of immunodeficiency (1.5-4.5 years) under natural course of perinatal HIV-infection determine the necessity of diagnosing (before 6-12 months) and wide prescription of antiretroviral therapy needed by 95.9 1.4% of children in the age of 3-3.5 years.

THE PSEUDOVIRUS-CELL-BASED SYSTEM FOR THE TESTING OF ANTIRETROVIRAL COMPOUNDS

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The pseudovirus-cell-based system for the testing of antiretroviral compounds consists of two principal components:

- Lentiviral vector pseudotyped with a homo- or heterologic envelope protein;
- Target cells corresponding to the cell type tropism of a particular Env protein.

Currently, we are using the lentiviral vector carrying eGFP reporter gene under the control of cellular promotor. The lentiviral capsid is pseudotyped with G protein of vesicular stomatitis virus (VSV-G), which enables a broad range of target cells to be transduced by pseudovirus.

However, the eGFP reporter can easily be replaced by luciferase reporter gene, as well as other surface glycoproteins from different types of viruses can be used for pseudotyping in order to assay infection in specific cell types.

The experimental setting is as follows: target cells are split in 96-well plates and are preincubated with tested inhibitor compound for 1-6 h. Infection is made by spinoculation of virus onto the cells in a swinging-bucket centrifuge, usually, when the cells are 60-80% confluent. A triplicate of wells is provided for each inhibitor concentration. Positive control triplicate contains pseudovirus without inhibitor compound. Negative control triplicate is mock-infected with growth medium containing the same amount of solvent, in which the inhibitor is dissolved (usually, DMSO or PBS).

Infected cells are grown for the period of 2-3 days following which the cells are trypsinised, fixed in 0.5% formaldehyde and run on cells sorter. The efficience of inhibition is expressed as percentage of GFP-positive cells in a triplicate, while the amount of cells in non-inhibited triplicate (positive control) is considered to be 100%. Usually,

the experiments are run with 2 different MOI (multiplicity of infection) – physiological (0.1-0.2 i.u./cell) and superphysiological (1.0 i.u./cell and higher). Inhibition curve is constructed for each compound. Data obtained for AZT and its phosphonate derivatives show god correlation with experimental data for the same compounds tested in HIV-1 infected lymphoid cells MT-4.

NEUTRALIZATION OF *B. ANTHRACIS* SPORES BY NEW DISINFECTANT

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Epidemiological situation with anthrax is far from being stabilized as demonstrated by numerous outbreaks of the disease during last decade. Disinfection of anthrax foci dictates necessity to develop, test and produce new disinfectants: long-stored, effective, low toxic and safe for environment.

Ecologically safe disinfectant based on specific virulent bacterial phages, spore germinant and specific substance (know-how) for neutralization of anthrax bacillus was developed.

The efficacy of disinfectant was tested in soil and on surfaces. The tests of disinfectant sprayed on surfaces contaminated by *B. anthracis* spores demonstrated 50% decrease of biological concentration of vaccine strain *B. anthracis* (STI-1) after 30 minutes. After 60 minutes the germination of spores and their lysis was observed (99.9%). The full effect of initiated spores' biodegradation (100%) was observed after second treatment by disinfectant after about 120 minutes.

The tests on the columns with different types of soils demonstrated that active anthrax spores neutralization by disinfectant occurs up to depth 50 cm (inactivation 86.3%). Process of spores neutralization in soil starts in 1 hour after treatment by preparation (inactivation 57%); in 3 hours inactivation reached 78.1% and after 24 hours 99.9% of spores were inactivated. High enough alanine doze for initiation of spore germination is required for effective neutralization ability of phage disinfectant. Also the efficacy of disinfectant depends on such factors as soil humidity, temperature and pH. The optimal ranges for disinfectant application are: soil humidity 50-80%, soil temperature 10˚C-45˚C, and soil pH 7.2-7.4. The most effective spore neutralization by disinfectant occurs in gray woodland and black earth soils comparing to other soil types.

In contrast to chemical disinfectants, the concentration of active component (virulent phages) of preparation increases after treating of objects and soil contaminated by *B. anthracis* spores in $4x10^3$ – $5x10^3$ times in geometric progression, while the concentration of e.g. active chlorine decreases in 2 times in 24 hours.

