

**“Burden and prevention of Viral
Hepatitis in Bulgaria.”**

Viral Hepatitis Prevention Board Meeting
Sofia, Bulgaria, 24-25 March 2011.

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Content

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

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Pubmed MEDLINE search on {(Bulgaria OR Bulgarian) AND (Hepatitis OR HAV OR HBV OR HCV OR HDV OR HEV)} in all fields and published since 2000 was performed. A second search on these results was performed in Endnote with 'Epidemiology' or 'Prevalence' or 'Prevention' or 'vaccin*' or 'control' or 'Diagnostics' or 'surveillance'. Only the references and the abstracts related to Bulgaria were selected.

3. Hepatitis Bibliography of the Speakerspag. 14

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

1. Bulgaria general background

(Source World factbook: <https://www.cia.gov/library/publications/the-world-factbook/geos/bu.html>)



Population:

7,093,635 (July 2011 est.)

Age structure:

0-14 years: 13.9% (male 506,403/female 480,935)

15-64 years: 67.9% (male 2,367,680/female 2,446,799)

65 years and over: 18.2% (male 522,343/female 769,475) (2011 est.)

Median age:

total: 41.9 years

male: 39.6 years

female: 44 years (2011 est.)

Population growth rate:

-0.781% (2011 est.)

Birth rate:

9.32 births/1,000 population (2011 est.)

Death rate:

14.32 deaths/1,000 population (July 2011 est.)

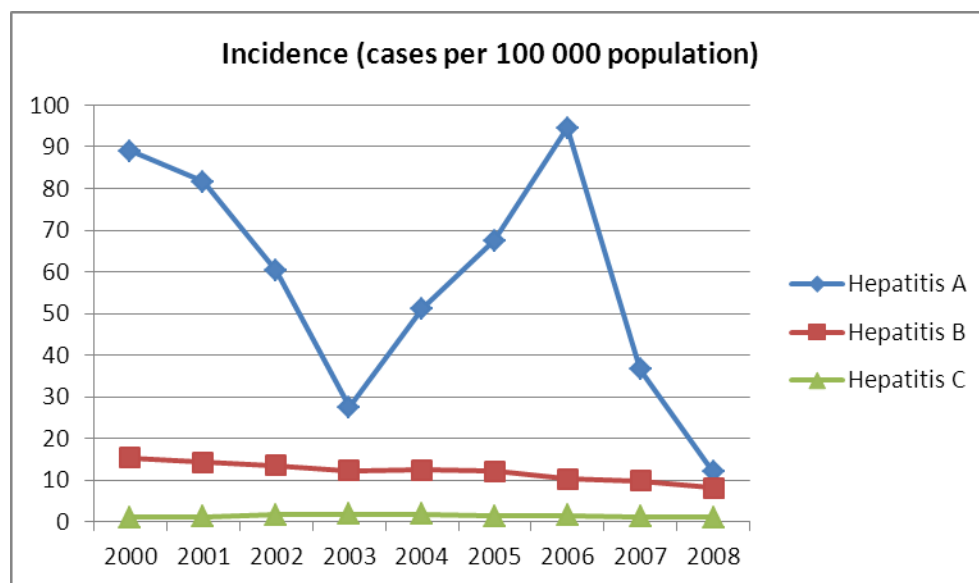
Net migration rate:

-2.82 migrant(s)/1,000 population (2011 est.)

Hepatitis epidemiological data

(Source: WHO Cisd database)

	Bulgaria								
	2000	2001	2002	2003	2004	2005	2006	2007	2008
	Hepatitis A								
2 - Hepatitis A - Incidence (cases per 100 000 population)	88,92	81,6	60,22	27,49	51,22	67,51	94,49	36,64	11,96
6011 - Hepatitis A - Number of cases	7119	6485	4753	2155	3990	5225	7266	2800	908
	Hepatitis B								
9009 - Hepatitis B - Incidence (cases per 100 000 population)	15,36	14,27	13,61	12,31	12,44	12,15	10,25	9,85	8,22
9008 - Hepatitis B - Number of cases	1230	1134	1074	965	969	940	788	753	624
	Hepatitis C								
6015 - Hepatitis C - Incidence (cases per 100 000 population)	1,1	1,3	1,66	1,85	1,87	1,37	1,57	1,28	1,17
6014 - Hepatitis C - Number of cases	88	103	131	145	146	106	121	98	89



