VHPB country meeting

Elimination of Viral Hepatitis in Hungary:

Lessons learnt and the way forward

BUDAPEST, HUNGARY

30-31 October 2019

Prepared by

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Content

This pre-meeting document contains general background information on Hungary and the current hepatitis situation. Furthermore a list of selected abstracts/references from a Pubmed MEDLINE search on different search terms.

This document should guide you in the preparation of the meeting, it should not be considered as complete literature review, but hopefully it will give an overview of what has been published on the topics of the meeting.

Inhoud

1. Meeting objectives

- *Provide an overview of the current viral hepatitis situation in Hungary: surveillance systems, epidemiology, screening, burden, prevention and the cascade of care*
- *Discuss achievements and challenges in the prevention of viral hepatitis, the possible implementation of new prevention strategies in Hungary*
- *Discuss the development, the implementation of a National hepatitis plan.*
- *Assess the needs to achieve the goal of eliminating viral hepatitis as a major public health threat by 2030 as set out in the WHO Global Strategy and WHO Europe Action Plan, building on the UN Sustainable Development Goals' (SDG) commitments.*
- *Discuss successes, issues and barriers to overcome, and the way forward.*

Target audience:

- *National Public health experts, Healthcare workers, Academics involved in prevention and control of viral hepatitis*
- *VHPB advisors*
- *observers*

Intended Impact

- Putting prevention and control of viral hepatitis on the national public health agenda, discuss the current situation and the way forward to contribute to Hungarian fight against hepatitis and to achieve the elimination of hepatitis by 2030

Meeting venue

Danubius Hotel Helia Budapest, Hungary

2. General background

2.1 Hungary – General information

Hungary is a country in Central Europe. Spanning 93,030 square kilometres (35,920 sq mi) in the Carpathian Basin, it borders Slovakia to the north, Ukraine to the northeast, Austria to the northwest, Romania to the east, Serbia to the south, Croatia to the southwest, and Slovenia to the west. With about 10 million inhabitants, Hungary is a medium-sized member state of the European Union. The official language is Hungarian, which is the most widely spoken Uralic language in the world, and among the few non-Indo-European languages to be widely spoken in Europe. Hungary's capital and largest city is Budapest; other major urban areas include Debrecen, Szeged, Miskolc, Pécs and Győr.

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Demographics data	
Population	9 825 704 (July 2018 est)
GDP (PPP) per capita	$ 29 600 (2017 est.)
GDP	$ 139.2 billion (2017 est.)
Unemployment rate	4.2% (2017 est.)
Population growth	-0.26%% (2018 est.)
Birth rate:	8.9 births/1,000 population (2018 est.)
Death rate:	12.8 deaths/1,000 population (2018 est.)
Net migration rate	1.3 migrant(s)/1,000 population (2018 est.)
Health expenditures	7.4% of GDP (2014)
Physicians density:	3.23 physicians/1,000 population (2016)
Life expectancy at birth	total population: 76,3 years

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

2.2 Hepatitis in Hungary

1.2.1 VHPB survey

VHPB survey on prevention and control of viral hepatitis in 53 European countries in 2014 – November 2014: http://www.vhpb.org/files/html/Meetings_and_publications/Other_VHPB_documents/SURVEY2014.pdf

1.2.2 WHO data

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Prevention and Control of Viral Hepatitis in Europe in 2014: the case of HUNGARY

Country profile

- Population (in millions) (year): 9,9 (2014)[a]
- Gross national income per capita (int $) (year): 20 930 (2012)[b]
- Most recent seroprevalence data:

	% HBsAg + (year)	% Anti-HCV + (year)
General population	-	-
Blood donors (first time)	0.3% (2008)[d]	0.3% (2008)[d]
Pregnant women	-	-
Risk groups		
Injecting drug users	0.4% (2007)[c]	22.6 % (2008)[1]
Prisoners	1.5% (2007-2009)[1]	4.9% (2007-2009)[2]
Migrants (Roma)	-	23.4% (2004)[c]

Screening[e]

Recommended for following groups:	Hep B	Hep C
Blood and organ donors	Yes (since 1966)	Yes (since 1992)
Pregnant women	Yes (since 1995)	No
Injecting drug users	Yes (2005)	Yes (since 2005)
STI clinic patients	No	No
Haemodialysis patients	Yes	No
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[g]		Target	Since/Period
Universal	No		
Risk group	Yes	close contacts of Hepatitis A patients (free of charge) Travellers to an endemic region; chronic liver disease; outbreak areas, residents close communities; IDU	2009 1997; 1998; 1999
Hepatitis[g,h]			
Universal	Yes	Adolescent (14y)	1999-ongoing
Catch-up	No		
Risk group	Yes	Haemodialysis patients, occupational risk; neonates born to HBsAg+ mothers; contacts HBsAg+ patient; Medical school student	1986; 1995; 1996; 1996

Treatment

National guidelines for clinicians available	
Hepatitis B	Yes (2014)[3]
Hepatitis C	Yes (2014)[4]
Drugs available for hepatitis C treatment[4]	
Ribavirin	Yes
Pegylated interferon	Yes
Interferon alpha	yes
Telaprevir	Yes
Boceprevir	Yes
Simeprevir	No
Sofosbuvir	Yes
Others: *(specify)*	
Number of patients treated for hepatitis B	
Number of patients treated for hepatitis C	

Impact

Figure 1: Hepatitis B vaccination coverage [i] and impact on acute hepatitis B incidence [j,k]

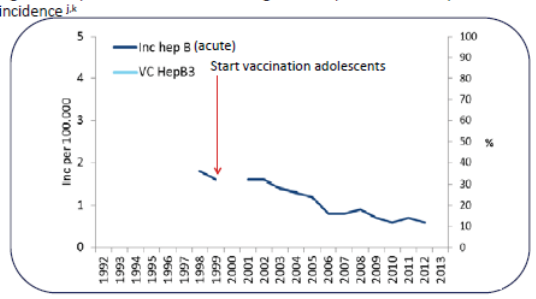
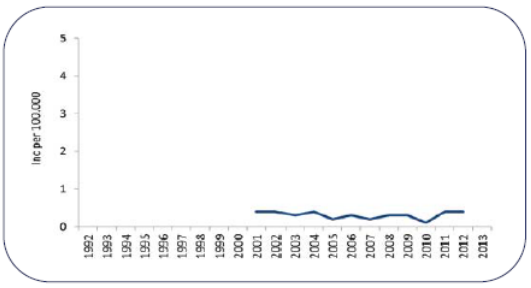


Figure 2: Introduction of activities and impact on acut hepatitis C incidence [j,k]



Specific issues and future challenges

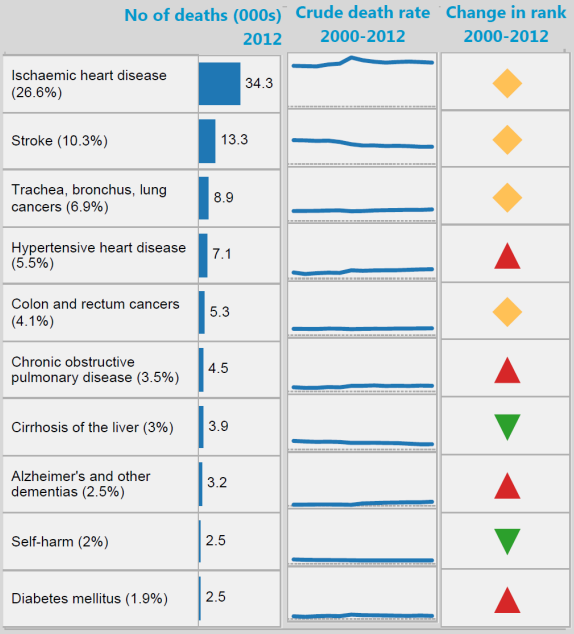
Country contact: **Dr. Csohán Ágnes** [csohan.agnes@oek.antsz.hu]

(source: http://www.who.int/gho/countries/hun.pdf?ua=1)

Hungary: WHO statistical profile

Top 10 causes of death

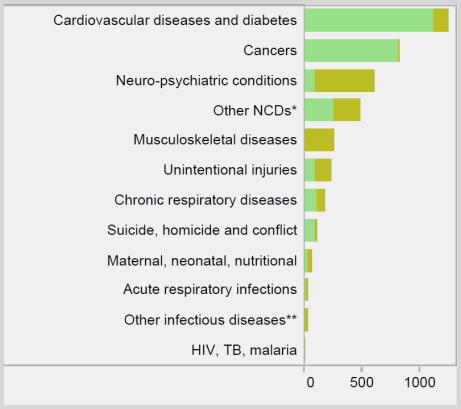
Ischaemic heart disease was the leading cause of death, killing 34.3 thousand people in 2012



Burden of disease, 2012

Disability-adjusted life years (DALYs) are the sum of years of life lost due to premature mortality (YLL) and years of healthy life lost due to disability (YLD).

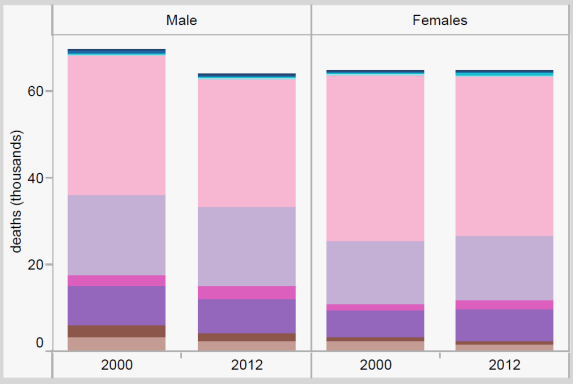
DALYs, YLL and YLD (thousands) by broad cause group



*Other noncommunicable diseases (NCDs) including non-malignant neoplasms; endocrine, blood and immune disorders; sense organ, digestive, genitourinary, and skin diseases; oral conditions; and congenital anomalies.
** Infectious diseases other than acute respiratory diseases, HIV, TB and malaria.

YLL YLD

Deaths by broad cause group



Causes
- HIV, TB, malaria
- Acute respiratory infections
- Other infectious diseases
- Maternal, neonatal, nutritional
- Cardiovascular diseases and diabetes
- Cancers
- Chronic respiratory diseases
- Other NCDs
- Suicide, homicide and conflict
- Unintentional injuries

Probability of dying, 2012

Probability of dying between relevant exact ages, for a person experiencing the 2012 age-specific mortality risks throughout their life.

Before age 15, all causes	Male	3%
	Female	3%
Before age 70, all causes	Male	55%
	Female	32%
Between ages 15 and 49, from maternal causes	Female	0%
Between ages 30 and 70, from 4 major noncommunicable diseases (NCDs)~	Both sexes	24%

~Cancers, cardiovascular diseases, chronic respiratory diseases and diabetes

Source: Country statistics and global health estimates by WHO and UN partners
For more information visit the Global Health Observatory (http://who.int/gho/mortality_burden_disease/en/)
Last updated: January 2015

WHO CISID database info (http://data.euro.who.int/cisid/?TabID=399572)

Hepatitis A

6012 - Hepatitis A - Incidence (cases per 100 000 population)											
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Hungary	1.68	1.07									

6011 - Hepatitis A - Number of cases											
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Hungary	168	107									

Hepatitis B

9009 - Hepatitis B - Incidence (cases per 100 000 population)											
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Hungary	0.88	0.66		0.67	0.53	0.62					

9008 - Hepatitis B - Number of cases											
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Hungary	88	66		67	53	62					

Hepatitis C

6015 - Hepatitis C - Incidence (cases per 100 000 population)											
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Hungary	0.34	0.31									

6014 - Hepatitis C - Number of cases											
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Hungary	34	31									

Immunization coverage

Source: http://apps.who.int/immunization_monitoring/globalsummary/coverages?c=HUN

World Health Organization

WHO vaccine-preventable diseases: monitoring system. 2019 global summary

Coverage time series for Hungary (HUN)

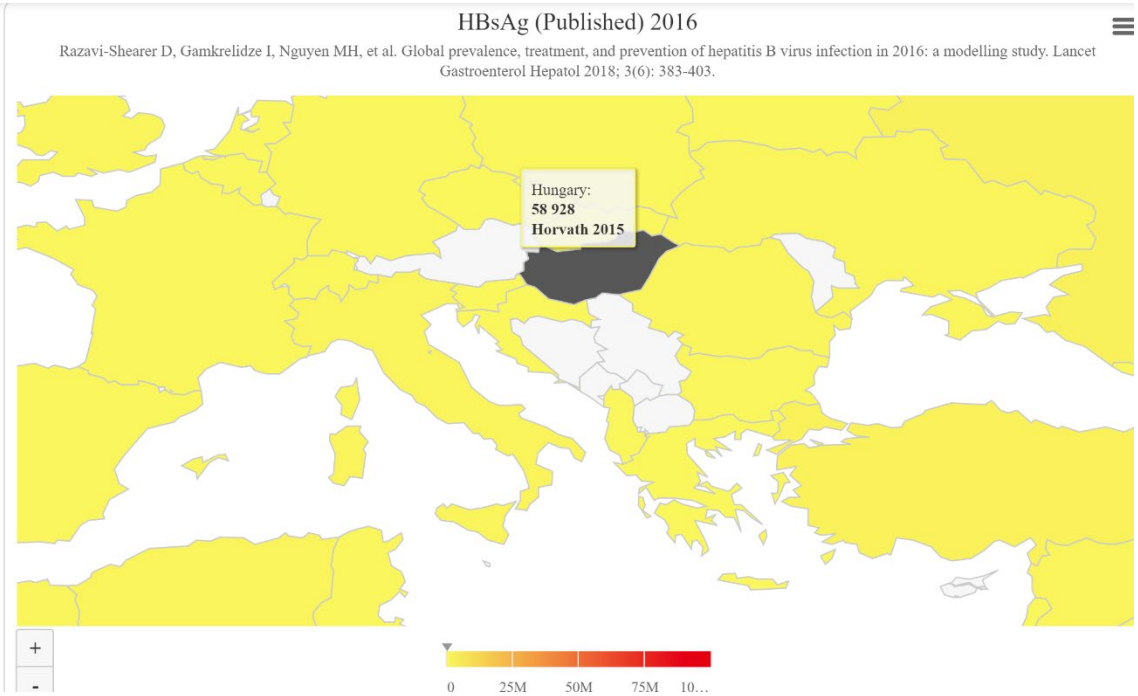
Last updated 15-July-2019 (data as of 1-July-2019)
Next overall update Winter 2019

Vacciness	2018	2017	2016	2015	2014	2013	2012	2011	2010	2009	2008	2007	2006	2005	2004	2003	2002	2001	2000	1999	1998	1997	*1995*	*1990*	*1985*	*1980*
BCG	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99	100	99
DTP1	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	_	100	100	_	_	_	_
DTP3	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99	99	99
HepB3	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	100	_	_	_	_	_	_
Hib3	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	_	_	_	_	_	_
IPV1	100	100	100	100	100	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_
MCV1	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99	99	99
MCV2	100	100	100	100	100	99	99	100	100	99	100	100	100	99	100	100	100	100	100	_	_	_	_	_	_	_
PCV1	100	100	100	98	96	95	_	93	89	82	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_
PCV2	100	100	100	96	95	94	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_
PCV3	100	100	98	91	93	92	90	84	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_
Pol3	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	99	99	99	98
RCV1	100	100	100	100	100	100	100	100	100	100	100	_	_	_	100	_	_	_	_	_	_	_	_	_	_	_
TT2+	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	100	100	_	_	_

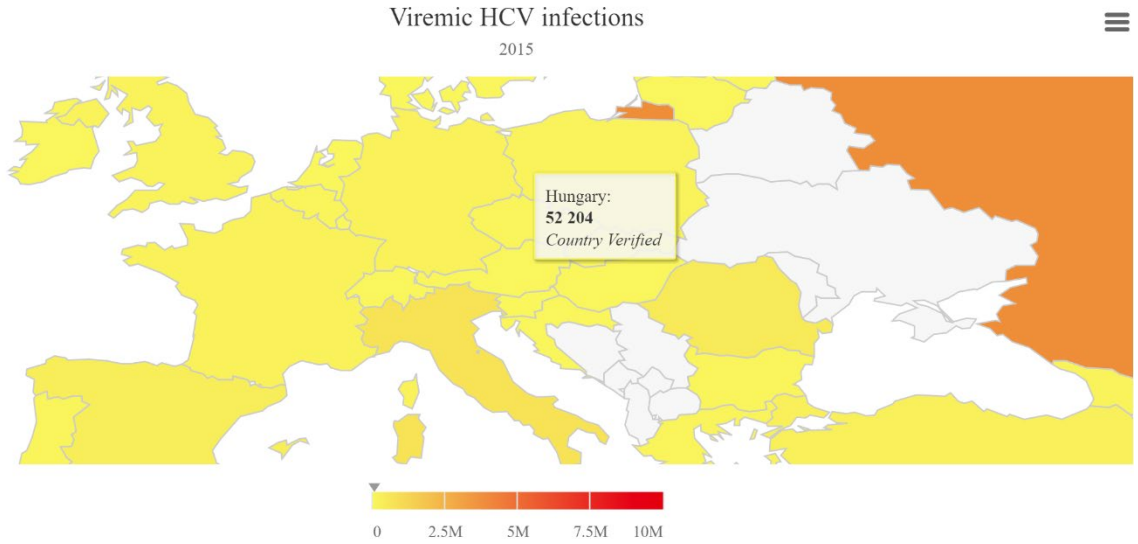
No Hungarian data available in the Global Health Observatory data repositoryat:
http://apps.who.int/gho/data/node.main.A828?lang=en

1.2.3 Centre of disease control - Polaris observatory

Hepatitis B (https://cdafound.org/polaris-hepb-map/)



Hepatitis C (http://cdafound.org/polaris-hepc-map/)



Hungary

Györgyi Tokodi, Péter Gaál

Governance

In Hungary vaccination programmes are regulated by Decree No. 18/1998 (VI. 3.) NM of the Minister of Welfare on the Prevention and Control of Infectious Diseases and Epidemics. The Decree specifies a so-called vaccination guideline,[1] which has, since 2017, been issued by the Ministry of Human Capacities, to update all the necessary knowledge on vaccination, including the practical tasks regarding the implementation of the vaccination programmes, general and specific indications and contraindications of vaccines, the storage and use of vaccines, registration and reporting requirements, as well as other provisions and recommendations on a yearly basis.

The Decree categorizes vaccinations into five main groups:

1. **Mandatory, free-of-charge routine childhood immunizations** (tuberculosis, diphtheria, pertussis, tetanus, poliomyelitis, **measles**, rubella, mumps, *Haemophilus influenzae* type B, hepatitis B, Streptococcus pneumoniae);

2. **Mandatory, free-of-charge immunization where there is risk of infection** (people living in the vicinity of typhoid, diphtheria, pertussis, **measles**, rubella, mumps; hepatitis A patients; people at risk of tetanus or rabies infection; newborns of hepatitis B carrier mothers; health workers and students);

1 Article 4, section (2). Before 2017 the vaccination guideline was issued by the National Centre of Epidemiology, which was integrated into the National Public Health Institute.

3. **Voluntary, free-of-charge immunization where there is risk of infection** (diphtheria; hepatitis B (e.g. family members of people with hepatitis B infection; patients on dialysis; oncology patients; IV drug users); **influenza**; HPV for girls aged 12+);

4. **Mandatory** (e.g. yellow fever) **and optional** (e.g. hepatitis A) **vaccination for travellers**; and

5. **Occupation-related mandatory vaccination** (e.g. tetanus, tick-borne encephalitis, hepatitis B).

The minister responsible for health (the Minister for Human Capacities) is assigned the power to control and supervise the prevention and elimination of communicable diseases, which is delegated to the national chief medical officer.[2] The national chief medical officer is authorized to act on their own where there is a risk of epidemics.[3] Local official activities are under the scope of authority of County and District Government Offices.[4] The deputy state secretary for the affairs of the chief medical officer is responsible for the development of national immunization programmes, and the coordination and supervision of implementation via the Communicable Diseases Prevention and Surveillance Unit under the Department of Hospital Hygiene and Communicable Disease Control, as well as the Clinical and Epidemiological Microbiology Directorate of the National Public Health Institute.[5]

In Hungary all vaccination programmes are nationwide, but their implementation is organized on a territorial basis through the public health departments and units of County and District Government Offices. However, the immunization calendar applies nationwide and the same vaccine schedule and vaccines are used in the whole country.

The electronic epidemiological surveillance database is maintained by the Department of Hospital Hygiene and Communicable Disease Control of the Ministry of Human Capacities, and updated with data from the field. For mandatory childhood vaccination, the most important actor, responsible for preparing the monthly reports, is the health visitor (mother and child health nurse). The Health Visitor Service is organized on a territorial basis. Each health visitor is responsible for a district and is charged with the preventive care of inhabitants, including pregnant women, post-partum women and children under the age of 6 in their homes, and school children aged 6+ years in schools. The health visitor keeps track of those who are obliged to be vaccinated and maintains a vaccination register for them. If there is a missed vaccination, the health visitor sends a written notification. After three failed attempts, the health visitor is obliged to report the case to the District Government Office.

The health visitor has to report completed vaccinations, failed vaccinations over two months, and the emigration and immigration of persons liable for vaccination.

The District Government Offices integrate and electronically transfer the data provided by health visitors to the electronic epidemiological surveillance register of the Ministry for Human Capacities, in particular to the Department of Hospital Hygiene and Communicable Disease Control. This means that vaccination coverage data are up-to-date and available at every level (national, county and district).

The same process applies to communicable disease surveillance, the only difference being that patients are reported by the medical doctors who detect the disease. The list of communicable diseases, the reporting of which is mandatory, is determined by the same decree.[6]

Given that the system is mandatory and based on the place of residence, there are no targeted measures for specific groups of the population and no special incentive schemes in place. Parents who fail to vaccinate their children can be fined. The fine or the implementation of the mandatory vaccination can be enforced by the Hungarian tax authority.

For mandatory childhood immunization, the vaccination coverage rates are calculated using administrative information, mainly the data reported by health visitors to the electronic epidemiological surveillance database. The denominator is the total number of children obliged to be vaccinated in the given year, because they reached the vaccination age.

2 Article 2, section (1).
3 Article 2, section (2).
4 Article 3, section (1).
5 Order No. 51/2017 (X. 25.) EMMI of the Minister of Human Capacities.
6 Decree No. 18/1998 (VI. 3.) NM of the Minister of Welfare, Article 16/A, Annex 1.

Table 1 Coverage of the second dose of the measles vaccine, 2010–2017

	2010	2011	2012	2013	2014	2015	2016	2017
Coverage (%)	99.5	99.5	99.4	99.3	99.4	99.6	99.7	99.7

Source: Department of Hospital Hygiene and Communicable Disease Control, Ministry of Human Capacities

Table 2 Measles cases, 2006–2017

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Cases	1	0	0	1	0	0	1	1	0	0	0	36

Source: http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/Country_slides_measles.pdf?ua=1

Vaccination coverage

In Hungary mandatory, free-of-charge vaccination against **measles** (group 1 vaccination) was introduced in 1969, as a result of which most persons aged under 47 years have received at least one shot. Since 1989, to achieve long-term protection, children have received two shots, the first at the age of 15 months and the second at the age of 11 years. Thanks to the mandatory vaccination programmes, the territory-based Health Visitor Service, and the strict reporting system, immunization coverage is excellent in Hungary (*see* Table 1), and measles cases are extremely rare.

Table 2 shows the trend regarding the number of measles cases. Between 2006 and 2016 there were no indigenous cases in Hungary, and only imported cases occurred. In 2017 a small outbreak took place in a small hospital near the border, where a foreign measles patient was treated and a few health workers and patients contracted the disease. In 2018, 18 imported, or import-related, cases were reported.

