



VHPB meeting

Prevention and control of Viral Hepatitis in the Baltic States: lessons learnt and the way forward

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Greet Hendrickx
VHPB Secretariat

Executive VHPB Secretariat, Vaccine and Infectious disease Institute, University of Antwerpen, Campus Drie Eiken, Universiteitsplein 1, BE-2610 Antwerpen, Belgium,
☎ +32 (0)3 265 26 64 📠 +32 (0)3 265 26 40 @: Greet.Hendrickx@uantwerpen.be

Content

This pre-meeting document contains general background information of the countries and the reported current hepatitis situation. Furthermore a list of selected abstracts/ references from a Pubmed MEDLINE search on different search terms. The references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author's name.

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List of publications achieved via speakers form when this form was not provided a Pubmed MEDLINE search was performed on Name of the speaker in [Author]. If more than 10 references only the most recent articles are shown.

1. General Background

1.1 Estonia



(Source World factbook
<https://www.cia.gov/library/publications/resources/the-world-factbook/geos/en.html>) and Wikipedia
<http://en.wikipedia.org/wiki/>)

Estonia Estonian: Eesti officially the Republic of Estonia (Estonian: Eesti Vabariik), is a country in the Baltic region of Northern Europe. It is bordered to the north by the Gulf of Finland, to the west by the Baltic Sea, to the south by Latvia (343 km), and to the east by Lake Peipus and Russia (338.6 km). Across the Baltic Sea lies Sweden in the west and Finland in the north. The territory of Estonia consists of a mainland and 2,222 islands and islets in the Baltic Sea, covering 45,339 km² (17,505 sq mi) of land, and is influenced by a humid continental climate.



	Demographics data
Population	1,313,271
GDP (PPP) per capita	27,994\$
GDP	\$25.953 million
Unemployment rate	7%
Population growth	-0.55% (2015 est.)
Birth rate:	10.51 births/1,000 population (2015 est.)
Death rate:	12.4 deaths/1,000 population (2015 est.)
Net migration rate	-3.6 migrant(s)/1,000 population (2015 est.)
Health expenditures	5.7% of GDP (2013)
Physicians density:	3.24 physicians/1,000 population (2012)
Life expectancy at birth	total population: 76.47 years

1.2 Latvia



Latvia officially the Republic of Latvia (Latvian: Latvijas Republika), is a country in the Baltic region of Northern Europe, one of the three Baltic states. It is bordered by Estonia to the north, Lithuania to the south, Russia to the east, and Belarus to the southeast, as well as a maritime border to the west with Sweden.

Latvia has 2,070,371 inhabitants and a territory of 64,589 km² (24,938 sq mi). The country has a temperate seasonal climate.

(Source World factbook <https://www.cia.gov/library/publications/resources/the-world-factbook/geos/en.html>) and Wikipedia <http://en.wikipedia.org/wiki/>)



	Demographics data
Population	1,986,705
GDP (PPP) per capita	\$23,700 (2014)
GDP	\$48.19 billion
Unemployment rate	10.8%
Population growth	-1.06% (2015 est.)
Birth rate:	10 births/1,000 population (2015 est.)
Death rate:	14.31deaths/1,000 population (2015 est.)
Net migration rate	-6.26 migrant(s)/1,000 population (2015 est.)
Health expenditures	5.7% of GDP (2013)
Physicians density:	3.58 physicians/1,000 population (2012)
Life expectancy at birth	total population: 74.23 years

1.3 Lithuania



Source World factbook
<https://www.cia.gov/library/publications/resources/the-world-factbook/geos/en.html>) and Wikipedia
<http://en.wikipedia.org/wiki/>

Lithuania officially the Republic of Lithuania (Lithuanian: Lietuvos Respublika), is a country in Northern Europe. One of the three Baltic states, it is situated along the southeastern shore of the Baltic Sea, to the east of Sweden and Denmark. It is bordered by Latvia to the north, Belarus to the east and south, Poland to the south, and Kaliningrad Oblast (a Russian exclave) to the southwest. Lithuania has an estimated population of 2.9 million people as of 2015, and its capital and largest city is Vilnius. Lithuanians are a Baltic people



	Demographics data
Population	2,884,433
GDP (PPP) per capita	\$27,100 (2014)
GDP	\$79.63 billion
Unemployment	10.7%
Population growth	-1.04% (2015 est.)
Birth rate:	10.1 births/1,000 population (2015 est.)
Death rate:	14.27 deaths/1,000 population (2015 est.)
Net migration rate	-6.27 migrant(s)/1,000 population (2015 est.)
Health expenditures	6.2% of GDP (2013)
Physicians density:	4.12 physicians/1,000 population (2012)
Life expectancy at birth	total population: 74.69 years

2. Hepatitis

2.1 Estonia

2.1.1 VHPB survey

VHPB survey on prevention and control of viral hepatitis in 53 European countries in 2014 – November 2014 (www.vhpb.org)

PREVENTION AND CONTROL OF VIRAL HEPATITIS IN EUROPE IN 2014: THE CASE OF ESTONIA

Country profile

- Population (in millions) (year): 1.3 (2014)^a
- Gross national income per capita (int \$) (year): 24 230 (2013)^b
- Most recent seroprevalence data:

	% HBsAg + (year)	% Anti-HCV + (year)
General population	-	-
Blood donors (first time)	0.2 % (2008) ^d	0.7 % (2008) ^d
Pregnant women	-	-
Risk groups		
Injecting drug users	21.3 % (2004) ¹	96.2 % (2004) ¹
Health care workers	-	5 % (1998) ²
Haemodialysis patients	-	10.7 % (1998) ²

Screening^e

Recommended for following groups:	Hep B	Hep C
Blood and organ donors	Yes (since 1978) *	Yes (since 1994) *
Pregnant women	Yes (since 1996) *	No
Injecting drug users	No	No
STI clinic patients	No	No
Haemodialysis patients	No	No
Health care workers	No	No
MSM	No	No
Prison population	Yes (since 2013) **	Yes (since 2013) **
Migrants	No	No
Others	No	No

* Data source: North Estonia Medical Centre, Blood Center

** Data source: Prisons Department of the Ministry of Justice

National plan

There is no written national strategy or plan that focuses exclusively or primarily on the prevention and control of viral hepatitis.^f

Vaccination programs

Hepatitis A ^g	Target	Since/Period
Universal	No	
Risk group	Yes	Contacts of hepatitis patients, occupational risk, travellers to an endemic region
Hepatitis B ^{g,h}	Target	Since/Period
Universal	Yes	Newborn Adolescent (12y)
Catch-up	No	
Risk group	Yes	Occupational risk

Treatment

National guidelines for clinicians available ^f	Yes (since 2013)
Hepatitis B	Yes (since 2002, changes made in 2006, 2007, 2010 and 2012)
Hepatitis C	
Drugs available for hepatitis C treatment ^{1,f}	
Ribavirin	Yes
Pegylated interferon	Yes
Interferon alpha	Yes
Telaprevir	Yes
Boceprevir	Yes
Simeprevir	No
Sofosbuvir	No
Others: (specify)	No
Number of patients treated for hepatitis B	276 (2013) [‡]
Number of patients treated for hepatitis C	2049 (2013) [‡]

[‡] Included on the national essential medicines list or subsidized by the government

** Data source: West-Tallinn Central Hospital, Infectious Diseases Clinic

[‡] Data source: Estonian Insurance Fund

Impact

Figure 1: Hepatitis B vaccination coverage¹ and impact on hepatitis B incidence^{1,k}

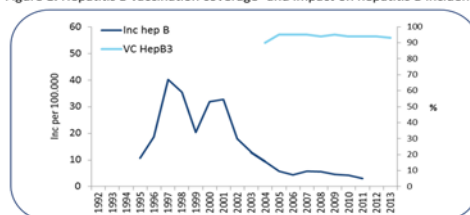
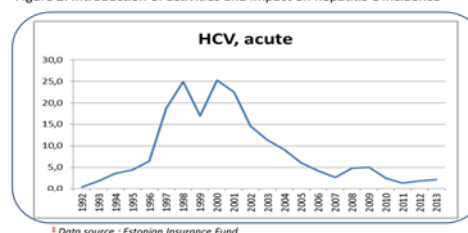


Figure 2: Introduction of activities and impact on hepatitis C incidence^{1,k}



[‡] Data source: Estonian Insurance Fund

Specific issues and future challenges

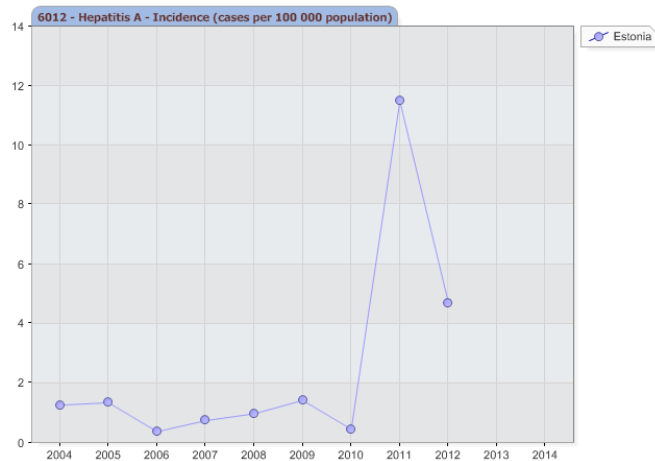
Vaccination programmes: HepB vaccination of newborns and adolescents(12 years old) is ongoing in 2014. From 2015 - continue vaccination of newborns and children, who was not vaccinated earlier. (source: Estonian Health Board)



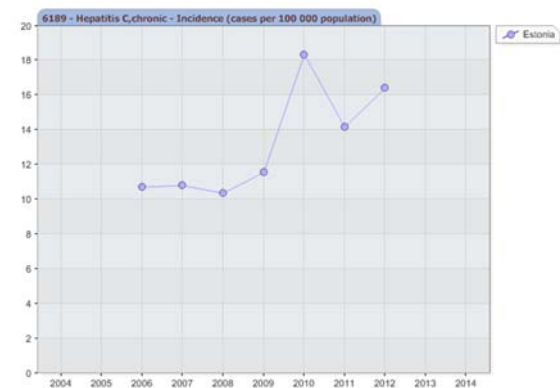
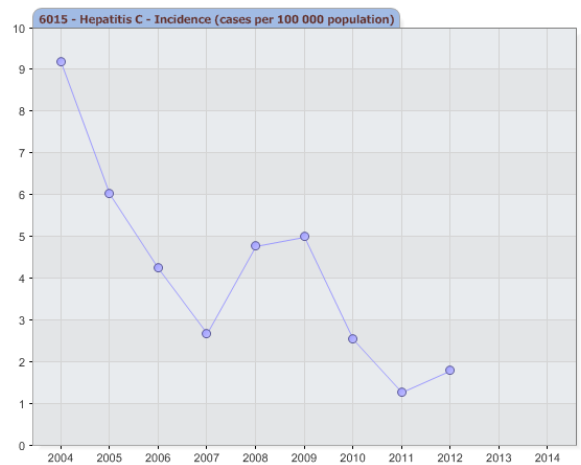
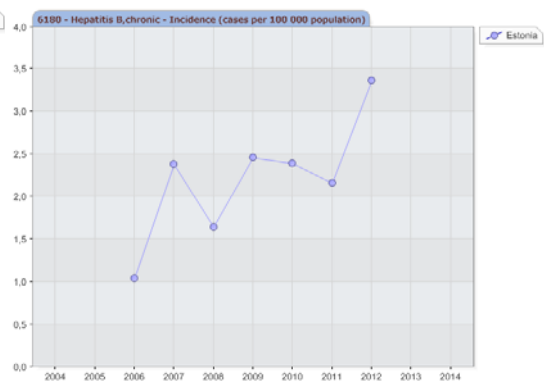
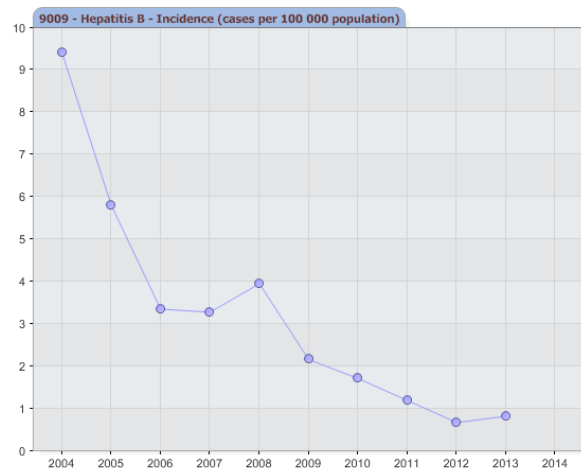
Country contact: Irina Filippova, Estonian Health Board, , irina.filippova@terviseamet.ee



WHO CISID database info (<http://data.euro.who.int/cisid/?TabID=375693>)



Chronic incidence / 100 000



2.1.2. Pubmed publications

RELATED Abstracts

Pubmed MEDLINE search on {(Hepatitis) AND (**Estonia**) } in all fields and filters used on this search 'last 10 years' on was performed. }. Manual selection. The references were manually sorted in the different subject in the EndNote database

Surveillance, diagnostics, screening

Ruutel, K., Lohmus, L. and Janes, J. "**Internet-based recruitment system for HIV and STI screening for men who have sex with men in Estonia, 2013: analysis of preliminary outcomes.**" Euro Surveill **2015** 20(15).

The aim of the current project was to develop an Internet-based recruitment system for HIV and sexually transmitted infection (STI) screening for men who have sex with men (MSM) in Estonia in order to collect biological samples during behavioural studies. In 2013, an Internet-based HIV risk-behaviour survey was conducted among MSM living in Estonia. After completing the questionnaire, all participants were offered anonymous and free-of-charge STI testing. They could either order a urine sample kit by post to screen for chlamydia infections (including lymphogranuloma venereum (LGV)), trichomoniasis, gonorrhoea and Mycoplasma genitalium infections, or visit a laboratory for HIV, hepatitis A virus, hepatitis B virus, hepatitis C virus and syphilis screening. Of 301 participants who completed the questionnaire, 265 (88%), reported that they were MSM. Of these 265 MSM, 68 (26%) underwent various types of testing. In the multiple regression analysis, Russian as the first language, previous HIV testing and living in a city or town increased the odds of testing during the study. Linking Internet-based behavioural data collection with biological sample collection is a promising approach. As there are no specific STI services for MSM in Estonia, this system could also be used as an additional option for anonymous and free-of-charge STI screening.

Ausmees, K., Selyutina, A., Kutt, K., Lippur, K., Pehk, T., Lopp, M., Zusinaite, E., Merits, A. and Kanger, T. "**Synthesis and biological activity of bimorpholine and its carbanucleoside.**" Nucleosides Nucleotides Nucleic Acids **2011** 30(11): 897-907.

A new enantiomerically pure carbacyclic nucleoside analogue with bimorpholine as a nonaromatic nucleobase was synthesized. The nucleoside analogue and bimorpholine were tested for cytotoxicity using an MTT assay and the xCELLigence System. Both assays revealed that compound 3 was highly cytotoxic at a 50 µM concentration while the cytotoxic effect of compound 1 was much less prominent. No antiretroviral activity was detected for this compound. In contrast, it acted as a potent inhibitor of hepatitis C virus (HCV) replication. Most likely this effect originates largely from the cytotoxicity of the compound; however, it is possible that a specific mechanism of HCV inhibition also exists.

Epidemiology

Ivanova, A., Tefanova, V., Reshetnjak, I., Kuznetsova, T., Geller, J., Lundkvist, A., Janson, M., Neare, K., Velstrom, K., Jokelainen, P., et al. "**Hepatitis E Virus in Domestic Pigs, Wild Boars, Pig Farm Workers, and Hunters in Estonia.**" Food Environ Virol **2015**.

While hepatitis E is a growing health concern in Europe, epidemiological data on hepatitis E virus (HEV) in Estonia are scarce. Along with imported HEV infections, autochthonous cases are reported from European countries. Both domestic and wild animals can be a source of human cases of this zoonosis. Here, we investigated the presence of anti-HEV antibodies and HEV RNA

in domestic pigs and wild boars, as well as in pig farm workers and hunters in Estonia. Anti-HEV antibodies were detected in 234/380 (61.6 %) of sera from domestic pigs and in all investigated herds, and in 81/471 (17.2 %) of meat juice samples from wild boars. HEV RNA was detected by real-time PCR in 103/449 (22.9 %) of fecal samples from younger domestic pigs and 13/81 (16.0 %) of anti-HEV-positive wild boar samples. Analysis of sera from 67 pig farm workers and 144 hunters revealed the presence of HEV-specific IgG in 13.4 and 4.2 % of the samples, respectively. No HEV RNA was detected in the human serum samples. Phylogenetic analyses of HEV sequences from domestic pigs and wild boars, based on a 245 bp fragment from the open reading frame 2 showed that all of them belonged to genotype 3. The present study demonstrates the presence of HEV in Estonian domestic pig and wild boar populations, as well as in humans who have direct regular contact with these animals. Our results suggest that HEV infections are present in Estonia and require attention.

Paat, G., Uuskula, A., Tefanova, V., Tallo, T., Priimagi, L. and Ahi, K. **"The trends and risk factors for hepatitis B occurrence in Estonia."** *Cent Eur J Public Health* **2009** 17(2): 108-111.

Hepatitis B virus (HBV) infection is prevalent worldwide and is a significant cause of morbidity and mortality. This article describes the trend in HBV occurrence in Estonia from 1990 to 2005 in Estonia, with the aim of highlighting key determinants in transmission dynamics, risk groups, and possible implications for prevention and control. A marked increase in reported numbers of new HBV cases occurred in mid 1990s (reaching 39 per 100,000 population) and decline thereafter. We present data on HBV prevalence from different population groups (persons with verified sexually transmitted infection, prisoners, medical personnel, blood donors and injection drug users). Special vaccination programmes introduced in Estonia have been successful in the prevention of HBV, however, we suggest that the main risk groups such as injection drug users (IDUs), men having sex with men (MSM) and HIV infected persons should be actively encompassed into HBV vaccination programme.

Tallo, T., Tefanova, V., Priimagi, L., Schmidt, J., Katargina, O., Michailov, M., Mukomolov, S., Magnius, L. and Norder, H. **"D2: major subgenotype of hepatitis B virus in Russia and the Baltic region."** *J Gen Virol* **2008** 89(Pt 8): 1829-1839.

Complete or almost complete hepatitis B virus (HBV) genomes were sequenced for 13 genotype A and 42 genotype D strains from the former USSR. The strains were classifiable within subgenotypes A2, D1, D2 and D3. Comparison of the deduced gene products for the four ORFs of 89 genotype D strains revealed 27 subgenotype-specific residues, and a region spanning residues 58-128 in the spacer region of the P gene could be used to distinguish between D1 and D4. This enabled the allocation to subgenotype of strains with partially sequenced genomes. D2 was dominating, while D3 was found in low frequency in the whole region. D1 was most prevalent in the Middle Asian Republics. Mean inter-subgenotype divergences between D1 and D2, D1 and D3 and D2 and D3 were 2.7, 3.4 and 3.4 %, respectively. The intra-subgenotype divergence was 0.4, 1.1, 1.0 and 1.8 % for A2, D1, D2 and D3, respectively. All D1 and D3 strains encoded subtype ayw2, whereas most D2 strains encoded ayw3. Two D2 strains encoded ayw4. Strains with identical S genes were closely related at the level of complete genomes and formed geographically specific clades with low intraclade divergences, possibly indicating past iatrogenic spread. It is not clear whether the finding of four subgenotypes in the area corresponds to separate introductions of the virus or to previous population migrations into the area. An earlier introduction of D3 compared with D2 was supported by its higher intra-subgenotype divergence, while the lower divergence within D1 is probably due to a more recent emergence.