On the basis of results obtained, preparation "Desantrax" is designed. This preparation is non toxically and ecologically friendly. It could be used both for emergency and for planning disinfection of natural loci.

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INFLUENZA – ASSOCIATED DEATHS IS ONE OF THE GLOBAL PROBLEM OF MODERN MEDICINE

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Influenza epidemics are associated with an excess of mortality from cardiovascular and respiratory diseases. The WHO estimated that these annual epidemics result in 3 to 5 million cases of severe illness and 250,000–500,000 deaths each year around the world. In the United States, influenza is responsible for 50 million illnesses and up to 47,200 deaths annually. Meanwhile in Russia accordingly official registration only 150-200 persons annually die from influenza. It is explained by the difference medical recording systems in the countries. In Russia deaths from influenza is registered when the fatal outcome occurs after manifestation of an acute infection. In the USA the concept of the "Delayed complications of influenza" is used. It means that all deaths from complications of cardiovascular and respiratory diseases if they occurred during influenza seasons or within two weeks after their ends are registered as delayed complications of influenza.

The objective of our research is to reveal statistical associations between mortality of exacerbations of chronic cardiovascular and respiratory diseases and incidence of influenza through 1999 - 2005 seasons in Moscow in the elderly.

Spearman rank correlations between a mortality from all cardiovascular diseases and influenza were- 0,7, for an acute myocardial infarction- 0,5, for ischemic heart diseases- 0,6, for cerebrovascular and respiratory diseases- 0,7 (all p values <0.001).There were no significant correlation associations between mortality from pulmonary heart disease and a repeated myocardial infarction.

Results of the analysis revealed**:** that the strongest associations are detected between incidence rate of influenza and mortality rate of ischemic heart disease for age groups 75-79, 80-84 and more than 85 years old (rank correlations - 0,85, 0,83 and 0,87 consequently). Between incidence rate of influenza and mortality rate of myocardial infarction for age groups 75-79 and more than 85 years old (rank correlations - 0,92 and 0,83 consequently), between incidence rate of influenza and mortality rate of cerebrovascular illnesses the strongest association for age groups 70-74, 80-84 and more than 85 years old (rank correlations - 0,85, 0,83 and 0,87 consequently), between incidence rate of influenza and mortality rate of bronchopulmonary pathology for age groups 70-74 and for 80-84 years old (rank correlations are 0,8 and 0,94 consequently), between incidence rate of influenza and mortality rate of pneumonia for age groups 65-69, 80-84 and more than 85 years old (rank correlations - 0,7, 0,77 and 0,74 consequently). All p values <0.001.

Thus, influenza is a dangerous infection for elderly persons with chronic cardiovascular and respiratory diseases because of strong associations between of mortality rate of ischemic heart diseases, acute incidence of myocardial infarction, cerebrovascular and respiratory diseases.

COMPARATIVE ANALYSES OF ORAL IMMUNOGENICITY OF THE TRANSGENIC CARROTS PRODUCING S OR M ANTIGENS OF HEPATITIS B VIRUS

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Raw storage roots of the transgenic carrot producing S (HBsAg) or M (preS2-HBsAg) antigens of hepatitis B virus (HBV) were used for oral immunization of BALB/c mice. The animals were immunized by feeding three times with 2-week intervals between each feeding. Analysis of mouse peripheral blood mononuclear cells starting from day 14 of experiment demonstrated the induction of an efficient HBsAg-specific T cell–mediated immune response in all the animals fed the transgenic carrot producing either HBV S or M antigen. However, the antibodies to HBsAg in blood plasma were detectable only in 11% of the animals immunized with the carrot producing S antigen and were undetectable in the case of M antigen–producing carrot. The antibodies to HBsAg were detected in the intestines of animals in the groups that received carrot producing S antigen (28%) and M antigen (11%). No antibodies to HBsAg were found in any blood or intestine samples of the control animals, fed the initial carrot or the carrot with inserted vector T-DNA.