Under the national **influenza** vaccination programme, vaccination is accessible free of charge for certain target groups on a voluntary basis (group 3 vaccination), including:

- *High-risk populations*, including people over the age of 60, pregnant women, chronic patients, such as patients with immune deficiency, chronic respiratory, cardiovascular and kidney diseases, and long-term care patients,
- *workers where influenza is an occupational hazard*, such as health and social care workers, people working in stock-raising, people working with immigrants, and people working in public education institutions.

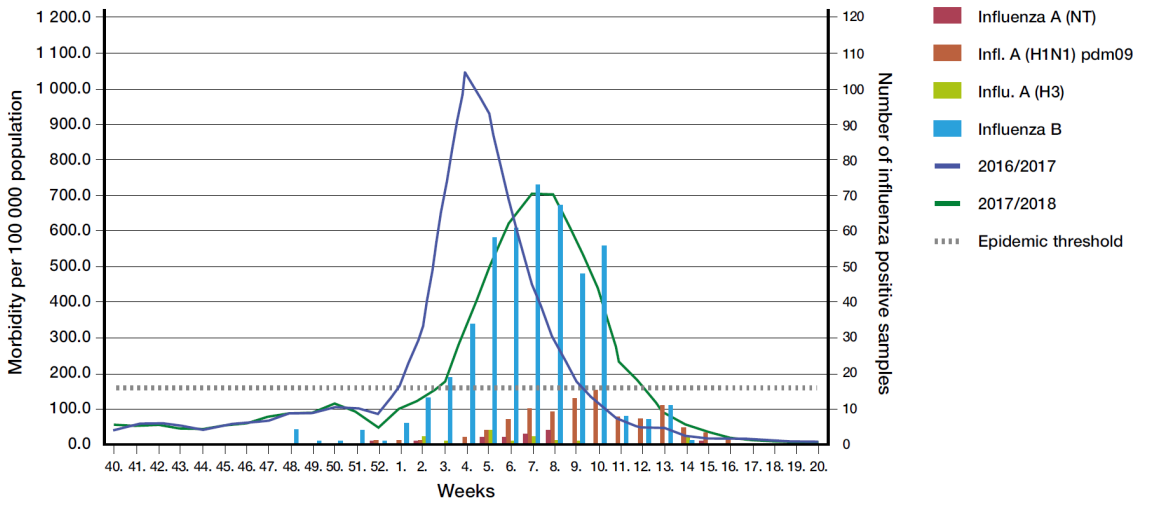
In addition to the national programmes, pharmacies offer several other vaccines that can be purchased by non-target groups.

In the 2017/18 influenza season the utilization of free-of-charge vaccines was 65.2%.[7] In 2017, 1.2 million vaccine doses were distributed among the target groups.

The Department of Hospital Hygiene and Communicable Disease Control of the Ministry of Human Capacities operates and maintains Influenza Sentinel Surveillance, which publishes the number of reported influenza-like illness consultations per 100 000 population and the number of virus detections. Influenza-like illness cases are reported by Sentinel general practitioners (roughly 20% of the total, and numbering 1351 in the 2017/18 season), on a weekly basis, by age groups. Of these family doctors, 100 regularly take samples from patients to identify the virus strain. Figure 1 shows an example of the weekly number of influenza-like illness cases and the number of specimens testing positive for influenza viruses for the 2017/18 influenza season.

7 Epinfo 20/19.

Figure 1 The number of patients with influenza-like illness who sought medical attention, per 100 000 population, and the number of influenza positive samples in Hungary, week 40 of 2017 – week 20, 2018



Source: Department of Hospital Hygiene and Communicable Disease Control

Provision

The provision of immunization is based on the vaccination guideline, which incorporates the professional guidelines according to which vaccination should be administered. The health service providers who administer the vaccines are supervised by and accountable to the District Government Offices.

Measles

Mandatory childhood vaccination for the entire child population between the ages of 0 and 6 years are administered by family paediatricians or family doctors, while childhood vaccinations for children over the age of 6 years are organized through the so-called school campaign vaccinations, which are administered by school health doctors. Contraindications are considered by the administering doctor.

Influenza

Influenza vaccines are administered by family doctors in primary care, or by occupational health doctors in the workplace, where influenza is an occupational hazard. They are obliged to report the utilization of free-of-charge influenza vaccines to the Government District Offices, which aggregate and transfer the data to the Department of Hospital Hygiene and Communicable Disease Control of the Ministry of Human Capacities.

Financing

With the exception of occupation-related mandatory vaccination, which has to be covered by employers, vaccines for mandatory vaccinations are free of charge. They are covered from the central government budget under the Ministry of Human Capacities.[8] With the exception of vaccination against influenza, HPV and pneumococcus,[9] voluntary vaccinations are excluded from the publicly funded benefit package, and the clients have to pay for them out-of-pocket, both for the vaccine and the vaccination service.[10] The service fee for administering the shot is set at HUF 2000, while it is free of charge for mandatory vaccinations. Publicly financed health service providers are paid for by the NHIFA depending on the type of service, e.g. primary care is capitated and outpatient specialist services are paid for by fee-for-service points.

Vaccines are procured centrally and distributed to the District Government Offices, which further distributes them among the relevant health service providers, such

8 Act CLIV of 1997, Article 142, section (2).
9 Government Decree No. 284/1997 (XII. 23.) Korm, Annex 2, item 16.
10 Act LXXXIII of 1997, Article 18, section (6), point (t).

as family paediatricians, family doctors or occupational health doctors. Family doctors usually pick up the vaccines in person from their local District Government Office.

Key barriers and facilitators

Hungary has a good immunization record, which is attributable to the well-organized system of addressing communicable diseases and the generally favourable attitude of the population towards vaccination and the prevention of infections. Nevertheless there are some threats to the existing system of public health, which can erode its firm organizational basis and might jeopardize current achievements:

- Since its establishment in 1991 the National Public Health and Medical Officer Service has undergone several reorganizations, the most recent of which was the organizational integration of its territorial units into the Government Office System and of the Office of the National Chief Medical Officer into the Ministry of Human Capacities. In contrast, the new Minister for Human Capacities has announced the re-establishment of the Office of the National Chief Medical Officer. Frequent major reorganizations are a risk for the disintegration of established processes and the loss of competent public health specialists.

- Despite recent improvements, Hungary is still facing a human resource crisis due to the emigration of qualified health workers. Shortages mostly affect the population in disadvantaged regions.

- In the case of mandatory childhood vaccination, coverage gaps are related to particular groups, such as children with anti-vaccination parents.[11] For this group, fines do not seem to be an effective corrective measure, and there are suspicions that certain anti-vaccination parents can obtain fake vaccination certificates from certain family paediatricians.[12]

- In terms of measles, imported cases (such as from Romania or Ukraine) seem to be the most important problem, and it is difficult for doctors to diagnose the disease because most of them have not encountered a single case for decades. On the other hand, outbreaks in neighbouring countries and in Hungary usually facilitate population awareness, because of the media coverage of such events.

11 www.ajbh.hu/documents/10180/2500969/Jelentés+az+óvodai+felvétel+védőoltások+elmaradása+miatti+elutasításáról+361_2016/c4de3125-7ec7-4fd8-8aba-2d0fe77421ae?version=1.0.

12 https://www.nlcafe.hu/csalad/20161105/gyermekorvos-kotelezo-vedooltas/.

Source: http://www.euro.who.int/__data/assets/pdf_file/0008/386684/vaccination-report-eng.pdf?ua=1

3. Presentations related references

Pubmed MEDLINE search on {(Hungar*) AND (Hepatitis OR HCV OR HBV)} in all [Abstract/title]

and filter:'last 10 years' on was performed.

The references were manually sorted in the different subjects in an EndNote

Session 1: Opening and objectives

Chairs: **Zsuzsa Schaff – Johannes Hallauer**

09:00 - 09:30 Welcome and opening of the meeting

Session 2: The health care system in Hungary

09:30 - 09:50 Introduction in the health care system of Hungary

Speaker (TBD)

09:50 - 10:10 Organization of infectious disease service

Speaker (TBD)

10:10 - 10:20 Questions

Session 3: Current viral hepatitis situation, epidemiology, screening, burden of disease in Hungary

10:20 - 10:50 Hepatitis surveillance and epidemiological situation

Epidemiology of hepatitis in Hungary

Dr. Cecilia Müller

Head, NNK

Hepatitis A - E

Other related references (Pubmed search):

Hettmann, A., et al. (2017). "**Phylogenetic analysis of a transfusion-transmitted hepatitis A outbreak**." Virus Genes **53**(1): 15-20.

A transfusion-associated hepatitis A outbreak was found in the first time in Hungary. The outbreak involved five cases. Parenteral transmission of hepatitis A is rare, but may occur during viraemia. Direct sequencing of nested PCR products was performed, and all the examined samples were identical in the VP1/2A region of the hepatitis A virus genome. HAV sequences found in recent years were compared and phylogenetic analysis showed that the strain which caused these cases is the same as that had spread in Hungary recently causing several hepatitis A outbreaks throughout the country.

Pischke, S., et al. (2019). "**Chronic Hepatitis E in Rheumatology and Internal Medicine Patients: A Retrospective Multicenter European Cohort Study.**" Viruses **11**(2).

Objectives: Hepatitis E virus (HEV) infection is a pandemic with regional outbreaks, including in industrialized countries. HEV infection is usually self-limiting but can progress to chronic hepatitis E in transplant recipients and HIV-infected patients. Whether other immunocompromised hosts, including rheumatology and internal medicine patients, are at risk of developing chronic HEV infection is unclear. Methods: We conducted a retrospective European multicenter cohort study involving 21 rheumatology and internal medicine patients with HEV infection between April 2014 and April 2016. The underlying diseases included rheumatoid arthritis (n = 5), psoriatic arthritis (n = 4), other variants of chronic arthritis (n = 4), primary immunodeficiency (n = 3), systemic granulomatosis (n = 2), lupus erythematosus (n = 1), Erdheim(-)Chester disease (n = 1), and retroperitoneal fibrosis (n = 1). Results: HEV infection lasting longer than 3 months was observed in seven (33%) patients, including two (40%) patients with rheumatoid arthritis, three (100%) patients with primary immunodeficiency, one (100%) patient with retroperitoneal fibrosis and one (100%) patient with systemic granulomatosis. Patients with HEV infection lasting longer than 3 months were treated with methotrexate without corticosteroids (n = 2), mycophenolate mofetil/prednisone (n = 1), and sirolimus/prednisone (n = 1). Overall, 8/21 (38%) and 11/21 (52%) patients cleared HEV with and without ribavirin treatment, respectively. One patient experienced an HEV relapse after initially successful ribavirin therapy. One patient (5%) was lost to follow-up, and no patients died from hepatic complications. Conclusion: Rheumatology and internal medicine patients, including patients treated with methotrexate without corticosteroids, are at risk of developing chronic HEV infection. Rheumatology and internal medicine patients with abnormal liver tests should be screened for HEV infection.

Reuter, G., et al. (2016). "**A novel avian-like hepatitis E virus in wild aquatic bird, little egret (Egretta garzetta), in Hungary**." Infect Genet Evol **46**: 74-77.

Hepatitis E virus (HEV), family Hepeviridae, has public health concerns because of its zoonotic potential; however, the host species spectrum, animal to animal transmissions, the natural chain of hepevirus infections and the genetic diversity of HEV in wildlife especially in birds are less known. Using random amplification and next generation sequencing technology a genetically divergent avian HEV was serendipitously identified in wild bird in Hungary. HEV RNA was detected with high faecal viral load (1.33x10(8)genomiccopies/ml) measured by real-time PCR in faecal sample from a little egret (Egretta garzetta). The complete genome of HEV strain little egret/kocsag02/2014/HUN (KX589065) is 6660-nt long including a 18-nt 5' end and a 103-nt 3' end (excluding the poly(A)-tail). Sequence analyses indicated that the ORF1 (4554nt/1517aa), ORF2 (1728nt/593aa) and ORF3 (339nt/112aa) encoded proteins of little egret/kocsag02/2014/HUN shared the highest identity (62.8%, 71% and 61.5%) to the corresponding proteins of genotype 1 avian (chicken) HEV in species Orthohepevirus B, respectively. This study reports the identification and complete genome characterization of a novel orthohepevirus distantly related to avian (chicken) HEVs at the first time in wild bird. It is important to recognize all potential hosts, reservoirs and spreaders in nature and to reconstruct the phylogenetic history of hepeviruses. Birds could be an important reservoir of HEV generally and could be infected with genetically highly divergent strains of HEV.

Adlhoch, C., et al. (2016). "**Hepatitis E virus: Assessment of the epidemiological situation in humans in Europe, 2014/15**." J Clin Virol **82**: 9-16.

BACKGROUND: Hepatitis E virus (HEV) is endemic in EU/EEA countries, but the understanding of the burden of the infection in humans is inconsistent as the disease is not under EU surveillance but subject to national policies. STUDY: Countries were asked to nominate experts and to complete a standardised questionnaire about the epidemiological situation and surveillance of HEV in their respective EU/EEA country. This study reviewed surveillance systems for human cases of HEV in EU/EEA countries and nominated experts assessed the epidemiology in particular examining the recent increase in the number of autochthonous cases. RESULTS: Surveillance systems and case definitions across EU/EEA countries were

shown to be highly variable and testing algorithms were unreliable. Large increases of autochthonous cases were reported from Western EU/EEA countries with lower case numbers seen in Northern and Southern European countries. Lack of clinical awareness and variability in testing strategies might account for the observed differences in hepatitis E incidence across EU/EEA countries. Infections were predominantly caused by HEV genotype 3, the most prevalent virus type in the animal reservoirs. CONCLUSION: Discussions from the expert group supported joint working across countries to better monitor the epidemiology and possible changes in risk of virus acquisition at a European level. There was agreement to share surveillance strategies and algorithms but also importantly the collation of HEV data from human and animal populations. These data collected at a European level would serve the 'One Health' approach to better informing on human exposure to HEV.

Banyai, K., et al. (2012). "**Putative novel genotype of avian hepatitis E virus, Hungary, 2010**." Emerg Infect Dis **18**(8): 1365-1368.

To explore the genetic diversity of avian hepatitis E virus strains, we characterized the near-complete genome of a strain detected in 2010 in Hungary, uncovering moderate genome sequence similarity with reference strains. Public health implications related to consumption of eggs or meat contaminated by avian hepatitis E virus, or to poultry handling, require thorough investigation.

Forgach, P., et al. (2010). "**Detection of hepatitis E virus in samples of animal origin collected in Hungary**." Vet Microbiol **143**(2-4): 106-116.

Hepatitis E virus (HEV) is an enterically transmitted human pathogen. HEV infections are mainly associated with acute, self-limited, icteric hepatitis with an average mortality rate of 1%. Animal reservoirs are considered to play an important role in the maintenance of the virus and in the spread of HEV to humans. HEV-induced seroconversion was described in several species, however clinical hepatitis in animals has not been observed to date. HEV strains from animals are genetically closely related to human HEV isolates, which supports the opinions on the zoonotic transmission of the virus. In this expansive study the occurrence of HEV was investigated in Hungarian wild and domesticated animal samples. HEV RNA was detected by reverse transcription-polymerase chain reaction in liver samples of wild boars, roe deer, and deer. The investigations of domestic swine samples detected HEV in 39% of the investigated Hungarian pig farms. Simultaneous investigation revealed no definite difference between liver and faeces samples of domestic pigs in the frequency of HEV positivity. The highest (36%) incidence of HEV infection was found among the 11-16-week-old pigs. Samples from domestic cattle and rodents collected in pig farms, forests and meadows were tested negative for HEV RNA. Phylogenetic analysis of partial sequences amplified within the ORF1 and ORF2 regions of selected strains revealed that the detected viruses belong to three subgroups of the third genogroup of HEV, and are closely related to human and swine HEV strains detected in different countries. The investigations revealed widespread distribution of HEV in Hungarian wild ungulate and domesticated swine populations, with considerable genetic diversity among the strains.

Hepatitis B and C:

Other related references (Pubmed search):

Gervain, J. (2018). "[**Analysis of hepatitis C virus type and subtype distribution in Hungary**]." Orv Hetil **159**(Suppl 2): 2-8.

INTRODUCTION: Hepatitis C virus (HCV) shows great structural variability. Based on genome sequencing and phylogenetical analysis, 7 types and 67 subtypes can be differentiated with varying geographical distribution. It is very important to determine the HCV type/subtype prior to starting direct antiviral therapy (DAA), which has been available since 2014, because the type, dose and optimal length of medication depends on these. AIM: In Hungary, the treatment of chronic HCV patients started in 1992 with the relevant special diagnostic tests

being carried out in our Molecular Diagnostic Laboratory. Determination of the nucleotide sequence of the Hungarian HCV1b NS5A/PKR-BR region and the type and subtype distribution of Hungarian patients have already been carried out. The current summary discusses the results of 6092 chronic HCV patients (175 serotypes, 5917 genotypes) based on age, gender, regions and genotype distribution changes over the period between 1996 and 2017. METHOD: Serotyping (1996-1999). Genotyping: hybridization (2000-2016), real-time PCR (2016-; Cobas 4800 HCV GT). RESULTS: Genotype distribution: GT1a: 5.6%; GT1b: 84.6%; GT1a + 1b: 5.1%; GT2: 0.1%; GT3: 1.8%; GT4: 0.1%; mixed: 1.6%; GT1 (non-differentiated subtype): 1,1%. Women/men ratio: 52%/48%. The most common age category is 50-60 years (37% of all cases). There was no genotype asymmetry among the four Hungarian regions and Budapest. Over time, the prevalence of genotype 3 increased from 1.6% to 2.8% and the number of patients under the age of 40 doubled. CONCLUSION: There have been no substantial changes in the HCV type/subtype distribution in Hungary over the past 20 years, 1b remaining the most common. The introduction of real-time PCR method for genotyping has resulted in a major quality improvement including only a few mixed subtype results leading to more efficient drug selection. Orv Hetil. 2018; 159(Suppl 2): 2-8.

Urbanek, P., et al. (2016). "**Epidemiology of HCV infection in the Central European region**." Clin Exp Hepatol **2**(1): 2-6.

Opinion leaders in each of four countries in the Central European region summarize the available data on hepatitis C virus (HCV) epidemiology. The overall prevalence of anti-HCV antibody reactivity in this region varies between 0.2% and 2.1%, the most prevalent HCV genotype is GT 1. The commonest route of transmission is intravenous drug abuse at present.

Madalinski, K., et al. (2015). "**Epidemiology of HCV infection in Central and Eastern Europe**." Przegl Epidemiol **69**(3): 459-464, 581-454.

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.

Liakina, V., et al. (2015). "**Historical epidemiology of hepatitis C virus (HCV) in select countries - volume 3**." J Viral Hepat **22 Suppl 4**: 4-20.

Detailed, country-specific epidemiological data are needed to characterize the burden of chronic hepatitis C virus (HCV) infection around the world. With new treatment options available, policy makers and public health officials must reconsider national strategies for infection control. In this study of 15 countries, published and unpublished data on HCV prevalence, viraemia, genotype, age and gender distribution, liver transplants and diagnosis and treatment rates were gathered from the literature and validated by expert consensus in each country. Viraemic prevalence in this study ranged from 0.2% in Iran and Lebanon to 4.2% in Pakistan. The largest viraemic populations were in Pakistan (7 001 000 cases) and Indonesia (3 187 000 cases). Injection drug use (IDU) and a historically unsafe blood supply were major risk factors in most countries. Diagnosis, treatment and liver transplant rates varied widely between countries. However, comparison across countries was difficult as the

number of cases changes over time. Access to reliable data on measures such as these is critical for the development of future strategies to manage the disease burden.

Muhlemann, B., et al. (2018). "**Ancient hepatitis B viruses from the Bronze Age to the Medieval period**." Nature **557**(7705): 418-423.

Hepatitis B virus (HBV) is a major cause of human hepatitis. There is considerable uncertainty about the timescale of its evolution and its association with humans. Here we present 12 full or partial ancient HBV genomes that are between approximately 0.8 and 4.5 thousand years old. The ancient sequences group either within or in a sister relationship with extant human or other ape HBV clades. Generally, the genome properties follow those of modern HBV. The root of the HBV tree is projected to between 8.6 and 20.9 thousand years ago, and we estimate a substitution rate of 8.04 x 10(-6)-1.51 x 10(-5) nucleotide substitutions per site per year. In several cases, the geographical locations of the ancient genotypes do not match present-day distributions. Genotypes that today are typical of Africa and Asia, and a subgenotype from India, are shown to have an early Eurasian presence. The geographical and temporal patterns that we observe in ancient and modern HBV genotypes are compatible with well-documented human migrations during the Bronze and Iron Ages(1,2). We provide evidence for the creation of HBV genotype A via recombination, and for a long-term association of modern HBV genotypes with humans, including the discovery of a human genotype that is now extinct. These data expose a complexity of HBV evolution that is not evident when considering modern sequences alone.

Muhlemann, B., et al. (2018). "**Author Correction: Ancient hepatitis B viruses from the Bronze Age to the Medieval period.**" Nature **562**(7726): E4.

In Fig. 2 of this Letter, the 'E' and 'G' clade labels were inadvertently reversed, and in Table 2 the genotype of DA27 was 'D1' instead of 'D5'. These have been corrected online.

Gelley, F., et al. (2013). "[**Hepatitis C virus recurrence after liver transplantation in Hungary. Trends over the past 10 years**]." Orv Hetil **154**(27): 1058-1066.

INTRODUCTION: Management of hepatitis C virus recurrence is a challenge after liver transplantation. AIM: The aim of the authors was to analyse the outcome of liver transplantation performed in hepatitis C virus positive patients during the past ten years and to compare recent data with a previous report of the authors. METHOD: The authors retrospectively evaluated the data (donors, recipients, perioperative characteristics, patient and graft survival, serum titer of hepatitis C virus RNA, histology) of 409 patients who underwent liver transplantation between 2003 and 2012. RESULTS: 156 patients were transplanted due to hepatitis C virus associated liver cirrhosis (38%). Worse outcome was observed in these patients in comparison to hepatitis C virus negative recipients. The cumulative patient survival rates at 1, 5, and 10 year were 80%, 61%, 51% in the hepatitis C virus positive group and 92%, 85%, 79% in the hepatitis C virus negative group, respectively ($p<0.001$). The cumulative graft survival rates at 1, 5 and 10 year were 79%, 59% and 50% in hepatitis C virus positive and 89%, 80% and 70% in hepatitis C virus negative patients ($p<0.001$). Hepatitis C virus recurrence was observed in the majority of the patients (132 patients, 85%), mainly within the first year (83%). The authors observed recurrence within 6 months in 71 patients (56%), and within 3 months in 26 patients (20%). The mean hepatitis C virus recurrence free survival was 243 days. Higher rate of de novo diabetes was detected in case of early recurrence. The cumulative patient survival rates at 1, 3, 5, 10 years were 98%, 89.5%, 81% and 65% when hepatitis C virus recurrence exceeded 3 months and 64%, 53%, 30.5% and 30.5% in patients with early recurrence ($p<0.001$). CONCLUSIONS: Poor outcome of liver transplantation in hepatitis C virus positive patients is still a challenge. Hepatitis C virus recurrence is observed earlier after liver transplantation in comparison with a previous report of the authors. De novo diabetes occurs more frequently in case of early recurrence. Despite an immediate start of antiviral treatment, early recurrence has a significant negative impact on the outcome of transplantation.