Tallo, T., Norder, H., Tefanova, V., Krispin, T., Schmidt, J., Ilmoja, M., Orgulas, K., Pruunsild, K., Priimagi, L. and Magnius, L. O. **"Genetic characterization of hepatitis C virus strains in Estonia: fluctuations in the predominating subtype with time."** *J Med Virol* **2007** 79(4): 374-382.

During the last decade, there has been a dramatic increase in intravenous drug use in young adults in Estonia with an increased incidence of both hepatitis B and C as a consequence. Since genetic data are limited regarding hepatitis C virus (HCV) strains in Estonia, the aim of the study

was to characterize HCV strains in different risk groups to determine their relatedness to strains from other geographical regions. Three hundred fifty-three anti-HCV positive sera collected during 1994-2004 from hospitalized patients, blood donors and health care workers were used as source of HCV RNA. Two hundred nine (59%) of the sera were positive for HCV RNA by PCR directed to the 5'-UTR region. For 174 strains the HCV subtype was determined by analyses of the NS5B and/or the 5'UTR-core regions. 1b (71%) was the most common subtype followed by 3a (24%), 2c (2%), 1a (1%), and 2a (1%). The 1b and 3a strains were similar to strains from other regions of the former USSR. Within genotype 1b there were several HCV lineages. However, for 3a there seemed to be two separate introductions into Estonia. There was a relative shift from subtype 1b to 3a in 1999-2000 with a further replacement of 3a with 1b in intravenous drug users in 2001 and onwards ($P < 0.05$). However, both subtypes were found to co-circulate in the community independent of risk factors. One patient was infected with the 2k/1b recombinant presumed to originate from St. Petersburg being the first isolate of this recombinant recovered outside Russia.

Prevention

Meriste, S., Lutsar, I., Tamm, E. and Willems, P. **"Safety and immunogenicity of a primary course and booster dose of a combined diphtheria, tetanus, acellular pertussis, hepatitis B and inactivated poliovirus vaccine."** *Scand J Infect Dis* **2006** 38(5): 350-356.

Primary immunization at 3, 4.5, and 6 months and boosting between 15 and 27 months of age with combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus (DTPa-HBV-IPV) vaccine was compared with separate administration of DTPa-HBV and IPV to healthy children (trials DTPa-HBV-IPV-019/033). Antibody titres were measured before and 1 month after primary and booster courses. Solicited local and general symptoms were recorded using diary cards. One month after primary vaccination, all children in both groups developed antibody titres above the assay cut-off for all vaccine components. Significantly higher anti-diphtheria, anti-pertactin (PRN) and anti-polio GMTs were measured following DTPa-HBV-IPV than DTPa-HBV plus IPV. Prior to boosting similar seroprotection/seropositivity rates were recorded in both groups. After boosting all children had seroprotective levels of diphtheria, tetanus, polio and HBV. Criteria for pertussis vaccine response were fulfilled in most children. Significantly higher anti-PRN GMTs were measured following DTPa-HBV-IPV than DTPa-HBV plus IPV. There was no difference between groups in the incidence or intensity of local and general symptoms after primary or booster vaccination, except for fever which was more frequent after the booster dose in the combined vaccine group. Both vaccine regimens were well tolerated and immunogenic, however the combined administration has the advantage of being administered as a single injection.

Risk groups

Soodla, P., Rajasaar, H., Avi, R., Zilmer, K., Kink, K., Novikova, L., Huik, K., Maimets, M. and Lutsar, I. **"Design and structure of the Estonian HIV Cohort Study (E-HIV)."** *Infect Dis (Lond)* **2015** 47(11): 772-779.

BACKGROUND: Estonia is experiencing the new Eastern Europe human immunodeficiency virus (HIV) epidemic, with the highest incidence of new infections in the EU. We describe demographic changes, HIV-related laboratory parameters and co-infections during the concentrated HIV epidemic using the Estonian HIV Cohort Study (E-HIV) database, founded in 2009. METHODS: All 3750 subjects in the E-HIV database on December 31, 2013 were included. Subjects were divided into risk groups: people who inject drugs (PWIDs), sexual transmission (heterosexual/homosexual), and other (perinatal) or unknown risk group. Subjects diagnosed before 2009 (first period) and after (second period) were analyzed separately. RESULTS: The

mean age at diagnosis has increased from 22.8 years (interquartile range (IQR) = 19.5-27.2) to 29.7 years (IQR = 25.3-36.2) ($p < 0.001$) between the first and second periods. PWIDs were younger than other transmission groups (23.2 vs 27.1; $p < 0.001$). There is a statistical difference in the route of transmission among genders, with overall increasing sexual transmission. The most common AIDS-defining illness was tuberculosis (0.5%). HIV/hepatitis C (HCV) co-infection was diagnosed in 42% of cases. The population median CD4 + cell count at diagnosis has declined over the years; in total 53% have been late presenters. Half of the patients are receiving antiretroviral treatment (cART). The most common combinations are nucleoside reverse transcriptase inhibitor (NRTI) backbone plus protease inhibitors (PIs) (57%) or NRTI backbone + non-NRTIs (42%). **CONCLUSION:** The E-HIV enables us to fill the gap in the lack of data on the course of the new Eastern European HIV epidemic. These data demonstrate that the HIV epidemic in Estonia is moving from PWIDs to the general population, suggesting that prevention measures and testing guidelines should be revised.

Perlman, D. C., Jordan, A. E., Uuskula, A., Huong, D. T., Masson, C. L., Schackman, B. R. and Des Jarlais, D. C. **"An international perspective on using opioid substitution treatment to improve hepatitis C prevention and care for people who inject drugs: Structural barriers and public health potential."** *Int J Drug Policy* **2015**.

People who inject drugs (PWID) are central to the hepatitis C virus (HCV) epidemic. Opioid substitution treatment (OST) of opioid dependence has the potential to play a significant role in the public health response to HCV by serving as an HCV prevention intervention, by treating non-injection opioid dependent people who might otherwise transition to non-sterile drug injection, and by serving as a platform to engage HCV infected PWID in the HCV care continuum and link them to HCV treatment. This paper examines programmatic, structural and policy considerations for using OST as a platform to improve the HCV prevention and care continuum in 3 countries-the United States, Estonia and Viet Nam. In each country a range of interconnected factors affects the use OST as a component of HCV control. These factors include (1) that OST is not yet provided on the scale needed to adequately address illicit opioid dependence, (2) inconsistent use of OST as a platform for HCV services, (3) high costs of HCV treatment and health insurance policies that affect access to both OST and HCV treatment, and (4) the stigmatization of drug use. We see the following as important for controlling HCV transmission among PWID: (1) maintaining current HIV prevention efforts, (2) expanding efforts to reduce the stigmatization of drug use, (3) expanding use of OST as part of a coordinated public health approach to opioid dependence, HIV prevention, and HCV control efforts, (4) reductions in HCV treatment costs and expanded health system coverage to allow population level HCV treatment as prevention and OST as needed. The global expansion of OST and use of OST as a platform for HCV services should be feasible next steps in the public health response to the HCV epidemic, and is likely to be critical to efforts to eliminate or eradicate HCV.

Jarlais, D. D. **"Systematic review research on needle/syringe programs and opiate substitution programs in low- and middle-income countries."** *J Food Drug Anal* **2013** 21(4): S59-S61.

Persons who inject drugs (PWID) are at an elevated risk for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection. In many high-income countries, needle and syringe exchange programs (NSPs) have been associated with reductions in blood-borne infections. However, we do not have a good understanding of the effectiveness of NSP in low/middle-income and transitional-economy countries. A systematic literature review based on PRISMA guidelines was utilized to collect primary study data on coverage of NSP programs and changes in HIV and HCV infection over time among PWID in low- and middle-income and transitional countries (LMICs). Included studies reported laboratory measures of either HIV or HCV and at least 50% coverage of the local injecting population (through direct use or through secondary exchange). We also included national reports on newly reported HIV cases for countries that had national level data for PWID in conjunction with NSP scale-up and implementation. Studies of 11 NSPs with high-coverage from Bangladesh, Brazil, China, Estonia, Iran, Lithuania, Taiwan, Thailand, and Vietnam were included in the review. In five studies, HIV prevalence decreased (range -3% to -15%) and in three studies HCV prevalence decreased (range -4.2% to -10.2%). In

two studies, HIV prevalence increased (range +5.6% to +14.8%). HCV incidence remained stable in one study. Of the four national reports of newly reported HIV cases, three reported decreases during NSP expansion, ranging from -30% to -93.3%, whereas one national report documented an increase in cases (+37.6%). Estimated incidence among new injectors decreased in three studies, with reductions ranging from -11/100 person years at risk to -16/100 person years at risk. While not fully consistent, the data generally support the effectiveness of NSP in reducing HIV and HCV infection in low/middle-income and transitional-economy countries. If high coverage is achieved, NSP appear to be as effective in LMICs as in high-income countries. Additional monitoring and evaluation research is needed for NSPs where reductions in HIV/HCV infection among PWID are not occurring in order to identify and correct contributing problems.

Huik, K., Avi, R., Carrillo, A., Harper, N., Pauskar, M., Sadam, M., Karki, T., Krispin, T., Kongo, U. K., Jermilova, T., et al. **"CCR5 haplotypes influence HCV serostatus in Caucasian intravenous drug users."** *PLoS One* **2013** 8(7): e70561.

BACKGROUND: Up to 90% HIV-1 positive intravenous drug users (IDUs) are co-infected with HCV. Although best recognized for its function as a major co-receptor for cell entry of HIV, CC chemokine receptor 5 (CCR5) has also been implicated in the pathogenesis of HCV infection. Here, we investigated whether CCR5 haplotypes influence HIV-1 and HCV seropositivity among 373 Caucasian IDUs from Estonia. **METHODS:** Of these IDUs, 56% and 44% were HIV and HCV seropositive, respectively, and 47% were coinfectd. 500 blood donors seronegative for HIV and HCV were also evaluated. CCR5 haplotypes (HHA to HHG*2) were derived after genotyping nine CCR2-CCR5 polymorphisms. The association between CCR5 haplotypes with HIV and/or HCV seropositivity was determined using logistic regression analysis. Co-variables included in the models were length of intravenous drug use, HBV serostatus and copy number of CCL3L1, the gene encoding the most potent HIV-suppressive chemokine and ligand for CCR5. **RESULTS:** Compared to IDUs seronegative for both HCV and HIV (HCV-/HIV-), IDUs who were HCV+/HIV- and HCV+/HIV+ were 92% and 82%, respectively, less likely to possess the CCR5-HHG*1 haplotype, after controlling for co-variables ($P(\text{adjusted}) = 1.89 \times 10^{-4}$ and 0.003, respectively). This association was mostly due to subjects bearing the CCR5 HHE and HHG*1 haplotype pairs. Approximately 25% and <10% of HCV-/HIV- IDUs and HCV-/HIV- blood donors, respectively, possessed the HHE/HHG*1 genotype. **CONCLUSIONS:** Our findings suggest that HHG*1-bearing CCR5 genotypes influence HCV seropositivity in a group of Caucasian IDUs.

Des Jarlais, D. C., Feelemyer, J. P., Modi, S. N., Abdul-Quader, A. and Hagan, H. **"High coverage needle/syringe programs for people who inject drugs in low and middle income countries: a systematic review."** *BMC Public Health* **2013** 13: 53.

BACKGROUND: Persons who inject drugs (PWID) are at an elevated risk for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection. In many high-income countries, needle and syringe exchange programs (NSP) have been associated with reductions in blood-borne infections. However, we do not have a good understanding of the effectiveness of NSP in low/middle-income and transitional-economy countries. **METHODS:** A systematic literature review based on PRISMA guidelines was utilized to collect primary study data on coverage of NSP programs and changes in HIV and HCV infection over time among PWID in low-and middle-income and transitional countries (LMICs). Included studies reported laboratory measures of either HIV or HCV and at least 50% coverage of the local injecting population (through direct use or through secondary exchange). We also included national reports on newly reported HIV cases for countries that had national level data for PWID in conjunction with NSP scale-up and implementation. **RESULTS:** Studies of 11 NSPs with high-coverage from Bangladesh, Brazil, China, Estonia, Iran, Lithuania, Taiwan, Thailand and Vietnam were included in the review. In five studies HIV prevalence decreased (range -3% to -15%) and in three studies HCV prevalence decreased (range -4.2% to -10.2%). In two studies HIV prevalence increased (range +5.6% to +14.8%). HCV incidence remained stable in one study. Of the four national reports of newly reported HIV cases, three reported decreases during NSP expansion, ranging from -30% to -93.3%, while one national report documented an increase in

cases (+37.6%). Estimated incidence among new injectors decreased in three studies, with reductions ranging from -11/100 person years at risk to -16/100 person years at risk.

CONCLUSIONS: While not fully consistent, the data generally support the effectiveness of NSP in reducing HIV and HCV infection in low/middle-income and transitional-economy countries. If high coverage is achieved, NSP appear to be as effective in LMICs as in high-income countries. Additional monitoring and evaluation research is needed for NSPs where reductions in HIV/HCV infection among PWID are not occurring in order to identify and correct contributing problems.

Uuskula, A., Fischer, K., Raudne, R., Kilgi, H., Krylov, R., Salminen, M., Brummer-Korvenkontio, H., St Lawrence, J. and Aral, S. **"A study on HIV and hepatitis C virus among commercial sex workers in Tallinn."** *Sex Transm Infect* **2008** 84(3): 189-191.

INTRODUCTION: Estonia is confronted by a dramatic expansion of the initially injection drug use-driven HIV epidemic. Little is known about HIV occurrence in population groups at high risk other than injection drug users. OBJECTIVE: To obtain data on the prevalence of HIV and hepatitis C virus (HCV) among female sex workers (FSW) in Tallinn. DESIGN: An unlinked, anonymous, cross-sectional survey of FSW recruited in Tallinn from October 2005 to May 2006. METHODS: 227 FSW were recruited for the survey and biological sample collection (HIV, HCV antibodies detection) using a combination of time-location, community and respondent-driven sampling. RESULTS: Among 227 women the HIV and HCV prevalences were 7.6% (95% CI 4.6% to 12.5%) and 7.9% (95% CI 4.5% to 12.6%), respectively. HIV prevalence was higher among FSW working in the street (odds ratio (OR) 6.4; 95% CI 1.1 to 35.6) and at the brothels and apartments supervised by the organised sex industry (OR 5.0; 95% CI 1.3 to 18.4). The duration of sex work was negatively associated with HIV prevalence (OR 0.78; 95% CI 0.63 to 0.97). CONCLUSIONS: Prevention needs of FSW in this area include increasing rates of HIV testing and putting in place effective programmes that can help extend HIV prevention behaviours across a range of sexual and drug use risk behaviours.

Uuskula, A., McNutt, L. A., Dehovitz, J., Fischer, K. and Heimer, R. **"High prevalence of blood-borne virus infections and high-risk behaviour among injecting drug users in Tallinn, Estonia."** *Int J STD AIDS* **2007** 18(1): 41-46.

The HIV epidemic in Estonia is rapidly expanding, and injection drug users (IDUs) are the major risk group contributing to the expansion. A convenience sample of 159 IDUs visiting syringe-exchange programmes (SEPs) was selected to quantify the association of HIV-risk behaviours and blood-borne infections. A high prevalence of HIV, hepatitis B core antibody (HBVcore), hepatitis B surface antigen (HbsAg) and hepatitis C virus antibodies (56, 85.1, 21.3, and 96.2%, respectively) was associated with high-risk injections, unsafe sexual behaviour and alcohol abuse. These findings emphasize the importance of evidence-based secondary prevention among the HIV-infected, especially given the uncertain sustainability of antiretroviral and substance abuse treatments.

Uuskula, A., Heimer, R., Dehovitz, J., Fischer, K. and McNutt, L. A. **"Surveillance of HIV, hepatitis B virus, and hepatitis C virus in an estonian injection drug-using population: sensitivity and specificity of testing syringes for public health surveillance."** *J Infect Dis* **2006** 193(3): 455-457.

Surveillance of bloodborne infections among injection drug users (IDUs) can be accomplished by determining the presence of pathogen markers in used syringes. Parallel testing of returned syringes and venous blood from IDUs was conducted to detect antibodies to human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). Syringe surveillance for HIV yielded a sensitivity and specificity of 92% and 89%, respectively, and provided a reasonable estimate of the prevalence of HIV among participants. Because sensitivity for HBV (34%) and HCV (55%) was low, syringe testing may be useful for surveillance of hepatitis over time but not for estimation of prevalence.

Tefanova, V., Tallo, T., Kutsar, K. and Priimgi, L. **"Urgent action needed to stop spread of hepatitis B and C in Estonian drug users."** *Euro Surveill* **2006** 11(1): E060126 060123.

Ruutel, K. and Uuskula, A. **"HIV epidemic in Estonia in the third decade of the AIDS era."** *Scand J Infect Dis* **2006** 38(3): 181-186.

This article describes current trends of HIV/AIDS and related conditions in Estonia, with the aim of highlighting key determinants in transmission dynamics and risk groups, problems and barriers of combating HIV/AIDS, and possible implications for prevention and control. Throughout the transition period Estonia has experienced major changes in political, economic, and social structure which all have contributed to increased violence, high-risk sexual behaviour, and substance abuse. Incidences of hepatitis B, C and sexually transmitted infections (STIs) increased in the early 1990s. HIV outbreaks were first detected among injecting drug users (IDUs) in 2000 and are still concentrated among this population group. High rates of sexual risk behaviour and inadequate knowledge regarding prevention of disease transmission in Estonia emphasizes the threat of a sex-related and STI facilitated driven HIV epidemic. To prevent further spread of HIV it is necessary to implement harm reduction interventions among IDUs. However, without effective management of socioeconomic and administrative barriers to health care and other services, an explicit policy on drugs will not reach marginalized groups and will not be able to prevent a further spread of these interrelated epidemics.

Treatment and Clinical

Dontsenko, I., Kerbo, N., Pullmann, J., Plank, S., Vozelevskaja, N. and Kutsar, K. **"Preliminary report on an ongoing outbreak of hepatitis A in Estonia, 2011."** *Euro Surveill* **2011** 16(42).

Since the beginning of August 2011, an outbreak of hepatitis A has been detected in Estonia. The majority of laboratory-confirmed cases (n = 66) were notified between 4 August and 3 October 2011 and were linked to Viljandi county. The outbreak is still ongoing.

Vali, T., Tein, A., Tikk, T. and Sillakivi, T. **"Surgical complications accompanying liver transplantation in Estonia."** *Transplant Proc* **2010** 42(10): 4455-4456.