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EPIDEMIOLOGICAL SITUATIONS ON CHOLERA IN TAJIKISTAN

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Cholera disease remains a problem of international scope. Epidemiological events on cholera at the present stage links with bringing to the European countries to endemic cholera homes, since the development of international travel, tourism, trade, migration and population increases. For cholera real epidemic danger are these countries in which formed the true endemic foci. According to most scholars, endemic establishment and spread of cholera is only possible in countries with contributing to the social and environmental conditions (poor public improvement, the low level of material security of the population at large, etc.). The cholera is still a disease of underdeveloped regions in the social attitude. Much attention is paid to sanitary protection area of the sliding and the spread of cholera from abroad. In connection with the growing volume of trade-economic, cultural, tourism and migration processes to the

foreign countries, including those which are vulnerable to cholera, there is a constant threat to its delivery to the territory of Tajikistan. Comprehensive assessment of epidemic manifestations of cholera takes into account the following indicators:

- An analysis of the human on infection and the provision of cholera vibrio choleric of environmental and surface waters.
- Climate and geographical features. Special attention is given to areas bordering with countries vulnerable to cholera, in the waters that originated abroad (territory of Tajikistan from the south is the border with Afghanistan and has been in recent time a lot of bridges built among the river Pyanj, and this contributes to a very large migration of people from one side to another and vice versa, and ultimately the number of beds is not precluded by the sliding of infection).
- Transport links, migration, sanitation and hygiene condition of the territory (water, sewage, sanitary clean-up) (taking into account not sufficient to ensure high quality drinking water especially rural areas and this will ultimately create a favorable environment for the development of the disease).
- The nature and terms of recreation and domestic water use.
- Customs of indigenous people.
- Preparedness and the interaction of treatment and preventive care, sanitation, local Antiplague healthcare and institutional medical services for complications of epidemic cholera.

Currenrly the territory of Tajikistan the epidemies of cholera occurred in the late second and in all subsequent epidemics. Identify ways of carrying cholera in Tajikistan was not possible. Individual cases vibriocarriering have occurred in the city of Khujand. After a drift of cholera from Afghanistan to the Pyanj water, thanks to the smooth conduct of anti-epidemic measures at identifying sources of infection, the epidemic process has been restricted and suppressed. In 1993 the epidsituation of cholera dramatically worsened. The main reason was the unstable political and economic environment, the weakening of health - sanitation, migration processes have become intense and various groups and segments of the population. In 1993 cases of cholera have occurred in the 10 areas of Tajikistan, including parts of the Khatlon region, as well as in several districts of republican subordination (Lenin and Hissar). In total 175 patients were registered and 118 of them were cases of vibrio carrying. In 1994 in Dushanbe it was reported 2 cases of cholera and 11 cases vibrio carrying. All cases registered among residents of Dushanbe, which returned from Karachi in 10 August 1994, including 50 tourists. Thanks to the measures taken, the further spread of infection on the territory was averted. It should be noted that in most areas of the Republic of Tajikistan are nit under study of the open water in the presence of cholera vibrio except regional centers government epidemic control laboratories. This is all due to the fact that laboratories in areas located in the adapted premises. Communication with the decline of the economic situation in the Republic in recent years, the equipment is in poor condition. In many laboratories the autoclaves are out of service, there is only one thermostat that is not enough. Almost the entire laboratory does not provide diagnostic media, serum, sacharose. In 2009, when checking the state of preparedness for prevention antiepidemic carrying cholera in 15 districts of the Republic has been established. Many areas are not staffed by specialists, medical doctors and laboratory technicians are not trained in the modern laboratories for cholera diagnosis. So, it should be noted that all the laboratories are needed to purchase by the equipment, diagnostics, trainings, and repairing.

MICROBIOLOGICAL MONITORING OF RESISTANCE OF NOSOCOMIAL PATHOGENS TO ANTIMICROBIALS IN REPUBLIC OF BELARUS

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The microbiological monitoring allows to increase efficiency of microbiological diagnostics, rational antimicrobial chemotherapy by improving control over them. Creation of actually functioning national surveillance system for containment of antimicrobial resistance is an important task of public health services. The National reference center for microbiological monitoring of resistance to antibiotics, antiseptics and disincentive agents has been successfully operating since 2003 in Belarus. The National reference centre works in close conjunction with selected microbiological laboratories located in all regions of the country and collects information on distribution of hospital bacteria, their resistance patterns to antimicrobials, investigates hospital isolates from five Belarusian regions (Minsk, Gomel, Grodno, Homel, Brest).