2. Hepatitis in Bulgaria

Pubmed MEDLINE search on {(Bulgaria OR Bulgarian) AND (Hepatitis OR HAV OR HBV OR HCV OR HDV OR HEV)} in all fields and published from 2000 on, was performed. A second search on these results was performed in Endnote with {'Epidemiology' or 'Prevalence' or 'Prevention' or 'vaccin*' or 'control' or 'Diagnostics' or 'surveillance'}. After a manual search only the references and the abstracts really related to Bulgaria were selected and the abstracts only related to treatment were deleted. In total 23 references are mentioned in this background document, the references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author's

Vatev, N. T., M. V. Atanasova, et al. (2009). "**Seroprevalence of hepatitis A viral infection in Plovdiv, Bulgaria.**" *Folia Med (Plovdiv)* **51**(1): 70-3.

INTRODUCTION: Hepatitis A occurs throughout the world, albeit with different endemicity. The level of endemicity is determined for each country from the annual incidence rate and from the age-specific seroprevalence of anti-HAVt. AIM: To assess the anti-HAVt seroprevalence in 180 people with no hepatitis A history. The study also aimed at determining the susceptibility of the separate individuals to the disease. PATIENTS AND METHODS: Two groups of people with no history of hepatitis A were studied; the study subjects were randomly selected from two quarters of Plovdiv--one with poor hygienic and sanitary conditions and the other with normal ones. The study was performed using Dia Sorin kits and equipment. RESULTS: Ninety-three subjects were included in Group I; 84 (90.23%) of these were anti-HAVt positive. Group II included 87 subjects of which 39 (44.83%) tested positive. The mean anti-HAVt seroprevalence for the whole sample (n=180) was 68.33%. CONCLUSIONS: The established mean seroprevalence of anti-HAVt is typical for countries with intermediate level of hepatitis A endemicity. The epidemiology of the disease, however, is completely different for each one of the groups. This finding makes it necessary that different preventive approach be used for each one of these groups, specifically related to the individual susceptibility to the disease--something that is not done in everyday practice.

Boykinova, O. B., Y. D. Stoilova, et al. (2009). "**Epidemiological, immunological and clinical characteristics of acute hepatitis C.**" *Folia Med (Plovdiv)* **51**(1): 61-9.

The aim of the study was to make a clinical and epidemiological and immunological characteristic of patients with acute hepatitis C infection (AHC). PATIENTS AND METHODS: The study included 178 patients with AHC; they were studied in terms of clinical course, biochemical constellations, T and B lymphocyte subpopulations, level of TNF-alpha in the blood serum, presence of autoantibodies, and the outcome of the disease in a five-year follow-up period. METHODS: anti-HCV (EIA), HCV-RNA (PCR), HCV genotyping; ALT, AST, AP, gamma-GT; ultrasonography and liver biopsy. RESULTS: AHC incidence increased six-fold between 2000 and 2006. The prevalence of the disease among intravenous drug-users (IDUs) was 46.07%. Young people (31.71 +/- 1.21) and males (67.98%) were prevalent. The genotype HCV-1 was prevalent. AHC ran with icterus in 70.22% of all