The purpose of this study was to evaluate surgical complications accompanying the introduction of orthotopic liver transplantation (OLT) in Estonia. Between 1999 and 2009, we performed the first 12 liver transplantations. Eight patients were males and four were females of age range 12 to 67 years. Their diagnoses were cholestatic disease (n = 5); tumor (n = 3); hepatitis C virus cirrhosis (n = 2); Budd-Chiari syndrome (n = 1); and cystic fibrosis (n = 1). Technical complications occurred in 7/12 patients. The early vascular complications in two patients were a suprahepatic vena cava lesion occurring at liver extraction, which resulted in uncontrolled suprahepatic bleeding after liver perfusion; the recipient died during transplantation. The other case displayed a right intrahepatic portal venous thrombosis, which was treated successfully with thrombolysis and anticoagulant therapy. Early biliary complications of biliary leaks occurred in three patients: two had undergone duct-to-duct reconstructions, which were treated by endoscopic retrograde cholangiography that successfully managed the anastomotic and recipient cystic duct leaks with a papillotomy and stenting. In one patient with a duct-to-jejunum anastomosis, a bile leak stopped at 3 weeks but he needed surgical therapy 2 years later due to an anastomotic stricture. Severe decubitus occurred in the lumbosacral region of the subjects with operating times of 14 hours. They required necrectomy and plastic surgery. One of them with postoperative intra-abdominal hypertension also displayed wound eventration requiring reoperations. The rate of hepatic (5/12) and extrahepatic (3/12) surgical complications, as well as of 1-year survival (9/12), in our period of implementation of OLT were satisfactory to continue OLT development in Estonia.

Research

Karelson, M., Dobchev, D. A., Karelson, G., Tamm, T., Tamm, K., Nikonov, A., Mutso, M. and Merits, A. **"Fragment-based development of HCV protease inhibitors for the treatment of hepatitis C."** *Curr*

Comput Aided Drug Des **2012** 8(1): 55-61.

A novel computational technology based on fragmentation of the chemical compounds has been used for the fast and efficient prediction of activities of prospective protease inhibitors of the hepatitis C virus. This study spans over a discovery cycle from the theoretical prediction of new HCV NS3 protease inhibitors to the first cytotoxicity experimental tests of the best candidates. The measured cytotoxicity of the compounds indicated that at least two candidates would be suitable further development of drugs.

Ausmees, K., Selyutina, A., Kutt, K., Lippur, K., Pehk, T., Lopp, M., Zusinaite, E., Merits, A. and Kanger, T.

"Synthesis and biological activity of bimorpholine and its carbanucleoside." Nucleosides Nucleotides Nucleic Acids **2011** 30(11): 897-907.

A new enantiomerically pure carbacyclic nucleoside analogue with bimorpholine as a nonaromatic nucleobase was synthesized. The nucleoside analogue and bimorpholine were tested for cytotoxicity using an MTT assay and the xCELLigence System. Both assays revealed that compound 3 was highly cytotoxic at a 50 μ M concentration while the cytotoxic effect of compound 1 was much less prominent. No antiretroviral activity was detected for this compound. In contrast, it acted as a potent inhibitor of hepatitis C virus (HCV) replication. Most likely this effect originates largely from the cytotoxicity of the compound; however, it is possible that a specific mechanism of HCV inhibition also exists.

Paat, G., Uuskula, A., Tefanova, V., Tallo, T., Priimagi, L. and Ahi, K. **"The trends and risk factors for hepatitis B occurrence in Estonia."** Cent Eur J Public Health **2009** 17(2): 108-111.

Hepatitis B virus (HBV) infection is prevalent worldwide and is a significant cause of morbidity and mortality. This article describes the trend in HBV occurrence in Estonia from 1990 to 2005 in Estonia, with the aim of highlighting key determinants in transmission dynamics, risk groups, and possible implications for prevention and control. A marked increase in reported numbers of new HBV cases occurred in mid 1990s (reaching 39 per 100,000 population) and decline thereafter. We present data on HBV prevalence from different population groups (persons with verified sexually transmitted infection, prisoners, medical personnel, blood donors and injection drug users). Special vaccination programmes introduced in Estonia have been successful in the prevention of HBV, however, we suggest that the main risk groups such as injection drug users (IDUs), men having sex with men (MSM) and HIV infected persons should be actively encompassed into HBV vaccination programme.

Thjodleifsson, B., Olafsson, I., Gislason, D., Gislason, T., Jogi, R. and Janson, C. **"Infections and obesity: A multinational epidemiological study."** Scand J Infect Dis **2008** 40(5): 381-386.

Viral infections have been associated with the aetiology of obesity in animal models. This study investigates the association between 7 serological markers of infections and body mass index (BMI) in a population based sample. Individuals ($n=985$, mean age 42 ± 9.7 (28-55) y, mean BMI $25.594.2$) from Iceland, Sweden and Estonia underwent a structured interview and blood sampling. IgG antibodies were measured against *Helicobacter pylori* and the cagA protein, hepatitis A virus, *Toxoplasma gondii*, herpes simplex virus 1, *Chlamydia pneumoniae*, Epstein-Barr virus and cytomegalovirus. High-sensitive C-reactive protein (CRP) was measured as a marker of systemic inflammation. A significant positive association between being overweight (BMI 25 kg/m^2) and IgG antibodies was found for *Helicobacter pylori* (OR 1.86, CI 1.34-2.60) and *Chlamydia pneumoniae* (OR 1.39, CI 1.03-1.88) and combined seropositivity had synergistic effect (OR 2.54 (1.62-3.97)). CRP was positively related to BMI ($p<0.0001$), whereas no significant association was found between CRP and IgG antibodies against *Helicobacter pylori* and/or *Chlamydia pneumoniae* and CRP. The results suggest that infections with *Chlamydia pneumoniae* and *Helicobacter pylori* are both significantly and synergistically associated with overweight and this association is not related to indicators of systemic inflammation.

Nikonov, A., Juronen, E. and Ustav, M. **"Functional characterization of fingers subdomain-specific monoclonal antibodies inhibiting the hepatitis C virus RNA-dependent RNA polymerase."** J Biol Chem **2008** 283(35): 24089-24102.

The hepatitis C virus (HCV) RNA-dependent RNA polymerase (RdRp), encoded by nonstructural protein 5B (NS5B), is absolutely essential for the viral replication. Here we describe the development, characterization, and functional properties of the panel of monoclonal antibodies (mAbs) and specifically describe the mechanism of action of two mAbs inhibiting the NS5B RdRp activity. These mAbs recognize and bind to distinct linear epitopes in the fingers subdomain of NS5B. The mAb 8B2 binds the N-terminal epitope of the NS5B and inhibits both primer-dependent and de novo RNA synthesis. mAb 8B2 selectively inhibits elongation of RNA chains and enhances the RNA template binding by NS5B. In contrast, mAb 7G8 binds the epitope that contains motif G conserved in viral RdRps and inhibits only primer-dependent RNA synthesis by specifically targeting the initiation of RNA synthesis, while not interfering with the binding of template RNA by NS5B. To reveal the importance of the residues of mAb 7G8 epitope for the initiation of RNA synthesis, we performed site-directed mutagenesis and extensively characterized the functionality of the HCV RdRp motif G. Comparison of the mutation effects in both in vitro primer-dependent RdRp assay and cellular transient replication assay suggested that mAb 7G8 epitope amino acid residues are involved in the interaction of template-primer or template with HCV RdRp. The data presented here allowed us to describe the functionality of the epitopes of mAbs 8B2 and 7G8 in the HCV RdRp activity and suggest that the epitopes recognized by these mAbs may be useful targets for antiviral drugs.

Kiiver, K., Merits, A., Ustav, M. and Zusinaite, E. **"Complex formation between hepatitis C virus NS2 and NS3 proteins."** *Virus Res* **2006** 117(2): 264-272.

Hepatitis C virus (HCV) NS2 and NS3 proteins as well as the NS3 protease cofactor NS4A are essential for the replication of the virus. The presence of in vivo heterodimeric complex between HCV NS2 and NS3 has been suggested by biochemical studies. Detailed characterization of the interactions between these viral proteins is of great importance for better understanding their role in viral replication cycle and represents attractive target for antiviral agents. In this study, we demonstrated in vivo interactions between HCV NS2 and NS3 proteins using an epitope tagging technique. For this purpose NS2, NS3 and NS4A were expressed in fusion with two different tags in Cos7 cells. Immunofluorescence analysis and co-immunoprecipitation with tag-specific antibodies revealed the existence of biologically important NS3/NS4A and NS3/NS2 complexes. Similar complexes were detected also in Huh7 cells infected with Semliki Forest virus vectors expressing NS2 and NS3 or NS23 precursor polyprotein. The formation of complex between NS2 and NS3 was found not to depend on whether the proteins were expressed individually or in form of common precursor. This observation suggests the existence of direct interaction between these two proteins that may have importance for the formation of the whole HCV replication complex.

Zusinaite, E., Metskula, K. and Salupere, R. **"Autoantibodies and hepatitis C virus genotypes in chronic hepatitis C patients in Estonia."** *World J Gastroenterol* **2005** 11(4): 488-491.

AIM: To determine the prevalence of several autoantibodies in chronic hepatitis C patients, and to find out whether the pattern of autoantibodies was associated with hepatitis C virus (HCV) genotypes. METHODS: Sera from 90 consecutive patients with chronic hepatitis C were investigated on the presence of anti-nuclear (ANA), anti-mitochondrial (AMA), anti-smooth muscle (SMA), anti-liver-kidney microsomal type 1 (LKMA1), anti-parietal cell (PCA), anti-thyroid microsomal (TMA), and anti-reticulin (ARA) autoantibodies. The autoantibodies were identified by indirect immunofluorescence. HCV genotypes were determined by a restriction fragment length polymorphism analysis of the amplified 5' noncoding genome region. RESULTS: Forty-six (51.1%) patients were positive for at least one autoantibody. Various antibodies were presented as follows: ANA in 13 (14.4%) patients, SMA in 39 (43.3%), TMA in 2 (2.2%), and ARA in 1 (1.1%) patients. In 9 cases, sera were positive for two autoantibodies (ANA and SMA). AMA, PCA and LKMA1 were not detected in the observed sera. HCV genotypes were distributed as follows: 1b in 66 (73.3%) patients, 3a in 18 (20.0%), and 2a in 6 (6.7%) patients. CONCLUSION: A high prevalence of ANA and SMA can be found in chronic hepatitis C patients. Autoantibodies are present at low titre (1:10) in most of the cases. Distribution of the autoantibodies show no differences in the sex groups and between patients infected with different HCV genotypes.

2.2 Latvia

2.2.1 VHPB survey

VHPB survey on prevention and control of viral hepatitis in 53 European countries in 2014 – November 2014 (www.vhpb.org)

PREVENTION AND CONTROL OF VIRAL HEPATITIS IN EUROPE IN 2014: THE CASE OF LATVIA

Country profile

- Population (in millions) (year): 2 (2014)^a
- Gross national income per capita (int \$) (year): 22 970(2013)^b
- Most recent seroprevalence data:

	% HBsAg + (year)	% Anti-HCV + (year)
General population	-	2.4 % (2011) ¹
Blood donors (first time)	0.5 % (2013) ²	1.5% (2013) ²
Pregnant women	0.7% (2008) ³	-
Risk groups		
Injecting drug users	3.0% (2013) ⁴	83.7% (2013) ⁴
Men having sex with men	8.8% (2013) ⁵	2.0% (2013) ⁵
Prison population	7% (2014) ⁶	34% (2014) ⁶
STI clinic patients	-	-

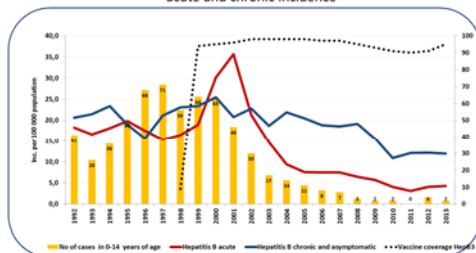
Screening

Recommended for following groups:	Hep B	Hep C
Blood and organ donors	Yes (since 1979)	Yes (since 1994)
Pregnant women	Yes (since 1990)	No
Injecting drug users	No	No
STI clinic patients	No	No
Haemodialysis patients	No	No
Health care workers	Yes, if not vaccinated, (since 2000)	No
Men having sex with men	No	No
Prison population	No	No
Migrants	No	No
Others	Household and other contacts after exposure ⁸ (since 2006)	Household and other contacts after exposure ⁸ (since 2006)

National plan

Action Plan for the Elimination of HIV Infection, Sexually Transmitted Infections and Hepatitis B and C for 2015-2017 (under development).

Figure 1: Hepatitis B vaccination coverage and impact on hepatitis B acute and chronic incidence¹⁰



Vaccination programs

Hepatitis A		Target	Since/Period
Universal	No		
Risk group	No		
Hepatitis B ⁷			
Universal	Yes	Infant (0-24 hours after birth) (2,4,6 and 12 months of age)	1997-2009 2010-ongoing
Catch-up	Yes	14y	2006-ongoing
Risk group	Yes	Neonates born to HBsAg+ or not tested mothers (0-12 hours after birth); HCW and other occupational risk; Haemodialysis patients;	2000-ongoing 2009-ongoing;

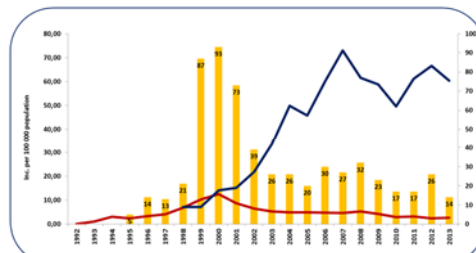
Treatment

National guidelines for clinicians available	Yes (updated in 2010)
Hepatitis B	Yes (2005, currently is being updated)
Hepatitis C	
Drugs available for hepatitis C treatment*	
Ribavirin	Yes (since 2005)
Pegylated interferon	Yes (since 2005)
Interferon alpha	Yes (since 1994)
Telaprevir	No
Boceprevir	No
Simeprevir	No
Sofosbuvir	No
Daclatasvir	No
Abt450/R	No
Ombitasvir	No
Dasabuvir	No
Number of patients treated for hepatitis B	128 (2013) ⁹
Number of patients treated for hepatitis C	799 (2013) ⁹

*included on the national essential medicines list or subsidized by the government

Impact

Figure 2 Impact on hepatitis C acute and chronic incidence¹⁰



Specific issues and future challenges

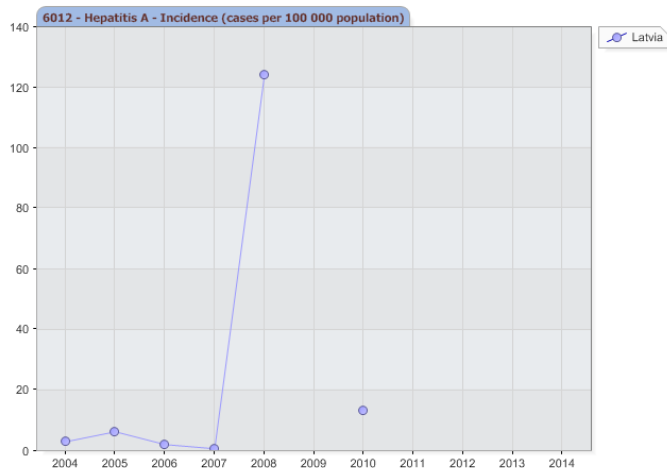
- Assessment to testing for hepatitis C in primary care and effective drug treatment should be a highly prioritised.
- Vaccination against hepatitis B (and A) for risk group – HCV-infected individuals, prisoners and employees in prisons.
- Screening programs for people who inject drugs, prisoners, men having sex with men, STI clinic patients.
- The elimination of blood borne virus associated with healthcare services, beauty treatment services, dental care, tattoo, community nursing, etc



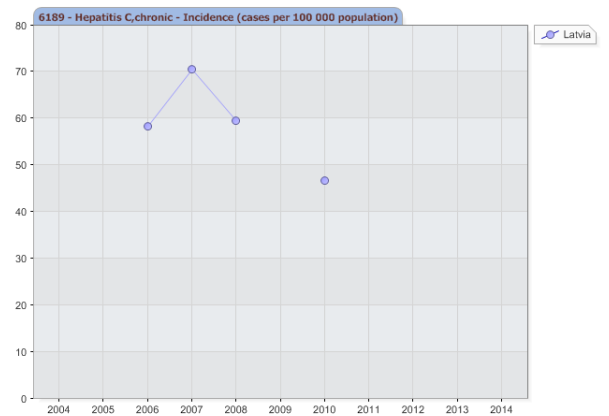
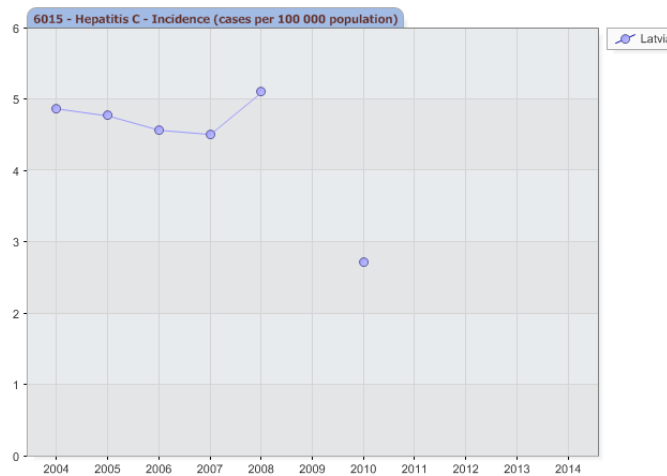
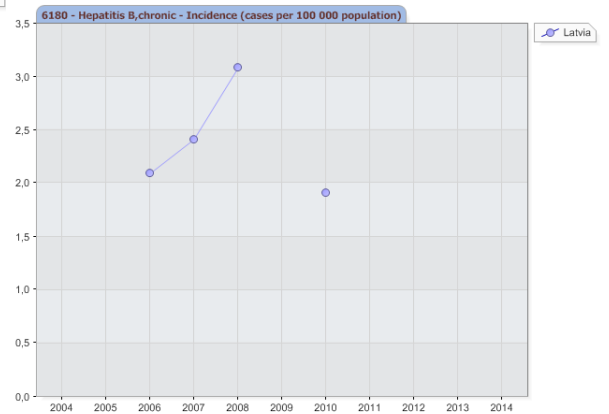
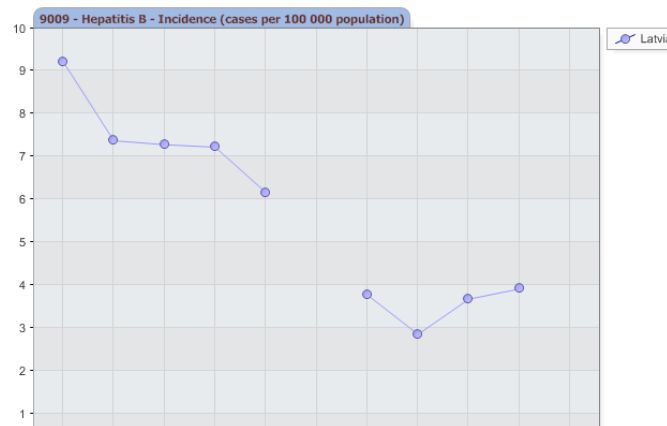
Country contact: The Centre for Disease Prevention and Control (CDPC) of Latvia, <http://www.spkc.gov.lv/about-SPKC/>, e-mail: projects@spkc.gov.lv



WHO CISID database info (<http://data.euro.who.int/cisid/?TabID=375693>)



Chronic incidence / 100 000



2.2.2 Pubmed publications

Pubmed MEDLINE search on {(Hepatitis) AND (Latvia) } in all fields and filters used on this search 'last 10 years' on was performed. }. Manual selection. The references were manually sorted in the different subject in the EndNote database

Surveillance, diagnostics, screening

Perevoscikovs, J., Lenglet, A., Lucenko, I., Steinerte, A., Payne Hallstrom, L. and Coulombier, D. **"Assessing the risk of a community outbreak of hepatitis A on blood safety in Latvia, 2008."** *Euro Surveill* **2010** 15(33): 19640.