In 2003-2009 yy different types of pathological specimens were studied: sputum, pleural liquid, tracheal aspirations, blood, urine, stool feces etc collected. For microbiological monitoring of resistance different approaches were used: ATB-expression, VITEK 2 Compact 30 (BioMerieux), genetic analysis.

7530 strains of microorganisms were isolated. 818 species of bacteria and fungi are identified. Most frequently identified microorganisms were*: Staphylococcus spp*.- 38.8%; *Escherichia spp*. – 17.7%; *Pseudomonas spp*.. – 6.3%; *Klebsiella spp*. – 6.0, *Candida spp*. – 5.8%; *Enterobacter spp*. – 4.0%; *Streptococcus spp* – 3.9%; *Citrobacter spp*. – 3.5%, *Proteus spp. – 3.3%*. Increasing resistance of *S. aureus* to ampicillin (39%), oxacillin (73%), cefuroxime (14%) was observed. In 2003-2009 significant increase in resistance of *E. coli* was detected to moxalactam (19%), aztreonam (16%), ciprofloxacin (16%), ticarcillin/clav.acid (15%), amikacin (14%), gentamicin (13%), imipenem (11%), netilmicin (10%). In 1996-97 the isolation frequency of resistant *Candida spp.* was 2-5%, whereas in 2003-2009 these indexes have increased in 2 and more times (9-14%). Analysis of dynamics of *P. aeruginosa* resistance to antimicrobials from 2003 to 2009 has revealed the increase in resistant variants to ticarcillin/clav.acid (55%), imipenem (30%), aztreonam (68%), gentamicin (77%), netilmicin (86%), ciprofloxacin (51%). In 2006-1007 yy *Staphylococcus spp.* carrying mec A gene comprised 33 % (71 isolates of 218). The majority of the tested MRSA harbored SCCmec type III (69%). SCCmec types I, II, IV, V were detected less frequent in 10%, 8%, 8%, 5% of isolates correspondingly. Most of MRSA strains (85%) carried *hlg g* and *luk E* - the genetic determinants of γ-hemolysins, leukocidin E. 1,1% of MRSA were positive for *etaA* gene controlling exfoliative toxins A. Most of MRSA produced capsules of either serotype 5 (28%) or serotype 8 (65,5%) but not capsules of type 1. All MRSA with SCCmec V harbored Panton-Valentine leukocidin gene. Studied MRSA strains did not carry *tsst* gene controlling toxic shock syndrome toxin.

Increase in resistance to antimicrobials in microorganisms from 2003 to 2009 witness to necessity of carrying out constant monitoring of multidrug resistance, including introduction of hospital formularies for the practical doctors, control of antibiotics usage in hospitals and other measures that meet the demands of ultimate goal of containment of antimicrobial resistance.

THE PROBLEM OF ANTHRAX IN THE SOUTH OF THE KYRGYZ REPUBLIC AND POSSIBLE SOLUTIONS

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The number of anthrax cases has sharply increased in the south of the Kyrgyz Republic in recent years. This is due to the climatic and geographic conditions of the south of the republic. Very hot and in some areas humid climate and significant range of the heights from the sea level (from 400 up to 7495 metres) in the south of the republic create favorable conditions for multiplication of various kinds of microbes, notably soil zoonotic ones. Therefore, all kinds of extremely dangerous infections, namely comma, plague and anthrax bacilli are frequently recorded in the south of the republic. Among these infections anthrax is a matter of deep concern for us.

Report of the Republican Department of State Sanitary-and-Epidemiologic Surveillance, Report of Republican Center for Quarantine and Extremely Dangerous Infections, Report of Republican Department of State Veterinary Control, Report of Antiplague Department of the Southern Regional Agency for State Veterinary Control of the Kyrgyz Republic, and statistics from 1960 to 2008; findings of investigation of xenobiotic environmental pollution. Collection of samples and laboratory examinations were conducted in accordance with guidelines "Directions and instructional lines for laboratory, clinical diagnostics, prevention and treatment of anthrax" (Moscow, 1980). To detect capsule generation bacteriological analyses with the aid of accelerated bioassay and luminous-serologic method were conducted. Bacterioscopies of samples, inoculation of media were also performed. Hemolytic and phosphatase activities were examined.