cases, while it was anicteric in 29.78%; ALT-activity was high--it was mean 1007.94 +/- 59.87 U/l; intrahepatic cholestasis was found in 38.80%. A light form of the disease was found in 43.26%, mild--in 50.56%, and severe--in 6.18%, without reaching acute liver failure. In the acute stage of the disease, an increase of helper/inducer CD3+CD4+ ($p = 0.001$), memory T helper CD4+CD29+ ($p < 0.0001$), activated CD3+HLA-DR+ ($p < 0.0001$), mature CD3+ T cells ($p < 0.05$), naive CD2+T ($p < 0.01$), and B-lymphocytes CD19+ ($p < 0.001$) was found, together with a non-significant increase of the suppressor/cytotoxic CD3+CD8+ T lymphocytes in comparison with the controls. The total killer CD56+ were reduced, as well as the MHC restricted killer cells CD8+CD56+. TNF-alpha was elevated in the serum in the light and mild forms ($p < 0.0001$). The participation of non-organ-specified antibodies (NOSAs) was minimal. Anti-MLA titer was 1/80 in two patients. Five years after the outset of AHC, a spontaneous viral clearance was established in 36.67% and chronic hepatitis in 63.33%. **CONCLUSION:** Despite the initially activated immune cellular response strongly correlating with a well expressed cytolytic syndrome around 2/3 of the AHC patients develop a chronic form of the disease.

Hens, N., M. Aerts, et al. (2008). "**Estimating the impact of vaccination using age-time-dependent incidence rates of hepatitis B.**" Epidemiol Infect **136**(3): 341-51.

The objective of this study was to model the age-time-dependent incidence of hepatitis B while estimating the impact of vaccination. While stochastic models/time-series have been used before to model hepatitis B cases in the absence of knowledge on the number of susceptibles, this paper proposed using a method that fits into the generalized additive model framework. Generalized additive models with penalized regression splines are used to exploit the underlying continuity of both age and time in a flexible non-parametric way. Based on a unique case notification dataset, we have shown that the implemented immunization programme in Bulgaria resulted in a significant decrease in incidence for infants in their first year of life with 82% (79-84%). Moreover, we have shown that conditional on an assumed baseline susceptibility percentage, a smooth force-of-infection profile can be obtained from which two local maxima were observed at ages 9 and 24 years.

Kojouharova, M. and A. Kurchatova (2008). "**The Effectiveness of the Universal Infant Immunization Against Hepatitis B in Bulgaria.**" International Journal of Infectious Diseases **12**: E152-E152.

Ivanova, L. and V. Russev (2007). "**Chronic liver diseases and parenterally transmitted hepatitis viruses.**" European Journal of Inflammation **5**(1): 1-6.

Hepatitis B virus (HBV), hepatitis C virus (HCV) and hepatitis D virus (HDV) are the leading cause of chronic liver diseases. The aims of the present study are to determine the etiological relationship of HBV and HCV in patients with chronic liver disease in North-Eastern Bulgaria and prevalence of dual and triple infections. A total of 434 patients were investigated for HBsAg, 402 of whom were also tested for anti-HCV. The HBsAg positive subjects were tested for anti-HDV and 32 of them also for HbeAg/anti-Hbe. Separated commercial

ELISA kits were used. HBsAg was detected in 132 (30.4%); 10.6% were co-infected with HDV Anti-HCV was detected in 15.4%. Five of 132 HbsAg positive patients (3.78%) were simultaneously HBV and HCV positive. Two patients out of 132 (1.52%) were positive to HBV, HCV and HDV Our data indicate that HBV infection was the main cause of chronic liver diseases in NorthEastern Bulgaria, and 10.6% of the patients suffered from severe disease because of co-infection with HDV HCV plays the same role in 15.4% of the cases. Recently, we observed dually infected (HBV and HCV) and triple infected (HBV, HCV, HDV) patients suffering from severe chronic liver diseases.

Mekouchinov, K., E. Marinova, et al. (2007). "**Spread of hepatitis B and C viruses among healthy people in Bulgaria.**" International Journal of Antimicrobial Agents **29**: S541-S541.

Stefanova-Petrova, D. V., A. H. Tzvetanska, et al. (2007). "**Chronic hepatitis C virus infection: prevalence of extrahepatic manifestations and association with cryoglobulinemia in Bulgarian patients.**" World J Gastroenterol **13**(48): 6518-28.