10:50 - 11:15 Coffee Break

Chairs: **Gabriella Pár – Rui Tato Marinho**

11:15 - 11:40 Disease Burden in Hungary: chronic viral hepatitis and liver disease in Hungary

Prof. Istvan Tornai

Associate Professor, University of Debrecen, Department of Medicine, Division of Gastroenterology, Hungary

References proposed by speaker:

1. Lengyel G, Gervain J, Pár G, Szalay F, Hunyady B, Schneider F, Nemesánszky E, Tusnádi A, Bányai T, Gyulay K, Tornai I: **Real-world virologic response rates and prediction of outcomes with peginterferon alfa-2a/ribavirin in Hungarian HCV genotype 1 patients**. J Gastroenterol Pancreatol Liv Dis. 2014, 1 (4): 1-8.
2. Varga M, Csefkó K, Bányai T, Martyin T, Lakatos P, Nagy I, Pálvölgyi A, Tusnádi A, Szabó A, Lesch M, Sipos B, Budai A, Enyedi J, Lombay B, Karádi L, Váczi Zs, Jancsik V, Weisz Gy, Palatka K, Tornai I: **Treatment of hepatitis C virus infected patients with cirrhosis in real-life conditions in Hungary with the two pegylated interferon.** (in Hungarian). Lege Artis Medicinae 2014, 24: 569-576.
3. Tornai I, Gervain J, Hunyady B, Lengyel G, Nemesánszky E, Princz Gy, Schneider F, Szalay F, Schuller J: **Influence of cumulative ribavirin dose on the sustained virological response of patients with chronic hepatitis C receiving peginterferon alfa-2a – ribavirin combination treatment (RIBADOSE study**). (in Hungarian). Cent Eur J Gastroenterol Hepatol 2017, 3:157-163.
4. Papp R, Papp M, Tornai I, Vitális Zs: **Incidence of hepatocellular carcinoma and consequent lessons for its management in Northeastern Hungary** (in Hungarian). Orv Hetil 2016, 157:1793-1801.

Other related references (Pubmed search):

Papp, R., et al. (2016). "[**Incidence of hepatocellular carcinoma and consequent lessons for its management in Northeastern Hungary**]." Orv Hetil 157(45): 1793-1801.

INTRODUCTION: The increasing incidence and poor prognosis of hepatocellular carcinoma places huge burden on healthcare. AIM: After reviewing literature on epidemiological trends, risk factors, diagnosis and management options for hepatocellular carcinoma, the authors investigated results of treatment and survival data of patients in Northeastern Hungary. METHOD: In a retrospective study, the authors analyzed medical records of 187 patients with hepatocellular carcinoma (etiology, presence of cirrhosis, stage of the tumor, treatment and disease outcome). RESULTS: Seventy-one patients (38%) had known cirrhosis at the diagnosis of hepatocellular carcinoma, while in 52 patients (28%) the presence of cirrhosis was established at the time of the diagnosis of hepatocellular carcinoma. Fifteen patients (8%) had no cirrhosis and in 49 patients (26%) no data were available regarding cirrhosis. Etiological factors were alcohol consumption (52%), viral hepatitis (41%) and metabolic syndrome (44%). In cases of metabolic syndrome, hepatocellular carcinoma frequently occurred without cirrhosis. In 83% of the cases, the tumor was discovered in an advanced stage. Median survival time was significantly associated with tumor stage (Barcelona A stage vs. B/C vs. D: 829 vs. 387 vs. 137 days, respectively $p<0.001$) but not with disease etiology (virus 282 days, metabolic syndrome 335 days and alcohol 423 days, $p = 0.65$). CONCLUSIONS: High mortality of hepatocellular carcinoma was mainly attributed to the delayed diagnosis of the disease. Screening of patients with cirrhosis could only result in a partial improvement since in a great proportion cirrhosis was diagnosed simultaneously with the tumor. Screening of diabetic and obese patients by ultrasonography should be

considered. Management of baseline liver disease is of importance in the care of hepatocellular carcinoma. Orv. Hetil., 2016, 157(45), 1793-1801.

Petrovski, B. E., et al. (2011). "**Behaviour does not fully explain the high risk of chronic liver disease in less educated men in Hungary**." Eur J Public Health **21**(5): 662-666.

BACKGROUND: Hungary has among the highest mortality rates from chronic liver disease (CLD) and cirrhosis in Europe. Usually, conventional behavioural factors are hypothesized as the cause of the high risk of CLD. METHODS: A case-control study was performed with 287 cases and 892 controls to study the relationship between socio-economic and behavioural factors and the risk of CLD. Liver disease was verified by physical examination and blood tests. Blood samples were collected for detecting hepatitis B, C and E virus infection. Information on exposure factors was recorded by the participating physicians and by self-administered questionnaire. Simple regression analysis was used to study the relationship between CLD/cirrhosis and potential risk factors as alcohol intake (amount and source), problem drinking, cigarette smoking, physical activity, viral hepatitis infections, socio-economic factors (education, financial and marital status). Multiple regression analysis was used to identify whether the effect of socio-economic factors is fully mediated by health behaviour (smoking, alcohol consumption, physical activity). RESULTS: The univariate analysis showed that heavy alcohol consumption, problem drinking, former and heavy cigarette smoking, single, separated or divorced marital status, bad or very bad perceived financial status and lower education significantly increased the risk of CLD/cirrhosis. The effect of marital status and of education did not change after adjustment for behavioural factors, but the effect of perceived financial status disappeared. CONCLUSIONS: The effect of low socio-economic status on the risk of CLD/cirrhosis is only partially explained by conventional behavioural risk factors in Hungary.

Par, A. (2010). "[**Hepatitis B virus (HBV) infection and hepatocarcinogenesis**]." Orv Hetil **151**(26): 1045-1053.

Hepatitis B virus is one of the most important etiologic factors of hepatocellular carcinoma. The present review discusses the molecular mechanisms of virus-induced carcinogenesis, indirect and direct effects of the infection. The cell damage-evoked regeneration and proliferation, as well as the viral proteins that induce chromosomal, genetic and epigenetic changes, play a key role in the multistep process leading to malignant cell transformation. Integration of HBV DNA in to the host DNA, activation of oncogenes and inactivation of tumor suppressor genes are of basic significance. The hepatitis B virus related complications such as cirrhosis and hepatocellular carcinoma can be prevented by vaccination or eradication of the virus with antiviral therapy.

Tornai, I. (2010). "[**Role of environmental factors in the etiology of hepatocellular carcinoma**]." Orv Hetil **151**(28): 1132-1136.

Chronic B and C virus hepatitis (HBV and HCV) are the most important risk factors in the development of hepatocellular carcinoma (HCC). About 40-50% of HCC is induced by these two chronic viral infections. Prevalence of HCC is slowly increasing in the United States and in Western-Europe, whereas alcohol consumption is gradually decreasing in the majority of these countries. However, the most important environmental risk factor for HCC is still the heavy long-term alcohol use. The risk of cirrhosis and HCC increases linearly, wherever ethanol intake is greater than 60 g/day for men and women. Aflatoxin, which contaminates grains, mostly in China and Africa, is a well-known mycotoxin. Since geographical distribution of aflatoxin as well as HBV overlaps with each other, they have a synergistic effect on inducing HCC. Cigarette smoking has also hepatocarcinogenic effect, which is significantly enhanced by the concomitant alcohol use or chronic viral hepatitis. Obesity, non-alcoholic fatty liver and steatohepatitis as well as diabetes mellitus together also form a significant risk for HCC, due to the gradually increasing number of patients. Insulin resistance and oxidative stress are the major pathogenetic mechanisms leading to hepatic cell injury in these patients.

Oral contraceptive drugs may also play a role in the development of HCC. The long-term exposure to organic solvents is also a risk factor for HCC. Dietary antioxidants, selenium, statins and coffee drinking have protective effect against HCC.

Feher, J. and G. Lengyel (2010). "[**Hepatocellular carcinoma: occurrence, risk factors, biomarkers**]." Orv Hetil **151**(23): 933-940.

Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related death worldwide. Primary hepatocellular carcinoma can be found most frequently (80-90 %) in patients with liver cirrhosis. The most frequent causes of liver cirrhosis are chronic hepatitis B and C virus infections and chronic alcohol consumption. The occurrence of hepatocellular carcinoma is about 3-15 % in patients with alcoholic liver disease. Other predisposing causes can be: non-alcoholic steatohepatitis (NASH), obesity, diabetes mellitus, autoimmune hepatitis, intrahepatic biliary inflammations (primary biliary cirrhosis, primary sclerosing cholangitis), copper and iron metabolic diseases (Wilson-disease, haemochromatosis), congenital alpha-1-antitripsin deficiency. The causative role of hepatitis B es C viruses have been well established in the pathogenesis of liver cancer. Other pathogenic factors are smoking, and different chemical agents. Treatment options for these patients have previously been limited to best supportive care and palliative therapy. Beside surgical treatment (resection, liver transplantation) the invasive radiologic therapy also has been widely used. The effectiveness of targeted therapy with monoclonal antibodies or small-molecule kinase inhibitors has now been demonstrated for the treatment of different tumors. In year 2007, sorafenib, a multitargeted kinase inhibitor was introduced to clinical practice and found to prolong survival significantly for patients with advanced HCC.

11:40 - 12:00

Overview of Hepatitis surveillance and Epidemiology in Europe

Erika Duffell

ECDC

Epidemiological objectives

To monitor:

- The incidence and routes of transmission of newly diagnosed cases of hepatitis B and C in the general and vulnerable populations;
- the prevalence of chronic hepatitis B and C virus infection to determine burden of infection (and estimate the proportion undiagnosed) in the general and vulnerable populations;
- the proportion of chronic hepatitis B and C cases that are engaged in care (continuum of care);
- the proportion of newly diagnosed chronic hepatitis B and C presenting late.

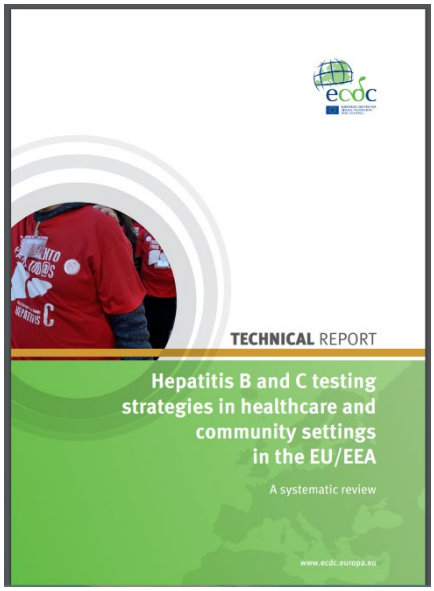
To determine:

- The genotype and sequence distributions of newly acquired hepatitis B and hepatitis C viruses to better follow transmission patterns, the emergence of resistance and vaccine escape mutants and potentially more virulent virus strains (priority on hepatitis C infections);
- and describe the proportion of co-infections (HIV/HBV/HCV/HDV)nd describe the proportion of co-infections (HIV/HBV/HCV/HDV);
- the proportion of HCV re-infections (especially among key risk groups with high incidence e.g. PWIDs)

Programme objectives

- To provide data to inform, strengthen and improve the development, evaluation and monitoring of national and EU level hepatitis B and C primary prevention and control programmes (e.g. vaccination, harm reduction);
- To monitor the burden of chronic hepatitis B and C infection and their continuum of care to inform, strengthen and improve the development, evaluation and monitoring of secondary prevention programmes (e.g. screening and high quality care pathways);
- To identify emerging population groups at risk (and changes over time) and in need for targeted prevention measures;
- To report on patient safety from healthcare associated infection and healthcare worker safety from occupational transmission;
- To better describe the prevalence of hepatitis in vulnerable populations – for Hepatitis B: especially MSM, IDU, CSW, migrants and for Hepatitis C: especially IDU, prisoners, blood and blood product recipients, migrants;
- To detect and monitor any multi-state outbreaks of viral hepatitis with respect to source, time, person, population and place in order to provide a rationale for public health action.

https://www.ecdc.europa.eu/en/about-uswho-we-workdisease-and-laboratory-networks/european-network-hepatitis-b-and-c-surveillance



The scope of this project was to provide an overview of different effective testing strategies for hepatitis B and C and their outcomes in the EU/EEA, covering all relevant population groups and settings. A systematic review was performed to collect, synthesise and analyse available data on HBV/HCV testing outcomes and acceptability measures from EU/EEA countries.

Other related references (Pubmed search):

Mason LMK, Veldhuijzen IK, Duffell E, van Ahee A, Bunge EM, Amato-Gauci AJ, Tavoschi L. **Hepatitis B and C testing strategies in healthcare and community settings in the EU/EEA: A systematic review**. Journal of viral hepatitis. 2019.

> An estimated 9 million individuals are chronically infected with hepatitis B virus (HBV) and hepatitis C virus (HCV) across the European Union/European Economic Area (EU/EEA), many of which are yet to be diagnosed. We performed a systematic review to identify interventions effective at improving testing offer and uptake in the EU/EEA. Original research articles published between 1 January 2008 and 1 September 2017 were retrieved from PubMed and EMBASE. Search strings combined terms for HBV/HCV, intervention, testing and geographic terms (EU/EEA). Out of 8331 records retrieved, 93 studies were selected. Included studies reported on testing initiatives in primary health care (9), hospital (12), other healthcare settings (31) and community settings (41). Testing initiatives targeted population groups such as migrants, drug users, prisoners, pregnant women and the general population. Testing targeted to populations at higher risk yielded high coverage rates in many settings. Implementation of novel testing approaches, including dried blood spot (DBS) testing, was associated with increased coverage in several settings including drug services, pharmacies and STI clinics. Community-based testing services were effective in reaching populations at higher risk for infection, vulnerable and hard-to-reach populations. In conclusion, our review identified several successful testing approaches implemented in healthcare and community settings, including testing approaches targeting groups at higher risk, community-based testing services and DBS testing. Combining a diverse set of testing opportunities within national testing strategies may lead to higher impact both in terms of testing coverage and in terms of reduction, on the undiagnosed fraction.

Mason LM, Duffell E, Veldhuijzen IK, Petriti U, Bunge EM, Tavoschi L. **Hepatitis B and C prevalence and incidence in key population groups with multiple risk factors in the EU/EEA: a systematic review**. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2019;24(30).

> BackgroundPeople living with HIV (PLHIV) and people in prison are population groups with a potentially high risk and/or prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection.AimWe conducted a systematic review in order to find prevalence and incidence estimates in these populations in the European Union/European Economic Area (EU/EEA).MethodsOriginal research articles published between January 2005 and February 2017 were retrieved from PubMed and Embase in February 2017.ResultsFifty-two articles were included, providing 97 estimates of HBV/HCV infection prevalence or incidence. Estimates of HBV infection prevalence ranged between 2.9% and43.4% in PLHIV and 0.0% and 25.2% in people in prison. Estimates of HCV infection prevalence ranged from 2.9% to 43.4% in PLHIV and 0.0% to 25.2% in people in prison. Incidence estimates ranged between 0.0 and 2.5 cases per 100 person-years for HBV infection in PLHIV. No such data was available for people in prison. HCV infection incidence ranged between 0.3 and 0.9 cases per 100 person-years in PLHIV and between 1 and 1.2 cases per 100 person-years in people in prison. Prevalence estimates were generally higher than in the general population, especially for HCV infection and among groups with multiple risk factors.ConclusionsPLHIV, people in prison and groups with multiple risk factors, have a high prevalence of HBV and HCV and may be at ongoing risk of infection. These groups should be among the populations prioritised and targeted for active case finding and prevention programmes in the EU/EEA.

Falla AM, Hofstraat SHI, Duffell E, Hahne SJM, Tavoschi L, Veldhuijzen IK. **Hepatitis B/C in the countries of the EU/EEA: a systematic review of the prevalence among at-risk groups**. BMC

infectious diseases. 2018;18(1):79.

BACKGROUND: In 2016, the World Health Organisation set a goal to eliminate viral hepatitis by 2030. Robust epidemiological information underpins all efforts to achieve elimination and this systematic review provides estimates of HBsAg and anti-HCV prevalence in the European Union/European Economic Area (EU/EEA) among three at-risk populations: people in prison, men who have sex with men (MSM), and people who inject drugs (PWID). METHODS: Estimates of the prevalence among the three risk groups included in our study were derived from multiple sources. A systematic search of literature published during 2005-2015 was conducted without linguistic restrictions to identify studies among people in prison and HIV negative/HIV sero-status unknown MSM. National surveillance focal points were contacted to validate the search results. Studies were assessed for risk of bias and high quality estimates were pooled at country level. PWID data were extracted from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) repository. RESULTS: Despite gaps, we report 68 single study/pooled HBsAg/anti-HCV prevalence estimates covering 23/31 EU/EEA countries, 42 of which were of intermediate/high prevalence using the WHO endemicity threshold (of >/=2%). This includes 20 of the 23 estimates among PWID, 20 of the 28 high quality estimates among people in prison, and four of the 17 estimates among MSM. In general terms, the highest HBsAg prevalence was found among people in prison (range of 0.3% - 25.2%) followed by PWID (0.5% - 6.1%) and MSM (0.0% - 1.4%). The highest prevalence of anti-HCV was also found among people in prison (4.3% - 86.3%) and PWID (13.8% - 84.3%) followed by MSM (0.0% - 4.7%). CONCLUSIONS: Our results suggest prioritisation of PWID and the prison population as the key populations for HBV/HCV screening and treatment given their dynamic interaction and high prevalence. The findings of this study do not seem to strongly support the continued classification of MSM as a high risk group for chronic hepatitis B infection. However, we still consider MSM a key population for targeted action given the emerging evidence of viral hepatitis transmission within this risk group together with the complex interaction of HBV/HCV and HIV.

Aspinall EJ, Hutchinson SJ, Goldberg DJ, Valerio H, Mozalevskis A, Noori T, . . . Tavoschi L. **Monitoring response to hepatitis B and C in EU/EEA: testing policies, availability of data on care cascade and chronic viral hepatitis-related mortality - results from two surveys (2016)**. HIV medicine. 2018;19 Suppl 1:11-5.

OBJECTIVES: The World Health Organization (WHO) developed a European Regional Action Plan (EAP) to fast-track action towards the goal of eliminating viral hepatitis. Robust monitoring is essential to assess national programme performance. The purpose of this study was to assess the availability of selected monitoring data sources in European Union/European Economic Area (EU/EEA) Member States (MS). METHODS: Availability of data sources at EU/EEA level was assessed using two surveys distributed to 31 EU/EEA MS in 2016. The two surveys covered (A) availability of policy documents on testing; testing practices and monitoring; monitoring of diagnosis and treatment initiation, and; (B) availability of data on mortality attributable to chronic viral hepatitis. RESULTS: Just over two-thirds of EU/EEA MS responded to the surveys. 86% (18/21) reported national testing guidance covering HBV, and 81% (17/21) covering HCV; while 33% (7/21) and 38% (8/21) of countries, respectively, monitored the number of tests performed. 71% (15/21) of countries monitored the number of chronic HBV cases diagnosed and 33% (7/21) the number of people treated. Corresponding figures for HCV were 48% (10/21) and 57% (12/21). 27% (6/22) of countries reported availability of data on mortality attributable to chronic viral hepatitis. CONCLUSIONS: The results of this study suggest that sources of information in EU/EEA Member States to monitor the progress towards the EAP milestones and targets related to viral hepatitis diagnosis, cascade of care and attributable mortality are limited. Our analysis should raise awareness among EU/EEA policy makers and stimulate higher prioritisation of efforts to improve the monitoring of national viral hepatitis programmes.

Hofstraat SHI, Falla AM, Duffell EF, Hahne SJM, Amato-Gauci AJ, Veldhuijzen IK, Tavoschi L. **Current prevalence of chronic hepatitis B and C virus infection in the general population, blood donors**

and pregnant women in the EU/EEA: a systematic review. Epidemiology and infection. 2017;145(14):2873-85.

This systematic review aimed at estimating chronic hepatitis B (HBV) and C virus (HCV) prevalence in the European Union (EU) and Economic Area (EEA) countries in the general population, blood donors and pregnant women. We searched PubMed(c), Embase(c) and Cochrane Library databases for reports on HBV and HCV prevalence in the general population and pregnant women in EU/EEA countries published between 2005 and 2015. Council of Europe data were used for HBV and HCV blood donor prevalence. HBV general population estimates were available for 13 countries, ranging from 0.1% to 4.4%. HCV general population estimates were available for 13 countries, ranging from 0.1% to 5.9%. Based on general population and blood donor estimates, the overall HBV prevalence in the EU/EEA is estimated to be 0.9% (95% CI 0.7-1.2), corresponding to almost 4.7 million HBsAg-positive cases; and the overall HCV prevalence to be 1.1% (95% CI 0.9-1.4), equalling 5.6 million anti-HCV-positive cases. We found wide variation in HCV and HBV prevalence across EU/EEA countries for which estimates were available, as well as variability between groups often considered a proxy for the general population. Prevalence estimates are essential to inform policymaking and public health practice. Comparing to other regions globally, HBV and HCV prevalence in the EU/EEA is low.

Duffell EF, van de Laar MJ, Amato-Gauci AJ. **Enhanced surveillance of hepatitis B in the EU, 2006-2012**. Journal of viral hepatitis. 2015;22(7):581-9.

Robust epidemiological information on hepatitis B is important to help countries plan prevention and control programmes and evaluate public health responses to control transmission. European Centre Disease Prevention and Control (ECDC) introduced enhanced surveillance of hepatitis B at EU/EEA level in 2011 to collate routine surveillance data from national notification systems. Analysis of the data collected for the years 2006-2012 shows a high burden of hepatitis B across Europe with 110 005 cases reported over the period with the majority of these cases being chronic infections. The most commonly reported routes of transmission in acute cases included heterosexual transmission, nosocomial transmission, injecting drug use and transmission among men who have sex with men. Mother-to-child transmission was the most common route reported for chronic cases. Trends over time were difficult to analyse as national reporting practices changed, but data suggest a downward trend in acute cases, which probably reflects the impact of the widespread implementation of vaccination programmes. Notifications of chronic infection varied across countries and showed discrepancy with the expected results based on findings from recent prevalence surveys. This indicated that notifications mirror local testing practices rather than real occurrence of disease. Improving the quality of the data and considering reported notifications alongside other data sources, such as local screening practices and vaccination policies, will improve the utility of the data.

Duffell EF, van de Laar MJ, Amato-Gauci AJ. **Enhanced surveillance of hepatitis C in the EU, 2006 - 2012**. Journal of viral hepatitis. 2015;22(7):590-5.

Hepatitis C is a major public health issue across Europe, and with rapidly evolving developments in the therapeutic field, it is essential that countries have access to epidemiological information. In 2011, The European Centre for Disease Prevention and Control (ECDC) introduced enhanced surveillance of hepatitis C across EU/EEA countries collecting routine data from national notification systems using standardized case definitions. Data collected from 2006 to 2012 indicate a high burden of disease with great variation in reported cases between countries. Most cases occurred among young adult males, and although injecting drug use dominated across all cases, there were increasing numbers of acute cases reported among men who have sex with men. Geographically, the reported data were the inverse of what may be expected based on findings from recent prevalence surveys in a number of EU/EEA countries. Unexpectedly, low figures were reported through notification systems in some southern and eastern European countries where prevalence is known from surveys to be high. This discrepancy highlights the limitation of surveillance data for a disease

such as hepatitis C which is largely asymptomatic until a late stage, so that notifications reflect testing practices rather than real occurrence of disease. Further improvements to the quality of the data are important to increase data utility. Improved understanding of national testing practices is necessary to allow a better interpretation of surveillance results. Additional epidemiological studies alongside routine case-based reporting in notification systems should also be considered to better estimate the true disease burden across Europe.

Duffell EF, van de Laar MJ. **Survey of surveillance systems and select prevention activities for hepatitis B and C, European Union/European Economic Area, 2009**. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2015;20(13):17-24.