Post-transfusion hepatitis A virus (HAV) infection worldwide is considered a sporadic event. An outbreak of HAV infection occurred in Latvia between the end of 2007 and throughout 2008 with more than 2,800 confirmed cases reported over a 13-month period (incidence of 123 per 100,000 population). The majority of reported HAV infection cases were in people over 18 years of age and in people living in the capitalcity, Riga. We estimated that the crude risk for HAV contamination of whole blood supplies in Riga between February and October 2008 ranged from 1.4 to 10.6 per 10,000 donated units. In people under 40 years of age, the risk of receiving an infectious blood transfusion was more than 3.0 per 10,000 recipients between August and October 2008 during the peak of the outbreak. We conclude that there is a previously under-recognised impact of HAV on blood safety during widespread outbreaks of this disease. Estimating the risk of contamination of blood supplies during an infectious disease outbreak scenario is important for fine tuning risk assessments and potentially improving public health practices.

Perevoscikovs, J., Lucenko, I., Magone, S., Brila, A., Curikova, J. and Vennema, H. **"Community-wide outbreak of hepatitis A in Latvia in 2008 - an update."** *Euro Surveill* **2009** 14(3).

An outbreak of hepatitis A has been ongoing in Latvia with 2,817 confirmed cases reported between 20 November 2007 and 31 December 2008. Initially the spread of infection was due to transmission among drug users and other high-risk groups, as well as several outbreaks in Riga (affecting a school and a restaurant), but in the second half of the year led to a community-wide increase in the number of cases. Molecular analysis of 100 strains showed that 95 belonged to genotype IA, of which 89 were identical and six were single nucleotide variants of the same sequence.

Perevoscikovs, J., Lucenko, I., Magone, S., Brila, A. and Curikova, J. **"Community-wide outbreak of hepatitis A in Latvia, in 2008."** *Euro Surveill* **2008** 13(40).

Since November 2007, an increase in the number of reported hepatitis A cases has been observed in Latvia. The aim of this report is to provide an update on the descriptive epidemiology of hepatitis A in Latvia and suggest some possible explanations of the recent increase in incidence.

Epidemiology

Tolmane, I., Rozentale, B., Keiss, J., Arsa, F., Brigis, G. and Zvaigzne, A. **"The prevalence of viral hepatitis C in Latvia: a population-based study."** *Medicina (Kaunas)* **2011** 47(10): 532-535.

BACKGROUND AND OBJECTIVE: Chronic viral hepatitis C (VHC) is one of the most discussed infectious diseases worldwide. The number of infected persons worldwide is approximately 170 million, and in Europe, it exceeds 9 million. The aim of this study was to determine the prevalence of antibodies to hepatitis C virus (anti-HCV prevalence) and prevalence of HCV

viremia (HCV-RNA prevalence) in Latvia. MATERIAL AND METHODS: A multistage randomized selection was used. A total of 42 primary care physicians (PCPs) were randomly selected from the register of PCPs from different regions of Latvia. From each PCP register, 60 subjects were selected (1651 individuals in total) and invited for the anti-HCV test with a screening method (ELISA). In case of positive results, antibodies were confirmed by the Western blot test, and all these subjects were tested for HCV-RNA by polymerase chain reaction. RESULTS: Of the 1459 subjects tested, 57 were positive for anti-HCV (3.9%; 95% CI 3% to 5%); 35 of them were positive for anti-HCV with a confirmatory test (2.4%; 95% CI, 1.7% to 3.3%): 19 men and 16 women (3.8% and 1.7%, respectively; $P=0.011$). The results of HCV RNA test were positive in 25 subjects (1.7%; 95% CI, 1.2% to 2.5%): 15 men and 10 women (3% and 1% respectively, $P=0.019$). CONCLUSIONS: The prevalence of anti-HCV and HCV-RNA in Latvia was found to be 2.4% and 1.7%, respectively. The prevalence of anti-HCV and HCV-RNA was higher in men than women.

Perevoscikovs, J., Lucenko, I., Magone, S. and Brila, A. **"Increase in hepatitis A cases in Latvia, in 2008, including an ongoing outbreak associated with a restaurant in Riga--preliminary report."** *Euro Surveill* 2008 13(20).

Prevention

Risk groups

Lieshout-Krikke, R. W., Zaaijer, H. L. and Prinsze, F. J. **"The yield of temporary exclusion of blood donors, exposed to emerging infections abroad."** *Vox Sang* 2013 104(1): 12-18.

BACKGROUND AND OBJECTIVES: Emerging infections abroad pose a threat to the safety of blood, donated by travelling blood donors. In this study, the yield of donor deferral after travelling was evaluated, by comparing the estimated numbers of infected donors returning from various affected areas. METHODS: A deterministic model was applied to calculate the number of infected donors, returning from six areas affected by outbreaks: Greece - Macedonia (West Nile fever), Italy - Emilia Romagna (West Nile fever), Thailand (chikungunya), Latvia (hepatitis A), central Turkey (Sicilian sandfly fever) and Italy - Tuscany (Toscana sandfly fever). RESULTS: The estimated number of infections among returning blood donors was surprisingly low, ranging from 0.32 West Nile virus-infected donors per year returning from Macedonia (Greece) to approximately 0.005 infected donors per year returning respectively from Tuscany (sandfly fever), Latvia (hepatitis A) and central Turkey (sandfly fever). CONCLUSION: The yield of the temporary exclusion of blood donors travelling to a specific, affected area is low, but the continuous monitoring of emerging infections and the timely assessment of new threats are laborious and imperfect. Safety measures may be instituted after the greatest threat of a new outbreak has passed. A general deferral of travelling donors may be more appropriate than targeted measures. It can be argued that all donors who stayed outside their country or continent of residency should be deferred for 4 weeks.

Aceijas, C., Hickman, M., Donoghoe, M. C., Burrows, D. and Stuijke, R. **"Access and coverage of needle and syringe programmes (NSP) in Central and Eastern Europe and Central Asia."** *Addiction* 2007 102(8): 1244-1250.

OBJECTIVE: To estimate access, activity and coverage of needle and syringe programmes (NSP) in Central and Eastern Europe and Central Asia. METHODS: Two data sets ('regional' and 'high-coverage sites') were used to estimate NSP provision (availability/number of sites), NSP utilization (syringes distributed/year), needle and syringe distribution (needles/syringes distributed/IDU/year), IDU reached (number/percentage of IDU contacted/year), regular reach (five or more contacts/month) and syringe coverage (percentage of injections/IDU/year administrable with new injecting equipment). RESULTS: Regional data set: results from 213 sites in 25 countries suggested that Czech Republic, Poland, Russia and Ukraine had > 10 NSP during 2001/2. Czech Republic, Kazakhstan, Latvia, Russia, Slovakia and Ukraine had >or= 10,000 IDU in contact with NSP. Ten countries reached >or= 10% of the estimated IDU

population. The 25 countries distributed approximately 17 million syringes/needles. Eight countries distributed > 0.5 million syringes/year. Syringe coverage (assuming 400 injections/IDU/year) was < 5% in 19 countries, 5-15% in five and > 15% in Macedonia. Overall syringe coverage was 1.2% and when assuming 700 injections/IDU/year it decreased to 0.7%. Syringe coverage for the IDU population in contact with NSP was \leq 15% in 10 countries, 15-60% in 11 and > 60% in Croatia, Macedonia, Moldova and Tajikistan. Overall syringe coverage for the population in contact with NSP was 9.8%. High-coverage data set: Soligorsk, Pskov and Sumy's NSP reached 92.3%, 92.2% and 73.3% of their estimated IDU population, respectively (regular reach: 0.2%, 1.8% and 22.7%). The distribution levels were 47.2, 51.7 and 94.2 syringes/IDU/year, respectively. CONCLUSION: The evidence suggests suboptimal levels of NSP implementation, programme activity and coverage. This paper provides a baseline for development of indicators that could be used to monitor NSP. Strategies to increase coverage that may go beyond NSP are urgently required, as is research into understanding how NSP can contribute to better syringe coverage among IDU.

Treatment and Clinical

Piekuse, L., Kreile, M., Zarina, A., Steinberga, Z., Sondore, V., Keiss, J., Lace, B. and Krumina, A.

"Association between inherited monogenic liver disorders and chronic hepatitis C." *World J Hepatol* 2014 6(2): 92-97.

AIM: To determine the frequencies of mutations that cause inherited monogenic liver disorders in patients with chronic hepatitis C. METHODS: This study included 86 patients with chronic hepatitis C (55 men, 31 women; mean age at diagnosis, 38.36 \pm 14.52 years) who had undergone antiviral therapy comprising pegylated interferon and ribavirin. Viral load, biochemical parameter changes, and liver biopsy morphological data were evaluated in all patients. The control group comprised 271 unrelated individuals representing the general population of Latvia for mutation frequency calculations. The most frequent mutations that cause inherited liver disorders [gene (mutation): ATP7B (H1069Q), HFE (C282Y, H63D), UGT1A1 (TA)7, and SERPINA1 (PiZ)] were detected by polymerase chain reaction (PCR), bidirectional PCR allele-specific amplification, restriction fragment length polymorphism analysis, and sequencing. RESULTS: The viral genotype was detected in 80 of the 86 patients. Viral genotypes 1, 2, and 3 were present in 61 (76%), 7 (9%), and 12 (15%) patients, respectively. Among all 86 patients, 50 (58%) reached an early viral response and 70 (81%) reached a sustained viral response. All 16 patients who did not reach a sustained viral response had viral genotype 1. Case-control analysis revealed a statistically significant difference in only the H1069Q mutation between patients and controls (patients, 0.057; controls, 0.012; odds ratio, 5.514; 95%CI: 1.119-29.827, $P = 0.022$). However, the H1069Q mutation was not associated with antiviral treatment outcomes or biochemical indices. The (TA) 7 mutation of the UGT1A1 gene was associated with decreased ferritin levels (beta regression coefficient = -295.7, $P = 0.0087$). CONCLUSION: Genetic mutations that cause inherited liver diseases in patients with hepatitis C should be studied in detail.

Kuznetsova, T., Tallo, T., Brjalin, V., Reshetnjak, I., Salupere, R., Priimagi, L., Katargina, O., Smirnova, M., Jansons, J. and Tefanova, V. **"Amino Acid Polymorphisms Within the Entire HCV NS5A Region in Estonian Chronic HCV 1b Patients With Different Treatment Response."** *Hepat Mon* 2013 13(12): e14481.

BACKGROUND: A substantial proportion of hepatitis C virus (HCV)-1b infected patients do not respond to pegylated interferon-alpha plus ribavirin (PegIFNalpha/RBV) combination therapy that was partially associated with mutations in the non-structural 5A (NS5A) protein.

OBJECTIVES: Analysis of NS5A polymorphisms in HCV genotype 1b pre-treatment serum samples from Estonian patients and their effect on the treatment response. PATIENTS AND METHODS: Twenty-nine complete NS5A sequences obtained from patients with chronic HCV-1b infection who had received combined therapy with PegIFNalpha-2a/RBV were analyzed and compared with the prototype strain HCV-J. Twelve patients achieved a sustained virological

response (SVR), 15 were non-SVR and 2 patients stopped treatment because of side effects. RESULTS: No significant difference in total number of amino acid mutations was observed between isolates from SVR and non-SVR patients in any known regions of the NS5A protein. However, specific amino acid substitutions at positions 1989 and 2283 correlated significantly with SVR, mutations at positions 1979, 2107, 2171 and 2382 were associated with non-response to treatment and amino acid substitution at position 2319 was observed in relapsers. At phylogenetic analysis, NS5A nucleotide sequences have been subdivided into four groups characterized by the different treatment response. Twenty-four novel nucleotide polymorphisms and 11 novel amino acid polymorphisms were identified based on the phylogenetic tree topology. CONCLUSIONS: Specific amino acid substitutions correlating with the treatment response were found. Polymorphisms revealed by phylogenetic analysis may define the signature patterns for treatment susceptible and treatment resistant strains prevalent in Estonia.

Tolmane, I., Rozentale, B., Keiss, J., Ivancenko, L., Subnikova, N., Reinholde, Z., Kozlovskaja, I., Sumlaninova, N., Laivacuma, S. and Simanis, R. **"Interleukin 28B Gene Polymorphism and Association with Chronic Hepatitis C Therapy Results in Latvia."** *Hepat Res Treat* **2012** 2012: 324090.

Introduction. With the standard treatment of chronic hepatitis C, sustained virological response (SVR) can be achieved only in half of all patients. Interleukin-28B appears to be involved in the control of HCV infection, and the genetic polymorphism of the encoding IL-28B gene may determine the efficacy of clearance of HCV. The aim of this paper was to detect IL-28B gene polymorphism in Latvia and to analyze therapy results. This is the first study on IL-28B gene polymorphism in Latvia. Material and Methods. There were 159 chronic viral hepatitis C patients included in the study. In order to detect IL-28B gene polymorphism, we used molecular biology techniques and methods: classical DNA separation, amplification by PCR, and standard sequencing. Genotype was defined as CC, CT, TC, or TT type. 142 patients were treated with the standard of care treatment. Results were analyzed according to IL-28B polymorphism. Results. There were 53 patients (33%) with CC genotype, 84 patients (53%) with CT/TC genotype, and 22 patients (14%) with TT genotype. 34 patients (74%) in CC genotype subgroup achieved SVR versus 50 patients (52%) in non-CC subgroups. In patients with genotype 1, SVR was achieved in 16 patients (84%) in CC subgroup versus 30 patients (47.6%) in non-CC subgroups, $P = 0.007$. Conclusions. The most common genotype of IL28B in Latvia is CT/TC, with an incidence of 53%. Patients with CC genotype achieved SVR more often than CT or TT subgroups. IL28B gene polymorphism therefore is a strong predictor of treatment result.

Research

Strods, A., Ose, V., Bogans, J., Cielens, I., Kalnins, G., Radovica, I., Kazaks, A., Pumpens, P. and Renhofa, R. **"Preparation by alkaline treatment and detailed characterisation of empty hepatitis B virus core particles for vaccine and gene therapy applications."** *Sci Rep* **2015** 5: 11639.

Hepatitis B virus (HBV) core (HBc) virus-like particles (VLPs) are one of the most powerful protein engineering tools utilised to expose immunological epitopes and/or cell-targeting signals and for the packaging of genetic material and immune stimulatory sequences. Although HBc VLPs and their numerous derivatives are produced in highly efficient bacterial and yeast expression systems, the existing purification and packaging protocols are not sufficiently optimised and standardised. Here, a simple alkaline treatment method was employed for the complete removal of internal RNA from bacteria- and yeast-produced HBc VLPs and for the conversion of these VLPs into empty particles, without any damage to the VLP structure. The empty HBc VLPs were able to effectively package the added DNA and RNA sequences. Furthermore, the alkaline hydrolysis technology appeared efficient for the purification and packaging of four different HBc variants carrying lysine residues on the HBc VLP spikes. Utilising the introduced lysine residues and the intrinsic aspartic and glutamic acid residues exposed on the tips of the HBc spikes for chemical coupling of the chosen peptide and/or nucleic acid sequences ensured a standard and easy protocol for the further development of versatile HBc VLP-based vaccine and gene therapy applications.

Lange, M., Fiedler, M., Bankwitz, D., Osburn, W., Viazov, S., Brovko, O., Zekri, A. R., Khudyakov, Y., Nassal, M., Pumpens, P., et al. **"Hepatitis C virus hypervariable region 1 variants presented on hepatitis B virus capsid-like particles induce cross-neutralizing antibodies."** *PLoS One* **2014** 9(7): e102235.

Hepatitis C virus (HCV) infection is still a serious global health burden. Despite improved therapeutic options, a preventative vaccine would be desirable especially in undeveloped countries. Traditionally, highly conserved epitopes are targets for antibody-based prophylactic vaccines. In HCV-infected patients, however, neutralizing antibodies are primarily directed against hypervariable region I (HVRI) in the envelope protein E2. HVRI is the most variable region of HCV, and this heterogeneity contributes to viral persistence and has thus far prevented the development of an effective HVRI-based vaccine. The primary goal of an antibody-based HCV vaccine should therefore be the induction of cross-reactive HVRI antibodies. In this study we approached this problem by presenting selected cross-reactive HVRI variants in a highly symmetric repeated array on capsid-like particles (CLPs). SplitCore CLPs, a novel particulate antigen presentation system derived from the HBV core protein, were used to deliberately manipulate the orientation of HVRI and therefore enable the presentation of conserved parts of HVRI. These HVRI-CLPs induced high titers of cross-reactive antibodies, including neutralizing antibodies. The combination of only four HVRI CLPs was sufficient to induce antibodies cross-reactive with 81 of 326 (24.8%) naturally occurring HVRI peptides. Most importantly, HVRI CLPs with AS03 as an adjuvant induced antibodies with a 10-fold increase in neutralizing capability. These antibodies were able to neutralize infectious HCVcc isolates and 4 of 19 (21%) patient-derived HCVpp isolates. Taken together, these results demonstrate that the induction of at least partially cross-neutralizing antibodies is possible. This approach might be useful for the development of a prophylactic HCV vaccine and should also be adaptable to other highly variable viruses.

Krams, I. A., Skrinda, I., Kecko, S., Moore, F. R., Krama, T., Kaasik, A., Meija, L., Lietuviētis, V. and Rantala, M. J. **"Body height affects the strength of immune response in young men, but not young women."** *Sci Rep* **2014** 4: 6223.

Body height and other body attributes of humans may be associated with a diverse range of social outcomes such as attractiveness to potential mates. Despite evidence that each parameter plays a role in mate choice, we have little understanding of the relative role of each, and relationships between indices of physical appearance and general health. In this study we tested relationships between immune function and body height of young men and women. In men, we report a non-linear relationship between antibody response to a hepatitis-B vaccine and body height, with a positive relationship up to a height of 185 cm, but an inverse relationship in taller men. We did not find any significant relationship between body height and immune function in women. Our results demonstrate the potential of vaccination research to reveal costly traits that govern evolution of mate choice in humans and the importance of trade-offs among these traits.

Sominskaya, I., Skrastina, D., Petrovskis, I., Dishlers, A., Berza, I., Mihailova, M., Jansons, J., Akopjana, I., Stahovska, I., Dreilina, D., et al. **"A VLP library of C-terminally truncated Hepatitis B core proteins: correlation of RNA encapsidation with a Th1/Th2 switch in the immune responses of mice."** *PLoS One* **2013** 8(9): e75938.

An efficient pBR327- and P_{trp}-based E. coli expression system was used to generate a large-scale library of virus like particles (VLP) formed by recombinant hepatitis B virus (HBV) core (HBc) protein derivatives. To construct the library, the gene of HBc protein of the genotype D/subtype ayw2 virus was gradually truncated from the 3'-end and twenty-two HBc variants (with truncation up to 139 aa) were expressed at high levels. The proteins were purified by salt precipitation and gel filtration. Background RNA binding was observed for VLPs formed by HBc1-149, which lacked all C-terminal Arg blocks, and the addition of three Arg residues (HBc1-152) only slightly increased RNA binding. The presence of two Arg blocks (proteins HBc1-162 and HBc1-163) resulted in approximately half of the typical level of RNA binding, and the presence of three blocks (protein HBc1-171) led to approximately 85% of the typical level of

binding. Only a small increase in the level of RNA binding was found for the HBc1-175 VLPs, which contained all four Arg blocks but lacked the last 8 aa of the full-length HBc protein. VLPs containing high levels of RNA had higher antigenicity according to an ELISA with anti-HBc mAbs than the VLPs formed by HBc variants without C-terminal Arg blocks and lacking RNA. The results indicate that the VLPs were stabilised by nucleic acids. The immunogenicity in BALB/c mice was comparable for VLPs formed by different HBc proteins, but a clear switch from a Th1 response to a Th2 response occurred after the loss of encapsidated RNA. We did not observe significant differences in lymphocyte proliferation in vitro for the tested VLP variants; however, the loss of RNA encapsidation correlated with a decreased level of IFN-gamma induction, which is a measure of the potential CTL activity of immunogens.