AIM: To assess the prevalence of extrahepatic manifestations in Bulgarian patients with chronic hepatitis C virus (HCV) infection and identify the clinical and biological manifestations associated with cryoglobulinemia.
METHODS: The medical records of 136 chronically infected HCV patients were reviewed to assess the prevalence of extrahepatic manifestations. Association between cryoglobulin-positivity and other manifestations were identified using chi2 and Fisher's exact test. Risk factors for the presence of extrahepatic manifestations were assessed by logistic regression analysis.
RESULTS: Seventy six percent (104/136) of the patients had at least one extrahepatic manifestation. Clinical manifestations included fatigue (59.6%), kidney impairment (25.0%), type 2 diabetes (22.8%), paresthesia (19.9%), arthralgia (18.4%), palpable purpura (17.6%), lymphadenopathy (16.2%), pulmonary fibrosis (15.4%), thyroid dysfunction (14.7%), Raynaud's phenomenon (11.8%), B-cell lymphoma (8.8%), sicca syndrome (6.6%), and lichen planus (5.9%). The biological manifestations included cryoglobulin production (37.5%), thrombocytopenia (31.6%), and autoantibodies: anti-nuclear (18.4%), anti-smooth muscle (16.9%), anti-neutrophil cytoplasm (13.2%) and anti-cardiolipin (8.8%). All extrahepatic manifestations showed an association with cryoglobulin-positivity, with the exception of thyroid dysfunction, sicca syndrome, and lichen planus. Risks factors for the presence of extrahepatic manifestations (univariate analysis) were: age \geq 60 years, female gender, virus transmission by blood transfusions, longstanding infection (\geq 20 years), and extensive liver fibrosis. The most significant risks factors (multivariate analysis) were longstanding infection and extensive liver fibrosis. **CONCLUSION:** We observed a high prevalence of extrahepatic manifestations in patients with chronic HCV infection. Most of these manifestations were associated with impaired lymphoproliferation and cryoglobulin production. Longstanding infection and extensive liver fibrosis were significant risk factors for the presence of extrahepatic manifestations in HCV patients.

Pekova, L., I. Mladenova, et al. (2007). "**Clinical features of acute hepatitis C of nosocomial origin in Bulgaria.**" Panminerva Med **49**(2): 98-100.

Pekova, L. M., P. Teocharov, et al. (2007). "**Clinical course and outcome of a nosocomial outbreak of hepatitis C in a urology ward.**" J Hosp Infect **67**(1): 86-91.

This paper describes a prospective study of the clinical course and outcome of a nosocomial outbreak of hepatitis C virus (HCV) infection in six male urology patients at a hospital in Stara Zagora, Bulgaria. These patients had been previously hospitalised in the urology ward, during which all had received intravenous therapy. Approximately three weeks later, all six were admitted to the infectious diseases unit with acute hepatitis, shown to be caused by HCV genotype 1b. The diagnosis was confirmed by polymerase chain reaction during the first week of their hospital stay. Infected patients were followed up for 30 months following diagnosis and 54 potential contacts for 6 months post-exposure. Four patients recovered completely; one developed chronic HCV infection and one died. The latter already had cirrhosis due to co-infection with hepatitis B virus. The investigation established the index case as a patient with chronic hepatitis C, who had been an in-patient on the same ward at the same time. The most likely route of transmission was intravenous heparin flushes administered with a common syringe. Contrary to the common assumption that acute HCV infection often leads to chronic disease, only one chronic case was observed during the 30-month period of investigation.

Vassilev, Z. P., H. Hagan, et al. (2006). "**Needle exchange use, sexual risk behaviour, and the prevalence of HIV, hepatitis B virus, and hepatitis C virus infections among Bulgarian injection drug users.**" Int J STD AIDS **17**(9): 621-6.

At a time when the rates of HIV, hepatitis C virus (HCV), and hepatitis B virus (HBV) infections have risen among injection drug users (IDUs) in other countries in the region, little is known about the prevalence of these infections among Bulgarian injectors and about their sexual risk behaviours. IDUs (n = 773) in a community-based needle exchange programme (NEP) and two major drug treatment facilities in Sofia completed a structured interview and were tested for HIV, HBV, and HCV antibodies. While HCV prevalence in the sample was 73.9%, HBV and HIV prevalence was low -6% and 0.5%, respectively. Having more than 10 sexual partners, having sex with someone with hepatitis C or another IDU, and never using a condom with another IDU were common among those who were recruited through NEP. As 40% of the IDUs reported using NEP, it appears that needle exchange provides an opportunity to reach high-risk populations and prevent sexual transmission of blood-borne pathogens.