Hepatitis B and C viral infections are leading causes of hepatic cirrhosis and cancer. The incidence and prevalence of both hepatitis B and C varies across European countries. European wide surveillance data help to understand the dynamic epidemiology of hepatitis B and C, which is important for the implementation and effectiveness of prevention and control activities.Comparison of surveillance data between countries in Europe is hampered by the differences in national healthcare and reporting systems. This report presents the results of a survey in 2009 which was undertaken to collect baseline information on surveillance systems and core prevention programmes for hepatitis B and C in individual European Union/ European Economic Area countries. The results provide key information to aid the interpretation of surveillance data, and while indicating heterogeneity in national surveillance systems and programmes, they highlight the potential of these systems. This resource has supported the implementation of a standardised European enhanced surveillance programme.

12:00 – 12:10 Question and discussion

12:10 - 12:30 *Treatment and follow up of HCV-related liver disease (Dr Mihály Makara) & Chronic HCV diagnostic methods in Hungary 1992-2019 (Dr Judit Gervain)*

Dr. Mihály Makara, Dr. Gervain Judit

References proposed by speaker:

1. Par, A., Gervain, J., Gógl, A. **Hepatitis C virus infection: Pathogenesis, diagnosis and treatment** (1998) Scandinavian Journal of Gastroenterology 33:107-114
2. Pawlotsky J.M. **Use and interpretation of virological test for Hepatitis C.** (2002) Hepatology 36:S65-73
3. Smith DB., Bukh J., Kuiken C., et al**. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assigment web resource**. (2014) Hepatology 59:318-327
4. Gajdán, L., Mag, M., Gervain, J.: **Contrast enhanced ultrasonography for characterisation of focal liver lesions**. [A kontrasztanyagos ultrahangvizsgálatok alkalmazása gócos májbetegségekben.] (2017) Central European Journal of Gastroenterology and Hepatology Vol 3:22-24.
5. Hunyady, B., Gerlei, Z., Gervain, J., Horvath, G., Lengyel, G., Par, A., Peter, Z., Rokusz, L., Schneider, F., Szalay, F., Tornai, I., Werling, K., Makara, M. **Screening, diagnosis, treatment, and follow up of hepatitis C virus related liver disease. National consensus guideline in Hungary from 26 March 2018** [A hepatitis C-virus-fertőzes szűrese, diagnosztikaja, antiviralis terapiaja, kezeles utani gondozasa. Magyar konszenzusajanlas. Ervenyes: 2018. március 16-tól] (2018) Central European Journal of Gastroenterology and Hepatology Vol4: 53-56.

Other related references (Pubmed search):

Bechini, A., et al. (2015). "**Identification of hepatitis B and C screening and patient management guidelines and availability of training for chronic viral hepatitis among health professionals in six European countries: results of a semi-quantitative survey**." BMC Infect Dis **15**: 353.

BACKGROUND: As part of the EU funded project "HEPscreen", the aim of this study is to identify hepatitis B and C screening and patient management guidelines, to assess the awareness of these among health professionals (HPs) and to explore the availability of hepatitis B/C training programmes for HPs in Germany, Italy, the Netherlands, the UK, Spain and Hungary. METHODS: A comprehensive literature search through the main scientific databases was performed to retrieve guidelines, following which an online survey was developed and sent to HPs in six areas of health care, including public health, to verify whether HPs are aware of these guidelines, to retrieve additional guidelines and to find out whether specific professional training is available. RESULTS: Twelve national guidelines were identified through the literature search. Of the 268 respondents, 80 % were aware of hepatitis B guidelines and 73 % were aware of hepatitis C guidelines in their country. The national guidelines identified through the literature search were mentioned by 1/3 of HPs in the UK and Germany, 13 % of HPs in the Netherlands, 14 % in Italy and 4 % in Spain. An additional 41 hepatitis B/C related guidance documents were retrieved through the online survey: 15 in the UK, seven in Hungary, six in Italy, five in the Netherlands, four in Germany and four in Spain. Availability of training programmes to improve skills and knowledge in viral hepatitis was most often reported in the Netherlands, with 82 % indicating availability and just 10 % indicating no availability, and least commonly in Italy, with 42 % indicating yes but 40 % indicating no. Availability was also reported by the majority in the UK, Hungary and Spain, while in Germany the majority selected unsure. CONCLUSIONS: Results suggest that the scientific databases are not the most important information source of best clinical practice for many HPs. Implementation of best practices requires that guidelines are specifically designed and actively promoted among those who are to follow them. Training can disseminate these best practice recommendations and raise awareness of guidelines. It is therefore encouraging that diverse training about hepatitis B/C is available to the different professional groups.

Leblebicioglu, H., et al. (2018). "**Availability of hepatitis C diagnostics and therapeutics in European and Eurasia countries**." Antiviral Res **150**: 9-14.

BACKGROUND: Treatment with direct acting antiviral agents (DAAs) has provided sustained virological response rates in >95% of patients with chronic hepatitis C virus (HCV) infection. However treatment is costly and market access, reimbursement and governmental restrictions differ among countries. We aimed to analyze these differences among European and Eurasian countries. METHODS: A survey including 20-item questionnaire was sent to experts in viral hepatitis. Countries were evaluated according to their income categories by the World Bank stratification. RESULTS: Experts from 26 countries responded to the survey. As of May 2016, HCV prevalence was reported as low (</=1%) in Croatia, Czech Republic, Denmark, France, Germany, Hungary, the Netherlands, Portugal, Slovenia, Spain, Sweden, UK; intermediate (1-4%) in Azerbaijan, Bosnia and Herzegovina, Italy, Kosovo, Greece, Kazakhstan, Romania, Russia, Serbia and high in Georgia (6.7%). All countries had national guidelines except Albania, Kosovo, Serbia, Tunisia, and UK. Transient elastography was available in all countries, but reimbursed in 61%. HCV-RNA was reimbursed in 81%. PegIFN/RBV was reimbursed in 54% of the countries. No DAAs were available in four countries: Kazakhstan, Kosovo, Serbia, and Tunisia. In others, at least one DAA combination with either PegIFN/RBV or another DAA was available. In Germany and the Netherlands all DAAs were reimbursed without restrictions: Sofosbuvir and sofosbuvir/ledipasvir were free of charge in Georgia. CONCLUSION: Prevalence of HCV is relatively higher in lower-middle and upper-middle income countries. DAAs are not available or reimbursed in many Eurasia and European countries. Effective screening and access to care are essential for reducing liver-related morbidity and mortality.

Jarcuska, P., et al. (2016). "**Evaluation of hepatic fibrosis - access to non-invasive methods, national practice/guidelines in Central Europe**." Clin Exp Hepatol **2**(1): 12-15.

Noninvasive methods have improved diagnostic tools of liver fibrosis. Although liver biopsy is the gold standard for diagnosis of hepatis fibrosis, the noninvasive tests are usually much

less expensive than liver biopsy, better tolerated, and can be repeated without any risk for the patient. Two groups of these noninvasive tests are included in clinical practice: serum biomarkers and elastography. In our paper we summarize noninvasive diagnostic options for liver fibrosis in the Czech Republic, Hungary, Poland and Slovakia. Noninvasive diagnostic methods, especially elastography, are widely accessible in all countries.

Gervain, J. (2014). "[**The diagnosis of hepatitis C virus infection**]." Orv Hetil **155**(26): 1019-1023.

The successful therapy of hepatitis C viral infection requires that the illness is diagnosed before the development of structural changes of the liver. Testing is stepwise consisting of screening, diagnosis, and anti-viral therapy follow-up. For these steps there are different biochemical, serological, histological and molecular biological methods available. For screening, alanine aminotransferase and anti-HCV tests are used. The diagnosis of infection is confirmed using real-time polymerase chain reaction of the viral nucleic acid. Before initiation of the therapy liver biopsy is recommended to determine the level of structural changes in the liver. Alternatively, transient elastography or blood biomarkers may be also used for this purpose. Differential diagnosis should exclude the co-existence of other viral infections and chronic hepatitis due to other origin, with special attention to the presence of autoantibodies. The outcome of the antiviral therapy and the length of treatment are mainly determined by the viral genotype. In Hungary, most patients are infected with genotype 1, subtype b. The polymorphism type that occurs in the single nucleotide located next to the interleukin 28B region in chromosome 19 and the viral polymorphism type Q80K for infection with HCV 1a serve as predictive therapeutic markers. The follow-up of therapy is based on the quantitative determination of viral nucleic acid according to national and international protocols and should use the same method and laboratory throughout the treatment of an individual patient.

Schaff, Z. (2011). "[**The value of liver biopsy in chronic hepatitis**]." Orv Hetil **152**(22): 856-858.

Liver needle biopsies played important role in determining the various forms of chronic hepatitis, the activity of inflammation and the degree of fibrosis. A breakthrough in their evaluation was provided by the so-called Knodell Histology Activity Index (HAI) system, which expressed the dynamics of the process and histological characteristics of therapy response. The HAI system underwent several modifications, the most widely used being the Desmet, Ishak modifications as well as the METAVIR scoring system. These systems examine necroinflammation and degree of fibrosis separately, namely the grade and stage of chronic hepatitis. Determination of fibrosis has become the subject of discussion lately, since the amount of connective tissue deposition (collagen fiber, extracellular matrix) is not clearly identifiable with the stage of chronic hepatitis. Histological evaluation of the liver remains decisive in determining the effect of the various new therapeutic drugs, in particular the protease and polymerase inhibitors of certain nonstructural proteins of the hepatitis C virus. It can be established however, that in recent years liver biopsies have become rather a selective than routine technique.

Gervain, J. (2010). "[**Symptoms of hepatocellular carcinoma. Laboratory tests used for its diagnosis and screening**]." Orv Hetil **151**(35): 1415-1417.

Early stage hepatocellular carcinoma is a symptom-free disease. Local and general symptoms occur due to the growth of the tumor tissue and the infiltration of the surrounding blood vessels. Illness progression is indicated by the development of abdominal discomfort, cachexia, therapy-resistant decompensation of previously compensated cirrhosis and in severe cases, the thrombosis of the portal vein or the hepatic veins. Characteristic laboratory findings are the quickly deteriorating blood and liver function tests results, the occurrence of haemostatic disorders and occasional hypoglycemia and/or hypercalcemia. To clarify the etiology and to identify high risk patients, we need to differentiate alcohol-, drug- or chemical-induced hepatic disorders, viral hepatitis B, C and Delta, metabolic disorders and non-alcoholic steatohepatitis. In the case of focal hepatic lesions, persistently elevated alfa

fetoprotein levels have a high diagnostic value. At levels over 200 ng/ml, the positive predictive value is >90%. Other, less commonly measured biomarkers are the glycosilated alfa fetoprotein-L3 and the vitamin K-deficiency induced des-gamma-carboxy prothrombin. The risk of tumor occurrence is multiple in patients with HbeAg positive chronic hepatitis B if the virus is of genotype C with mutations in the 1762 and 1764 locations of the core promoter region. Abdominal ultrasound and measurement of alfa fetoprotein is recommended every 6 months for high risk individuals, or every 3-4 months over an 18-24 months period for patients with hepatic lesions of <1cm and of unknown malignancy.

12:30 - 12:40 *Questions*

12:40 - 13:30 LUNCH

Chairs: Ferenc Szalay – Vladimir Chulanov

13:30 - 13:45 *Hepatitis in Risk groups in Hungary*

Screening programmes among injecting drug users in Hungary

Anna Horváth-Tarján – Maria Dudas

Other related references (Pubmed search):

Treso, B., et al. (2013). "**Molecular epidemiology of hepatitis C virus genotypes and subtypes among injecting drug users in Hungary**." Euro Surveill **18**(47).

The aim of this study was to determine the geographical distribution of hepatitis C virus genotypes/subtypes among people who inject drugs (PWID) recruited at 22 needle exchange sites and drug outpatient services in all seven Planning and Statistical Regions of Hungary. Of 198 such PWID, 147 (74.2%), 45 (22.7%) and six (3.0%) carried genotype 1, 3 or 4, respectively, and 31 (72.1%) of the 43 genotype 1 sequences were of subtype 1a. Genotype 3 was significantly more prevalent in provincial towns than in the capital, Budapest. Injecting for a longer period and an older age both correlated with a higher prevalence of genotype 3, suggesting possible future changes in genotype distribution. The distributions of hepatitis C virus genotypes/ subtypes differed significantly between the tested PWID and the general population. The identification of genotype 3 reflected its worldwide occurrence among PWID. Our results underline the importance of genotyping before treatment, especially among people who have ever injected drugs in Hungary.

Tarjan, A., et al. (2017). "**HCV prevalence and risk behaviours among injectors of new psychoactive substances in a risk environment in Hungary-An expanding public health burden**." Int J Drug Policy **41**: 1-7.

BACKGROUND: In Hungary a large increase in injecting new psychoactive substances (NPS) coincided with decreasing harm reduction efforts and rising HCV infection. We describe these, and assess changes in HCV prevalence and risk behaviours, 2011-2014, among NPS injectors, using 2011-2015 syringe exchange programme (SEP) data as a key contextual ('risk environment') variable. METHODS: We conducted repeated national sero-behavioural surveys in people who inject drugs (PWID) injecting in the last month and attending SEPs or drug treatment centres (n=399, 2011; 384, 2014), using face-to-face interviews and dried blood-spot samples. Prevalence of injected drugs and SEP coverage (2011-2015) were assessed through our national SEP monitoring system and using population size estimates. RESULTS: NPS injecting tripled among PWID attending SEPs in Hungary (2011: 26%; 2015: 80%). Among NPS injectors, HCV prevalence, sharing syringes and sharing any injecting equipment (last month), doubled (2011-2014: 37%-74%, 20%-48%, 42%-71%, respectively), significantly exceeding prevalence in other PWID groups. Among young NPS injectors (aged<25), HCV prevalence increased 7-fold (12%-76%), among new injectors

(injecting<2years) 4-fold (13%-42%), coupled with high levels of equipment sharing (79% and 72% respectively). Not using a condom at last intercourse (79%), ever-imprisonment (65%) and last-year homelessness (57%) were highly prevalent among NPS injectors (2014). The number of syringes distributed per estimated PWID nationally fell from 114 to 81 (2011-2014) and dropped to 28 in 2015. CONCLUSION: NPS injectors in Hungary are at severe risk of blood-borne infections due to high levels of injecting and sexual risk behaviours within a high-risk environment, including continuously low SEP provision, imprisonment and homelessness. An HIV outbreak cannot be excluded. Stronger investment in evidence-based prevention measures, with special focus on young and new injectors, and expansion of hepatitis C treatment are urgently needed.

Racz, J., et al. (2016). "**New cases of HIV among people who inject drugs in Hungary: False alarm or early warning?**" Int J Drug Policy **27**: 13-16.

Between 2009 and the first quarter of 2014, only one case of HIV (contracted outside Hungary) was detected among PWIDs in Hungary. However, more recent evidence suggests increased sharing of injecting paraphernalia among PWIDs. This is linked to the emergence of new designer drugs that require frequent injection, alongside funding cuts to the Hungarian needle exchange program (NEP) which has reduced access to sterile injecting equipment. During the past five years in Hungary, drug use has become increasingly discussed in moral as opposed to public health terms, and drug consumption has been re-criminalized. The largest NEP in Hungary was closed because of political pressure and government funding for regular HCV/HIV testing/counselling and seroprevalence studies among PWIDs has been stopped. This paper describes the detection of two new cases of HIV infection in PWIDs attending two NEPs in Budapest in May 2014. These new cases may indicate an unfolding HIV outbreak among PWIDs-similar to those reported in Greece and Romania. Yet the question remains: If no further HIV cases are detected, is this because there are no new cases or because there are no testing facilities for PWID?

Tarjan, A., et al. (2015). "**Emerging Risks Due to New Injecting Patterns in Hungary During Austerity Times.**" Subst Use Misuse **50**(7): 848-858.

As a consequence of the massive restructuring of drug availability, heroin injection in Hungary was largely replaced by the injecting of new psychoactive substances (NPS) starting in 2010. In the following years in our sero-prevalence studies we documented higher levels of injecting paraphernalia sharing, daily injection-times, syringe reuse, and HCV prevalence among stimulant injectors, especially among NPS injectors. Despite the increasing demand, in 2012 the number of syringes distributed dropped by 35% due to austerity measures. Effects of drug market changes and the economic recession may have future epidemiological consequences. Study limitations are noted and future needed research is suggested.

Gyarmathy, V. A. and P. Sarosi (2015). "**Hepatitis C prevalence among people who inject drugs in Hungary.**" Lancet Infect Dis 15(11): 1261-1262.

Treso, B., et al. (2013). "**Molecular epidemiology of hepatitis C virus genotypes and subtypes among injecting drug users in Hungary**." Euro Surveill 18(47).

The aim of this study was to determine the geographical distribution of hepatitis C virus genotypes/subtypes among people who inject drugs (PWID) recruited at 22 needle exchange sites and drug outpatient services in all seven Planning and Statistical Regions of Hungary. Of 198 such PWID, 147 (74.2%), 45 (22.7%) and six (3.0%) carried genotype 1, 3 or 4, respectively, and 31 (72.1%) of the 43 genotype 1 sequences were of subtype 1a. Genotype 3 was significantly more prevalent in provincial towns than in the capital, Budapest. Injecting for a longer period and an older age both correlated with a higher prevalence of genotype 3, suggesting possible future changes in genotype distribution. The distributions of hepatitis C virus genotypes/ subtypes differed significantly between the tested PWID and the general

population. The identification of genotype 3 reflected its worldwide occurrence among PWID. Our results underline the importance of genotyping before treatment, especially among people who have ever injected drugs in Hungary.

Gazdag, G., et al. (2012). "**Referral of intravenous drug users for antiviral treatment: effectiveness of hepatitis C case-finding programmes**." Cent Eur J Public Health 20(3): 223-225.

BACKGROUND: Hepatitis C infection (HCI) case-finding programmes aim to identify infected persons in a well-defined population. This study assessed the effectiveness of three HCI case-finding programmes for intravenous drug users by examining the rate of their referral to antiviral treatment. METHODS: The Hepatology Outpatient Clinic of Szent Laszlo Hospital examines and treats all intravenous drug users who are found positive in HCI case-finding programmes in Budapest. The medical records of patients who visited the Hepatology Outpatient Clinic of Szent Laszlo Hospital between 1 January 2006 and 31 December 2008 were screened and records indicating a history of drug abuse were selected. These records were matched against the databases of the hepatitis case-finding programmes and the records that appeared in both datasets were analyzed. RESULTS: Of the 234 intravenous drug users identified as hepatitis C virus positive in the Budapest case-finding programmes, only 21 attended the Hepatology Outpatient Clinic of Szent Laszlo Hospital and only two started antiviral treatment, but their hepatitis C virus positive status had already been known at the time of screening. CONCLUSION: In this study, not a single patient with drug abuse whose hepatitis C virus positive status was identified in one of the HCI case-finding programmes was referred for antiviral treatment.

Gyarmathy, V. A. and J. Racz (2011). "[**Human immunodeficiency virus (HIV) and Hepatitis C virus (HCV) testing among injecting drug users**]." Orv Hetil 152(4): 124-130.

In Hungary, there is a need for widely accessible HIV and HCV testing and counseling for injecting drug users. Theoretically, free and confidential rapid HIV and HCV testing would be the most suitable for this purpose. Low threshold agencies, such as needle and syringe programs, would provide ideal premises for such a testing system, Here, participants would be able to undergo regular testing every six months. Making rapid testing widely available raises the following three main issues: 1. validity of the testing results (or: the verification of positive rapid test results), 2. circumstances of taking blood (or: legislation regarding drawing blood), and 3. cost effectiveness (or: how important is it to prevent an HIV epidemic). The authors propose the establishment of a system that offers screening using rapid tests and which would be an expansion of a currently existing system of HIV and HCV testing based on finger prick blood. The current system would thus serve as a means to verify the results of the rapid tests. At the same time, there is a need to obtain permission from a public health body to enable in needle and syringe programs the provision of rapid testing and testing of blood using finger pricks. In many countries, test results are given to injecting drug users not by doctors but by trained social workers - such a system could also be established in Hungary. If preventing an HIV epidemic in Hungary is a priority, then wide access to rapid HIV testing is justified. Widely accessible free and confidential rapid HIV and HCV testing and counseling - combined with screening and verification using finger prick blood - may function not only as a testing and counseling service but also as a good quality public health monitoring system. Such a system, however, requires regular financial support from the government.

Gyarmathy, V. A., et al. (2011). **"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 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. and A. Neaigus (2011). "**The association between social marginalisation and the injecting of alcohol amongst IDUs in Budapest, Hungary**." Int J Drug Policy 22(5): 393-397.

BACKGROUND: Alcohol injecting may cause intense irritation, serious vein damage, and additional risks. What little is known about alcohol injecting points to the potential role of social marginalisation. METHODS: Injecting drug users (N=215) were recruited between October 2005 and December 2006 in Budapest, Hungary from non-treatment settings. Multivariate logistic regression models identified correlates of lifetime alcohol injecting. RESULTS: About a quarter (23%) reported ever injecting alcohol-only 3% reported injecting alcohol in the past 30 days. In multivariate analysis, six variables were statistically significantly associated with ever injecting alcohol: male gender, being homeless, ever sharing cookers or filters and injecting mostly in public places showed a positive association, whilst Roma ethnicity and working at least part time showed a negative association. CONCLUSIONS: Our study suggests that alcohol injecting is more of a rare event than a so far undiscovered research and prevention priority. Still, providers of harm reduction services should be aware that alcohol injecting happens, albeit rarely, especially amongst socially marginalised IDUs, who should be counselled about the risks of and discouraged from alcohol injecting.

Gyarmathy, V. A. and J. Racz (2010). "[**Epidemiology of hepatitis C and human immunodeficiency virus infections among injecting drug users in Hungary--what's next?]."** Orv Hetil 151(10): 365-371.

The prevalence of hepatitis C virus infection (HCV) is currently about 35% among injecting drug users in Budapest, Hungary, and it is under 20% outside of the capital, and no verified case of human immunodeficiency virus (HIV) have been detected so far. Mathematical models describe that the co-occurrence of HIV and HCV among injecting drug users is such under an HCV prevalence of about 35% the probability of an HIV epidemic is low, but above this threshold an, HIV epidemic is to be expected. According to these models, there is a looming probability of an HIV epidemic among injecting drug users in Hungary, especially in Budapest. There are four ways to prevent or delay such an epidemic: 1. substitution treatment programs; 2. legal access to injecting equipment; 3. free and confidential HIV and HCV counseling and rapid testing; and 4. hygienic injecting environment. In order to avoid a predicted HIV epidemic, epidemiological pattern of HCV among injecting drug users in Hungary requires both a comprehensive prevention response and the systematic monitoring of the epidemiological situation. The success of the prevention programs depends on two factors: 1. wide access; and 2. regular financial support from the government.

Gyarmathy, V. A. and J. Racz (2010). "[**Social networks, risk dyads, and their role in the epidemiology and prevention of drug related infectious diseases**]." Orv Hetil 151(32): 1289-1294.

In the case of risk behaviors where infection transmission occurs through social relationships (e.g. via sharing drugs and injecting equipment, or through sexual relations), prevention should follow (among others) the path of the social network. Previous studies have shown

that sharing of injecting equipment is more likely to occur in larger and denser networks and that more popular individuals are more likely to engage in risk behaviors, become infected or transmit infection. Primary targets of social network interventions are central individuals, and information diffuses from them to the more peripheral members of the network. The most effective preventions are those where social network interventions targeting high-risk, central individuals are complemented by concurrent individual counseling and/or dyad interventions. Injecting drug users in Hungary would also benefit from such a multifaceted prevention approach aiming to reduce risky injecting behavior. This population needs prevention, in whatever form available, to prevent the deterioration of the current HCV and HIV epidemiological situation in Hungary and the development of an HIV epidemic that will eventually spread over to the general population.