The goal of research: investigation of anthrax epizootiologic and epidemiologic situation in the southern regions of the Kyrgyz Republic and improvement of epidemiologic surveillance and epidemic control systems.

Before the dissolution of the USSR 13.9 cases of anthrax were annually recorded during 1960-1991. For the last 17 years anthrax morbidity rate has increased by 21.2 cases. Annual anthrax incidence during 1992-1996 was 50 cases, 129 cases in 1996-2001, 117 cases in 2002-2006, 65 cases in 2007-2008, i.e. 361 cases were recorded in the republic in 17 years after the dissolution of the USSR. Out of them, 29 cases (8%) of anthrax were recorded in the southern regions of the republic.

Since 2001 the number of anthrax affected settlements has increased by 57 (out of them, 51(89.5%) settlements in the southern regions of the republic) as compared to 1991, when such areas encountered 1183 settlements. Anthrax cases were occasionally recorded in one or two settlements in the Soviet times and first years of post-Soviet times. At present, anthrax cases are annually recorded in all the southern regions and cities of the Kyrgyz Republic, except four high-mountainous regions: Chatkal, Chon-Alay, Toguz-Torouz and Toktogul regions. In the last three years ten new anthrax foci were revealed in the Osh region.

Starting from 2007 anthrax has taken its severe course. Two patients were operated, three patients died. Moreover, contamination of the environment by various pesticides, salts of heavy metals, hydrocarbonic compounds and radioactive nuclides leads to mutability and virulence of microbes resulting in increase of the number of severe cases and fatal outcomes. Environmental contamination also contributes to generation of novel antibiotic-resistant types of microbes. During 1992-2008 more than 1200 cattle heads died. All fatal cases among people and animals were observed in the area heavily contaminated by pesticides.

The results of bacteriological investigation showed that in 1999 out of 90 tests anthrax was encountered in 3 cases (3.3%), in 2000-2001 – 116 tests - anthrax was not registered, in 2003 – 77 tests - 3 cases (3.8%), in 2004-68 tests-3 (4.4%), in 2005 – 56 tests -2 cases (3.5%), in 2006 – 123 tests- 1 case (0,8%), in 2007 – 62 tests – 2 (3.2%), in 2008 – 93 tests -11cases (11,82). Starting from the year 2008 anthrax bacilli have been found in animal meat and skin: 6 (35.2%) out of 17 tests showed the presence of anthrax bacillus as compared to 4 (5.3) out of 75 tests in 2007. Microbes isolated from the areas contaminated by pesticides were found to be much more antibiotic-resistant as compared to those isolated from ecologically pure areas. Thus, anthrax bacilli tend to be more frequently found in soil.

For prevention and control of anthrax in the Kyrgyz Republic information-analytic subsystem of epidemiologic surveillance was elaborated. To obtain necessary information and take measures in case of extremely dangerous disease, including anthrax, a networking was provided by ISTC (CSR046) in Institute of Medical Problems, Osh Antiplague Department and Osh Regional Veterinary Laboratory. All information received is propagated by Osh Aarhus Center among the farmers and NGOs to raise people awareness regarding anthrax situation in the region and possible counteractions to the disease. Frequent sessions on anthrax are conducted by the researches of the Institute of Medical Problems.

In conditions of the south of the Kyrgyz Republic anthrax tends to be frequently observed. Xenobiotic environmental contamination is probably considered to be one the factors affecting the state of anthrax bacillus in soil, but this assumption requires further investigation. Preventive measures should be directed on improvement of investigation strategy, organisation of regular monitoring and raise of population awareness.

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MOLECULAR EPIDEMIOLOGY OF HUMAN

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After the human genome sequenation, became apparent, that the huge field for analysis of various biological processes, exercised by proteins, was discovered. In this connection interesting that fact is, that, despite of the same genetic code of the pathogen, the infection at the different people proceeds variously, and, on the contrary, the completely different pathogenic agents produce similar clinical symptoms and contain similar structures of nucleic acids and proteins.