Magdzik, W. (2006). "[**Vaccination against hepatitis B and epidemiological situation of this disease in European countries in the years 1990-2001**]." Przeegl Epidemiol **60**(2): 179-84.

Programme of vaccination in 52 countries of European Region does not include vaccination against hepatitis B of newborns and infants in 13 countries (25,0%), of older children and adolescents in 28 countries (53,8%) and among them newborns, infants older children and adolescents in 8 countries (15,4%). The best coverage of vaccination was found in Italy, Bulgaria, Poland, Romain

and Lithuania. Number of cases of hepatitis B in the years 1990-2001 in 10 countries among 22 (45,4%), decreased in 6 countries (27,2%), increased in 4 countries (18,2%). The biggest improvement of epidemiological situation of hepatitis B was found in Poland.

Kojouharova, M. (2006). "**Current outbreak of hepatitis A in Bulgaria, 2006.**" Euro Surveill **11**(10): E061005 1.

Atanasova, M. V., I. A. Haydouchka, et al. (2004). "**Prevalence of antibodies against hepatitis C virus and hepatitis B coinfection in healthy population in Bulgaria. A seroepidemiological study.**" Minerva Gastroenterol Dietol **50**(1): 89-96.

AIM: Viral hepatitis C is often silent and is sometimes discovered only by routine serologic testing. We investigated healthy adults for seroprevalence of antibodies against hepatitis C virus (HCV), for markers of hepatitis B (HBV) coinfection and for risk factors of transmission blood borne viruses. METHODS: We performed a descriptive cross sectional study for the period 1999-2000. A caseload of 2,211 healthy randomly selected subjects (aged 10-69, both sexes) from a big Bulgarian city gave informed consent for participation and answered a standardized questionnaire. Serum samples were obtained and tested using ELISA method for anti-HCV antibodies, HBV markers (HBsAg, anti-HBc and anti-HBs antibodies), as well as for anti-HIV-1.2 antibodies. RESULTS: The overall anti-HCV seroprevalence was 1.08%, which coincides with the data submitted to WHO for the general Bulgarian population, as well as with the average data for Europe. Higher anti-HCV seroprevalence was ascertained with increasing age except in adolescents, in whom the anti-HCV positivity was high. A great part of the subjects with anti-HCV antibodies -- 62.5% had serological evidence for exposure to HBV. Anti-HCV carriage was in positive correlation with the summarized data for previous morbidity (surgery, blood transfusion and past liver disease), as well as with detecting markers for hepatitis B. In the studied caseload 0.68% had markers of double HCV and HBV infection. Nobody was found as seropositive for HIV-1.2. CONCLUSIONS: The results of our study suggest the need of more stringent measures for prevention and control of HCV infection, including screening focused on different groups of population, precise determination of risk factors for HCV transmission and offering of HBV vaccine to HCV positive individuals to reduce the high risk of double HCV and HBV infection.

Panchovska, M. S. (2004). "**Hepatitis C virus and hepatic abnormalities in Bulgarian patients with primary Sjogren's syndrome.**" Minerva Med **95**(3): 255.

Petrunov, B., M. Kojouharova, et al. (2002). "**EU project interreg II: Seroepidemiology study on hepatitis C and B viral infections prevalence in Bulgaria and Northern Greece.**" Journal of Hepatology **36**: 497.

Rakadjieva, T., J. Stoilova, et al. (2002). "**A study on the basic epidemiological parameters of viral hepatitis a in the region of Plovdiv, Bulgaria.**" Folia Med (Plovdiv) **44**(3): 11-4.