Gyarmathy, V. A., et al. (2010). "**Liquid drugs and high dead space syringes may keep HIV and HCV prevalence high - a comparison of Hungary and Lithuania**." Eur Addict Res 16(4): 220-228.

Despitevery 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). Wecompared 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.

Gazdag, G., et al. (2010). "**Barriers to antiviral treatment in hepatitis C infected intravenous drug users.**" Neuropsychopharmacol Hung 12(4): 459-462.

BACKGROUND: Nowadays intravenous drug use is the main source of hepatitis C transmission, but only a small proportion of those who acquired infection via intravenous drug use receive antiviral treatment. AIM: to assess the barriers of access to antiviral treatment of infected intravenous drug users. METHODS: A retrospective chart review was carried out in a hepatology outpatient clinic including all hepatitis C infected intravenous drug users in a 3-year period. RESULTS: Only one-third of the infected former intravenous drug users received antiviral treatment. The main barrier to antiviral treatment was the lack of abstinence. Former intravenous drug users in prison or in long-term drug rehabilitation institutes were more likely to enter antiviral treatment. CONCLUSIONS: The low proportion of patients entering antiviral treatment calls the attention to further improving the pretreatment management of this patient population. Special attention should be paid to the maintenance of abstinence.

13:45 - 14:00 *Screening in Prisoners*

Doc. Klara Werling

Other related references (Pubmed search):

Bielen, R., et al. (2018). "**Harm reduction and viral hepatitis C in European prisons: a cross-sectional survey of 25 countries**." Harm Reduct J 15(1): 25.

BACKGROUND: Current estimates suggest that 15% of all prisoners worldwide are chronically infected with the hepatitis C virus (HCV), and this number is even higher in regions with high rates of injecting drug use. Although harm reduction services such as opioid substitution

therapy (OST) and needle and syringe programs (NSPs) are effective in preventing the further spread of HCV and HIV, the extent to which these are available in prisons varies significantly across countries. METHODS: The Hep-CORE study surveyed liver patient groups from 25 European countries in 2016 and mid-2017 on national policies related to harm reduction, testing/screening, and treatment for HCV in prison settings. Results from the cross-sectional survey were compared to the data from available reports and the peer-reviewed literature to determine the overall degree to which European countries implement evidence-based HCV recommendations in prison settings. RESULTS: Patient groups in nine countries (36%) identified prisoners as a high-risk population target for HCV testing/screening. Twenty-one countries (84%) provide HCV treatment in prisons. However, the extent of coverage of these treatment programs varies widely. Two countries (8%) have NSPs officially available in prisons in all parts of the country. Eleven countries (44%) provide OST in prisons in all parts of the country without additional requirements. CONCLUSION: Despite the existence of evidence-based recommendations, infectious disease prevention measures such as harm reduction programs are inadequate in European prison settings. Harm reduction, HCV testing/screening, and treatment should be scaled up in prison settings in order to progress towards eliminating HCV as a public health threat.

Treso, B., et al. (2012). "**Prevalence and correlates of HCV, HVB, and HIV infection among prison inmates and staff, Hungary**." J Urban Health 89(1): 108-116.

The aim of this national, multicenter, cross-sectional study was to assess the prevalence of hepatitis B (HBV), hepatitis C (HCV), and human immunodeficiency viruses (HIV) among prisoners, and to identify related risk behaviors including injection drug use. Overall, 4,894 inmates from 20 prisons were enrolled. To have a comparison group, prison staff were also asked to take part. Altogether, 1,553 of the 4,894 inmates from seven prisons completed a questionnaire on risk behaviors. According to the survey, 1.5%, 4.9%, and 0.04% of the prisoners were tested positive for HBsAg, anti-HCV and anti-HIV, respectively. These prevalence data are among the lowest reported from prisons worldwide, although comparable to the Central European data. The prevalence of HBV, HCV, and HIV in the Hungarian prison staff was low (0.38%, 0.47%, and 0%, respectively). The rate of HCV infection was significantly higher among inmates who have ever injected drugs (22.5%) than among inmates who reported they had never injected drugs (1.1%). This first prevalence study of illegal drug injection-related viral infections among Hungarian prisoners points out that ever injecting drugs is the main reason for HCV infection among inmates. The opportunity to reach drug users infected with HCV for treatment underlines the importance of screening programs for blood-borne viruses in prisons.

14:00 - 14:15 *Screening in emergency units*

Prof. Istvan Tornai

Associate Professor, University of Debrecen, Department of Medicine, Division of Gastroenterology, Hungary

References proposed by speaker:

1. Hsieh YH, Rothman RE, Laeyendecker OB, Kelen GD, Avornu A, Patel EU, Kim J, Irvin R, Thomas DL, Quinn TC: **Evaluation of the Centers for Disease Control and Prevention Recommendations for Hepatitis C Virus Testing in an Urban Emergency Department**. Clinical Infectious Diseases 2016;62:1059-65.
2. Lyons MS, Kunnathur VA, Rouster SD, Hart KW, Sperling MI, Fichtenbaum CJ, Sherman KE: **Prevalence of Diagnosed and Undiagnosed Hepatitis C in a Midwestern Urban Emergency Department**. Clinical Infectious Diseases 2016;62:1066-71.

Other related references (Pubmed search):

Udvardy, M. (2018). "[**A new era of transfusion-transmitted pathogens, infections. Renewed need for updating standards for clinicans along with blood banking**]." Orv Hetil 159(37): 1495-1500.

Preparative and clinical transfusiology and transfusion, a majestic part of clinical medicine saved the life of hundred millions. However, bloodborne or transmitted infections became a serious issue in France in the 1980s, when many haemophiliacs were infected by HIV or hepatitis C virus by receiving plazma FactorVIII concentrates. This resulted in a quick and powerful development of screening as well as pathogen-inactivating methods, which reduced pathogen contamination and transmission to minimal levels. Times and pathogens are continously and rather quickly changing, so during the last decade many - not only egzotic - new pathogens and diseases were recognised, and some of them (e.g., Zyka virus, Ebola, hepatitis E virus, etc.) can also be transmitted by blood or blood-component transfusions, and in some instances they escape from standard screening and inactivation procedures. Hereby we try to focus and draw attention to some of these potentially pathogenic new bloodborne microbiological agents, and along with this we try to emphasize the significance of application of updated next generation screening and inactivation procedures. Interestingly a recent British trial, based on large population data, showed some evidence of a slight increase of non-Hodgkin lymphoma incidence in patients with multiple previous transfusions. Probably these facts are even more important in haemophiliacs, who receive prophylactic treatment 3 times weekly either by plasma factor concentrates derived from multiple donors or by gene synthetic factor sources. It is important that haemophiliac patient and family should receive the necessary information, and go for a fully informed consent based on the potential advantages and hazards of a particular treatment modality, the same way as in the chronic treatment of other diseases. Orv Hetil. 2018; 159(37): 1495-1500.

Szucs, M., et al. (2014). "**An archived serum sample as a clue for identifying the primary source of a nosocomial hepatitis C virus outbreak in a haemodialysis unit**." Arch Virol 159(9): 2207-2212.

Due to an unexpected technical error, patients at a dialysis unit who were seronegative for hepatitis C virus (HCV) were temporarily transferred to another dialysis unit next to a ward reserved for HCV-seropositive patients. In the following 7 months, 17 patients were diagnosed as anti-HCV positive. The aim of the study was to reveal the cause of this nosocomial infection. Anti-HCV-positive sera were further tested by molecular methods. Data collection and on-site epidemiologic inspections were carried out. The source of the nosocomial infection proved to be a seropositive patient treated at the unit, who died before the outbreak was recognized. The exact date of the infection was determined.

Dencs, A., et al. (2011). "**Phylogenetic investigation of nosocomial transmission of hepatitis C virus in an oncology ward**." J Med Virol 83(3): 428-436.

Nosocomial hepatitis C virus (HCV) infections have been reported from different health-care settings worldwide. Twenty patients, treated at the same oncology department, with no previous record of hepatitis C infection, tested positive for anti-HCV antibodies between November 2007 and June 2008. Twelve of the newly infected patients were found to be HCV RNA positive. The common origin of the infections was assumed. To investigate the relatedness of the detected viral strains phylogenetic analyses were performed using sequences from the NS5B and E1/E2 genome regions. A patient carrying HCV for years was also involved in the study. She was treated at the same oncology department and was considered a possible infectious source. The previous HCV carrier harbored subtype 1b, while all other patients were infected with subtype 1a. Sequences from the 12 newly infected patients formed two groups. The viral sequences within the groups were very closely related. A greater evolutionary distance was observed between the two groups; however, their relatedness could be demonstrated by sequences from both regions with high statistical support. The results indicated that nosocomial transmission occurred. The phylogenetic analyses suggested that the viruses originated from a common source, possibly a patient carrying highly divergent variants. This presumed infectious source could not be identified in the course of this study. The genotype distribution of Hungarian control sequences included

	in the analysis confirmed this conclusion, since HCV genotype 1a was found to be relatively uncommon. Dencs, A., et al. (2011). "**Phylogenetic analysis of a nosocomial transmission of hepatitis B virus at a paediatric haematology ward**." Acta Microbiol Immunol Hung 58(1): 23-29. A nosocomial Hepatitis B virus (HBV) outbreak at a paediatric onco-haematology unit was investigated using molecular biological methods to determine the origin of the infections. The National Reference Laboratory of Hepatitis Viruses received seven HBsAg positive sera from patients and one from the brother of a patient. A fragment of the preS1/preS2/S genes from all samples was amplified, the PCR products were sequenced and a rooted phylogenetic tree was constructed. All nucleotide sequences from the different patients were very similar and 6 of the 8 sequences were identical, suggesting a common origin of the infections. These sequences were closely related to those amplified from a nosocomial HBV epidemic in another hospital in Hungary. The on-scene investigation revealed several malpractices. The two hospital departments had close connections and some of the patients were treated in both institutions. Present report underlines the importance of developing screening protocols for hepatitis viruses and that of the introduction of regular training programs for health care professionals in the field of hospital hygiene.
14:15 - 14:30	*Screening by family doctors* ***Prof. Ferenc Szalay***
14:30 - 14:45	*HCV screening in homosexual communities* ***Dr. Eszter Újhelyi***
14:45 - 15:00	*Questions*
15:00 - 15:20	*Optimization of screening strategies for viral hepatitis* ***John Ward (Coalition for Global Hepatitis, The Task Force for Global Health)***

HEPATITIS C

Why People Born from 1945–1965 Should Get Tested

KNOW MORE HEPATITIS™

Why should people born from 1945-1965 get tested for hepatitis C?

People born from 1945–1965, sometimes referred to as baby boomers, are 5 times more likely to have hepatitis C than other adults. Hepatitis C can lead to liver damage, cirrhosis, and even liver cancer. Most people with hepatitis C do not know they are infected. Since many people can live with hepatitis C for decades without symptoms or feeling sick, testing is critical so those who are infected can get treated and cured.

While anyone can get hepatitis C, 3 in 4 people with hepatitis C were born from 1945–1965.

What should baby boomers know about hepatitis C?

Hepatitis C is a liver disease that results from infection with the hepatitis C virus. Some people who get infected are able to clear, or get rid of, the hepatitis C virus, but most people who get infected develop a chronic, or long-term, infection. Over time, chronic hepatitis C can cause serious health problems. In fact, hepatitis C is a leading cause of liver cancer and the leading cause of liver transplants. Treatments are now available that can cure hepatitis C.

CDC recommends that everyone born from 1945–1965 get tested for hepatitis C.

Why do people born from 1945-1965 have such high rates of hepatitis C?

The reason that people born from 1945–1965 have high rates of hepatitis C is not completely understood. Most baby boomers are believed to have become infected in the 1960s through the 1980s when transmission of hepatitis C was highest.

Hepatitis C is primarily spread through contact with blood from an infected person. Baby boomers could have gotten infected from medical equipment or procedures before universal precautions and infection control procedures were adopted. Others could have gotten infected from contaminated blood and blood products before widespread screening virtually eliminated the virus from the blood supply by 1992. Sharing needles or equipment used to prepare or inject drugs, even if only once in the past, could spread hepatitis C. Still, many people do not know how or when they were infected.

Continued on next page

CDC
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Getting tested for hepatitis C

The only way to know if you have hepatitis C is to get tested. A blood test, called a hepatitis C antibody test, can tell if a person has ever been infected with the hepatitis C virus. This test looks for antibodies to the hepatitis C virus. Antibodies are chemicals released into the bloodstream when someone gets infected.

When getting tested for hepatitis C, ask when and how test results will be shared. There are two possible antibody test results:

- **Non-reactive, or a negative,** means that a person does not have hepatitis C. However, if a person has been recently exposed to the hepatitis C virus, he or she will need to be tested again.
- **Reactive, or a positive,** means that hepatitis C antibodies were found in the blood and a person has been infected with the hepatitis C virus at some point in time. A reactive antibody test **does not** necessarily mean a person has hepatitis C. Once someone has been infected, they will always have antibodies in their blood. This is true if even if they have cleared the hepatitis C virus.

  A reactive antibody test requires an additional, follow-up test to determine if a person is currently infected with hepatitis C.

For more information

Talk to a health professional, call the health department, or visit www.cdc.gov/knowmorehepatitis.

Publication No. 220401

www.cdc.gov/knowmorehepatitis

Updated 2016

Other related references (Pubmed search):

Manjelievskaia J, Brown D, Shriver CD, Zhu K. **CDC Screening Recommendation for Baby Boomers and Hepatitis C Virus Testing in the US Military Health System**. Public Health Rep. 2017;132(5):579-84.

OBJECTIVES: Chronic hepatitis C virus (HCV) is the most common blood-borne infection in the United States, with an estimated 2.7 to 3.9 million cases as of 2014. In August 2012, the Centers for Disease Control and Prevention (CDC) recommended 1-time HCV testing of all baby boomers. The objectives of this study were to (1) determine the proportion of people screened for HCV in the US Department of Defense Military Health System before and after the CDC screening recommendation for baby boomers and (2) assess whether certain patient or system factors were associated with screening for HCV before and after August 2012. METHODS: We used a dataset containing 5% of beneficiaries randomly selected from the Military Health System Data Repository medical claims database for the period July 2011 through September 2013. RESULTS: Of 108 223 people eligible for HCV screening during the first period (July 2011 through July 2012), 1812 (1.7%) were screened. Of 109 768 people eligible during the second period (September 2012 through September 2013), 2599 (2.4%) were screened. HCV screening receipt was related to benefit type (Prime before August 2012: adjusted odds ratio [aOR] = 2.16; 95% confidence interval [CI], 1.89-2.46; Prime after August 2012: aOR = 1.93; 95% CI, 1.73-2.16) and care source (direct care before August 2012: aOR = 1.80; 95% CI, 1.57-2.07; direct care after August 2012: aOR = 2.45; 95% CI, 2.18-2.75); male sex (aOR = 1.17; 95% CI, 1.06-1.29) and black race (aOR = 1.20; 95% CI, 1.05-1.37) were associated with HCV testing only before August 2012. CONCLUSIONS: Interventions should be implemented to increase awareness and knowledge of the current national HCV testing recommendation among baby boomers to seek out testing and health care providers to perform screening.

Howell J, Pedrana A, Cowie BC, Doyle J, Getahun A, Ward J, . . . Hellard ME. **Aiming for the elimination of viral hepatitis in Australia, New Zealand, and the Pacific Islands and Territories: Where are we now and barriers to meeting World Health Organization targets by 2030**. Journal of gastroenterology and hepatology. 2019;34(1):40-8.

Viral hepatitis affects more than 320 million people globally, leading to significant morbidity and mortality due to liver failure and hepatocellular carcinoma (HCC). More than 248 million people (3.2% globally) are chronically infected with hepatitis B virus (HBV), and an estimated 80 million people (1.1% globally) are chronically infected with hepatitis C virus (HCV). In 2015, more than 700 000 deaths were directly attributable to HBV, and nearly 500 000 deaths were attributable to HCV infection; 2-5% of HBV-infected people develop HCC per annum irrespective of the presence of cirrhosis, whereas 1-5% HCV-infected people with advanced fibrosis develop HCC per annum. The rapidly escalating global mortality related to HBV and HCV related viral hepatitis to be the 7th leading cause of death worldwide in 2013, from 10th leading cause in 1990. Australia, New Zealand, and Pacific Island Countries and Territories fall within the World Health Organization Western Pacific Region, which has a high prevalence of viral hepatitis and related morbidity, particularly HBV. Remarkably, in this region, HBV-related mortality is greater than for tuberculosis, HIV infection, and malaria combined. The region provides a unique contrast in viral hepatitis prevalence, health system resources, and approaches taken to achieve World Health Organization global elimination targets for HBV and HCV infection. This review highlights the latest evidence in viral hepatitis epidemiology and explores the health resources available to combat viral hepatitis, focusing on the major challenges and critical needs to achieve elimination in Australia, New Zealand, and Pacific Island Countries and Territories.

Eckman MH, Ward JW, Sherman KE. **Cost Effectiveness of Universal Screening for Hepatitis C Virus Infection in the Era of Direct-Acting, Pangenotypic Treatment Regimens**. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association. 2019;17(5):930-9.e9.

BACKGROUND & AIMS: Most persons infected with hepatitis C virus (HCV) in the United States were born from 1945 through 1965; testing is recommended for this cohort. However, HCV incidence is increasing among younger persons in many parts of the country and treatment is recommended for all adults with HCV infection. We aimed to estimate the cost effectiveness of universal 1-time screening for HCV infection in all adults living in the United States and to determine the prevalence of HCV antibody above which HCV testing is cost effective. METHODS: We developed a Markov state transition model to estimate the effects of universal 1-time screening of adults 18 years or older in the United States, compared with the current guideline-based strategy of screening adults born from 1945 through 1965. We compared potential outcomes of 1-time universal screening of adults or birth cohort screening followed by antiviral treatment of those with HCV infection vs no screening. We measured effectiveness with quality-adjusted life-years (QALY), and costs with 2017 US dollars. RESULTS: Based on our model, universal 1-time screening of US residents with a general population prevalence of HCV antibody greater than 0.07% cost less than $50,000/QALY compared with a strategy of no screening. Compared with 1-time birth cohort screening, universal 1-time screening and treatment cost $11,378/QALY gained. Universal screening was cost effective compared with birth cohort screening when the prevalence of HCV antibody positivity was greater than 0.07% among adults not in the cohort born from 1945 through 1965. CONCLUSIONS: Using a Markov state transition model, we found a strategy of universal 1-time screening for chronic HCV infection to be cost effective compared with either no screening or birth cohort-based screening alone.

Nasrullah M, Sergeenko D, Gvinjilia L, Gamkrelidze A, Tsertsvadze T, Butsashvili M, . . . Averhoff F. **The Role of Screening and Treatment in National Progress Toward Hepatitis C Elimination - Georgia, 2015-2016**. MMWR Morbidity and mortality weekly report. 2017;66(29):773-6.

Georgia, a country in the Caucasus region of Eurasia, has a high prevalence of hepatitis C virus (HCV) infection. In April 2015, with technical assistance from CDC, Georgia embarked on the world's first program to eliminate hepatitis C, defined as a 90% reduction in HCV prevalence by 2020 (1,2). The country committed to identifying infected persons and linking them to care and curative antiviral therapy, which was provided free of charge through a partnership with Gilead Sciences (1,2). From April 2015 through December 2016, a total of 27,595 persons initiated treatment for HCV infection, among whom 19,778 (71.7%) completed treatment. Among 6,366 persons tested for HCV RNA >/=12 weeks after completing treatment, 5,356 (84.1%) had no detectable virus in their blood, indicative of a sustained virologic response (SVR) and cure of HCV infection. The number of persons initiating treatment peaked in September 2016 at 4,595 and declined during October-December. Broader implementation of interventions that increase access to HCV testing, care, and treatment for persons living with HCV are needed for Georgia to reach national targets for the elimination of HCV.

Ward JW. **Strategies for Expanding Access to HBV and HCV Testing and Care in the United States: The CDC Hepatitis Testing and Linkage to Care Initiative, 2012-2014**. Public Health Rep. 2016;131 Suppl 2:1-4.

Reilley B, Leston J, Hariri S, Neel L, Rudd M, Galope M, . . . Vellozzi C. **Birth Cohort Testing for Hepatitis C Virus - Indian Health Service 2012-2015**. MMWR Morbidity and mortality weekly report. 2016;65(18):467-9.

Hepatitis C virus (HCV) infection is a substantial and largely unrecognized public health problem. An estimated 3.5 million persons in the United States are currently living with HCV infection, at least half of whom are unaware of their infection (1-3). Persons born during 1945-1965 (the "baby boomer" birth cohort) have a sixfold higher prevalence (2.6%) than adults of other ages, and represent 81% of all persons chronically infected with HCV (4). Therefore, in addition to recommending testing for all persons at risk for HCV infection, CDC and the U.S. Preventive Services Task Force (USPSTF) recommend one-time HCV testing for the birth cohort (5,6). Compared with the national average, American Indian/Alaska Native (AI/AN) persons

have approximately twofold the rate of acute HCV incidence and HCV associated mortality (2). In June 2012, the Indian Health Service (IHS) implemented HCV testing in the 1945-1965 birth cohort and created a nationally standardized performance measure to monitor implementation of the recommendation. As of June 2015, the proportion of the birth cohort screened for HCV increased from a baseline of 7.9% (14,402/182,503) to 32.5% (68,514/211,014) among the AI/AN population served by IHS nationwide; provider training and the use of clinical decision tools were associated with increases in HCV testing. With this fourfold increase in testing in just 3 years, IHS needs to prepare for the challenges associated with increased identification of persons living with HCV infection.

Mera J, Vellozzi C, Hariri S, Carabin H, Drevets DA, Miller A, . . . Ward JW. **Identification and Clinical Management of Persons with Chronic Hepatitis C Virus Infection - Cherokee Nation, 2012-2015**. MMWR Morbidity and mortality weekly report. 2016;65(18):461-6.

An estimated 3.5 million persons in the United States are living with hepatitis C virus (HCV) infection, resulting in approximately 20,000 deaths each year, primarily from cirrhosis or hepatocellular carcinoma (1,2). American Indian/Alaska Native (AI/AN) populations have the highest incidence of acute HCV infection among all U.S. racial/ethnic groups and are at greater risk for HCV-related mortality compared with the general population (3). In 2013, new antiviral drugs became available that make possible 8-12 week treatment regimens with fewer adverse events and are able to achieve sustained virologic response (SVR) in >90% of treated patients (4), equivalent to a cure of HCV infection. Also of note, HCV testing recommendations were expanded in 2012 by CDC and in 2013 by the U.S. Preventive Services Task Force to include one-time testing of persons born during 1945-1965 (the "baby boomer" cohort) in addition to anyone at increased risk for HCV infection (5,6). Given the availability of new HCV drugs, expanded testing recommendations, and high incidence of HCV infection in AI/AN populations, in October 2012, Cherokee Nation Health Services (CNHS) implemented a tribal HCV testing policy.* As part of the policy, CNHS added a reminder in the electronic health record (EHR) for clinical decision support and provided HCV education to primary care clinicians. From October 2012 to July 2015, among 92,012 persons with at least one CNHS clinic encounter, the cumulative number who received HCV screening for the first time increased from 3,337 (3.6%) to 16,772 (18.2%). The largest percentage of HCV screening was among persons born during 1945-1965. Of 715 persons who tested positive for HCV antibodies, 488 (68.3%) were tested for HCV RNA; among those 488 persons, 388 (79.5%) were RNA positive and were thus confirmed to have chronic HCV infection. Treatment was initiated for 223 (57.5%) of the 388 with chronic infection; 201 (90.1%) completed treatment, of whom 180 (89.6%) achieved SVR. CNHS has successfully increased HCV testing and treatment and is now collaborating with CDC and other external partners to develop an HCV elimination program for the Cherokee Nation that might serve as a model for similar settings.