The molecular epidemiological characteristics of each person are a subject of our researches.

With the purpose to study of these features it is interesting to investigate a biological stuff (serum, wipes, swabs, blood and others) from each person on availability of the pathogen components (nucleic acid, proteins), and also clones of antibodies to immune significant antigenic determinants (specific markers), certain spectrum of pathogens of infection diseases. The pool of pathogens is defined by amount of the nosological forms, which are circulated in human population (approximately 1500).

The markers settle up by an International database of proteins and nucleic acids analysis, as well as empirically. The molecular probes for a hybridization of nucleic acids, and also recombinant and synthetic peptides are considered as structures capture the specific material from the analyzed samples. The macro and the micro methods, including nanotechnology and so-called microarray, widely use in scientific researches and in practice now. Many years of experience in this area has shown that in this case we can talk about construction of the antigenic maps for each person. The monitoring of the majority of the population of certain regions will be important not only for epidemiological analysis, but also for his prediction, that is the most important now.

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POLYMORPHISM Γ-IFN AND Γ-IFN RECEPTOR TYPE 1 GENES IN PATIENTS WITH CHRONICAL INFECTIOUS DISEASES - HERPES VIRUS INFECTION AND LYME BORELIOSIS

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In the world there is a growth of infectious diseases with multisystem clinical presentations involving the central and peripheral nervous system. Lyme disease and Herpes Viral infection is a chronic multi-system infectious disorder characterized by several stages and manifestations, affecting the skin, brain and nerves. The clinical outcome of these diseases depends on immune response during infection. Cytokines are regulators of the physiological and pathological immune response. IFN-gamma is immune interferon and it is produced by antigenspecific T-lymphocytes CD4+ and CD8+ and also natural killers after corresponding stimulation by antigenes and mitogens. The IFN-gamma receptor is normally expressed on the surface membrane of monocytes, macrophages, T cells, B cells, NK cells, neutrophils, fibroblasts and endothelial cells.

The aim of this study was to assesses SNP polymorphisms of the IFNG and IFNGR1 genes in patients with Herpes Virus and Lyme Disease. The study included a control group (n=40) of healthy subjects, patients with Alpha Herpes Virus (n=23) or Lyme disease (n=26). The role of two polymorphisms in the IFNG (SNPs +874, 5644) and IFNGR1 gene (SNPs +95, -270) were assesses by allele-specific PCR.

The +874 A/A genotype was found significantly more often in control subjects and patients with borreliosis compared to patients with herpes (30% and 38.5% vs. 8.7%, $p < 0.05$). No differences in genotype +874 distribution were found between the control group and patients with borreliosis ($p > 0.05$). The frequency of IFNG 5644 A/A genotype was significantly decreased in patients with Lyme disease compared to the control group (3.8% vs. 22.5%, $p < 0.05$) and decreased in patients with herpes compared to the control group (8.7% vs. 22.5%), although the latter decrease did not reach statistical significance.

There were significant differences between the control group and the Herpes Virus patients in frequency of IFNGR1 +95 genotypes. The frequency of genotype TT was increased in herpes patients (52%) in compare with control group 12.5% ($p < 0.05$). There was no statistically significant difference in SNP -270 IFNGR1 genotype frequencies between the studied groups.

Our study was shown that patients with Herpes Virus and Lyme Disease have a genetic defect in the IFNG and IFNGR1 genotypes. SNP +95 lies at the beginning of intron 1 and in close proximity to a splicing site. Changes in the nucleotide at the first intron can increase or decrease the binding of a particular transcription factor. The 3'UTR region (position 5644) plays an important role in the expression of many eukaryotic genes by governing mRNA stability, localizing mRNA, and regulating translation efficiency. Specific binding of the nuclear transcription factor-κB (NFkB) to the DNA sequence containing the +874 T allele has been reported; and nucleotide replacement in this point can effect on transcription process of IFN-γ gene and influence on the rate of IFN-γ production[6]. Studies of interferon gene polymorphisms may help to elucidate the complex network of interactive genes influencing the type and strength of immune responses to infections and may help identify host genetic factors responsible for control of infectious agents in humans.