INTRODUCTION: Infection with hepatitis A virus is of great importance to public health. The disease has a worldwide occurrence due to inadequate

sanitation and the variable seroprevalence rates in the community.

OBJECTIVE: The present report investigates the epidemiological features of hepatitis A in the region of Plovdiv and outlines the most important epidemiological features of the disease.

MATERIALS AND METHODS: In 1999 (a year with a lower hepatitis A prevalence) the basic epidemiological characteristics of the disease were studied: overall morbidity and mortality rates, age, sexual and seasonal distribution, and prevalence in rural and urban areas. The study was carried out in a cohort of 288 patients with hepatitis A admitted to the Clinic of Infectious Disease of the Medical University in Plovdiv. All patients were anti HAV IgM positive. Routine clinical, laboratory, epidemiological and statistical methods were used. Laboratory and serological tests were performed at the Center for Disease Control, Plovdiv and at the University Clinical Laboratory.

RESULTS: Of 423 patients with acute viral hepatitis 288 (68.09%) had hepatitis A. In 1999 the morbidity rate for the region of Plovdiv was 49.55 per hundred thousand (intermediate). Disease prevalence was the highest in preschool and early school age as well as in the age groups 20-29 (84.67 per hundred thousand) and 30-39 (71.59 per hundred thousand). Urban residents accounted for 79.85% of the cases. The male/female ratio was 1:1. 82.25% of the preschool children did not attend day-care centers. History of contact with sources of infection was elicited from 17.01% of the patients. Disease rates peaked in October through December (maximum in October).

CONCLUSIONS: Accumulated data could contribute to more effective disease control.

Nikolova, M., M. Liubomirova, et al. (2002). "**Clinical significance of antinuclear antibodies, anti-neutrophil cytoplasmic antibodies and anticardiolipin antibodies in heroin abusers.**" *Isr Med Assoc J* 4(11 Suppl): 908-10.

BACKGROUND: Different autoantibodies and immunologic abnormalities have been described in heroin abusers positive for human immunodeficiency virus, hepatitis B surface antigen, or hepatitis C virus, as well as in addicts with negative viral markers.

OBJECTIVES: To investigate the prevalence of different autoantibodies in heroin addicts.

METHODS: We studied 10 heroin addicts (8 males and 2 females aged 18-30 years) with a mean duration of heroin abuse of 46.5 months (range 6-96) for the presence of the following autoantibodies: antinuclear antibodies and anti-neutrophil cytoplasmic antibodies--using indirect immunofluorescent technique; ds-DNA, ss-DNA, Sm, RNP, Ro and La antibodies--using counter immunoelectrophoresis; and immunoglobulins G and M anticardiolipin and beta 2-glycoprotein-I antibodies--using enzyme-linked immunosorbent assay. All patients were tested for VDRL, HIV, HBsAG and anti-HCV antibodies.

RESULTS: Four patients were positive for ANA, of whom two were positive for anti-HCV and two for ANCA. Three patients were positive for IgM aCL, one of whom was positive for IgG beta 2 GPI with clinical data of acute renal failure in the course of heroin coma and antiphospholipid syndrome (deep vein thrombosis) and positive Sm and ds-DNA antibodies, and another had subacute endocarditis and biopsy-proven chronic tubulo-interstitial nephritis (in both these patients aCL gradually fell to normal levels after the cessation of heroin abuse). One patient was HBsAG positive with negative autoantibodies. All patients were HIV and VDRL negative.

CONCLUSION: Our data support the

importance of ANA and aCL determination as a predictor of some systemic complications in heroin addicts.

Van Damme, P. (2001). "**Hepatitis B: vaccination programmes in Europe--an update.**" *Vaccine* **19**(17-19): 2375-9.