Koneru A, Nelson N, Hariri S, Canary L, Sanders KJ, Maxwell JF, . . . Vellozzi C. **Increased Hepatitis C Virus (HCV) Detection in Women of Childbearing Age and Potential Risk for Vertical Transmission - United States and Kentucky, 2011-2014**. MMWR Morbidity and mortality weekly report. 2016;65(28):705-10.

Hepatitis C virus (HCV) infection is a leading cause of liver-related morbidity and mortality (1). Transmission of HCV is primarily via parenteral blood exposure, and HCV can be transmitted vertically from mother to child. Vertical transmission occurs in 5.8% (95% confidence interval = 4.2%-7.8%) of infants born to women who are infected only with HCV and in up to twice as many infants born to women who are also infected with human immunodeficiency virus (HIV) (2) or who have high HCV viral loads (3,4); there is currently no recommended intervention to prevent transmission of infection from mother to child (3). Increased reported incidence of HCV infection among persons aged </=30 years (5,6) with similar increases among women and men in this age group (6), raises concern about increases in the number of pregnant women with HCV infection, and in the number of infants who could be exposed to HCV at birth. Data from one large commercial laboratory and birth certificate data were used to investigate trends in HCV detection among women of childbearing age,* HCV testing among

children aged </=2 years, and the proportions of infants born to HCV-infected women nationally and in Kentucky, the state with the highest incidence of acute HCV infection during 2011-2014 (6). During 2011-2014, commercial laboratory data indicated that national rates of HCV detection (antibody or RNA positivity(dagger)) among women of childbearing age increased 22%, and HCV testing (antibody or RNA) among children aged </=2 years increased 14%; birth certificate data indicated that the proportion of infants born to HCV-infected mothers increased 68%, from 0.19% to 0.32%. During the same time in Kentucky, the HCV detection rate among women of childbearing age increased >200%, HCV testing among children aged </=2 years increased 151%, and the proportion of infants born to HCV-infected women increased 124%, from 0.71% to 1.59%. Increases in the rate of HCV detection among women of childbearing age suggest a potential risk for vertical transmission of HCV. These findings highlight the importance of following current CDC recommendations to identify, counsel, and test persons at risk for HCV infection (1,7), including pregnant women, as well as consider developing public health policies for routine HCV testing of pregnant women, and expanding current policies for testing and monitoring children born to HCV-infected women. Expansion of HCV reporting and surveillance requirements will enhance case identification and prevention strategies.

Mixson-Hayden T, Dawson GJ, Teshale E, Le T, Cheng K, Drobeniuc J, . . . Kamili S. **Performance of ARCHITECT HCV core antigen test with specimens from US plasma donors and injecting drug users**. Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology. 2015;66:15-8.

BACKGROUND: Hepatitis C virus (HCV) core antigen is a serological marker of current HCV infection. OBJECTIVES: The aim of this study was mainly to evaluate the performance characteristics of the ARCHITECT HCV core antigen assay with specimens from US plasma donors and injecting drug users. STUDY DESIGN: A total of 551 serum and plasma samples with known anti-HCV and HCV RNA status were tested for HCV core antigen using the Abbott ARCHITECT HCV core antigen test. RESULTS: HCV core antigen was detectable in 100% of US plasma donor samples collected during the pre-seroconversion phase of infection (anti-HCV negative/HCV RNA positive). Overall sensitivity of the HCV core antigen assay was 88.9-94.3% in samples collected after seroconversion. The correlation between HCV core antigen and HCV RNA titers was 0.959. CONCLUSIONS: HCV core antigen testing may be reliably used to identify current HCV infection.

15:20 - 15:30 Question and discussion

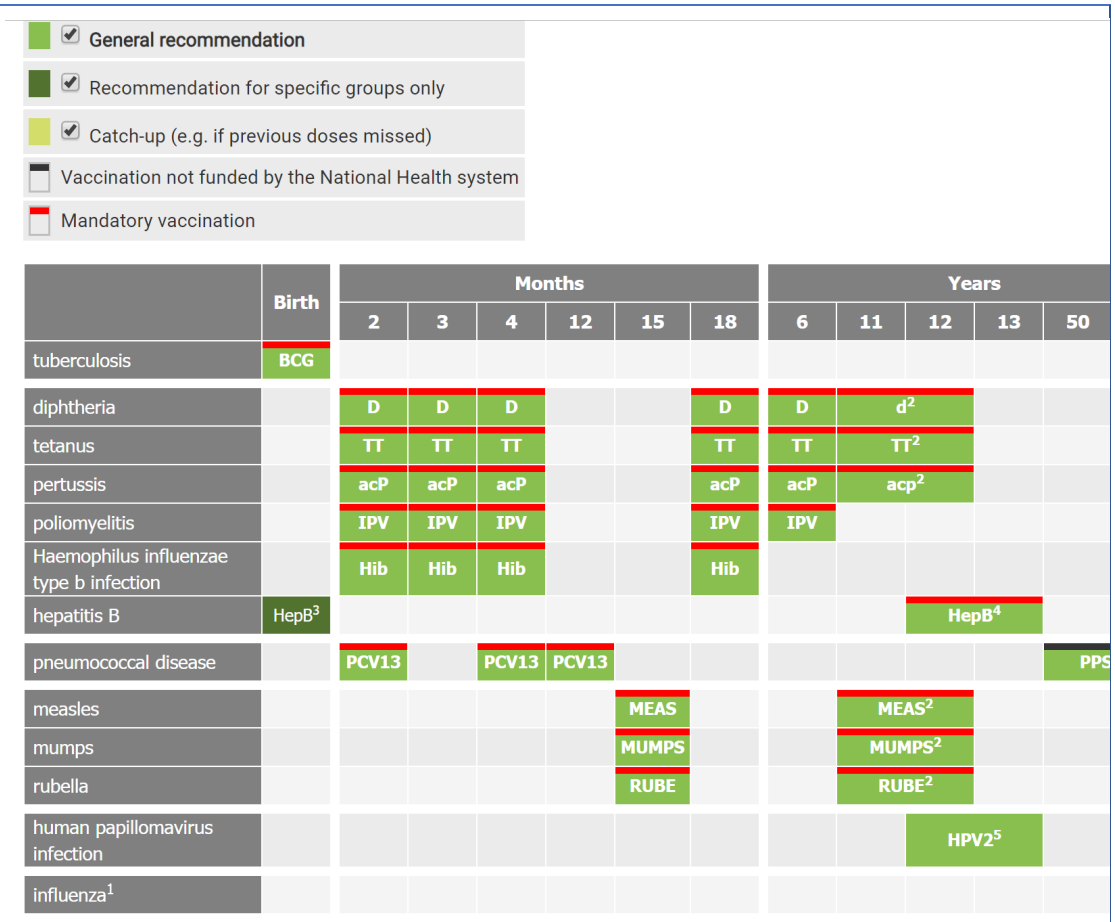
15:30 - 15:50 **Coffee Break**

Session 4: Prevention of viral hepatitis

Chairs: István Vályi-Nagy - Vana Papaevangelou

15:50 - 16:10 Vaccination programs in Hungary

Dr. Zsuzsanna Molnár



Footnotes:

1. Flue vaccination free of charge for vulnerable populations including people >60 and pregnant women
2. School-based vaccination in 6th grade
3. Babies born to a mother infected with hepatitis B or unknown immune status will be offered a first vaccine dose within 12 hours after birth and simultaneously immunoglobulin in case of HbsAg positive mother. Following vaccine doses are given 1 month later and the third dose, 6 months after first dose.
4. School-based vaccination in 7th grade
5. Girls-only vaccination offered in schools (seventh grade). Recommended only, but free of charge

Source: https://vaccine-schedule.ecdc.europa.eu/

16:10 - 16:30

Hepatitis vaccination worldwide: Lessons learnt and the way forward

Pierre Van Damme

Vaccine and Infectious Disease Institute, University, Antwerp, Belgium

Other related references (Pubmed search):

Chapter in Plotkin's Vaccines: Hepatitis B Vaccines,· January 2018 *with* 22 Reads,
DOI: 10.1016/B978-0-323-35761-6.00025-0. In book: Plotkin's Vaccines, pp.342-374.e17

Van Damme P, Dionne M, Leroux-Roels G, Van Der Meeren O, Di Paolo E, Salaun B, . . . Folschweiller N. **Persistence of HBsAg-specific antibodies and immune memory two to three decades after hepatitis B vaccination in adults**. Journal of viral hepatitis. 2019;26(9):1066-75.

The duration of protection after hepatitis B vaccination is not exactly known. This phase IV study evaluated antibody persistence and immune memory 20-30 years after adult immunization with recombinant hepatitis B vaccine (HBsAg vaccine, Engerix-B) in routine clinical practice. Men and women 40-60 years old, with documented evidence of vaccination with three or four HBsAg

vaccine doses 20-30 years earlier and without subsequent booster, were enrolled and received HBsAg vaccine as challenge dose. HBsAg-specific antibodies (anti-HBs) and frequencies of HBsAg-specific circulating memory B cells and CD4(+) T cells expressing combinations of activation markers (CD40L, IL2, IFNgamma, TNFalpha) were measured prechallenge, 7 and 30 days postchallenge. Of 101 participants in the according-to-protocol cohort for immunogenicity, 90.1% had anti-HBs concentrations >/= 10 mIU/mL prechallenge administration; 84.2% and 100% mounted an anamnestic response 7 and 30 days postchallenge, respectively. HBsAg-specific memory B and CD4(+) T cells expressing at least two activation markers were low prechallenge and increased markedly postchallenge. These results suggest sustained immune memory and long-term protection 20-30 years after a complete primary HBsAg vaccination course during adulthood, in line with current recommendations that a booster is not needed in fully vaccinated immunocompetent adults.

Whitford K, Liu B, Micallef J, Yin JK, Macartney K, Van Damme P, Kaldor JM. **Long-term impact of infant immunization on hepatitis B prevalence: a systematic review and meta-analysis**. Bulletin of the World Health Organization. 2018;96(7):484-97.

Objective: To conduct a systematic review and meta-analysis of the long-term impact of infant vaccination on the prevalence of hepatitis B virus (HBV) infection at the population level. Methods: We searched online databases for articles reporting comparisons between population cohorts aged >/= 15 years who were exposed or unexposed to infant HBV immunization programmes. We categorized programmes as universal or targeted to infants whose mothers were positive for hepatitis B surface antigen (HBsAg). We included studies reporting prevalence of hepatitis B core antibody (HBcAb), HBsAg, or both. We evaluated the quality of the study methods and estimated the relative reduction in the prevalence of infection. Findings: Of 26 studies that met the inclusion criteria, most were from China (20 studies). The prevalence of HBV infection in unvaccinated and universally vaccinated cohorts ranged from 0.6% (116 of 20 305 people) to 16.3% (60/367) and from 0.3% (1/300) to 8.5% (73/857), respectively. Comparing cohorts with universal vaccination to those without vaccination, relative prevalences were 0.24 (95% confidence interval, CI: 0.16-0.35) for HBsAg and 0.23 (95% CI: 0.17-0.32) for HBcAb. For populations with targeted vaccination, relative prevalences were 0.32 (95% CI: 0.24-0.43) and 0.33 (95% CI: 0.23-0.45), respectively. Conclusion: The residual burden of infection in cohorts offered vaccination suggests that longer-term evaluations of vaccination coverage, timeliness and other aspects of programme quality are needed. As HBV-vaccinated infant cohorts reach adulthood, ongoing analysis of prevalence in adolescents and young adults will ensure that elimination efforts are on track.

Van Damme P, Leroux-Roels G, Suryakiran P, Folschweiller N, Van Der Meeren O. **Persistence of antibodies 20 y after vaccination with a combined hepatitis A and B vaccine**. Human vaccines & immunotherapeutics. 2017;13(5):972-80.

Vaccination is the most effective and well-tolerated method of conferring long-term protection against hepatitis A and B viruses (HAV; HBV). Long-term studies are required to characterize the duration of protection and need for boosters. Following primary immunization of 150 and 157 healthy adults with 3-doses of combined hepatitis A/hepatitis B vaccine (HAB; Twinrix, GSK Vaccines, Belgium) at 0-1-6 months in 2 separate studies, we measured vaccine-induced antibody persistence against HAV and HBV annually for 20 y (Study A: NCT01000324; Study B: NCT01037114). Subjects with circulating anti-HAV antibodies < 15 mIU/mL or with anti-hepatitis B surface antigen < 10 mIU/mL were offered an additional monovalent hepatitis A and/or B vaccine dose (Havrix/Engerix-B, GSK Vaccines, Belgium). Applying the immunogenicity results from these studies, mathematical modeling predicted long-term persistence. After 20 y, 18 and 25 subjects in studies A and B, respectively, comprised the long-term according-to-protocol cohort for immunogenicity; 100% and 96.0% retained anti-HAV antibodies >/= 15 mIU/mL, respectively; 94.4% and 92.0% had anti-HBs antibodies >/= 10 mIU/mL, respectively. Between Years 16-20, 4 subjects who received a challenge dose of monovalent hepatitis A vaccine (N = 2) or hepatitis B vaccine (N = 2), all mounted a strong anamnestic response suggestive of immune memory despite low antibody levels. Mathematical modeling predicts that 40 y after

vaccination >/= 97% vaccinees will maintain anti-HAV >/= 15 mIU/mL and >/= 50% vaccinees will retain anti-HBs >/= 10 mIU/mL. Immunogenicity data confirm that primary immunization with 3-doses of HAB induces persisting anti-HAV and anti-HBs specific antibodies in most adults for up to 20 y; mathematical modeling predicts even longer-term protection.

Van Damme P. **Long-term Protection After Hepatitis B Vaccine**. The Journal of infectious diseases. 2016;214(1):1-3.

Kane MA, Roudot-Thoraval F, Guerin N, Papaevangelou V, Van Damme P. **Editorial on "What is a potentially damaging vaccination delay in children younger than 2 years?"**. Human vaccines & immunotherapeutics. 2016;12(8):2053-6.

Control of hepatitis B through routine infant immunization in more than 95% of countries has reduced the prevalence of chronic hepatitis carriers to less than 1%-2% in immunized cohorts of children even in high endemicity countries. In that context the authors of this editorial found the results of a paper by Gras et al in this issue concerning. They performed a Delphi survey of 37 French immunization experts and the results concluded that delayed hepatitis B immunization would cause "potential damage" only after 11 years. Large cohorts of French children and adolescents remain susceptible to hepatitis B infection. Given the high rates of immigration to France from areas of higher endemicity, the higher birth rate and degree of integration of these groups into the health system, plus the lower age of sexual debut and the use of injectable drugs in the general population, we cannot agree that a delay of 11 years is acceptable. Rates of adolescent immunization are quite low so relying on protection at this age will yield little in terms of population protection. Loss of confidence in Hepatitis B vaccine following disproved allegations that the vaccine caused Multiple Sclerosis persists in France, and we believe the results of this paper sends a damaging message to health workers and parents in France and beyond.

16:30 – 16:40 Question and discussion

Session 5: Control of viral hepatitis

16:40 - 17:00 **Hepatitis case finding – Screening programmes and cascade of care in Hungary**

Hepatitis research in Hungary, from identification to treatment

Prof. Zsuzsa Schaff

References proposed by speaker:

1. **Transmission of non-A, non-B hepatitis from man to chimpanzee.** Tabor E, Gerety RJ, Drucker JA, Seeff LB, Hoofnagle JH, Jackson DR, April M, Barker LF, Pineda-Tamondong G. Lancet 1(8062): 463-466, 1978
2. **Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome.** Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Science 244: 359-262, 1989
3. **Additional evidence for more than one agent of human non-A non-B hepatitis. Transmission and passage studies in chimpanzees.** Tabor E, Snoy P, Jackson DR, Schaff Z, Blatt PM, Gerety RJ. Transfusion 24: 224-230, 1984
4. Bradley DW et al: Non-A, **Non-B hepatitis in experimentally infected chimpanzees: Com morphology of virus-induced ultrastructural changes. In:** Hepatitis Viruses and Hepatoc Carcinoma: Approaches through molecular biology and ecology. Nishioka K, Blumberg BS, Koike K (eds). Academic Press Inc., New York, London, pp. 225-251, 1985

5. **Hepatitis C virus core protein shows a cytoplasmic localization and associates to cellular lipid storage droplets.** G Barba, F Harper, T Harada, M Kohara, S Goulinet, Y Matsuura, G Eder, Zs Schaff, M J Chapman, T Miyamura, and C Bréchot. Proc. Natl. Acad. Sci. USA 94: 1200-1205, 1997
6. **Hepatic inclusions during interferon therapy in chronic viral hepatitis.** Schaff Z, Hoofnagle JH, Grimley PM. Hepatology 6: 966-970, 1986

17:00 - 17:20

EASL Hepatitis treatment strategies in the framework of elimination of viral hepatitis as a public health threat

Mojca Maticic

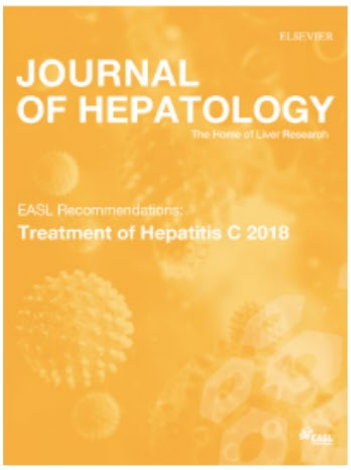
Head Department Viral Hepatitis, University medical Centre Ljubljana, Slovenia

References proposed by speaker:

European Association of the Strudy of the Liver

https://easl.eu/

1. **EASL CPG HCV**. J Hepatol 2018; 69: 461–511.

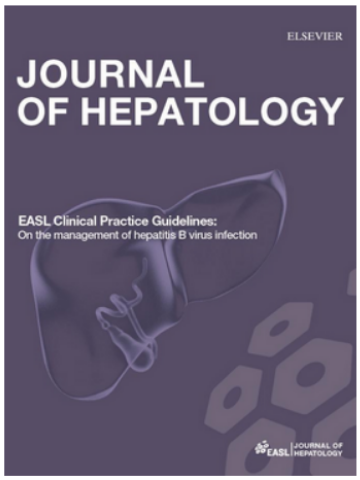


EASL RECOMMENDATIONS ON TREATMENT OF HEPATITIS C 2018

Hepatitis C virus (HCV) infection is a major cause of chronic liver disease, with approximately 71 million chronically infected individuals worldwide. Clinical care for patients with HCV-related liver disease has advanced considerably thanks to an enhanced understanding of the pathophysiology of the dis-ease, and because of developments in diagnostic procedures and improvements in therapy and prevention. These European Association for the Study of the Liver Recommendations on Treatment of Hepatitis C describe the optimal management of patients with acute and chronic HCV infections in 2018 and onwards.

http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/easl-recommendations-on-treatment-of-hepatitis-c-2018

2. **EASL CPG HBV**. J Hepatol 2017; 62: 370-98.



EASL 2017 CLINICAL PRACTICE GUIDELINES ON THE MANAGEMENT OF HEPATITIS B VIRUS INFECTION

Hepatitis B virus (HBV) infection remains a global public health problem with changing epidemiology due to several factors including vaccination policies and migration. This Clinical Practice Guideline presents updated recommendations for the optimal management of HBV infection. Chronic HBV infection can be classified into five phases: (I) HBeAg-positive chronic infection, (II) HBeAg-positive chronic hepatitis, (III) HBeAg-negative chronic infection, (IV) HBeAg-negative chronic hepatitis and (V) HBsAg-negative phase.

3. **EASL CPG HEV.** J Hepatol 2018; 68: 1256-
4. **WHO. Global Heaplt Sector on Viral Hepatizis.** Available at: http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_32-en.pdf?ua=1

Other related references (Pubmed search):

Hunyady, B., et al. (2016). "[**Efficacy and safety of boceprevir based triple therapy in Hungarian patients with hepatitis C genotype 1 infection, advanced stage fibrosis and prior treatment failure**]." Orv Hetil **157**(34): 1366-1374.

INTRODUCTION: During 2011 and 2013, 155 Hungarian hepatitis C genotype 1 infected patients, mostly with advanced liver fibrosis, who did not respond to prior peginterferon + ribavirin dual therapy, started boceprevir based triple therapy in an early access program. AIM AND METHOD: Efficacy and safety of the therapy was retrospectively assessed based on sustained virologic responses, as well as on frequency and type of serious adverse events and of those leading to therapy discontinuation. RESULTS: In an intent-to-treat analysis 39.4% patients (61/155) reached sustained virologic response. Amongst pervious relapsers, partial responders and null-responders 59.5%, 41.4 % and 22.9% ($p<0.05$ compared to the other two categories) reached sustained virologic response, respectively, while amongst non-cirrhotics and cirrhotics 52.5% and 31.3% ($p<0.05$ compared to the non-cirrhotics) achieved sutained virologic response, respectively. Six out of the 33 most difficult to cure patients (previous null responder and cirrhotic) have reached sustained virologic response (18.2%). Frequency of early discontinuations due to insufficient virologic response was 31.1%, while due to adverse event 10.3%. Reported frequency of serious adverse event was 9.8%. These events represented anemia, diarrhoea, depression, agranulocytosis, elevated aminotransferases, generalized dermatitis and severe gingivitis with loss of teeth, prolonged QT interval on ECG, generalized oedema and severe dyspnoea, uroinfection, exacerbation of Crohn's disease, Campylobacter pylori infection and unacceptable weakness and fatigue. Eight patients received transfusion, 4 patients erythropoietin and 1 granulocyte colony stimulating factor during therapy. No death has been reported. CONCLUSIONS: With boceprevir based triple therapy, one of the bests available in 2011-2013 in Hungary, a relevant proportion of hepatitis C infected patients with advanced liver fibrosis achieved sustained viral response. In this cohort, side-effects resembled those reported in registration studies, and resulted in therapy discontinuation with consequent treatment failure in a relevant number of patients. Efficacy and tolerability of boceprevir-based triple therapy are suboptimal, particularly in the most difficult to cure patient population. Orv. Hetil., 2016, 157(34), 1366-1374.

Makara, M., et al. (2013). "[**Organizational characteristics of treatment for chronic hepatitis in Hungary: Hepatitis Registry and Priority Index**]." Orv Hetil **154**(29): 1151-1155.

Hepatitis Registry was developed by the Hepatology Section of the Hungarian Gastroenterology Society with the contribution of the Foundation for Liver Patients. The main task was to register all interferon based treatments of chronic hepatitis C and B and to facilitate the preauthorization process. The registry helped to clarify the number and characteristics of hepatitis C patients waiting for triple therapy; 3000 previously failed patients are still eligible for protease inhibitor therapy, 40% of them already developed cirrhosis stage and 40% are null responders to the previous therapy. As a file is created for treatment authorization, the system counts automatically the Priority Index according to the calculation set in the guideline. Priority Index reflects the urgency of treatment. The most prominent parameter of the Index is the degree of fibrosis, but it also takes into account the progression rate, prognostic factors, and special situations.

Nemes, B., et al. (2012). "**Predictive factors of sustained virological response for recurrent hepatitis C virus after liver transplantation: the hungarian experience**." Transplant Proc **44**(7): 2162-2163.