Niedre-Otomere, B., Bogdanova, A., Bruvere, R., Ose, V., Gerlich, W. H., Pumpens, P., Glebe, D. and Kozlovska, T. **"Posttranslational modifications and secretion efficiency of immunogenic hepatitis B virus L protein deletion variants."** *Virology* **2013** 10: 63.

BACKGROUND: Subviral particles of hepatitis B virus (HBV) composed of L protein deletion variants with the 48 N-terminal amino acids of preS joined to the N-terminus of S protein (1-48preS/S) induced broadly neutralizing antibodies after immunization of mice with a Semliki Forest virus vector. A practical limitation for use as vaccine is the suboptimal secretion of such particles. The role of the N-terminal preS myristoylation in the cellular retention of full-length L protein is described controversially in the literature and the relation of these data to the truncated L protein was unknown. Thus, we studied the effect of preS myristoylation signal suppression on 1-48preS/S secretion efficiency, glycosylation and subcellular distribution. **FINDINGS:** The findings are that 1-48preS/S is secreted, and that removal of the N-terminal myristoylation signal in its G2A variant reduced secretion slightly, but significantly. The glycosylation pattern of 1-48preS/S was not affected by the removal of the myristoylation signal (G2A mutant) but was different than natural L protein, whereby N4 of the preS and N3 of the S domain were ectopically glycosylated. This suggested cotranslational translocation of 1-48preS in contrast to natural L protein. The 1-48preS/S bearing a myristoylation signal was localized in a compact, perinuclear pattern with strong colocalization of preS and S epitopes, while the non-myristoylated mutants demonstrated a dispersed, granular cytoplasmic distribution with weaker colocalization. **CONCLUSIONS:** The large deletion in 1-48preS/S in presence of the myristoylation site facilitated formation and secretion of protein particles with neutralizing preS1 epitopes at their surface and could be a useful feature for future hepatitis B vaccines.

Niedre-Otomere, B., Bogdanova, A., Skrastina, D., Zajackina, A., Bruvere, R., Ose, V., Gerlich, W. H., Garoff, H., Pumpens, P., Glebe, D., et al. **"Recombinant Semliki Forest virus vectors encoding hepatitis B virus small surface and pre-S1 antigens induce broadly reactive neutralizing antibodies."** *J Viral Hepat* **2012** 19(9): 664-673.

Most hepatitis B virus (HBV) vaccines consist of viral small surface (S) protein subtype adw2 expressed in yeast cells. In spite of good efficacy, HBV-genotype and subtype differences, escape mutants and insufficient Th1 activation remain potential problems. To address these problems, we generated recombinant Semliki Forest virus (rSFV) vectors encoding S protein, subtype adw2 or ayw2, or a fragment of the large surface protein, amino acids 1-48 of the pre-S1 domain, fused to S (pre-S1.1-48/S). The antigen loop in S protein and the selected pre-S1 sequences are known targets of neutralizing antibodies. BALB/c mice were immunized intravenously with 10(7) rSFV particles and 10(8) rSFV particles 3 weeks later. Antibodies induced by rSFV encoding S proteins reacted preferentially with subtype determinants of yeast-derived S antigen but equally well with patient-derived S antigen. Immunization with rSFV encoding pre-S1.1-48/S resulted in formation of pre-S1- and S-specific immunoglobulin G (IgG), while immunization with the isogenic mutant without S start codon induced pre-S1 antibodies only. Neutralizing antibodies were determined by mixing with plasma-derived HBV/ayw2 and subsequent inoculation of susceptible primary hepatocyte cultures from Tupaia belangeri. S/adw2 antisera neutralized HBV/ayw2 as effectively as antisera raised with S/ayw2. The pre-S1 antibodies also completely neutralized HBV infectivity. The IgG1/IgG2a ratios

ranged from 0.28 to 0.88 in the four immunized groups and were lowest for the pre-S1.1-48/S vector, indicating the strongest Th1 response. This vector type may induce subtype-independent and S-escape-resistant neutralizing antibodies against HBV.

Sominskaya, I., Skrastina, D., Dislers, A., Vasiljev, D., Mihailova, M., Ose, V., Dreilina, D. and Pumpens, P. **"Construction and immunological evaluation of multivalent hepatitis B virus (HBV) core virus-like particles carrying HBV and HCV epitopes."** *Clin Vaccine Immunol* 2010 17(6): 1027-1033.

A multivalent vaccine candidate against hepatitis B virus (HBV) and hepatitis C virus (HCV) infections was constructed on the basis of HBV core (HBc) virus-like particles (VLPs) as carriers. Chimeric VLPs that carried a virus-neutralizing HBV pre-S1 epitope corresponding to amino acids (aa) 20 to 47 in the major immunodominant region (MIR) and a highly conserved N-terminal HCV core epitope corresponding to aa 1 to 60 at the C terminus of the truncated HBcDelta protein (N-terminal aa 1 to 144 of full-length HBc) were produced in *Escherichia coli* cells and examined for their antigenicity and immunogenicity. The presence of two different foreign epitopes within the HBc molecule did not interfere with its VLP-forming ability, with the HBV pre-S1 epitope exposed on the surface and the HCV core epitope buried within the VLPs. After immunization of BALB/c mice, specific T-cell activation by both foreign epitopes and a high-titer antibody response against the pre-S1 epitope were found, whereas an antibody response against the HBc carrier was notably suppressed. Both inserted epitopes also induced a specific cytotoxic-T-lymphocyte (CTL) response, as shown by the gamma interferon (IFN- γ) production profile.

Alekseeva, E., Sominskaya, I., Skrastina, D., Egorova, I., Starodubova, E., Kushners, E., Mihailova, M., Petrakova, N., Bruvere, R., Kozlovskaya, T., et al. **"Enhancement of the expression of HCV core gene does not enhance core-specific immune response in DNA immunization: advantages of the heterologous DNA prime, protein boost immunization regimen."** *Genet Vaccines Ther* 2009 7: 7.

BACKGROUND: Hepatitis C core protein is an attractive target for HCV vaccine aimed to exterminate HCV infected cells. However, although highly immunogenic in natural infection, core appears to have low immunogenicity in experimental settings. We aimed to design an HCV vaccine prototype based on core, and devise immunization regimens that would lead to potent anti-core immune responses which circumvent the immunogenicity limitations earlier observed. METHODS: Plasmids encoding core with no translation initiation signal (pCMVcore); with Kozak sequence (pCMVcoreKozak); and with HCV IRES (pCMVcoreIRES) were designed and expressed in a variety of eukaryotic cells. Polypeptides corresponding to HCV 1b amino acids (aa) 1-98 and 1-173 were expressed in *E. coli*. C57BL/6 mice were immunized with four 25-microg doses of pCMVcoreKozak, or pCMV (I). BALB/c mice were immunized with 100 microg of either pCMVcore, or pCMVcoreKozak, or pCMVcoreIRES, or empty pCMV (II). Lastly, BALB/c mice were immunized with 20 microg of core aa 1-98 in prime and boost, or with 100 microg of pCMVcoreKozak in prime and 20 microg of core aa 1-98 in boost (III). Antibody response, [3 H]-T-incorporation, and cytokine secretion by core/core peptide-stimulated splenocytes were assessed after each immunization. RESULTS: Plasmids differed in core-expression capacity: mouse fibroblasts transfected with pCMVcore, pCMVcoreIRES and pCMVcoreKozak expressed 0.22 \pm 0.18, 0.83 \pm 0.5, and 13 \pm 5 ng core per cell, respectively. Single immunization with highly expressing pCMVcoreKozak induced specific IFN- γ and IL-2, and weak antibody response. Single immunization with plasmids directing low levels of core expression induced similar levels of cytokines, strong T-cell proliferation (pCMVcoreIRES), and antibodies in titer 103(pCMVcore). Boosting with pCMVcoreKozak induced low antibody response, core-specific T-cell proliferation and IFN- γ secretion that subsided after the 3rd plasmid injection. The latter also led to a decrease in specific IL-2 secretion. The best was the heterologous pCMVcoreKozak prime/protein boost regiment that generated mixed Th1/Th2-cellular response with core-specific antibodies in titer $\geq 3 \times 10^3$. CONCLUSION: Thus, administration of highly expressed HCV core gene, as one large dose or repeated injections of smaller doses, may suppress core-specific immune response. Instead, the latter is induced by a heterologous DNA prime/protein boost regiment that circumvents the negative effects of intracellular core expression.

2.3 Lithuania

2.3.1 VHPB survey

VHPB survey on prevention and control of viral hepatitis in 53 European countries in 2014 – November 2014 (www.vhpb.org)

PREVENTION AND CONTROL OF VIRAL HEPATITIS IN EUROPE IN 2014: THE CASE OF LITHUANIA

Country profile

- Population (in millions) (year): 2,9 (2014)^a
- Gross national income per capita (int \$) (year): 23 110 (2012)^b
- Most recent seroprevalence data:

	% HBsAg + (year)	% Anti-HCV + (year)
General population	-	2.8 % (2010) ¹
Blood donors (first time)	0.3 % (2008) ^d	0.6 % (2008) ^d
Pregnant women	-	-
Risk groups		
Injecting drug users	3.3 % (2006) ^c	79 % (2000) ² 94 % (2008) ⁴
Haemodialysis patients	14.4 % (2001) ³	15.4 % (2001) ³

Screening^e

Recommended for following groups:	Hep B	Hep C
Blood and organ donors	Yes (1969)	Yes (1993)
Pregnant women	No	No
Injecting drug users	No	No
STI clinic patients	No	No
Haemodialysis patients	Yes (since year ?)	Yes (since year ?)
Health care workers	No	No
Men having sex with men	No	No
Prison population	No	No
Migrants	No	No
Others	Occupational risk	Occupational risk

National plan

There is no written national strategy or plan that focuses exclusively or primarily on the prevention and control of viral hepatitis.^f

Vaccination programs

Hepatitis A		Target	Since/Period
Universal	No		
Risk group	No		
Hepatitis B^{g,h,i}			
Universal	Yes	Newborn Adolescents (12y)	1998-ongoing 2002-2010
Catch-up	No		
Risk group	Yes	Haemodialysis patients, occupational risk,	1998

Treatment

National guidelines for clinicians available ^f	
Hepatitis B	Yes (2005)
Hepatitis C	Yes (2008)
Drugs available for hepatitis C treatment ^j	
Ribavirin	Yes
Pegylated interferon	Yes
Interferon alpha	Yes
Telaprevir	YES
Boceprevir	No
Simeprevir	No
Sofosbuvir	No
Others: (specify)	?
Number of patients treated for hepatitis B	100
Number of patients treated for hepatitis C	600/year

^kincluded on the national essential medicines list or subsidized by the government

Impact

Figure 1: Hepatitis B vaccination coverage¹ and impact on hepatitis B incidence^{1,k}

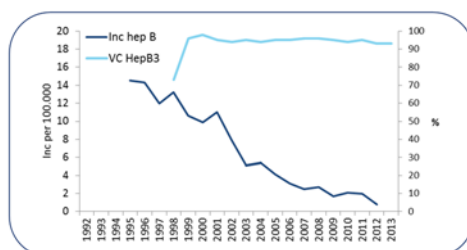
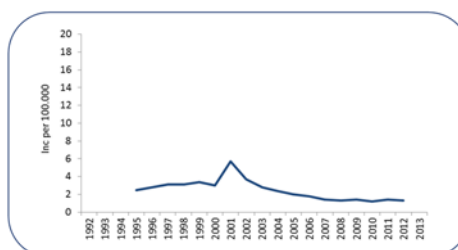


Figure 2: Introduction of activities and impact on hepatitis C incidence^{1,k}



Specific issues and future challenges

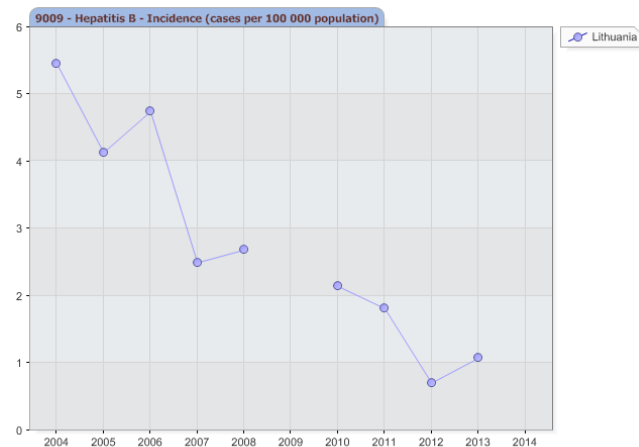
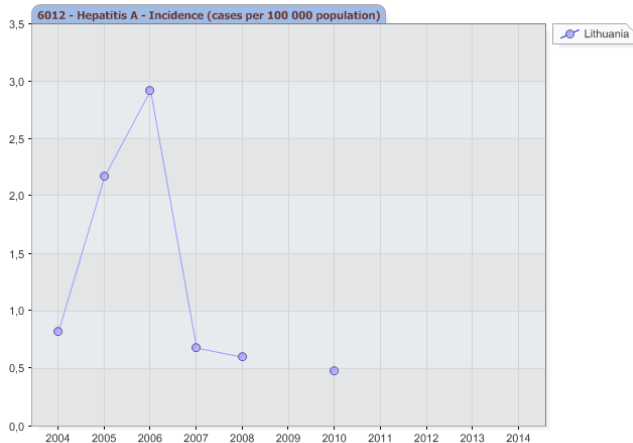
To complete by country if wanted.....



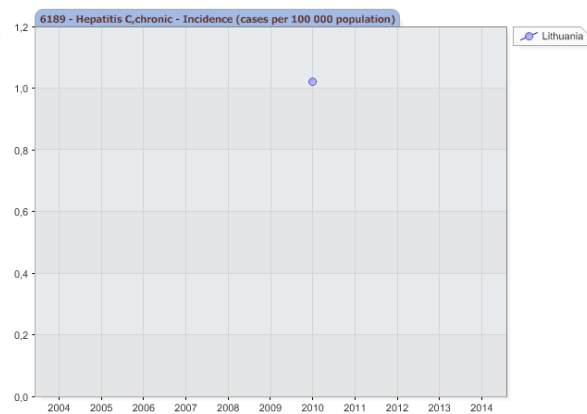
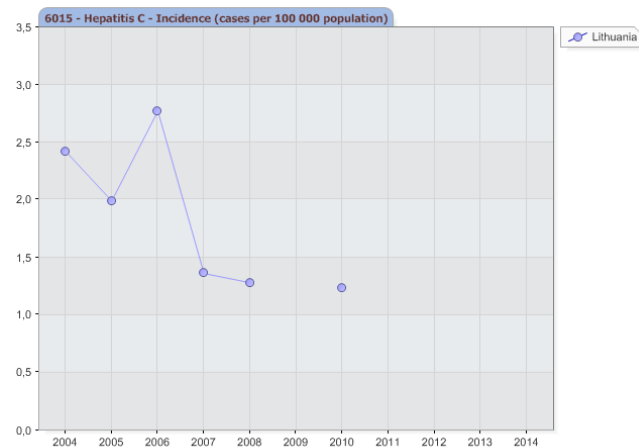
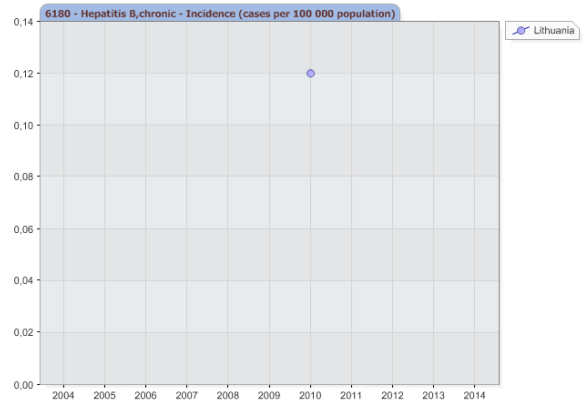
Country contact: Irma Caplinskiene, MD. Head of HIV/AIDS/STI and Hepatitis surveillance department
Centre for Communicable Diseases and AIDS. www.ulac.lt and irma.caplinskiene@ulac.lt



WHO CISID database info (<http://data.euro.who.int/cisid/?TabID=375693>)



Chronic –incidence cases/100 000



2.3.2 Pubmed publications

Pubmed MEDLINE search on {(Hepatitis) AND (Lithuania) } in all fields and filters used on this search 'last 10 years' on was performed. }. Manual selection. The references were manually sorted in the different subject in the EndNote database

Surveillance, diagnostics, screening

Laperche, S., Nubling, C. M., Stramer, S. L., Brojer, E., Grabarczyk, P., Yoshizawa, H., Kalibatas, V., El Elkyabi, M., Mofteh, F., Girault, A., et al. "**Sensitivity of hepatitis C virus core antigen and antibody combination assays in a global panel of window period samples.**" *Transfusion* **2015**.

BACKGROUND: Hepatitis C virus (HCV) antigen and antibody combination assays have been launched as a cost-effective alternative to nucleic acid testing (NAT) for reducing the antibody-negative window period (WP). Later, a HCV antigen chemiluminescence immunoassay (CLIA) became available. STUDY DESIGN AND METHODS: A panel composed of 337 HCV NAT-yield samples that were characterized for viral load (VL) and genotype was used to compare the sensitivity of two combination enzyme-linked immunosorbent assays (Monolisa, Bio-Rad; and Murex, formerly Abbott) and a HCV antigen CLIA (Abbott). Analytic sensitivity was compared with HCV RNA detection using Ultrio (Grifols) by testing serial dilutions of 10 genotype (gt)1 to gt4 samples. RESULTS: HCV antigen CLIA detected 92.4% of samples, whereas Monolisa and Murex detected 38.3 and 47.5%, respectively. In the HCV RNA VL range of 105 to 107 IU/mL, Monolisa and Murex detected 38% to 56% of gt1, 85% to 78% of gt2, and 21% to 37% of gt3. The overall geometric mean 50% limit of detection (range) of Ultrio on gt1 to gt4 dilution series was 3.5 (1.2-7.7) copies/mL, compared to 3.3×10^6 (4.4×10^5 - 2.7×10^7), 3.4×10^6 (2.2×10^5 - 4.2×10^7), and 2728 (415-7243) copies/mL for Monolisa, Murex, and HCV antigen CLIA, respectively. CONCLUSION: Analytical sensitivity of NAT was on average 1 million- and 780-fold higher than combination assays and HCV antigen CLIA, respectively. Relative sensitivities of combination assays differed for genotypes with Murex being more sensitive for gt1 and gt3 and Monolisa more sensitive for gt2. Although being less sensitive than NAT, combination assays could be considered in resource-limited settings since they detect 38% to 47% of seronegative WP donations.

Kalibatas, V. and Kalibatiene, L. "**The results of nucleic acid testing in remunerated and non-remunerated blood donors in Lithuania.**" *Blood Transfus* **2014** 12 Suppl 1: s58-62.