Researches have shown that gene polymorphism can influence on onset, a current, an outcome and success of therapy for many diseases. Also gene polymorphisms have an influence on gene expression. Probably that the great importance it has for chronic virus, bacterial and protozoal infections. Genotypes analysis will show association with sensitivity or resistance to infectious agents. Expression of cytokine gene is very important for correct functioning immune system, therefore studying of polymorphism of cytokine genes is an topical problem understanding infectious diseases.

EFFECTIVENESS OF VACCINATION OF SERVICEMEN AGAINST HEPATITIS A VIRUS

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The present research is devoted to the decision of a problem of a low level of population protection from a hepatitis A virus (HAV) infection. The purpose of the work was the estimation of effectiveness of vaccination of young replenishment soldiers of Russian Armed Forces. The “Avaxim” vaccine have been inoculated to 175 originally seronegative persons. We also studied 23 people who served more than one year. Level of anti-HAV antibodies was evaluated using both Russian and foreign test-systems.

Results of parallel evaluation of antibody level by the test-systems from two different manufacturers indicated, that Russian test-system has allowed to reveal protective antibodies in 50,0±10,17 % of cases, whereas the imported test-system - in 70,8 ±9,28 %. Antibodies after vaccination in servicemen of the third period of service (23 persons), as detected with different test-systems, were verified more often, than in young soldiers. Using Russian test-system, we have revealed the antibodies in 16 (69,6 ±9,47 %) cases. Nevertheless, the differences in a level of antibodies determined using Russian test-system among servicemen of the different periods of service are not statistically reliable (t=1,093; P = 0,274). Foreign test-system has revealed antibodies in all vaccinated soldiers of the third period of service that was reliably higher than in the group of young soldiers (t=2,400; P = 0,019).

The described phenomenon can be connected to decrease of organism resistance of young soldier replenishment at the expense of a significant stress of regulator systems during first months of a service. About half (48,8 %) of young soldiers had a significant functional difficulty of homeostasis system and decrease in reserves of the organism, shown in the form of reactions of sharp and chronic stress. In contrast, such symtoms were detected only in 21,0 % of soldiers of the third period of service. Therefore it is possible to suppose, that the stress of homeostasis systems of servicemen has affected the results of vaccination.

INFLUENZA A (H5N1) VACCINE IN HUNGARY: DEVELOPMENT, EVALUATION, PRODUCTION

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The vaccine was produced by the same method as the interpandemic influenza vaccine "FluvalAB" used in Hungary for the past 11 years. The method has been validated by meeting the requirements of EMEA related to interpandemic influenza vaccines each year since 1995. The virus strain (NIBRG-14), a reverse genetics–derived 2:6 reassortant between A/Viet Nam/1194/2004 (H5N1) and PR8, was obtained from the National Institute for Biologic Standards and Control, London. Hens' egg–grown, formaldehyde-inactivated, whole virus vaccine, developed and produced by the Omninvest Ltd. (Budapest, Hungary), was used. The vaccine contained 6 µg hemagglutinin per dose (as determined by single radial immundiffusion test) in 0.5-mL ampules. Purity was assessed by endotoxin content (determined by chromogenic endotoxin assay, using a modified limulus amoebocyte lysate and a synthetic color-producing substrate), which was considered acceptable in concentrations <0.1 IU/mL. The amount of ovalbumin was determined by ELISA, which was considered satisfactory in concentrations <10 ng/mL. Aluminum phosphate was used as adjuvant, in the amount of 0.31 mg Al per ampule; 0.1 mg/mL merthiolate was added as preservative. A total of 146 healthy volunteers >18 years of age (mean ± SD 42.07 ± 12.62 years). were enrolled in the study. Sixty-five male and 81 female volunteers participated. The injection administered 0.5 mL of vaccine intramuscularly. The injection was not repeated. Serum antibody titers were measured by hemagglutination inhibition (HI) by using chicken erythrocytes, following standard procedures. None of the study participants displayed measurable levels of HI antibodies before vaccination.

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