Recurrence of hepatitis C virus (HCV) after liver transplantation (OLT) occurs consistently. Early initiation of combined antiviral treatment (AVT) has become a standard treatment seeking to achieve sustained virological response (SVR). We evaluated the files of 108 HCV-positive patients between 2003 and 2010. Seventy-two (72) experienced recurrent HCV within 12 months, 31 of whom completed the AVT (43%) but 9 (29%) exhibited SVR. Factors with impacting SVR were male recipient, no fatty changes in the donor liver, short warm ischemia time, cyclosporine-based immunosuppression, neither infective, septic or bleeding complication nor acute rejection episode and a rapid viral response to AVT. De novo diabetes, and unsuccessful AVT prior to OLT were strongly associated with a a failed SVR. The 1- and 3-year cumulative patient survival rates trended to be better in cases of SVR compared with nonresponders (100% and 100% versus 94% and 89%; P = .07).

Werling, K., et al. (2010). "**Effect of liver steatosis on therapeutic response in chronic hepatitis C virus genotype 1 infected patients in hungary**." Pathol Oncol Res **16**(2): 149-157.

Hepatic steatosis seems a frequent histological alteration seen in chronic hepatitis C virus infected patients. There is still a lot to learn about the exact mechanism of effect of liver steatosis and its influence on the progression of liver diseases. Our study involved 96 chronic hepatitis C genotype 1 infected Hungarian patients who received pegylated interferon and ribavirin treatment for the first time. Degree of steatosis, viral and host factors influencing its development and its effect on the efficiency of antiviral treatment were determined. In 61 (64%) of patients the liver tissue showed varying degree of steatosis, which did not show relationship with level of alcohol consumption (p = 0.5792), diabetes mellitus (p = 0.5925) or body mass index (p = 0.9685) in type 1 chronic hepatitis C patients. Degree of steatosis and virus titer showed strong relationship (OR = 2.1). Significant relationship was also found between degree of hepatic steatosis and stage (p = 0.0119), as well as between therapeutic response to combined pegylated interferon + ribavirin treatment and steatosis (p = 0.0012). Our results demonstrated that steatosis has clinical significance in hepatitis C virus genotype 1 infected patients.

17:20 - 17:40	Question and discussion
19:30	**DINNER**

Thursday 31 October 2019

Session 6: National hepatitis plan and the different stakeholders

Chairs: Béla Hunyady – David Goldberg

08:30 - 08:50 **The Hungarian Hepatitis Committee. National program for chronic viral hepatitis elimination**

Prof. Béla Hunyady

Head of Gastroenterology Department, full professor; Somogy County Kaposi Mór Teching Hospital, Kaposvár and University of Pécs, Medical School, Pécs, Hungary

References proposed by speaker:

1. Barna TK, Ozsvár Zs, Szendrényi V, Gál Gy. **Hepatitis C-vírus ellenanyag előfordulása véradók szérumában**. Orv Hetil. 1996; 137(10):507–511.
2. Országos **Epidemiológiai Központ. Az intravénás kábítószer-használattal összefüggő hazai HIV-, illetve HCV-prevalencia 2014-ben**. EPINFO 2015; 22(18): 189–194.
3. Gervain J. Magyarországi C-**vírus-hepatitises betegek vírustípus- és szubtípusmegoszlásának elemzése**. Orv Hetil 2018; 159(Suppl 2): 2–8.
4. Hunyady B, Gerlei Z, Gervain J, et al. **Hepatitis C-vírus fertőzés szűrése, diagnosztikája, antivirális terápiája, kezelés utáni gondozása. Magyar konszenzusajánlás**. Érvényes: 2018. március 26-tól. Central European Journal of Gastroenterology and Hepatology 2018; 4(2): 53-68.
5. Makara M, Horváth G, Szalay F, et al. **A krónikus vírushepatitisek hazai ellátási rendszerének sajátosságai: Hepatitis Regiszter és a Prioritási** Index. Orv Hetil. 2013; 154(29): 1151–1155.
6. Hunyady B, Gervain J, Gógl Á, et al. **Nemzeti program a hepatitis C vírus fertőzés magyarországi felszámolásának előkészítésére**. MedicalOnline 2015. november 06. http://www.medicalonline.hu/cikk/nemzeti_program_a_hepatitis_c_virus_fertozes_magyarorszagi_felszamolasanak_elokeszitesere.
7. Horváth G, Gerlei Zs, Gervain J, et al**. A hepatitis B- és D-vírus-fertőzés diagnosztikája, antivirális kezelése. Magyar konszenzusajánlás**. Érvényes: 2017. szeptember 22-től. Orv Hetil. 2018; 159(Suppl 1): 24–37.

Other related references (Pubmed search):

Hunyady, B., et al. (2018). "[**Screening, diagnosis, treatment, and follow up of hepatitis C virus related liver disease. National consensus guideline in Hungary from 22 September 2017**]." Orv Hetil **159**(Suppl 1): 3-23.

The treatment of hepatitis C is based on a national consensus guideline updated six-monthly according to local availability and affordability of approved therapies through a transparent allocation system in Hungary. This updated guideline incorporates some special new aspects, including recommendations for screening, diagnostics, use and allocation of novel direct acting antiviral agents. The indication of therapy in patients with no contraindication is based on the demonstration of viral replication with consequent inflammation and/or fibrosis in the liver. Non-invasive methods (elastographies and biochemical methods) are preferred for liver fibrosis staging. The budget allocated for these patients is limited. Interferon-based or interferon-free therapies are available for the treatment. Due to their limited success rate as well as to their (sometimes severe) side-effects, the mandatory use of interferon-based therapies as first line treatment can not be accepted from the professional point of view. However, they can be used as optional therapy in treatment-naive patients with mild disease. As of interferon-free therapies, priority is given to those with urgent need based on a pre-defined scoring system reflecting mainly the stage of the liver disease, but considering also additional factors, i.e., hepatic decompensation, other complications, activity and progression

of liver disease, risk of transmission and other special issues. Approved treatments are restricted to the most cost-effective combinations based on the cost per sustained virological response value in different patient categories with consensus amongst treating physicians, the National Health Insurance Fund of Hungary and patients' organizations. Interferon-free treatments and shorter therapy durations are preferred. Orv Hetil. 2018; 159(Suppl 1): 3-23.

Horvath, G., et al. (2018). **"[Diagnosis and treatment of chronic hepatitis B and D. National consensus guideline in Hungary from 22 September 2017]."** Orv Hetil **159**(Suppl 1): 24-37.

Diagnosis and treatment of hepatitis B virus (HBV) and hepatitis D virus infection mean for the patient to be able to maintain working capacity, to increase quality of life, to prevent cancer, and to prolong life expectancy, while the society benefits from eliminating the chances of further transmission of the viruses, and decreasing the overall costs of serious complications. The guideline delineates the treatment algorithms from 22 September 2017 set by a consensus meeting of physicians involved in the treatment of these diseases. The prevalence of HBV infection in the Hungarian general population is 0,5-0,7%. The indications of treatment are based upon viral examinations (including viral nucleic acid determination), determinations of disease activity and stage (including biochemical, pathologic, and/or non-invasive methods), and excluding contraindications. To avoid unnecessary side effects and for a cost-effective approach, the guideline stresses the importance of quick and detailed virologic evaluations, the applicability of transient elastography as an acceptable alternative of liver biopsy in this regard as well as the relevance of appropriate consistent follow-up schedule for viral response during therapy. The first choice of therapy in chronic HBV infection can be pegylated interferon for 48 weeks or continuous entecavir or tenofovir therapy. The latter two must be continued for at least 12 months after hepatitis B surface antigen seroconversion. Lamivudine is no longer the first choice; patients currently taking lamivudine must switch if the response is inadequate. Appropriate treatment of patients taking immunosuppressive medications is highly recommended. Pegylated interferon based therapy is recommended for the treatment of concomitant hepatitis D infection. Orv Hetil. 2018; 159(Suppl 1): 24-37.

Hunyady, B., et al. (2017). **"[Screening, diagnosis, treatment, and follow up of hepatitis C virus related liver disease. National consensus guideline in Hungary from 15 October 2016]."** Orv Hetil **158**(Suppl 1): 3-22.

Treatment of hepatitis C is based on a national consensus guideline updated six-monthly according to local availability and affordability of approved therapies through a transparent allocation system in Hungary. This updated guideline incorporates some special new aspects, including recommendations for screening, diagnostics, use and allocation of novel direct acting antiviral agents. Indication of therapy in patients with no contraindication is based on demonstration of viral replication with consequent inflammation and/or fibrosis in the liver. Non-invasive methods (elastographies and biochemical methods) are preferred for liver fibrosis staging. The budget allocated for these patients is limited. Therefore, expensive novel direct acting antiviral combinations as first line treatment are reimbursed only, if the freely available, but less effective and more toxic pegylated interferon plus ribavirin dual therapy deemed to prone high chance of adverse events and/or low chance of cure. Priority is given to those with urgent need based on a pre-defined scoring system reflecting mainly the stage of the liver disease, but considering also additional factors, i.e., hepatic decompensation, other complications, activity and progression of liver disease, risk of transmission and other special issues. Approved treatments are restricted to the most cost-effective combinations based on the cost per sustained virological response value in different patient categories with consensus amongst treating physicians, the National Health Insurance Fund and patient's organizations. Interferon-free treatments and shorter therapy durations are preferred. Orv. Hetil., 2017, 158(Suppl. 1), 3-22.

Horvath, G., et al. (2017). "[**Diagnosis and treatment of chronic hepatitis B and D. National consensus guideline in Hungary from 15 October 2016**]." Orv Hetil **158**(Suppl 1): 23-35.

Diagnosis and treatment of HBV/HDV infection means for the patient to be able to maintain working capacity, to increase quality of life, to prevent cancer, and to prolong life expectancy, while society benefits from eliminating the chances of further transmission of the viruses, and decreasing the overall costs of serious complications. The guideline delineates the treatment algorithms for 2017 set by a consensus meeting of physicians involved in the treatment of these diseases. The prevalence of HBV infection in the Hungarian general population is 0.5-0.7%. The indications of treatment is based upon viral examinations (including viral nucleic acid determination), determinations of disease activity and stage (including biochemical, pathologic, and/or non-invasive methods), and excluding contraindications. To avoid unnecessary side effects and for cost-effective approach the guideline stresses the importance of quick and detailed virologic evaluations, the applicability of elastography as an acceptable alternative of liver biopsy in this regard, as well as the relevance of appropriate consistent follow up schedule for viral response during therapy. The first choice of therapy in chronic hepatitis B infection can be pegylated interferon for 48 weeks or continuous entecavir or tenofovir therapy. The latter two must be continued for at least 12 months after hepatitis B surface antigen seroconversion. Adefovir dipivoxil is recommended mainly in combination therapy. Lamivudine is no longer a first choice; patients currently taking lamivudine must switch if response is inadequate. Appropriate treatment of patients taking immunosuppressive medications is highly recommended. Pegylated interferon based therapy is recommended for the treatment of concomitant hepatitis D infection. Orv. Hetil., 2017, 158(Suppl. 1) 23-35.

Csete, J., et al. (2016). "Public health and international drug policy." Lancet **387**(10026): 1427-1480.

Hunyady, B., et al. (2015). "[**Hepatitis C: diagnosis, anti-viral therapy, after-care. Hungarian consensus guideline**]." Orv Hetil **156**(9): 343-351.

Approximately 70,000 people are infected with hepatitis C virus in Hungary, and more than half of them are not aware of their infection. From the point of infected individuals early recognition and effective treatment of related liver injury may prevent consequent advanced liver diseases and complications (liver cirrhosis, liver failure and liver cancer) and can increase work productivity and life expectancy. Furthermore, these could from prevent further spread of the virus as well as reduce substantially long term financial burden of related morbidity, as a socioeconomic aspect. Pegylated interferon + ribavirin dual therapy, which is available in Hungary since 2003, can clear the virus in 40-45% of previously not treated (naive), and in 5-21% of previous treatment-failure patients. Addition of a direct acting first generation protease inhibitor drug (boceprevir or telaprevir) to the dual therapy increases the chance of sustained viral response to 63-75% and 59-66%, respectively. These two protease inhibitors are available and financed for a segment of Hungarian patients since May 2013. Between 2013 and February 2015, other direct acting antivirals and interferon-free combination therapies have been registered for the treatment of chronic hepatitis C with a potential efficacy over 90% and typically with a short duration of 8-12 weeks. Indication of therapy includes exclusion of contraindications to the drugs and demonstration of viral replication with consequent liver injury, i.e., inflammation and/or fibrosis in the liver. Non-invasive methods (elastography and biochemical methods) are accepted and preferred for staging liver damage (fibrosis). For initiation of treatment accurate and timely molecular biology tests are mandatory. Eligibility for treatment is a subject of individual central medical review. Due to budget limitations therapy is covered only for a proportion of patients by the National Health Insurance Fund. Priority is given to those with urgent need based on a Hungarian Priority Index system reflecting primarily the stage of liver disease, and considering also additional factors, i.e., activity and progression of liver disease, predictive factors of treatment and other special issues. Approved treatments are restricted to the most cost-effective combinations based on the cost per sustained viral response value in different patient categories with consensus between professional organizations, National Health Insurance Fund and patient organizations. More expensive therapies might be available upon co-financing by the patient or a third party. Interferon-free treatments and shorter therapy durations preferred as much as financially feasible. A separate budget is allocated to cover interferon-free treatments for the most-in-

need interferon ineligible/intolerant patients, and for those who have no more interferon-based therapy option.

Hunyady, B., et al. (2014). "[**Diagnosis, treatment, and follow-up of hepatitis C-virus related liver disease. Hungarian national consensus guideline**]." Orv Hetil **155 Suppl**: 3-24.

Approximately 70 000 people are infected with hepatitis C virus in Hungary, more than half of whom are not aware of their infection. Early recognition and effective treatment of related liver injury may prevent consequent advanced liver diseases (liver cirrhosis and liver cancer) and its complications. In addition, it may increase work productivity and life expectancy of infected individual, and can prevent further viral transmission. Early recognition can substantially reduce the long term financial burden of related morbidity from socioeconomic point of view. Pegylated interferon + ribavirin dual therapy, which is available in Hungary since 2003, can kill the virus in 40-45% of previously not treated (naive), and in 5-21% of previous treatment-failure patients. Addition of two direct acting first generation protease inhibitor drugs (boceprevir and telaprevir) to the dual therapy increased the chance of sustained clearance of virus to 63-75% and 59-66%, respectively. These two protease inhibitor drugs are available and financed for a segment of Hungarian patients since May 2013. Indication of therapy includes exclusion of contraindications to the drugs and demonstration of viral replication with consequent liver injury, i.e., inflammation and/or fibrosis in the liver. For initiation of treatment as well as for on-treatment decisions accurate and timely molecular biology tests are mandatory. Staging of liver damage (fibrosis) non-invasive methods (transient elastography and biochemical methods) are acceptable to avoid concerns of patients related to liver biopsy. Professional decision for treatment is balanced against budget limitations in Hungary, and priority is given to those with urgent need using a national Priority Index system reflecting stage of liver disease as well as additional factors (activity and progression of liver disease, predictive factors and other special circumstances). All naive patients are given a first chance with dual therapy. Those with genotype 1 infection and with on-treatment or historic failure to dual therapy are eligible to receive protease inhibitor based triple therapy provided, they reach financial cutoff eligibility based on Priority Index. Duration of therapy is usually 48 weeks in genotype 1 with a response-guided potential to reduce duration for non-cirrhotic patients. Patients with non-1 genotypes are treated with dual therapy (without protease inhibitors) for a genotype and response driven duration of 16, 24, 48, or 72 week. Careful monitoring for early recognition and management of side-effects as well as viral response and potential breakthrough during protease-inhibitor therapy are recommended.

Horvath, G., et al. (2014). **"[Diagnosis and treatment of chronic hepatitis B and D. Hungarian national consensus guideline**]." Orv Hetil **155 Suppl**: 25-36.

Diagnosis and treatment of hepatitis B and D virus infections mean that the patient is able to maintain working capacity, increase quality of life, prevent cancer, and prolong life expectancy, while the society benefits from eliminating the chances of further transmission of the viruses, and decreasing the overall costs of serious complications. The guideline delineates the treatment algorithms for 2014, which is agreed on a consensus meeting of specialists involved in the treatment of the above diseases. The prevalence of hepatitis B virus infection in the Hungarian general population is 0.5-0.7%. The indications of treatment is based upon viral examinations (including viral nucleic acid determination), determinations of disease activity and stage (including biochemical, pathologic, and/or non-invasive methods), and excluding contraindications. To avoid unnecessary side effects and for cost-effective approach the guideline emphasizes the importance of quick and detailed virologic evaluations, the applicability of transient elastography as an acceptable alternative of liver biopsy in this regard, as well as the relevance of appropriate consistent follow up schedule for viral response during therapy. The first choice of therapy in chronic hepatitis B infection can be pegylated interferon for 48 weeks or continuous entecavir or tenofovir therapy. The latter two must be continued for at least 12 months after hepatitis B surface antigen seroconversion. Adefovir dipivoxil is recommended mainly in combination therapy. Lamivudine is no longer a first choice; patients currently taking lamivudine must switch if response is inadequate. Appropriate treatment of

patients taking immunosuppressive medications is highly recommended. Pegylated interferon based therapy is recommended for the treatment of concomitant hepatitis D infection.

Makara, M., et al. (2012). "[**Hungarian consensus guideline for the diagnosis and treatment of B, C, and D viral hepatitis**]." Orv Hetil **153**(10): 375-394.

More than 1% of the Hungarian population is infected with hepatitis B, C, or D viruses. Since 2006 the diagnostics and therapy of these infections are carried out in treatment centers according to national guidelines - since 2010 according to financial protocols. The consensus-based guidelines for 2012 are published in this paper. The guidelines stress the importance of quick and detailed virologic evaluations, the applicability of transient elastography as an acceptable alternative of liver biopsy in this regard, as well as the relevance of appropriate consistent follow up schedule for viral response during therapy. The first choice of therapy in chronic hepatitis B infection is pegylated interferon for 48 weeks or continuous entecavir therapy. The later must be continued for at least 6 months after hepatitis B surface antigen (HBsAg) seroconversion. Tenofovir disoproxil fumarat is not yet reimbursed by the National Health Insurance Fund. Adefovir dipivoxil is recommended mainly in combination therapy. Lamivudine is no longer a first choice; patients currently taking lamivudine must switch if response is inadequate. Appropriate treatment of patients taking immunosuppressive medications is highly recommended. Pegylated interferon based therapy is recommended for the treatment of concomitant hepatitis D infection. Treatment naive chronic hepatitis C patients should initially receive pegylated interferon and ribavirin dual combination therapy. In genotype 1 infection if response is insufficient at 4 or 12 weeks one of the two new direct acting antivirals (boceprevir or telaprevir) should be added. The length of treatment is usually 48 weeks; in cases of extended early viral response shorter courses are recommended. Previous treatment failure patients with genotype 1 infection should receive a protease inhibitor backed triple combination therapy, mostly for 48 weeks. However, relapsers without cirrhosis and with extended rapid viral response, shorter telaprevir based combination therapy is sufficient. Drug-drug interactions as well as emergence of viral resistance are of particular importance. For genotype 2 or 3 HCV infections 24 weeks, for genotype 4 infections 24, 48 or 72 weeks of pegylated interferon plus ribavirin therapy is recommended in general. The guidelines published here become protocols when published as official publications of the Hungarian Health Authority.

Judit, G., et al. (2010). "[**Protocol for the antiviral therapy of hepatitis C]."** Orv Hetil **151**(2): 66-72.

Gervain, J., et al. (2010). "[**Protocol for the antiviral therapy of hepatitis B and D**]." Orv Hetil **151**(1): 24-28.

08:50 - 09:10

Financial aspects of HCV elimination. Is it „cost saving”? Cost of screening and treatment.

Dr. Aron Zoltán Vincziczki

NEAK

Other related references (Pubmed search):

Marshall, A. D., et al. (2018). "**Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe**." Lancet Gastroenterol Hepatol **3**(2): 125-133.

All-oral direct-acting antiviral drugs (DAAs) for hepatitis C virus, which have response rates of 95% or more, represent a major clinical advance. However, the high list price of DAAs has led many governments to restrict their reimbursement. We reviewed the availability of, and national criteria for, interferon-free DAA reimbursement among countries in the European Union and European Economic Area, and Switzerland. Reimbursement documentation was reviewed between Nov 18, 2016, and Aug 1, 2017. Primary outcomes were fibrosis stage, drug

or alcohol use, prescriber type, and HIV co-infection restrictions. Among the 35 European countries and jurisdictions included, the most commonly reimbursed DAA was ombitasvir, paritaprevir, and ritonavir, with dasabuvir, and with or without ribavirin (33 [94%] countries and jurisdictions). 16 (46%) countries and jurisdictions required patients to have fibrosis at stage F2 or higher, 29 (83%) had no listed restrictions based on drug or alcohol use, 33 (94%) required a specialist prescriber, and 34 (97%) had no additional restrictions for people co-infected with HIV and hepatitis C virus. These findings have implications for meeting WHO targets, with evidence of some countries not following the 2016 hepatitis C virus treatment guidelines by the European Association for the Study of Liver.

09:10 - 09:30

Best practices: National Hepatitis approach of Slovenia

Mojca Maticic

Head Department Viral Hepatitis, University medical Centre Ljubljana, Slovenia

References proposed by speaker:

1. **Strategies to manage hepatitis C virus infection disease burden - volume 3.** Alfaleh FZ, Nugrahini N, Matičič M, et al. ECCMID 2018. Madrid, April 23, 2018. Poster #Mon-13. J Viral Hepat. 2015 Dec;22 Suppl 4:42-65. doi: 10.1111/jvh.12474.
2. **Hepatitis C virus genotypes in 1,504 patients in Slovenia, 1993-2007.** Seme K, Vrhovac M, Mocilnik T, Maticic M, Lesnicar G, Baklan Z, Volkar JM, Rajter M, Stepec S, Lunar M, Poljak M. J Med Virol. 2009 Apr;81(4):634-9. doi: 10.1002/jmv.21427.
3. **Prevalence, genotype distribution, and risk factors for hepatitis C infection among HIV-infected individuals in Slovenia: a 1986-2013 update.** Škamperle M, Seme K, Lunar MM, Maver PJ, Tomažič J, Vovko TD, Pečavar B, Matičič M, Poljak M. Acta Dermatovenerol Alp Pannonica Adriat. 2014;23(2):25-6.
4. **A national multidisciplinary healthcare network for treatment of hepatitis C in people who inject drugs in Slovenia**. Maticic M. BMC Infect Dis. 2014; 14(Suppl 6): S6. Published online 2014 Sep 19. doi: 10.1186/1471-2334-14-S6-S6

Other related references (Pubmed search):

Maticic M, Zorman JV, Gregorcic S, Schatz E, Lazarus JV. **Changes to the national strategies, plans and guidelines for the treatment of hepatitis C in people who inject drugs between 2013 and 2016: a cross-sectional survey of 34 European countries**. Harm reduction journal. 2019;16(1):32.

BACKGROUND: Hepatitis C virus (HCV) infection is the leading cause of cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC) worldwide. In Europe, people who inject drugs (PWID) represent the majority of HCV infections, but are often excluded from treatment. The aim of this study was to report on national HCV strategies, action plans and guidelines in European countries that include HCV treatment for the general population as well as for PWID. Data on access to direct-acting antivirals (DAAs) were also collected. METHODS: In 2016, 38 non-governmental organisations, universities and public health institutions that work with PWID in 34 European countries were invited to complete a 16-item online survey about current national HCV treatment policies and guidelines. Data from 2016 were compared to those from 2013 for 33 European countries, and time trends are presented. Differences in the data were analysed. Data from 2016 on general access to DAAs in PWID are presented separately. RESULTS: The response rate was 100%. Fourteen countries (42%) reported having a national HCV strategy covering HCV treatment; 12 of these addressed HCV treatment for PWID. Respondents from ten countries (29%) reported having a national HCV action plan. PWID were specifically included in seven of them. Twenty-nine countries (85%) reported having national HCV treatment guidelines. PWID were specifically included in 23 (79%) of them. Compared to 2013, respondents reported that an additional seven countries (25%) had national strategies, an additional eight countries (29%) had action plans and an additional six countries (19%) had HCV treatment guidelines. However, PWID were not included in two, four and six of those countries, respectively. DAAs were reported to be available in 91% of the study countries, with restrictions

reported in 71% of them. CONCLUSION: Respondents reported that fewer than half of the European countries in this study had a national HCV strategy and/or action plan, with even fewer including PWID. However, when compared to 2013, the number of such countries had slightly increased. Although PWID are often addressed in clinical guidelines, strategic action is needed to increase access to HCV treatment for this group and the situation should be regularly monitored.