BACKGROUND: In Lithuania, governmentally covered remuneration for whole blood donations prevails. Donors may choose to accept or reject the remuneration. The purpose of this study was to compare the rate of nucleic acid testing (NAT) discriminatory-positive markers for human immunodeficiency virus-1 (HIV-1), hepatitis B virus (HBV) and hepatitis C virus (HCV) in seronegative, first-time and repeat, remunerated and non-remunerated donations at the National Blood Centre in Lithuania during the period from 2005 to 2010. MATERIALS AND METHODS: All seronegative whole blood and blood component donations were individually analysed by NAT for HIV-1, HBV and HCV. Only discriminatory-positive NAT were classified. The prevalence of discriminatory-positive NAT per 100,000 donations in the donor groups and the odds ratios comparing the remunerated and non-remunerated donations were determined. RESULTS: Significant differences were observed for HBV NAT results: 47.42 and 26.29 per 100,000 remunerated first-time and repeat donations, respectively, compared to 10.6 and 3.58 per 100,000 non-remunerated first-time and repeat, seronegative donations, respectively. The differences were also significant for HCV NAT results: 47.42 and 51.99 for remunerated first-time and repeat donations, respectively, compared to 2.12 and 0 per 100,000 non-remunerated first-time and repeat, seronegative donations, respectively. No seronegative, discriminatory-positive NAT HIV case was found. The odds of discriminatory HBV and HCV NAT positive results were statistically significantly higher for both first-time and repeat remunerated donations

compared to first-time and repeat non-remunerated donations. DISCUSSION: First-time and repeat remunerated seronegative donations were associated with a statistically significantly higher prevalence and odds for discriminatory-positive HBV and HCV NAT results compared to first-time and repeat non-remunerated donations at the National Blood Centre in Lithuania.

Epidemiology

Madalinski, K., Zakrzewska, K., Kolakowska, A. and Godzik, P. "**Epidemiology of HCV infection in Central and Eastern Europe.**" *Przegl Epidemiol* **2015** 69(3): 459-464.

AIM OF STUDY: is the estimation of prevalence of HCV infection in fourteen Central and Eastern European countries (CEEC). MATERIAL AND METHODS: This review describes the comparative data of persons possessing anti-HCV antibodies and persons with HCV viremia (% of population and number) in fourteen Central and Eastern European countries (CEEC). The study was performed according to data on the ≥ 15 years of age populations obtained from the Statistical Offices of the countries. RESULTS: The prevalence of anti-HCV in populations varied between 0.27 and 3.5%. The lowest values were reported from Kosovo, Hungary, Germany and the Czech Republic; 0.3-0.6%. The highest values of anti-HCV antibodies were noted in Latvia, Lithuania and Romania; 2.4, 2.85 and 3.5%, respectively. From eight countries the percentages of persons with HCV viremia were available (0.2-3.5%). CONCLUSIONS: The paper gives an estimate of the number of people infected with HCV in the general population of 8 countries from the CSEEC region. This number is approximately ~1.16 million. KEY WORDS: Hepatitis C, anti-HCV antibodies, HCV-RNA, prevalence in general population and first-time blood donors; countries of Central and Eastern Europe.

Liakina, V. and Valantinas, J. "**Anti-HCV prevalence in the general population of Lithuania.**" *Med Sci Monit* **2012** 18(3): PH28-35.

BACKGROUND: The aim of this study was to assess risk factors for HCV acquisition and prevalence of anti-HCV in the general population of Lithuania. MATERIAL/METHODS: The study enrolled 1528 randomly selected adults from the 5 biggest cities of Lithuania and its rural regions. Screening for anti-HCV was performed by analysis of peripheral capillary blood with lateral flow immunochromatography and confirmation of positive cases by peripheral venous blood testing with 2-step chemiluminescent microparticle immunoassay. RESULTS: Anti-HCV prevalence in Lithuania is 2.78% and according to the standard European population the adjusted anti-HCV rate is 2.85%. It is more prevalent among men (crude rates: 4.02% males vs. 1.49% females, $p=.0030$) and this does not depend on age. Vilnius and Kaunas regions have higher infection rates than smaller rural regions (2.92% and 3.01% vs. 2.24%, 0.74% and 1.35%). Nowadays among our population HCV infection spreads mainly via intravenous drug use ($OR=42.5$, $p<.0001$). HCV transmission occurs through blood transfusions ($OR=6.4$, $p=.0002$), tooth removal ($OR=4.1$, $p=.0048$), childbirth ($OR=5.0$, $p=.0224$), multiple and a long-term hospitalization ($OR=3.0$, $p=.0064$), tattooing ($OR=4.4$, $p=.0013$), open traumas ($OR=3.7$, $p=.0009$) and intrafamilially ($OR=11.3$, $p=.0002$). CONCLUSIONS: 2.78% of the population is anti-HCV-positive. The anti-HCV rate is higher in Vilnius and Kaunas in comparison with other regions. HCV spreads mainly through intravenous drug use, but intrafamilial and some nosocomial routes are also important. The anti-HCV prevalence did not depend on age. Despite active prevention of nosocomial HCV transmission, the incidence of HCV infection does not decrease due to virus spread mostly in "trusted networks" of intravenous drug users.

Kurkela, S., Pebody, R., Kafatos, G., Andrews, N., Barbara, C., Bruzzone, B., Butur, D., Caplinskas, S., Davidkin, I., Hatzakis, A., et al. "**Comparative hepatitis A seroepidemiology in 10 European countries.**" *Epidemiol Infect* **2012** 140(12): 2172-2181.

The WHO recommends hepatitis A virus (HAV) immunization according to level of transmission and disease burden. We aimed to identify susceptible age groups by standardized serosurveys to inform HAV vaccination policy in participating countries: Belgium, Czech Republic, England,

Finland, Germany, Italy, Lithuania, Malta, Romania, and Slovakia. Each country tested national serum banks (n = 1854-6748), collected during 1996-2004, for anti-HAV antibodies. Local laboratory results were standardized to common units. Forty-one per cent of those aged <30 years and 6% of those aged ≥30 years were susceptible to HAV in Romania; compared to 70-94% and 26-71%, respectively, elsewhere. Romania reported high HAV incidence in children and young adults. Other countries reported HAV disease primarily in older risk groups. The results suggest low level of HAV transmission in most of Europe. Romania, however, appeared as an area with intermediate transmission. Vaccination of risk groups in countries with high susceptibility of young and middle-aged adults needs to be continued.

Liakina, V., Speiciene, D., Irnius, A. and Valantinas, J. **"Changes in hepatitis C virus infection routes and genotype distribution in a Lithuanian cohort with chronic hepatitis C."** *Med Sci Monit* 2009 15(4): PH17-23.

BACKGROUND: We evaluated the distribution of hepatitis C virus genotypes and determined their association with routes of infection according to the sex and age of the study subjects. **MATERIAL/METHODS:** We studied 1158 patients with chronic hepatitis C. Hepatitis C virus antibodies were detected with a microparticle enzyme immunoassay, hepatitis C virus ribonucleic acid was identified via polymerase chain reaction, and hepatitis C virus genotypes were determined with a line probe assay. An anonymous questionnaire completed by all subjects included the date of chronic hepatitis C diagnosis, the age and sex of the patient, the hepatitis C virus genotype and subtype, and possible routes of infection. **RESULTS:** Of the patients studied, 50.9% had more than 1 possible route of infection, 41.2% had a single route of infection, and 7.9% had an unknown route of infection. The most common hepatitis C transmission routes were intravenous drug use and tattoos in younger patients and surgery or long or multiple hospitalizations in older patients. The genotype distribution was as follows: genotype 1, 65.0% of patients; genotype 2, 26.3%; and genotype 3, 8.7%. The transmission of genotype 1 was associated primarily with surgery and that of genotype 3 was linked with intravenous drug use. **CONCLUSIONS:** Today, the main routes of hepatitis C virus transmission are intravenous drug use and tattoos. Some hepatitis C infections are associated with surgery or are acquired from a family member. The shift in transmission pathways predetermined the shift in hepatitis C virus genotypes from 1 to 3.

Merkinaitė, S., Lazarus, J. V. and Gore, C. **"Addressing HCV infection in Europe: reported, estimated and undiagnosed cases."** *Cent Eur J Public Health* 2008 16(3): 106-110.

The hepatitis C virus (HCV) is a major public health problem due to its high prevalence, high rate of onward transmission and health complications. As many as 85% of people infected with HCV may go on to become chronic carriers of the disease with the risk of developing liver cancer or cirrhosis. At present, it is the most common cause of chronic liver disease and liver transplantation in a number of countries, with an estimated 250,000 people dying annually from HCV-related causes. Despite the magnitude of the problem, the virus does not receive adequate attention from either the general public or from health policy-makers. This study assesses HCV prevalence from both estimated totals and undiagnosed cases in selected European countries. Secondary sources were assessed and experts in 17 European countries were interviewed about HCV prevalence, reporting strategies and transmission. Available data suggest that only between 10% and 40% of people with HCV in Europe are aware of their infection (up to 90% of the prevalent pool are undiagnosed in such countries as Germany or Poland). Though the virus affects people of all ages, races and backgrounds, in Europe, between 20% and 90% of new HCV cases have been identified among past or current injecting drug users (IDUs). It is of the utmost importance to improve both public awareness and access to early testing and counselling, with the goal of prevention of further infections, maintenance of health and provision of treatment to avoid cirrhosis and liver cancer. Additionally, as previous studies in central and eastern Europe show, evidence-based measures to prevent and manage HCV among IDUs, where most current transmission is concentrated, remain limited. Therefore, there is a strong need for intensified advocacy to put HCV higher on both public health and harm reduction agendas.

Deterding, K., Constantinescu, I., Nedelcu, F. D., Gervain, J., Nemecek, V., Srtuneky, O., Vince, A., Grgurevic, I., Bielawski, K. P., Zalewska, M., et al. **"Prevalence of HBV genotypes in Central and Eastern Europe."** *J Med Virol* **2008** 80(10): 1707-1711.

The importance of hepatitis B virus (HBV) genotypes for disease progression and response to interferon-alpha-based treatment is well established. While almost all patients in the Mediterranean area are infected with HBV genotype D, HBV genotype A is dominant in Northern Europe. However, the distribution of HBV genotypes is unknown for several Central and Eastern European countries. Data are described of 1313 HBsAg-positive patients recruited at 14 referral centers in eight countries. There were only very few cases of HBV genotype B, C, E, F, and H infection while HBV genotypes A and D were found in 42% and 48% of patients, respectively. Eight percent of patients had positive bands for more than one genotype using the hybridization assay. The frequency of genotype A was higher in Poland (77%) and the Czech Republic (67%) as compared to Hungary (47%), Lithuania (41%), Croatia (8%), and Germany (32%). In contrast, HBV genotype D was most frequent in Croatian, Romanian, and Russian patients with 80%, 67%, and 93% of cases, respectively. In conclusion, HBV genotype A versus D showed significantly different distribution patterns in Central and Eastern Europe which deserves consideration for national guidelines and treatment decisions.

Kupcinskas, L. **"Chronic hepatitis in West and East."** *Dig Dis* **2007** 25(3): 274-276.

The main etiologies of chronic hepatitis (CH) worldwide are viral B and C infections. Progression of CH to end-stage liver disease has a significant impact on mortality and need for liver transplantation worldwide. This review will focus on differences in etiology, prevalence, clinical outcomes of CH and impact on public health issues between developed Western and developing Eastern countries. Despite achievements in treatment and prevention of viral hepatitis in Western countries, processes of globalization contribute to further spread of the infections. Further efforts towards the elimination of hepatic B virus transmission throughout implementation of vaccination programs and primary prevention of hepatitis C infection are still of high importance, especially in developing world.

Stikleryte, A., Griskeviciene, J., Magnius, L. O., Zagminas, K., Norder, H. and Ambrozaitis, A.

"Characterization of HCV strains in an oncohematological pediatric department reveals little horizontal transmission but multiple introductions by un-screened blood products in the past." *J Med Virol* **2006** 78(11): 1411-1422.

Because several children were found infected with hepatitis C virus (HCV) at a pediatric oncohematological department in Vilnius, 474 children were tested for anti-HCV. Fifty-eight percent of 96 children treated with blood and plasma products manufactured before the introduction of anti-HCV screening of blood in Lithuania in 1994 were positive for anti-HCV versus 3.4% of those treated after 1994. The possible route of transmission for 45 of these was investigated by phylogenetic analyses within the NS5B region. Children treated before 1995 were infected with a multiplicity of strains of different subtypes, predominantly 1b found in 21 cases, 3a in 5 cases, 2 in 3 cases, 1a in 1 case, and not subtypeable genotype 1 strains in 2 cases. Children who had received blood products after 1994 were infected with only two subtypes, 1b in six and 3a in seven. Genetic analysis showed multiple introductions of HCV before 1995 and that horizontal spread between patients had occurred only to a minor extent at the department. However, two transmission chains involved children treated before 1995. Another chain involved five children treated after 1994. Since the most important risk factor for acquiring hepatitis C was blood products manufactured before the introduction of donor screening for anti-HCV, the spread between children would not have been revealed without molecular tools. These and the background strains provide the first reported sequence data on Lithuanian HCV strains. In general, these were shown to form autochthonous clades, except the 3a strains that were related to strains from the former USSR.

Prevention

Rimkuvienė, J., Puriene, A., Peciuliene, V. and Zaleckas, L. **"Percutaneous injuries and hepatitis B vaccination among Lithuanian dentists."** *Stomatologija* **2011** 13(1): 2-7.

The transmission of blood-borne viruses in dental offices is a potential hazard to patients and dental staff. The aim of the study was to clarify the current situation regarding hepatitis B virus vaccination, percutaneous injuries among members of the Lithuanian dental community. MATERIAL AND METHODS: A confidential, self administered questionnaire was sent to all 2235 Lithuanian general dental practitioners. The questionnaire collected data on sociodemographic characteristics, practice time, working place and environment, hepatitis B virus (HBV) vaccination, history of hepatitis B infection, and needlestick and sharp instruments injury (NSII). RESULTS: Overall response rate was 64.7% (87.4% of them were women; 64.1% were working in five major cities of Lithuania and 60.8% in private clinics. Mean age of respondents was 44.8 (range 23 - 74 years). As much as 95.3% dentists expressed concern about the risk of cross-infection from patients to themselves and their dental assistants. Respondents reported: complete immunization against HBV (35.9%); previous hepatitis infection (4.3%); needlestick and sharp instruments injury (78.5%); collecting medical history about HBV from patients (30.9%). CONCLUSIONS: Despite a high risk of needlestick and sharp instruments injury in the dental practice as well as high risk of HBV infection and the existence of strong rules and recommendations for routine HBV vaccination, vaccine coverage among Lithuanian dentists cannot be assumed to be adequate. Further continuing education programs and stronger control measures might be suggested.

Magdzik, W. **"[Vaccination against hepatitis B and epidemiological situation of this disease in European countries in the years 1990-2001]."** *Przegl Epidemiol* **2006** 60(2): 179-184.

Programme of vaccination in 52 countries of European Region does not include vaccination against hepatitis B of newborns and infants in 13 countries (25,0%), of older children and adolescents in 28 countries (53,8%) and among them newborns, infants older children and adolescents in 8 countries (15,4%). The best coverage of vaccination was found in Italy, Bulgaria, Poland, Romain and Lithuania. Number of cases of hepatitis B in the years 1990-2001 in 10 countries among 22 (45,4%), decreased in 6 countries (27,2%), increased in 4 countries (18,2%). The biggest improvement of epidemiological situation of hepatitis B was found in Poland.

Risk groups

Gyarmathy, V. A., Johnston, L. G., Caplinskiene, I., Caplinskas, S. and Latkin, C. A. **"A simulative comparison of respondent driven sampling with incentivized snowball sampling--the "strudel effect".**" *Drug Alcohol Depend* **2014** 135: 71-77.

BACKGROUND: Respondent driven sampling (RDS) and incentivized snowball sampling (ISS) are two sampling methods that are commonly used to reach people who inject drugs (PWID). METHODS: We generated a set of simulated RDS samples on an actual sociometric ISS sample of PWID in Vilnius, Lithuania ("original sample") to assess if the simulated RDS estimates were statistically significantly different from the original ISS sample prevalences for HIV (9.8%), Hepatitis A (43.6%), Hepatitis B (Anti-HBc 43.9% and HBsAg 3.4%), Hepatitis C (87.5%), syphilis (6.8%) and Chlamydia (8.8%) infections and for selected behavioral risk characteristics. RESULTS: The original sample consisted of a large component of 249 people (83% of the sample) and 13 smaller components with 1-12 individuals. Generally, as long as all seeds were recruited from the large component of the original sample, the simulation samples simply recreated the large component. There were no significant differences between the large component and the entire original sample for the characteristics of interest. Altogether 99.2% of 360 simulation sample point estimates were within the confidence interval of the original prevalence values for the characteristics of interest. CONCLUSIONS: When population characteristics are reflected in large network components that dominate the population, RDS and ISS may produce samples that have statistically non-different prevalence values, even though some isolated network components may be under-sampled and/or statistically significantly different from the main groups. This so-called "strudel effect" is discussed in the paper.

Jarlais, D. D. "Systematic review research on needle/syringe programs and opiate substitution programs in low- and middle-income countries." *J Food Drug Anal* **2013** 21(4): S59-S61.

Persons who inject drugs (PWID) are at an elevated risk for human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection. In many high-income countries, needle and syringe exchange programs (NSPs) have been associated with reductions in blood-borne infections. However, we do not have a good understanding of the effectiveness of NSP in low/middle-income and transitional-economy countries. A systematic literature review based on PRISMA guidelines was utilized to collect primary study data on coverage of NSP programs and changes in HIV and HCV infection over time among PWID in low- and middle-income and transitional countries (LMICs). Included studies reported laboratory measures of either HIV or HCV and at least 50% coverage of the local injecting population (through direct use or through secondary exchange). We also included national reports on newly reported HIV cases for countries that had national level data for PWID in conjunction with NSP scale-up and implementation. Studies of 11 NSPs with high-coverage from Bangladesh, Brazil, China, Estonia, Iran, Lithuania, Taiwan, Thailand, and Vietnam were included in the review. In five studies, HIV prevalence decreased (range -3% to -15%) and in three studies HCV prevalence decreased (range -4.2% to -10.2%). In two studies, HIV prevalence increased (range +5.6% to +14.8%). HCV incidence remained stable in one study. Of the four national reports of newly reported HIV cases, three reported decreases during NSP expansion, ranging from -30% to -93.3%, whereas one national report documented an increase in cases (+37.6%). Estimated incidence among new injectors decreased in three studies, with reductions ranging from -11/100 person years at risk to -16/100 person years at risk. While not fully consistent, the data generally support the effectiveness of NSP in reducing HIV and HCV infection in low/middle-income and transitional-economy countries. If high coverage is achieved, NSP appear to be as effective in LMICs as in high-income countries. Additional monitoring and evaluation research is needed for NSPs where reductions in HIV/HCV infection among PWID are not occurring in order to identify and correct contributing problems.

Tolmane, I., Rozentale, B., Keiss, J., Arsa, F., Brigis, G. and Zvaigzne, A. "The prevalence of viral hepatitis C in Latvia: a population-based study." *Medicina (Kaunas)* **2011** 47(10): 532-535.