In the eight years since the Global Advisory Group of the Expanded Program on Immunisation set 1997 as the target for integrating hepatitis B (HB) vaccination into national immunisation programs world-wide, more than 116 countries have included HB vaccine as part of their routine infant or adolescent immunisation programs. Meanwhile, many countries have performed economic evaluation studies, while others have initiated sero-epidemiological studies to generate input data for burden of disease calculation. These studies have indicated that epidemiological and economic arguments cannot be used to delay the implementation of universal hepatitis B vaccination. Some countries have improved their surveillance system and included viral hepatitis in the surveillance programs. Other have put hepatitis B vaccination on the political agenda. By the year 2000, following countries of the WHO European Region (51 countries) have implemented a universal hepatitis B immunisation programme: Andorra, Albania, Austria, Belarus, Belgium, Bulgaria, Estonia, France, Germany, Greece, Italy, Israel, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Luxembourg, Malta, Moldova, Monaco, Poland, Portugal, parts of the Russian Federation, Romania, Slovakia, Slovenia, San Marino, Spain, Switzerland, Turkey and Uzbekistan. The Netherlands and some other European countries are seriously studying the issues or are making budgetary provisions for introduction of HB vaccine into their vaccination programme. Most of the European countries, which now use the vaccine routinely, have started with adolescent or infant immunisation. Belgium (1999), France (1994) and Italy (1991) have begun with both adolescent and infant HB immunisation. France continues since 1st October 1998 with the infant immunisation programme only. The rewards of effective implementation of the programmes in these countries are becoming apparent; and their success offers an exemplary model for other countries. The deadline was 1997. Globally, work still remains to be done to support and implement interventions that will bring us closer to the WHO goal and to control, eliminate and eradicate hepatitis B in the coming generations at large. If all the 145 million infants born in 1991 had been vaccinated in this way, the number of chronic carriers would have been reduced by 7.5 million, and 1.8 million deaths prevented.

Kojouharova, M., P. Teoharov, et al. (2001). "**Safety and immunogenicity of a yeast-derived recombinant hepatitis B vaccine in Bulgarian newborns.**" *Infection* **29**(6): 342-4.

BACKGROUND: In 1998, Bulgaria adopted a recombinant DNA yeast-derived hepatitis B (HB) vaccine (Euvax B) for universal vaccination of all Bulgarian newborns on a 0-1-6 month schedule, the first dose to be given within 24 h of birth. **MATERIALS AND METHODS:** We evaluated the safety, immunogenicity and effectiveness of this vaccine in over 40,000 healthy infants from July 1998 to December 1999. Standard safety information was collected for all infants vaccinated, subsets being followed for solicited local and systemic adverse events (n = 200) and antibodies to HB surface

antigen (anti-HBsAg) 1-3 months after the third dose (n = 140). RESULTS: No serous adverse events were registered for any vaccinee, solicited local reactions were rare (< 1.5%), mild and transient. The overall geometric mean titer (GMT) was 1,012 mIU/ml (95% CI: 786; 1,302), the seroprotection rate being 98.6%. CONCLUSION: These surveillance data, obtained under the conditions of universal infant immunization show the novel recombinant HB vaccine, Euvax B, is safe and well-tolerated with an immunogenicity similar to other recombinant HB vaccines.

Popivanova, N. I., E. Ivanova, et al. (2001). "**Viral hepatitis B (VHB) in Bulgaria.**" Journal of Hepatology **34**: 164-165.

La Vecchia, C., F. Lucchini, et al. (2000). "**Trends in mortality from primary liver cancer in Europe.**" Eur J Cancer **36**(7): 909-15.

Upward trends in incidence and mortality from primary liver cancer have been reported from Japan, the USA and a few European countries. Thus, we systematically reviewed trends in age-standardised death certification rates from primary liver cancer between 1970 and 1996 in 20 European countries providing data for the World Health Organisation database. Overall age-standardised (world population) mortality rates were approximately stable or showed no consistent trends in seven countries, including Bulgaria and Hungary (with exceedingly high rates), Finland, The Netherlands and the UK. Moderate rises were observed in Austria, Germany and Switzerland, and much larger upward trends in France and Italy, particularly for males. Downward trends were observed in both sexes in Belgium, Spain, Ireland, Greece and several Scandinavian countries. The per cent change in rates per year ranged, for males, from -7.4% for Ireland and -5.1% for Spain to +4.4% for Italy and +8.6% for France. Trends were more favourable in women, with 15 out of 20 countries showing downward trends in rates, and moderately more favourable in middle age (45-64 years) and, in major European countries, in young adults (20-44 years of age). In conclusion, trends in liver cancer mortality in Europe are heterogeneous. The fall in mortality in countries like Spain may be largely explained by improvements in the distinction between primary and secondary liver neoplasms, whereas upward trends in Central Europe and Italy are likely to be, at least in part, real. Increases in infection with the hepatitis C virus, and improved and increased searches for liver cancer in cirrhotic patients are two of the likeliest explanations for these observations.