Lazarus JV, Pericas JM, Picchio C, Cernosa J, Hoekstra M, Luhmann N, . . . Dillon JF. **We know DAAs work, so now what? Simplifying models of care to enhance the hepatitis C cascade**. Journal of internal medicine. 2019;286(5):503-25.

Globally, some 71 million people are chronically infected with hepatitis C virus (HCV). Marginalized populations, particularly people who inject drugs (PWID), have low testing, linkage to care and treatment rates for HCV. Several models of care (MoCs) and service delivery interventions have the potential to improve outcomes across the HCV cascade of care, but much of the relevant research was carried out when interferon-based treatment was the standard of care. Often it was not practical to scale-up these earlier models and interventions because the clinical care needs of patients taking interferon-based regimens imposed too much of a financial and human resource burden on health systems. Despite the adoption of highly effective, all-oral direct-acting antiviral (DAA) therapies in recent years, approaches to HCV testing and treatment have evolved slowly and often remain rooted in earlier paradigms. The effectiveness of DAAs allows for simpler approaches and has encouraged countries where the drugs are widely available to set their sights on the ambitious World Health Organization (WHO) HCV elimination targets. Since a large proportion of chronically HCV-infected people are not currently accessing treatment, there is an urgent need to identify and implement existing simplified MoCs that speak to specific populations' needs. This article aims to: (i) review the evidence on MoCs for HCV; and (ii) distil the findings into recommendations for how stakeholders can simplify the path taken by chronically HCV-infected individuals from testing to cure and subsequent care and monitoring.

Chkhartishvili N, Holban T, Simonovic Babic J, Alexiev I, Maticic M, Kowalska J, Horban A. **State of viral hepatitis care in 16 countries of Central and Eastern European Region**. Central European journal of public health. 2019;27(3):212-6.

OBJECTIVES: Survey was conducted to assess state of viral hepatitis care in Central and Eastern Europe (CEE). METHODS: Representatives of 16 CEE countries completed on-line survey in April-May 2017 that collected information on basic epidemiology and availability of key services for HCV and HBV infections. Sources of information provided ranged from national surveillance data to expert opinion. RESULTS: The burden of viral hepatitis varied between countries, ranging from 6,500 to 2 million for HCV and from 10,000 to 3 million for HBV. Access to routine HCV RNA testing and genotyping was reported by 11 and 9 countries, respectively. HCV resistance testing was available in 7 countries. Direct acting antivirals (DAAs) were available in 13 countries, most frequently Sofosbuvir and Ledipasvir/Sofosbuvir (12 countries apiece) and Ombitasvir/Paritaprevir/Dasabuvir (9 countries). HBV DNA testing and HBV genotyping were routinely available in 10 and 7 countries, respectively. Eleven countries reported available treatment with Tenofovir. CONCLUSIONS: There are gaps in viral hepatitis care in CEE. Despite the availability of registered modern drugs for HCV and HBV, the access to treatment is limited. Ensuring quality health care is essential to reduce the epidemic and achieve the WHO's goal of eliminating viral hepatitis as a major public health challenge.

Marshall AD, Cunningham EB, Nielsen S, Aghemo A, Alho H, Backmund M, . . . Grebely J. **Restrictions for reimbursement of interferon-free direct-acting antiviral drugs for HCV infection in Europe**. The lancet Gastroenterology & hepatology. 2018;3(2):125-33.

All-oral direct-acting antiviral drugs (DAAs) for hepatitis C virus, which have response rates of 95% or more, represent a major clinical advance. However, the high list price of DAAs has led many governments to restrict their reimbursement. We reviewed the availability of, and national

criteria for, interferon-free DAA reimbursement among countries in the European Union and European Economic Area, and Switzerland. Reimbursement documentation was reviewed between Nov 18, 2016, and Aug 1, 2017. Primary outcomes were fibrosis stage, drug or alcohol use, prescriber type, and HIV co-infection restrictions. Among the 35 European countries and jurisdictions included, the most commonly reimbursed DAA was ombitasvir, paritaprevir, and ritonavir, with dasabuvir, and with or without ribavirin (33 [94%] countries and jurisdictions). 16 (46%) countries and jurisdictions required patients to have fibrosis at stage F2 or higher, 29 (83%) had no listed restrictions based on drug or alcohol use, 33 (94%) required a specialist prescriber, and 34 (97%) had no additional restrictions for people co-infected with HIV and hepatitis C virus. These findings have implications for meeting WHO targets, with evidence of some countries not following the 2016 hepatitis C virus treatment guidelines by the European Association for the Study of Liver.

Leblebicioglu H, Arends JE, Ozaras R, Corti G, Santos L, Boesecke C, . . . Salmon D. **Availability of hepatitis C diagnostics and therapeutics in European and Eurasia countries**. Antiviral research. 2018;150:9-14.

BACKGROUND: Treatment with direct acting antiviral agents (DAAs) has provided sustained virological response rates in >95% of patients with chronic hepatitis C virus (HCV) infection. However treatment is costly and market access, reimbursement and governmental restrictions differ among countries. We aimed to analyze these differences among European and Eurasian countries. METHODS: A survey including 20-item questionnaire was sent to experts in viral hepatitis. Countries were evaluated according to their income categories by the World Bank stratification. RESULTS: Experts from 26 countries responded to the survey. As of May 2016, HCV prevalence was reported as low (</=1%) in Croatia, Czech Republic, Denmark, France, Germany, Hungary, the Netherlands, Portugal, Slovenia, Spain, Sweden, UK; intermediate (1-4%) in Azerbaijan, Bosnia and Herzegovina, Italy, Kosovo, Greece, Kazakhstan, Romania, Russia, Serbia and high in Georgia (6.7%). All countries had national guidelines except Albania, Kosovo, Serbia, Tunisia, and UK. Transient elastography was available in all countries, but reimbursed in 61%. HCV-RNA was reimbursed in 81%. PegIFN/RBV was reimbursed in 54% of the countries. No DAAs were available in four countries: Kazakhstan, Kosovo, Serbia, and Tunisia. In others, at least one DAA combination with either PegIFN/RBV or another DAA was available. In Germany and the Netherlands all DAAs were reimbursed without restrictions: Sofosbuvir and sofosbuvir/ledipasvir were free of charge in Georgia. CONCLUSION: Prevalence of HCV is relatively higher in lower-middle and upper-middle income countries. DAAs are not available or reimbursed in many Eurasia and European countries. Effective screening and access to care are essential for reducing liver-related morbidity and mortality.

Lazarus JV, Stumo SR, Harris M, Hendrickx G, Hetherington KL, Maticic M, . . . Safreed-Harmon K. **Hep-CORE: a cross-sectional study of the viral hepatitis policy environment reported by patient groups in 25 European countries in 2016 and 2017**. Journal of the International AIDS Society. 2018;21 Suppl 2:e25052.

INTRODUCTION: The first World Health Organization (WHO) global health sector strategy on hepatitis B and C viruses (HBV and HCV) has called for the elimination of viral hepatitis as a major public health threat by 2030. This study assesses policies and programmes in support of elimination efforts as reported by patient groups in Europe. METHODS: In 2016 and 2017, hepatitis patient groups in 25 European countries participated in a cross-sectional survey about their countries' policy responses to HBV and HCV. The English-language survey addressed overall national response; public awareness/engagement; disease monitoring; prevention; testing/diagnosis; clinical assessment; and treatment. We performed a descriptive analysis of data and compared 2016 and 2017 findings. RESULTS: In 2017, 72% and 52% of the 25 European study countries were reported to not have national HBV and HCV strategies respectively. The number of respondents indicating that their governments collaborated with civil society on viral hepatitis control increased from 13 in 2016 to 18 in 2017. In both 2016 and 2017, patient groups reported that 9 countries (36%) have disease registers for HBV and 11 (44%) have disease registers for HCV. The number of countries reported to have needle and

syringe exchange programmes available in all parts of the country dropped from 10 (40%) in 2016 to 8 in 2017 (32%). In both 2016 and 2017, patient groups in 5 countries (20%) reported that HCV treatment is available in non-hospital settings. From 2016 to 2017, the reported number of countries with no restrictions on access to direct-acting antivirals for HCV increased from 3 (12%) to 7 (28%), and 5 fewer countries were reported to refuse treatment to people who are currently injecting drugs. CONCLUSIONS: The patient-led Hep-CORE study offers a unique perspective on the readiness of study countries to undertake comprehensive viral hepatitis elimination efforts. Viral hepatitis monitoring should be expanded to address policy issues more comprehensively and to incorporate civil society perspectives, as is the case with global HIV monitoring. Policy components should also be explicitly added to the WHO framework for monitoring country-level progress against viral hepatitis.

Hepatitis C virus prevalence and level of intervention required to achieve the WHO targets for elimination in the European Union by 2030: a modelling study. The lancet Gastroenterology & hepatology. 2017;2(5):325-36.

BACKGROUND: Hepatitis C virus (HCV) is a leading cause of liver-related morbidity and mortality worldwide. In the European Union (EU), treatment and cure of HCV with direct-acting antiviral therapies began in 2014. WHO targets are to achieve a 65% reduction in liver-related deaths, a 90% reduction of new viral hepatitis infections, and 90% of patients with viral hepatitis infections being diagnosed by 2030. This study assessed the prevalence of HCV in the EU and the level of intervention required to achieve WHO targets for HCV elimination. METHODS: We populated country Markov models for the 28 EU countries through a literature search of PubMed and Embase between Jan 1, 2000, and March 31, 2016, and a Delphi process to gain expert consensus and validate inputs. We aggregated country models to create a regional EU model. We used the EU model to forecast HCV disease progression (considering the effect of immigration) and developed a strategy to acehive WHO targets. We used weighted average sustained viral response rates and fibrosis restrictions to model the effect of current therapeutic guidelines. We used the EU model to forecast HCV disease progression (considering the effect of immigration) under current screening and therapeutic guidelines. Additionally, we back-calculated the total number of patients needing to be screened and treated to achieve WHO targets. FINDINGS: We estimated the number of viraemic HCV infections in 2015 to be 3 238 000 (95% uncertainty interval [UI] 2 106 000-3 795 000) of a total population of 509 868 000 in the EU, equating to a prevalence of viraemic HCV of 0.64% (95% UI 0.41-0.74). We estimated that 1 180 000 (95% UI 1 003 000-1 357 000) people were diagnosed with viraemia (36.4%), 150 000 (12 000-180 000) were treated (4.6% of the total infected population or 12.7% of the diagnosed population), 133 000 (106 000-160 000) were cured (4.1%), and 57 900 (43 900-67 300) were newly infected (1.8%) in 2015. Additionally, 30 400 (26 600-42 500) HCV-positive immigrants entered the EU. To achieve WHO targets, unrestricted treatment needs to increase from 150 000 patients in 2015 to 187 000 patients in 2025 and diagnosis needs to increase from 88 800 new cases annually in 2015 to 180 000 in 2025. INTERPRETATION: Given its advanced health-care infrastructure, the EU is uniquely poised to eliminate HCV; however, expansion of screening programmes is essential to increase treatment to achieve the WHO targets. A united effort, grounded in sound epidemiological evidence, will also be necessary. FUNDING: Gilead Sciences.

09:30 - 09:40	Questions and Discussion
09:40 - 10:00	Prevention and control activities by Civil society and patient organisation

Antalné Nagy

VIMOR Hepatitis patient organisation / Hungarian Liver Patients Association

http://www.vimor.hu/

	VIMOR Vírusos Májbetegek Országos Egyesülete
10:00 - 10:20	Role of politics and media in HCV elimination ***Dr.Péter Csányi*** Deputy secretary of Health - EMMI
10:20 - 10:30	Question and discussion
10:30 – 11:00	**Coffee Break**

Session 7: Groups discussion

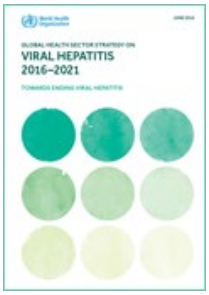
What are the needs to Eliminate viral hepatitis by 2030

Chairs: Mihály Makar – Daniel Lavanchy

11:00 - 11:20 WHO Global Strategy on Viral Hepatitis: progress towards elimination and good practices in the WHO European Region

Antons Mozalevskis

WHO Regional Office for Europe



WHO Elimination Goals

Global health sector strategy on viral hepatitis 2016-2021

This is the first global health sector strategy on viral hepatitis, a strategy that contributes to the achievement of the 2030 Agenda for Sustainable Development.

It covers the first six years of the post-2015 health agenda, 2016–2021, building on the Prevention and Control of Viral Hepatitis Infection: Framework for Global Action, and on two resolutions on viral hepatitis adopted by the World Health Assembly in 2010 and in 2014.

The strategy addresses all five hepatitis viruses (hepatitis A, B, C, D and E), with a particular focus on hepatitis B and C, owing to the relative public health burden they represent.

Global hepatitis Report 2017

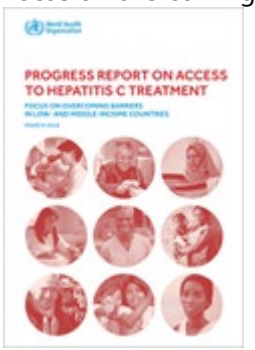
In May 2016, the World Health Assembly endorsed the *Global Health Sector Strategy (GHSS) on viral hepatitis 2016–2021*. The GHSS calls for the elimination of viral hepatitis as a public health threat by 2030 (reducing new infections by 90% and mortality by 65%).

This WHO *Global hepatitis report* describes, for the first time, the global and regional estimates on viral hepatitis in 2015, setting the baseline for tracking progress in implementing the new global strategy.

The report focuses on hepatitis B and C, which are responsible for 96% of all hepatitis mortality. It presents data along the five strategic directions (strategic information, interventions, equity, financing and innovation) – key pillars of the GHSS to facilitate monitoring of progress in countries, regions and globally, and to measure the impact of interventions on reducing new infections and saving lives between 2015 and 2030.

Progress report on access to hepatitis C treatment

Focus on overcoming barriers in low- and middle-income countries



Increased access to highly effective direct-acting antivirals (DAAs) for the treatment of infection with the hepatitis C virus (HCV) is revolutionizing the prospect of ending HCV epidemics. Globally, the number of people who initiated DAA-based treatment for HCV rose between 2015 and 2016, from approximately 1 million to 1.5 million.

This report updates the first edition, published in 2016, and reviews the progress countries have made in expanding access to life-saving DAAs. The report reviews the main challenges countries face and describes recent developments in relation to five key factors that determine access to DAA medicines: affordability, quality assurance, regulatory approval, government commitment and financing. It highlights key areas for action by ministries of health and other government decision-makers, pharmaceutical manufacturers and technical partners.

Action plan for the health sector response to viral hepatitis in the WHO European Region (2017)

This first Action plan for viral hepatitis in the WHO European Region adapts the Global Health Sector Strategy on Viral Hepatitis, 2016–2021 to the context of the European Region.

The plan was developed through a participatory process, finalized and endorsed at the 66th session of the WHO Regional Committee for Europe, along with resolution EUR/RC66/R10. While the Action plan addresses all five hepatitis viruses, its major focus is on hepatitis B and C, given the high public health burden they represent in the Region.

The goal of the Action plan is elimination of viral hepatitis as a public health threat in the WHO European Region by 2030 through the reduction of transmission, morbidity and mortality due to viral hepatitis and its complications, and by ensuring equitable access to comprehensive prevention, recommended testing, care and treatment services for all.

Fact sheets on sustainable developments goals: health target, Viral hepatitis

The facts sheets on the SDG health targets present key facts and figures, ongoing commitments, guidance on action, and indicators to monitor progress – in the context of the WHO European Region. They also provide specific highlights on how WHO/Europe supports its Member States in achieving these targets, and cover key SDG aspects such as equity, partnerships and intersectoral collaboration

References proposed by speaker:

1. Aspinall EJ, Hutchinson SJ, Goldberg DJ, Valerio H, Mozalevskis A, Noori T, Duffell E, Tavoschi L. **Monitoring response to hepatitis B and C in EU/EEA: testing policies, availability of data on care cascade and chronic viral hepatitis-related mortality - results from two surveys (2016).** HIV Med. 2018 Feb;19 Suppl 1:11-15. doi: 10.1111/hiv.12599.
2. Hutin Y, Low-Beer D, Bergeri I, Hess S, Garcia-Calleja JM, Hayashi C, Mozalevskis A, Rinder Stengaard A, Sabin K, Harmanci H, Bulterys M. Viral **Hepatitis Strategic Information to Achieve Elimination by 2030: Key Elements for HIV Program Managers.** JMIR Public Health Surveill. 2017 Dec 15;3(4):e91. doi: 10.2196/publichealth.7370.
3. Duffell EF, Hedrich D, Mardh O, Mozalevskis A. **Towards elimination of hepatitis B and C in European Union and European Economic Area countries: monitoring the World Health Organization's global health sector strategy core indicators and scaling up key interventions.** Euro Surveill. 2017 Mar 2;22(9). pii: 30476. doi: 10.2807/1560-7917.ES.2017.22.9.30476.

Other related references (Pubmed search):

Par, A. and G. Par (2018). "[**Three decades of the hepatitis C virus from the discovery to the potential global elimination: the success of translational researches**]." Orv Hetil **159**(12): 455-465.

More than 25 years after the discovery of hepatitis C virus, the development of the direct acting antivirals can lead to the regional or long-term global elimination of the virus with over 90% efficacy. This is the success of basic and clinical translational research. Yet, some unsolved challanges remain, such as the great number of unidentified patients who are not aware of their condition, the limited access to the therapy due to the high prices of the drugs, and the treatment of resistance-associated variants. In addition, the lack of vaccine is also an obstacle. In 2016, the World Health Organization (WHO) developed the first global health sector strategy for the elimination of viral hepatitis by 2030. Its evidence-based guidelines are primarily targeted at the national hepatitis programme managers who are responsible for the national testing and treatment plans. According to these recommendations, it is of basic importance to perform focused risk-based testing in higher-risk populations and after diagnosis to start treatment as "cure as prevention", furthermore, to limit the risk of reinfection. We review the events of the HCV story from the discovery to these days, including virology, epidemiology, pathogenesis, diagnosis and therapy. Orv Hetil. 2018; 159(12): 455-465.

Hunyady, B., et al. (2015). "[In Process Citation]." Orv Hetil **156 Suppl 1**: 3-23.

Approximately 70,000 people are infected with hepatitis C virus in Hungary, and more than half of them are not aware of their infection. From the point of infected individuals early recognition and effective treatment of related liver injury may prevent consequent advanced liver diseases and complications (liver cirrhosis, liver failure and liver cancer) and can increase work productivity and life expectancy. From a socioeconomic aspect, this could also prevent further spread of the virus as well as reduce substantially long term financial burden of related morbidity. Pegylated interferon + ribavirin dual therapy, which is available in Hungary since 2003, can clear the virus in 40-45% of previously not treated (naive), and in 5-21% of previous treatment-failure patients. Addition of a direct acting first generation protease inhibitor drug (boceprevir or telaprevir) to the dual therapy increases the chance of sustained viral response to 63-75% and 59-66%, respectively. These two protease inhibitors are available and financed for a segment of Hungarian patients since May 2013. Between 2013 and February 2015, other direct acting antiviral interferon-free combination therapies have been registered for the treatment of chronic hepatitis C, with a potential efficacy over 90% and typical short duration of 8-12 weeks. Indication of therapy includes exclusion of contraindications to the drugs and demonstration of viral replication with consequent liver injury, i.e., inflammation and / or fibrosis in the liver. Non-invasive methods (elastography and biochemical methods) are accepted and preferred for staging liver damage (fibrosis). For initiation of treatment as well as for on-treatment decisions, accurate and timely molecular biology tests are mandatory. Eligibility for treatment is a subject of individual central medical review. Due to budget limitations therapy is covered only for a proportion of patients by the National Health Insurance Fund. Priority is given to those with urgent need based on a Hungarian Priority Index system reflecting primarily the stage of liver disease, and considering also additional factors, i.e., activity and progression of liver disease, predictive factors of treatment and other special issues. Approved treatments are restricted to the most cost-effective combinations based on the cost per sustained viral response value in different patient categories with consensus between professional organizations, National Health Insurance Fund and patient organizations. More expensive therapies might be available upon co-financing by the patient or a third party. Interferon-free treatments and

	shorter therapy durations preferred as much as financially feasible. A separate budget is allocated to cover interferon-free treatments for the most-in-need interferon ineligible/intolerant patients, and for those who have no more interferon-based therapy option. Orv. Hetil., 2015, 156(Suppl. 1), 3-23.
11:20 – 12:30	Groups or Panel discussion: Assess the needs to achieve the WHO's Regional office for Europe- targets for elimination viral hepatitis in Hungary by 2030 Group 1 - Epidemiological surveillance, screening, monitoring and analysis of the effectiveness of prevention and treatment programs, informing the public Group 2 -Prevention of viral hepatitis: improvement of vaccine prevention programs, prevention in high-risk groups, prevention in health care settings Group 3 - Treatment of viral hepatitis: recommendations based on epidemiology and disease burden data, increasing access to treatment, coverage of the most affected groups Group 4 – Funding of screening, prevention and treatment programs: mechanisms for ensuring sustainable financing, prospects for reducing prices for medicines, financing of treatment in outpatient settings Group 5 - Innovations in health care: research priorities, mechanisms to promote scientific development, accelerate the introduction of promising developments in the practice
12:30 – 13:00	Presentation outcome of the groups sessions
13:00 – 14:30	**Lunch**

Session 8: Conclusion of the meeting

Chairs: Zsuzsa Schaff – Daniel Shouval

14:40 – 15:30	Conclusion of the meeting + Final discussion ***David FizSimons*** Independent researcher & rapporteur, Prévessin-Moens, France

4. Speakers information

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 AND 'hepatitis'. If more than 10 references were available only the most recent articles are shown. Speakers are listed alphabetically.

PÉTER CSÁNYI

Deputy Secretary of State, Ministry of Health, Hungary

From pubmed search: no publications retrieved.

MARIA DUDAS

Epidemiologist, Department of Communicable Disease Epidemiology and Infection Control in National Public Health Center, Hungary.

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ERIKA DUFFELL

ECDC

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DAVID FITZSIMONS

Independent researcher, Prévessin-Moens, France

Rapporteur

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ANNA HORVÁTH-TARJÁN

Sociologist/researcher and scientific analyst at the Hungarian Reitox National Focal Point to the EMCDDA

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BÉLA HUNYADY

Head of Gastroenterology Department, full professor; Somogy County Kaposi Mór Teching Hospital, Kaposvár and University of Pécs, Medical School, Pécs, Hungary

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GERVAIN JUDIT

Head of Division of Hepato-Pancreatology and Molecular Diagnostics Laboratory, Szent György University Teaching Hospital Székesfehérvár, Hungary

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MIHÁLY MAKARA

Consultant, Central Hospital of Southern Pest National Institute of Hematology and Infectious Diseases, Hungary

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MOJCA MATICIC

Head Department Viral Hepatitis, University medical Centre Ljubljana, Slovenia

EASL Policy and Public Health Committee Member

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