BACKGROUND AND OBJECTIVE: Chronic viral hepatitis C (VHC) is one of the most discussed infectious diseases worldwide. The number of infected persons worldwide is approximately 170 million, and in Europe, it exceeds 9 million. The aim of this study was to determine the prevalence of antibodies to hepatitis C virus (anti-HCV prevalence) and prevalence of HCV viremia (HCV-RNA prevalence) in Latvia. MATERIAL AND METHODS: A multistage randomized selection was used. A total of 42 primary care physicians (PCPs) were randomly selected from the register of PCPs from different regions of Latvia. From each PCP register, 60 subjects were selected (1651 individuals in total) and invited for the anti-HCV test with a screening method (ELISA). In case of positive results, antibodies were confirmed by the Western blot test, and all these subjects were tested for HCV-RNA by polymerase chain reaction. RESULTS: Of the 1459 subjects tested, 57 were positive for anti-HCV (3.9%; 95% CI 3% to 5%); 35 of them were positive for anti-HCV with a confirmatory test (2.4%; 95% CI, 1.7% to 3.3%): 19 men and 16 women (3.8% and 1.7%, respectively; $P=0.011$). The results of HCV RNA test were positive in 25 subjects (1.7%; 95% CI, 1.2% to 2.5%): 15 men and 10 women (3% and 1% respectively, $P=0.019$). CONCLUSIONS: The prevalence of anti-HCV and HCV-RNA in Latvia was found to be 2.4% and 1.7%, respectively. The prevalence of anti-HCV and HCV-RNA was higher in men than women.

Gyarmathy, V. A., Neaigus, A., Li, N., Ujhelyi, E., Caplinskiene, I., Caplinskas, S. and Latkin, C. A. "Infection disclosure in the injecting dyads of Hungarian and Lithuanian injecting drug users who self-reported being infected with hepatitis C virus or human immunodeficiency virus." *Scand J Infect Dis* **2011** 43(1): 32-42.

The aim of this study was to assess the prevalence and correlates of disclosure to network members of being hepatitis C virus (HCV)- or human immunodeficiency virus (HIV)-infected

among injecting dyads of infected injection drug users (IDUs) in Budapest, Hungary and Vilnius, Lithuania. Multivariate generalized estimating equations (GEE) were used to assess associations. Very strong infection disclosure norms exist in Hungary, and HCV disclosure was associated with using drugs and having sex within the dyad. Non-ethnic Russian IDUs in Lithuania were more likely to disclose HCV infection to non-Roma, emotionally close and HCV-infected network members, and to those with whom they shared cookers, filters, drug solutions or rinse water or got used syringes from, and if they had fewer non-IDU or IDU network members. Ethnic Russian Lithuanian IDUs were more likely to disclose HCV if they had higher disclosure attitude and knowledge scores, 'trusted' network members, and had lower non-injecting network density and higher injecting network density. HIV-infected Lithuanian IDUs were more likely to disclose to 'trusted' network members. Disclosure norms matched disclosure behaviour in Hungary, while disclosure in Lithuania to 'trusted' network members suggests possible stigmatization. Ongoing free and confidential HCV/HIV testing services for IDUs are needed to emphasize and strengthen disclosure norms, and to decrease stigma.

Gyarmathy, V. A., Neaigus, A., Li, N., Ujhelyi, E., Caplinskiene, I., Caplinskas, S. and Latkin, C. A. **"Liquid drugs and high dead space syringes may keep HIV and HCV prevalence high - a comparison of Hungary and Lithuania."** *Eur Addict Res* **2010** 16(4): 220-228.

Despite very similar political, drug policy and HIV prevention backgrounds, HIV and HCV prevalence is considerably different in Hungary (low HIV and moderate HCV prevalence) and Lithuania (high HCV and moderate HIV prevalence). We compared the drug use profile of Hungarian (n = 215) and Lithuanian (n = 300) injecting drug users (IDUs). Overall, compared with IDUs in Hungary, IDUs in Lithuania often injected opiates purchased in liquid form ('shirka'), used and shared 2-piece syringes (vs. 1-piece syringes) disproportionately more often, were less likely to acquire their syringes from legal sources and had significantly more experience with injected and less experience with non-injected drugs. It may not be liquid drugs per se that contribute to a higher prevalence of HCV and/or HIV, but it is probably factors associated with the injecting of liquid drugs, such as the wide-spread use and sharing of potentially contaminated 2-piece syringes acquired often from non-legal sources, and syringe-mediated drug sharing with 2-piece syringes. Scaling up substitution therapy, especially heroin replacement, combined with reducing the supply of liquid drugs may decrease the prevalence of high-risk injecting behaviours related to the injecting of liquid drugs and drug injecting-related infections among IDUs in Lithuania.

Gailiene, G. and Cenenkiene, R. **"[Professional biological risk factors of health care workers]."** *Medicina (Kaunas)* **2009** 45(7): 530-536.

Health care workers are attributed to the group at highest risk of biological factors, as they are daily exposed to fluids of the human body. The risk of sharps injuries and exposure to blood is associated with bloodborne infections. The aim of this study was to determine the frequency and type of professional biological risk factors, to evaluate the use of personal protective devices, application of immunoprophylaxis to health care workers in the surgical departments. **METHODS.** A retrospective study was carried out from January to June 2006. Data were collected in the surgical departments of Hospital of Kaunas University of Medicine. An anonymous questionnaire survey was performed. **RESULTS.** More than half (51.4%) of the respondents experienced sharps injuries, 62.1% were exposed to biological fluids, and 39.6% of the workers experienced both injury and exposure. In all cases, the hands were injured during sharps injuries. Exposure of healthy skin and eyes to biological fluids occurred in 63% and 20% of the cases, respectively. Majority of exposures were blood splashes (60%). Physicians most frequently experienced sharps injury during the surgery (79.3%), nurses - during the preparation of instruments (35.1%), supporting staff - disposing the waste (75.8%). Commonly physicians were injured by surgical needles (72.4%), nurses - by needlestick (72.4%), and supporting staff - by glass waste (60.6%). Majority of the respondents (86%) were not vaccinated with HB vaccine. No personal protective equipment was used by 14.5% of the respondents during sharps injuries and 5% during exposures. **CONCLUSIONS.** More than half of the respondents experienced sharps injury or exposure to biological fluids during the study

period. Physicians and nurses experience sharps injury and exposure to biological fluids more commonly as compared to supporting staff. Hepatitis B vaccination is insufficient among health care workers.

Kalibatas, V. "**Payment for whole blood donations in Lithuania: the risk for infectious disease markers.**" *Vox Sang* 2008 94(3): 209-215.

BACKGROUND AND OBJECTIVES: In Lithuania, remuneration for whole blood donations still prevails, with the government covering payment for the donors. The payment per donation in cash is equal to 40 litas (euro11.6); it is offered to all blood donors and accepted by the majority of them. Donors who gave blood and received the payment are treated as remunerated donors; those who gave blood and did not take the payment are treated as non-remunerated ones. The purpose of this study was to assess the risk of payment for whole blood donations and to analyse the prevalence of infectious diseases markers per 100 remunerated and non-remunerated, first-time and regular whole blood donations, and to compare the risk ratios of infectious disease markers of remunerated and non-remunerated whole blood donations in 2005 and 2006 at the National Blood Center in Lithuania. **MATERIALS AND METHODS:** Whole blood donors were categorized as follows: (i) first-time donor, remunerated; (ii) first-time donor, non-remunerated; (iii) regular donor, remunerated; and (iv) regular donor, non-remunerated. The blood donations were analysed for the presence or absence of the following infectious disease markers: anti-hepatitis C virus (anti-HCV), hepatitis B surface antigen (HBsAg), anti-human immunodeficiency virus (anti-HIV (1)/(2)) and syphilis. Only confirmed infectious disease markers were classified. To assess the risk of payment for whole blood donations, the prevalence of infectious disease markers per 100 donations in the different donor groups and the risk ratios between the remunerated and non-remunerated donations were determined. **RESULTS:** The prevalence per 100 first-time remunerated donations was: for anti-HCV 1.84 (2005) and 2.98 (2006); for HBsAg 1.73 (2005) and 2.03 (2006); for syphilis 0.67 (2005) and 1.03 (2006). The prevalence per 100 first-time non-remunerated donations was: for anti-HCV 0.93 (2005) and 0.98 (2006); for HBsAg 1.57 (2005) and 1.33 (2006); for syphilis 0.29 (2005) and 0.47 (2006). The first-time donors who were remunerated for whole blood donations had a significantly higher prevalence of infectious disease markers per 100 donations and a higher risk ratio for at least three infectious disease markers (HBsAg, anti-HCV and syphilis) as compared to first-time donors who were non-remunerated. The regular donors who were non-remunerated for whole blood donations had the lowest prevalence of all infectious disease markers: anti-HCV -0.03 (2005) and 0.04 (2005); syphilis -0.06 (2005) and 0.02 (2006); and any positive cases of HBsAg and anti-HIV (1)/(2) were found both in 2005 and 2006. No statistically significance differences in incidence and risk ratio existed when comparing the regular donations who were remunerated and non-remunerated. **CONCLUSION:** The payment for whole blood donors provides a higher risk for infectious disease markers of first-time donations at the National Blood Center in Lithuania.

Kalibatas, V. "**[The results of nucleic acid testing for viruses in individual donor test and its importance for the safety of blood]**." *Medicina (Kaunas)* 2008 44(10): 791-798.

SUMMARY: The aim of the study was to evaluate the results of nucleic acid testing for viruses in an individual donor test in National Blood Center; the objectives--to analyze the prevalence of infectious disease markers per 100 seronegative remunerated and non-remunerated, first-time and regular whole-blood donations and to assess the odds ratio in detecting the infectious disease markers among remunerated and non-remunerated donations. **MATERIALS AND METHODS:** All seronegative (for compulsory hepatitis B surface antigen, antibodies against hepatitis C, and antibodies against HIV-1/2 tests) whole-blood donations were tested by Procleix Ultrio (Tigris, Chiron) system at the National Blood Center in 2005-2007 in order to identify HIV-1, hepatitis C, and hepatitis B viruses. **RESULTS:** There were 152229 seronegative whole-blood donations tested by nucleic acid test of viruses in individual donor tests (ID-NAT). In 152146 cases, no infectious disease marker was found, and in 83 cases (or 0.05% of all seronegative whole blood donations), infectious disease markers were determined and confirmed. The prevalences of hepatitis C virus (determined by HCV-NAT method) per 100

seronegative blood donations were as follows: 0.061 among first-time remunerated donations and 0.042 among regular remunerated donations. The prevalences of hepatitis B virus (determined by HBV-NAT method) per 100 seronegative blood donations were as follows: 0.111 among first-time remunerated donations, 0.062 among regular remunerated donations, 0.014 among first-time non-remunerated donations, and 0.005 among regular non-remunerated donations. The remunerated donations showed the higher odds ratios in determining the infectious disease marker by ID-NAT test, comparing with non-remunerated ones. CONCLUSIONS: 1. The prevalence of hepatitis B and hepatitis C viruses, determined by ID-NAT test, per 100 seronegative whole-blood donations is statistically significantly higher in remunerated donations. 2. The remunerated donations had the higher odds ratios in determining the infectious disease marker by ID-NAT test, comparing with non-remunerated ones. 3. In order to maximize the safety of blood and blood products, the continuity of promotion of non-remunerated whole-blood donations program should be ensured, and a compulsory blood donor testing for nucleic acids of viruses in an individual donor test should be introduced.

Kupcinskas, L., Petrauskas, D., Petrenkiene, V. and Saulius, K. **"Prevalence of hepatitis B virus chronic carriers and risk factors for hepatitis B virus infection among Lithuanian army soldiers."** *Mil Med* **2007** 172(6): 625-627.

The aim of this study was to evaluate the prevalence of hepatitis B serological markers (hepatitis B virus (HBV) superficial antigen (HBsAg)) and risk factors for HBV infection among Lithuanian Army soldiers. The study was carried out in Lithuanian military subunits in 2003. Serum samples were drawn from 1,830 soldiers (average age, 21.6 (0.707) years) and tested for hepatitis B infection markers (HBsAg). Questionnaires were used to obtain information about risk factors associated with HBV infection. A total of 1.97% of soldiers was seropositive for HBsAg. The prevalence rate of HBV infection was related to military subunit ($p > 0.05$). Most of the HBsAg-positive soldiers (53.8%) served 4 to 6 months. Among soldiers who were offered to use drugs, the prevalence of HBsAg was 4.3%; in the remaining group, the prevalence was 1.9%. No association was found between other risk factors for HBV infection and the prevalence rate of the hepatitis B marker. Study data proved the need for health promotion, prophylactic vaccination, and monitoring programs at the Lithuanian Armed Forces.

Treatment and Clinical

Ahmed, W., Arif, A., Alam, E. and Qureshi, H. **"Response to different conventional interferons in treatment of chronic hepatitis C."** *J Ayub Med Coll Abbottabad* **2012** 24(3-4): 120-123.

BACKGROUND: Sustained virological response to interferon therapy is a great challenge for patients of chronic Hepatitis C. Over 20 brands of interferons are available in the local market with each claiming over 80% response and a wide variation in the cost thus creating confusion for treating physicians as to which drug should be selected. METHODS: Chronic Hepatitis C patients attending outpatients department of Pakistan Medical Research Centre JPMC from January 1998-December 2010 were evaluated. Complete blood count, liver function tests, serum proteins, HCV-RNA were done in all cases before starting therapy. Side effects were also noted. RESULTS: Total of 851 cases received interferon 3 MIU three times a week for 6 months. There were 638 (75%) males and 213 (25%) females, mean age was 36.1 +/- 10.4 years. All were HCV-RNA positive prior to treatment, at the end of 6 months 666 (78.3%) became negative while 185 (21.7%) were non-responders with positive HCV RNA. End of treatment response (ETR) showed 84.7% with Bioferon (Argentina), 83.8% Hebron (Cuba), 82.2% INF (Argentina), 82.1% Ceron (China), 81% Viteron (Korea), 80.7% Leveron (Argentina), 81.5% Hepaferon, 79.1% Anferon (China), 77.4% Intron (Belgium), 75% Green alpha (Korea), 74% Roferon (Switzerland), 67.3% Uniferon (Lithuania), and 68.4% with others. Post-treatment 211 cases were lost to follow-up. In remaining 358/640 (55.9%) negative for HCV-RNA, at six months follow up, whereas 98 (15.3%) relapsed. Sustained virological response (SVR) Ceron 68.2%, Hebron 66.3%, Bioferon 65.2%, Leveron 60.5%, Intron 60.3%, Viteron 57%, Anferon 53.3%, Green alpha, Roferon, Hepaferon, and others 50%, INF 48.5% and Uniferon 41.9%. Average cost of these

interferons was Rs. 6,000/month, except Hepaferon 5,000/month, Roferon 10,600/month. CONCLUSIONS: ETR ranged from 74-84.7% and SVR 41.9% to 68.2% and > 60% SVR was observed with Ceron, Hebron, Bioferon, Leveron, Intron and were cost effective.

Vanagas, G., Padaiga, Z. and Mickeviciene, A. **"Cost-effectiveness and cost-utility of the treatment of chronic hepatitis B with peginterferon alfa-2a, interferon alfa, and lamivudine in Lithuania."** *Medicina (Kaunas)* **2010** 46(12): 835-842.

BACKGROUND: Chronic hepatitis B infection is an important health care problem worldwide. According to the World Health Organization, 10% to 15% of population is infected with hepatitis B virus. Nearly 100 new cases of acute hepatitis B are annually registered in Lithuania, but official statistics covers only 8-25% of all disease incidence. The aim of this study was to evaluate the cost-effectiveness of the treatment of chronic hepatitis B with peginterferon alfa-2a and compare it to treatment with interferon alfa and lamivudine in Lithuania. MATERIAL AND METHODS: A Markov model was used to evaluate long-term cost-effectiveness of the treatment with peginterferon alfa-2a and to compare it with treatment with interferon alfa and lamivudine. Peginterferon alfa-2a was administered by subcutaneous injections at a dosage of 180 mug every week for 48 weeks; interferon alfa, 6 million IU three times a week for 24 weeks; and lamivudine, 100 mg per day from 48 weeks to 5 years for HBeAg-positive chronic hepatitis B and 100 mg per day up to 5 years in HBeAg-negative chronic hepatitis B. RESULTS: Treatment with peginterferon alfa-2a gained 1.179 life years as compared to 0.658 life years gained with treatment with interferon alfa; incremental costs per incremental life-year gained (LYG) were 51,256.92 Lt (14,845.03 euro). Treatment with peginterferon alfa-2a gained 0.545 quality-adjusted life-years (QALYs) with incremental costs per incremental QALY of 48,980.08 Lt (14,185.61 euro). Treatment with peginterferon alfa-2a had twice higher cost-effectiveness than treatment with interferon alfa: 50,4167.00 Lt (146,016.85 euro) vs. 954,020.08 Lt (276,303.31 euro), respectively. Costs for a complete response were also twice lower. Treatment with peginterferon alfa-2a gained 0.757 incremental LYG more compared to lamivudine (48-week course). Comparing incremental cost-effectiveness using peginterferon alfa-2a for treatment, incremental costs per incremental LYG were 41,993.67 Lt (12,162.21 euro); additionally there was a gain of 0.792 incremental QALYs, while incremental costs for incremental QALY were 40,096.19 Lt (11,612.66 euro). Complete response costs were 83,515.98 Lt (24,187.89 euro) less compared to lamivudine (48-week course). CONCLUSIONS: Treatment of chronic hepatitis B prolongs patients' overall survival and quality-adjusted life. Peginterferon alfa-2a was the most effective drug registered in Lithuania for CHB treatment.

Paskonis, M., Masalaite, L., Buivydiene, A., Sokolovas, V., Jurgaitis, J., Jurevicius, S., Mikalauskas, S., Gutasukas, M., Spuras, J., Sarkaite, R., et al. **"Orthotopic liver transplantation: the first experience and results of the Vilnius University Hospital Santariskiu Klinikos."** *Ann Transplant* **2010** 15(1): 14-24.

BACKGROUND: Liver transplantation has become the treatment of choice for chronic and acute end-stage liver failure as well as for selected cases of malignancies and metabolic disorders. We report our first experience of the orthotopic liver transplantation. MATERIAL/METHODS: Between 2005 and 2008 16 cadaveric orthotopic liver transplantations in 16 adults (12 males, 4 females, mean age 44 years) were performed. Main indications for orthotopic liver transplantation were cholestatic liver disease (31%), viral-induced cirrhosis (25%), alcoholic liver disease (19%), hepatocellular carcinoma associated with hepatitis virus infection (13%), autoimmune cirrhosis (6%), cryptogenic acute liver failure (6%). Mean follow-up was 15 month (range: 4 days - 43 month). RESULTS: Intraabdominal haemorrhage was observed in 6 patients (37.5%). Vascular complications were observed in 3 patients (18.75%). Biliary complication were observed in 3 patients (18.75%). Overall 1 year patient survival was 87,5%. Four (25%) patients died during follow-up. All patients died because of sepsis and multiorgan system failure. CONCLUSIONS: Our first results showed that secret of successful liver transplantation is perfect interdisciplinary team approach, including selection of the recipient and timing of transplantation, the operative procedure itself, prevention and treatment of complications, the perioperative anaesthesiological and intensive-care management, and careful follow up after transplantation.

Adukauskienė, D., Dockienė, I., Naginiene, R., Kevelaitis, E., Pundzius, J. and Kupcinskas, L. **"Acute liver failure in Lithuania."** *Medicina (Kaunas)* **2008** 44(7): 536-540.