2. Hepatitis Bibliography of the Speakers

List of publications achieved via speakers form when this form was not available a Pubmed MEDLINE search was performed on Name of the speaker in [Author]-field and 'Hepatitis' in [all fields]. If more than 10 references only the most recent articles are shown.
Non hepatitis related references are formatted in grey.

MIRA KOJOUHAROVA, *National Centre of Infectious and Parasitic Diseases*

1. Kojouharova M, Kurchatova, A. **The Effectiveness of the Universal Infant Immunization Against Hepatitis B in Bulgaria.** *International Journal of Infectious Diseases* 2008;12:E152-E.
2. Kojouharova M; Editorial team. **Current outbreak of hepatitis A in Bulgaria, 2006.** *Euro Surveill.* 2006 Oct 5;11(10):E061005.1.
3. Kojouharova M, Teoharov P, Bahtchevanova T, Maeva I, Eginlian A, Deneva M. **Safety and immunogenicity of a yeast-derived recombinant hepatitis B vaccine in Bulgarian newborns.** *Infection.* 2001 Dec;29(6):342-4.

STEVEN WIERSMA, *WHO*

1. Wiersma ST, McMahon B, Pawlotsky JM, Thio CL, Thursz M, Lim SG, Ocamo P, Esmat G, Maimuna M, Bell D *et al*: **Treatment of chronic hepatitis B virus infection in resource-constrained settings: expert panel consensus.** *Liver Int* 2010.
2. Jacobsen KH, Wiersma ST: **Hepatitis A virus seroprevalence by age and world region, 1990 and 2005.** *Vaccine* 2010, **28**(41):6653-6657.
3. Wiersma ST: **Hepatitis B vaccine continues to provide long-term protection to healthcare workers.** *J Hepatol* 2009, **51**(4):826; author reply 826-827.
4. Dumolard L, Gacic-Dobo M, Shapiro CN, Wiersma S, Wang SA: **Implementation of Newborn Hepatitis B Vaccination-Worldwide, 2006 (Reprinted from MMWR, vol 57, pg 1249-1252, 2008).** *Jama-J Am Med Assoc* 2009, **301**(1):29-31.
5. Hendrickx G, Van Herck K, Vorsters A, Wiersma S, Shapiro C, Andrus JK, Roper AM, Shouval D, Ward W, Van Damme P: **Has the time come to control hepatitis A globally? Matching prevention to the changing epidemiology.** *J Viral Hepatitis* 2008, **15**:1-15.
6. Kham DD, Ojima T, Nymadawa P, Tsend N, Lkhagvasuren T, Wiersma S, Uehara R, Watanabe M, Oki I, Nakamura Y: **Seroepidemiology of**

hepatitis B virus infection among children in Mongolia: Results of a nationwide survey. *Pediatr Int* 2007, **49**(3):368-374.

7. Hollinger FB, Bell B, Levy-Bruhl D, Shouval D, Wiersma S, Van Damme P: **Hepatitis A and B vaccination and public health.** *J Viral Hepatitis* 2007, **14**:1-5.
8. Davaalkham D, Ojima T, Wiersma S, Lkhagvasuren T, Nymadawa P, Uehara R, Watanabe M, Oki I, Nakamura Y: **Administration of hepatitis B vaccine in winter as a significant predictor of the poor effectiveness of vaccination in rural Mongolia: evidence from a nationwide survey.** *J Epidemiol Commun H* 2007, **61**(7):578-584.
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