OBJECTIVES: Acute liver failure (ALF) is a life-threatening condition that can rapidly progress into coma and death due to the cerebral edema and multi-organ dysfunction. The ALF etiology and risk factors have been investigated in West Europe, North America, and Asia; however, there are still no published data about the causes and prognosis of ALF in Central and East European countries. The aim of our study was to analyze the causes, outcomes, and prognostic factors of ALF in patients referred to tertiary care center in Lithuania. **MATERIAL AND METHODS:** A total of 28 consecutive patients admitted to the tertiary care center (one of two university-level medical centers in Lithuania) over the period of January 1996 and December 2004 and who fulfilled the entry criteria of ALF (presence of hepatic encephalopathy (HE) and prothrombin international normalized ratio (INR) >1.5) were included into a prospective study. **RESULTS:** In our study the most frequent causes of ALF were acute viral hepatitis B (21.4%), drug-induced hepatitis (21.4%), and indeterminate hepatitis (17.9%); other etiologies included Budd-Chiari syndrome (10.7%), ischemic hepatitis (10.7%), Wilson's disease (7.1%), *Amanita phalloides*-induced liver damage (3.6%), acute fatty liver of pregnancy (3.6%), and malignant infiltration of the liver (3.6%). Among patients with drug-induced liver injury, only one case of acetaminophen poisoning was diagnosed. Clinical status of 9 persons in all patients with ALF corresponded to criteria for liver transplantation (LT) (one liver transplantation was performed), 6 of them had contraindications, and 13 patients did not fulfill requirements for urgent LT. The patients' survival rate in these groups was 11.1%, 16.7% and 69.2%, respectively. In 27 non-transplanted patients univariate analysis revealed the grade of HE on the day of enrolment, total serum bilirubin, pH, and prothrombin INR as risk factors for death from ALF. Multivariate logistic regressive analysis determined only prothrombin INR >3.24 and serum pH <or=7.29 as independent predictors of lethal outcome in ALF. **CONCLUSIONS:** Acute viral hepatitis B, drug-induced liver injury, and indeterminate hepatitis are the main ALF causes in Lithuania. In non-transplanted patients, the main predictors of lethal outcome were severe coagulopathy and metabolic acidosis. Improvement of liver donation system for urgent liver transplantation is essential requirement for amelioration of ALF patient's survival.

Research

Pleckaitė, M., Bremer, C. M., Gedvilaitė, A., Kucinskaite-Kodze, I., Glebe, D. and Zvirbliene, A. **"Construction of polyomavirus-derived pseudotype virus-like particles displaying a functionally active neutralizing antibody against hepatitis B virus surface antigen."** *BMC Biotechnol* **2015** 15: 85.

BACKGROUND: Virus-like particles (VLPs) can be efficiently produced by heterologous expression of viral structural proteins in yeast. Due to their repetitive structure, VLPs are extensively used for protein engineering and generation of chimeric VLPs with inserted foreign epitopes. Hamster polyomavirus VP1 represents a promising epitope carrier. However, insertion of large sized protein sequences may interfere with its self-assembly competence. The co-expression of polyomavirus capsid protein VP1 with minor capsid protein VP2 or its fusion protein may result in pseudotype VLPs where an intact VP1 protein mediates VLP formation. In the current study, the capacity of VP1 protein to self-assemble to VLPs and interact with the modified VP2 protein has been exploited to generate pseudotype VLPs displaying large-sized antibody molecules. **RESULTS:** Polyomavirus-derived pseudotype VLPs harbouring a surface-exposed functionally active neutralizing antibody specific to hepatitis B virus (HBV) surface antigen (HBsAg) have been generated. The pseudotype VLPs consisting of an intact hamster polyomavirus (HaPyV) major capsid protein VP1 and minor capsid protein VP2 fused with the anti-HBsAg molecule were efficiently produced in yeast *Saccharomyces cerevisiae* and purified by density-gradient centrifugation. Formation of VLPs was confirmed by electron microscopy. Two types of pseudotype VLPs were generated harbouring either the single-chain fragment

variable (scFv) or Fc-engineered scFv on the VLP surface. The antigen-binding activity of the purified pseudotype VLPs was evaluated by ELISA and virus-neutralization assay on HBV-susceptible primary hepatocytes from *Tupaia belangeri*. Both types of the pseudotype VLPs were functionally active and showed a potent HBV-neutralizing activity comparable to that of the parental monoclonal antibody. The VP2-fused scFv molecules were incorporated into the VLPs with higher efficiency as compared to the VP2-fused Fc-scFv. However, the pseudotype VLPs with displayed VP2-fused Fc-scFv molecule showed higher antigen-binding activity and HBV-neutralizing capacity that might be explained by a better accessibility of the Fc-engineered scFv of the VLP surface. **CONCLUSIONS:** Polyomavirus-derived pseudotype VLPs harbouring multiple functionally active antibody molecules with virus-neutralizing capability may represent a novel platform for developing therapeutic tools with a potential application for post-exposure or therapeutic treatment of viral infections.

Kucinskaite-Kodze, I., Pleckaityte, M., Bremer, C. M., Seiz, P. L., Zilnyte, M., Bulavaite, A., Mickiene, G., Zvirblis, G., Sasnauskas, K., Glebe, D., et al. **"New broadly reactive neutralizing antibodies against hepatitis B virus surface antigen."** *Virus Res* **2015**.

Hepatitis B virus (HBV) surface antigen (HBsAg) is considered to be the most important target for the diagnosis and immune prophylaxis of HBV infection. HBsAg-specific monoclonal antibodies (MAbs) are extensively used for studying the complex structure of the HBsAg, mapping the neutralizing epitopes and development of HBV diagnostic tests. However, the efficiency of anti-HBV binding strongly depends on the epitope structure and MAb capability to recognize different HBV variants. In the current study, 9 MAbs against yeast-expressed HBsAg of ayw2 serotype were generated and 7 of them were shown to recognize a linear epitope comprising amino acid (aa) residues 119-GPCRTCT-125 within the main antigenic "a" determinant of HBsAg. One MAb of the highest affinity (clone HB1) was selected for detailed cross-reactivity studies, generation of recombinant single-chain antibody (scFv) and molecular modelling of antibody-epitope interaction. The importance of each aa residue within the identified MAb epitope was determined by alanine substitution study that revealed aa residues C(121), T(123), C(124) and T(125) as essential for binding. These aa residues are highly conserved among HBV variants. In contrast, alanine substitution of G119, P120 and R122 had no or minor influence on the reactivity with the MAb. Certain aa residues at position 122 (either R or K) define different HBV serotypes (either d or y), therefore, the affinity of the MAb HB1 for the epitope with R122K substitution was determined to evaluate its diagnostic potential. The MAb recognized both epitope variants with high affinity. Sequence alignment of the MAb epitope within different HBV strains demonstrated that the shortest peptide recognized by the MAb 121-CR(K)TCT-125 is identical among different human HBV genotypes (HBV A-F, H) and monkey HBV species (HBVCP, HBVGO, HBVGB, WMHBV). In line with these data, the MAb HB1 was cross-reactive in Western blot with a large panel of antigens derived from different HBV genotypes. Recombinant scFv consisting of immunoglobulin VH and VL regions joined by a 20 aa-long linker was generated by cloning the respective cDNA sequences from hybridoma HB1. The recombinant scFv generated in *E. coli* recognized the same epitope as the parental MAb HB1. Cloning of HB1 VH and VL regions allowed determination of their primary structure and subsequent computer modeling of antibody-epitope interaction. The generated molecular models of HB1 variable region with its target peptides were in accordance with experimental data showing the importance of certain aa residues in antibody binding. In conclusion, the current study describes new HBsAg-specific antibodies with HBV-neutralizing potency and a broad cross-reactivity against different HBV strains. The generated MAb HB1 will be of great value in diagnostic and research settings, while the recombinant HB1-derived scFv represents a promising "building block" for producing anti-HBV tools with a potential biopharmaceutical application.

Gedvilaite, A., Kucinskaite-Kodze, I., Lasickiene, R., Timinskas, A., Vaitiekaite, A., Ziogiene, D. and Zvirbliene, A. **"Evaluation of Trichodysplasia Spinulosa-Associated Polyomavirus Capsid Protein as a New Carrier for Construction of Chimeric Virus-Like Particles Harboring Foreign Epitopes."** *Viruses* **2015** 7(8): 4204-4229.

Recombinant virus-like particles (VLPs) represent a promising tool for protein engineering. Recently, trichodysplasia spinulosa-associated polyomavirus (TSPyV) viral protein 1 (VP1) was efficiently produced in yeast expression system and shown to self-assemble to VLPs. In the current study, TSPyV VP1 protein was exploited as a carrier for construction of chimeric VLPs harboring selected B and T cell-specific epitopes and evaluated in comparison to hamster polyomavirus VP1 protein. Chimeric VLPs with inserted either hepatitis B virus preS1 epitope DPAFR or a universal T cell-specific epitope AKFVAAWTLKAAA were produced in yeast *Saccharomyces cerevisiae*. Target epitopes were incorporated either at the HI or BC loop of the VP1 protein. The insertion sites were selected based on molecular models of TSPyV VP1 protein. The surface exposure of the insert positions was confirmed using a collection of monoclonal antibodies raised against the intact TSPyV VP1 protein. All generated chimeric proteins were capable to self-assemble to VLPs, which induced a strong immune response in mice. The chimeric VLPs also activated dendritic cells and T cells as demonstrated by analysis of cell surface markers and cytokine production profiles in spleen cell cultures. In conclusion, TSPyV VP1 protein represents a new potential carrier for construction of chimeric VLPs harboring target epitopes.

Razanskas, R. and Sasnauskas, K. **"Interaction of hepatitis B virus core protein with human GIPC1."** *Arch Virol* **2010** 155(2): 247-250.

Up to now, little is known about hepatitis B virus core protein (HBc) interactions with host-cell proteins, although such interactions might be essential for virus propagation and pathogenicity. In this work, a human liver cDNA library was screened for proteins interacting with HBc. Among several HBc-interacting partners selected, it interacted most strongly with the human protein GIPC1. A common protein interaction domain, PDZ, was identified as the region that is sufficient for the interaction with HBc. The core protein has a putative C-terminal PDZ-interacting motif, and this sequence proved to be important for the interaction with GIPC1.

Razanskas, R. and Sasnauskas, K. **"A novel human protein is able to interact with hepatitis B virus core deletion mutant but not with the wild-type protein."** *Virus Res* **2009** 146(1-2): 130-134.

Hepatitis B virus mutants with in-frame deletions in the central part of the core gene are associated with a severe course of infection in long-term immunosuppressed renal transplant recipients. In this study, yeast two-hybrid system was employed to investigate interaction capabilities of two core mutants with deleted 77-93 and 86-93 amino acids. The same mutant and wild-type (WT) protein pairs which form core-like particles inside bacterial cells were able to interact also in two-hybrid system. To find host proteins possibly involved in enhanced pathogenesis of the mutant variants, a human hepatocyte cDNA library was screened for proteins interacting with the mutant but not with the WT core protein. A human protein of unknown function FLJ20850 interacted specifically with the mutant proteins. An attempt to determine interacting regions revealed that FLJ20850 was unable to interact without significant parts of its C- or N-end, and introduced deletion in the central region conferred interaction capability to the WT core protein.

Simanis, R., Lejniece, S., Sochnevs, A., Eglite, J., Chernevskā, G., Kovalova, Z., Gardovska, D., Jeruma, A., Kuse, V. and Viksna, L. **"Natural clearance of hepatitis C virus in hemophilia patients."** *Medicina (Kaunas)* **2008** 44(1): 15-21.

OBJECTIVE: The objective of this study was to investigate the prevalence of HCV (hepatitis C virus) infection in hemophilia patients in Latvia and to analyze association between natural clearance of HCV and human leukocyte antigen (HLA) class II genes. **MATERIAL AND METHODS:** From 61 hemophilic patients participating in this study, 38 were adults and 23 were pediatric patients younger than 18 years. To analyze association between HLA class II alleles and natural clearance of HCV, the gene frequency was compared in hemophilia patients group and the control group of 60 healthy subjects, all men. Serum HCV RNA was qualitatively determined and HLA class II alleles were identified by polymerase chain reaction (PCR) method. **RESULTS:** HCV infection is common among hemophilia patients in Latvia. Antibodies to HCV were found in 45 of 61 (74%) hemophilia patients. In 41% of hemophilia patients (18 of 44),

HCV infection resolved spontaneously. Children cleared HCV more frequently than adults (7 of 11 comparing to 11 of 33, respectively; OR=3.50; P<0.05). The frequency difference was found to be statistically significant when comparing HLA alleles distribution in the sample of hemophilia patients who naturally cleared HCV (n=18) and in the control group (n=60) (corresponding frequency of HLA-DRB1*07 allele - 4 (11.11%) and 9 (1.67%); OR=7.38; P<0.05). CONCLUSIONS: Natural clearance of HCV infection is frequently found in hemophilia patients in Latvia. Children are more likely to clear virus naturally than adults. There is an association between natural clearance of HCV and HLA allele DRB1*07 in hemophilia patients.

Guobuzaitė, A., Chokshi, S., Balciuniene, L., Voinic, A., Stikleryte, A., Zagminas, K., Ambrozaitis, A. and Naoumov, N. **"Viral clearance or persistence after acute hepatitis C infection: interim results from a prospective study."** *Medicina (Kaunas)* **2008** 44(7): 510-520.

OBJECTIVE: Hepatitis C virus infection (HCV) has a high rate of chronic evolution; however, the underlying mechanisms remain to be elucidated. We investigated natural clinical, virological, and immunological course of acute HCV infection in order to identify possible prognostic factors of spontaneous resolution and to gain more understanding of early characteristics responsible for viral clearance or persistence. MATERIALS AND METHODS: Eight patients with acute symptomatic hepatitis C were prospectively followed up for more than 6 months (range, 8-14 months). None of the individuals received antiviral therapy during the study period. We analyzed biochemical, virological, and immunological parameters of these patients detected at different time-points of the follow-up. Plasma HCV RNA was quantitated using TaqMan real-time polymerase chain reaction. Virus-specific CD4(+) T cells were enumerated by interferon-gamma (IFN-gamma) ELISpot assay. RESULTS: Two of eight individuals resolved HCV spontaneously, while the remaining patients developed chronic HCV infection. HCV RNA became undetectable within 14 days of the study, followed by a rapid alanine aminotransferase normalization in patients with resolved infection. On the contrary, chronically infected subjects demonstrated persistent viremia or intermittently undetectable HCV-RNA, accompanied by polyphasic alanine aminotransferase profile throughout the study. Patients with self-limited hepatitis C displayed the strongest virus-specific CD4(+) T (IFN-gamma) cell reactivity within the first weeks of the follow-up, while persistently infected subjects initially showed a weak antiviral CD4(+) T (IFN-gamma) cell response. CONCLUSIONS: In most cases, acute hepatitis C progresses to chronic disease. Viral clearance within the first month after clinical presentation accompanied by monophasic alanine aminotransferase profile could predict recovery. Early and strong CD4(+)/Th1 immune response against HCV might play an important role in the disease resolution.

3. Bibliography of the Speakers

List of publications achieved via speaker's form, when this form was not available a Pubmed MEDLINE search was performed on Name of the speaker in [Author]-field. If more than 10 references were available only the most recent articles are shown.

LAIMUTĖ VAIDELIENĖ, *Ministry of health of the republic of Lithuania (Vice-minister)*

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IRINA FILIPPOVA *Health Board, CD Surveillance and control department*

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JURIJS PEREVOSCIKOVs, *Head of the Department of Infectious Diseases Risk Analysis and Prevention, Centre for Disease Prevention and Control of Latvia*

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VYTAUTAS USONIS *Head, Clinic of Children Diseases. Faculty of Medicine, Vilnius University*

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JANA FELDMANE, *Head division of Environmental Health, Department of public Health Ministry of Health*

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JEVGENIA EPŠTEIN, *Health Board, CD Surveillance and control department*

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RAINA NIKIFOROVA, *epidemiologist, Department of Infectious Diseases Surveillance and Immunization, Centre for Disease Prevention and Control of Latvia*

From speaker's form: No publication reported

SAULIUS CAPLINSKAS, *Director, Centre for Communicable Diseases and AIDS*

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1. Gyarmathy VA, Johnston LG, Caplinskiene I, Caplinskas S, Latkin CA. **A simulative comparison of respondent driven sampling with incentivized snowball sampling--the "strudel effect".** *Drug Alcohol Depend* 2014;**135**:71-77.
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IRMA CAPLINSKIENE, *Head of HIV/AIDS/STI and Hepatitis Surveillance*

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KRISTI HUIK, *Tartu University.*

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JOANA BIKULČIENĖ, *hepatitis screening in the Lithuanian, blood donors, National Blood Center*

From speakers form:

NO publications reported – but presentation related info:

1. Institute of Hygiene, Blood donors register, Report 2015 III quarter
http://www.hi.lt/uploads/pdf/padaliniai/KDR/KDR_statistika_2015_III_ketv.pdf
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ANITA DAUGAVVANAGA, *hepatitis screening in the Latvian blood donor centre.*

.Head of The State Blood Donor Center,

From speakers form:

1. Common European Standarts and Criteria for the \inspection of Blood Establishments „Audit/ Inspection- Training Guide’’, 2010
2. Professional magazine of medicine „DOCTUS’’, 2006

KRISTI RÜÜTEL, *Head, Infectious Diseases and Drug Monitoring Department, National Institute for Health Development*

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ALJONA KURBATOVA *Head of the Infectious Diseases and Drug Abuse Prevention Department National Institute for Health Development*

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LIVA GRAMATINA, *Senior health promotion coordinator, Department of Health promotion, Centre for Disease Prevention and Control. "Hepatitis prevention in the context of HIV prevention point work"*

From speaker's form: NO publications reported

TATIANA KUZNETSOVA, *National Institute for Health Development*

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1. Ivanova A, Tefanova V, Reshetnjak I, Kuznetsova T, Geller J, Lundkvist Å, Janson M, Neare K, Velström K, Jokelainen P, Lassen B, Hütt P, Saar T, Viltrop A, Golovljova I. **Hepatitis E Virus in Domestic Pigs, Wild Boars, Pig Farm Workers, and Hunters in Estonia**. *Food Environ Virol.* 2015 Jul 4.

IRINA SOMINSKAYA - *Latvian Biomedical Research and Study Centre*

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VALENTINA LIAKINA - *Centre of Hepatology, Gastroenterology and Dietetics, Clinic of Gastroenterology, Nephrourology and Surgery, Faculty of Medicine, Vilnius University, Lithuania.*

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1. Liakina V, Hamid S, Tanaka J, Olafsson S, Sharara AI, Alavian SM, et al. **Historical epidemiology of hepatitis C virus (HCV) in select countries** - volume 3.// J Viral Hepat. 2015 Dec;22 Suppl 4:4-20.
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7. Liakina V, Valantinas J. **Anti-HCV prevalence in the general population of Lithuania.**// Medical Science Monitor 2012;18(3): PH28-35.
8. Juran BD, Hirschfield GM, Invernizzi P, Atkinson EJ, Li Y, Xie G, et al. **ImmunoChip analyses identify a novel risk locus for primary biliary cirrhosis at 13q14, multiple independent associations at four established risk loci and epistasis between 1p31 and 7q32 risk**

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RITA KOROTINSKA, *Epidemiologist of Department of Infectious Diseases Risk Analysis and Prevention, Centre for Disease Prevention and Control of Latvia*
From speakers form: No publication reported

KRISTAPS KAUGURS

(10 recent articles –from Pubmed search [Kaugurs K [author]: no publications reported

ANTONS MOZALEVSKIS (*World Health Organization Regional Office for Europe Focal Point for Viral Hepatitis*)

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LIUDMILA MOSINA (*World Health Organization Regional Office for Europe*)

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LIGITA JANCORIENE *Vilnius University, Hospital Santariskiu*

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DAVID FITZSIMONS, rapporteur, Prévessin, France

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