• VIRAL HEPATITIS

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Lessons learnt and the way forward	ŀ
Athens, Greece, November 15-16, 2007.	'

Editorial

This issue of Viral Hepatitis reviews topics covered at the Viral Hepatitis Prevention Board (VHPB) autumn meeting "Prevention and control of viral hepatitis in Greece: Lessons learnt and the way forward", held on November 15-16, 2007 in Athens, Greece.

This VHPB "country" meeting brought together scientists, doctors and public health experts responsible for the prevention and control of viral hepatitis in Greece who reviewed existing surveillance systems for infectious diseases; provided an update of the epidemiological situation on viral hepatitis; and evaluated current prevention and control measures on viral hepatitis in Greece, with a view to identify successes, problems and barriers to overcome, and the way forward. Several lessons were learnt from presentations and discussions during the meeting, which led to the formulation of recommendations on the basis of existing strengths and future challenges to be faced.

In particular, the low level of public health expenditure in Greece, coupled with the high involvement of the private sector in immunization practices, were identified as factors of social inequities, leaving unvaccinated populations unprotected.

Also, the need for reliable data on Hepatitis A (HAV), Hepatitis B (HBV) and Hepatitis C (HCV) incidence at national level was recognized, with particular attention to be paid to higher rates observed among immigrants. Several approaches taken to study national seroprevalence and overcome the limitations of existing surveillance systems were discussed.

In terms of immunization policies, the need for timely HBV vaccination, especially in infants during the first months of life to prevent horizontal intrafamilial transmission, was emphasized; a decision regarding the introduction of HAV routine vaccination in Greece should be reconsidered based on recent epidemiological data.

Finally, the unique opportunities offered by the nationwide ongoing HBV-HCV cohort study were underlined in terms of enhanced prevention and improved treatment for both diseases while the importance of strengthened follow-up of HBV/HCV-HIV coinfected patients and reinforced prevention measures was also stressed.

Vana Papaevangelou and Pierre Van Damme on behalf of the Viral Hepatitis Prevention Board

Breaking news:

Greece decided to implement routine hepatitis A vaccination.

Supported by the discussions and information presented during the meeting the Greece National Advisory Committee for Immunisation decided to include hepatitis A vaccination into the National Immunization Programme, as of January 23, 2008. Within the National Immunization Programme hepatitis A vaccine is now offered free of charge to all children.

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MEETING NEWS

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Prevention and control of viral hepatitis in Greece: Lessons learnt and the way forward Athens, Greece, November 15-16, 2007

The Health Care system in Greece

The current Greek Health Care (HC) System is a complex, mixed system, integrating elements from the *Bismarck* model (financed mainly by social insurance) and *Beveridge* model (financed mainly by state taxes) [1]. Health services are divided into 3 sectors (see Figure below):

- The Greek National Health System (NHS/ESY) was implemented in Greece in 1983 in an effort to establish the *Beveridge* model, however, this was never accomplished because Social Insurance services refused to be included in the services of the NHS.
- Since then, Social Insurance Services have remained independent and operated outside the NHS. Almost 50% of the Greek population is ensured via the IKA Foundation, which is the most important entity among Social Insurance Services.
- The Private sector is of major importance in the Greek HC system. Private services are paid directly out-of-pocket or through private health insurances. Approximately 10% of the Greek population has an additional private insurance while social insurance is mandatory for all Greeks.

Organization and financing of health services



The organization of the primary HC services in Greece is summarized in the following Figure:



Once the NHS was established in 1983, the initial target was to organize primary HC throughout the country. However, after setting up primary HC centers in rural areas, the system was never extended to cities, due to lack of involvement of Social Insurance Services. Therefore, in urban areas, only public medical dispensaries or public hospitals with outpatient departments are available today.

The Social Security system established polyclinics in cities (mainly IKA-funded), and in addition, \sim 3500 physicians are contracted with a social insurance foundation.

During the last years, local authorities have started to set up and operate a limited number of primary HC centers (polyclinics or medical dispensaries). The growth of the private health services was most prominent in the primary HC sector [2], which now constitutes over 60,000 private physicians and many diagnostic centers. Together with Italy, this represents the highest ratio of doctors/population in Europe.

In 2004, the hospital infrastructure in Greece counted 319 hospitals. Of these, 44% were large public hospitals and 54% were small private hospitals. This accounted for a total of more than 50,000 hospital beds (69% public; 28% private), which largely covers the current needs.

Over the last 25 years, the ratio public/private expenditure has evolved to approximately 50/50. The public health expenditure in Greece is currently the lowest in Europe (5.3% of Gross National Product in 2005). Public health expenditure is mainly used for financing of hospitals (55%), followed by primary HC (24%) and pharmaceuticals (16%). On the other hand, most private expenditures cover primary HC (66%) while 16% is for purchase of drugs and only 14% for hospitals. This large difference in public versus private health financing is mainly due to the fact that public primary HC was never completed in cities. Since only IKA-funded HC centers are available in urban areas, but with lower quality of services, most Greeks living in cities are forced to rely on private sector for primary HC. Recently, the same trend has also been observed in rural areas where attendance at private primary HC centers has increased.

The main issues encountered with the Greek HC system can be summarized as follows:

- Greece has the lowest level of public health expenditure in Europe.
- As a consequence, the public budget is inadequate to cover HC resources, mainly leading to shortage of nurses in public hospitals (only 1 nurse/bed).
- Administration framework is complex with responsibilities fragmented between ministries.
- The management of public hospitals is inadequate due to its political character.
- Primary HC is not sufficiently organized.
- At national level, there is a lack of organized prevention and health promotion, and underuse of diagnostic testing. Life expectancy in Greece was 77 years in 1991, ranking as second highest within the EU; while it has now dropped to 7th position, with 79 years, this slight gain is mainly due to decreased child mortality rather than increased adult life expectancy (still high rates of smokers, obese individuals, etc.)
- The private sector, playing a major role, is poorly regulated, with no evaluation and control.
- The weight of the private sector leads to social inequities in the access to health services. This is reflected in low life expectancy, high morbidity and mortality associated with low socio-economic status.

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Based on a presentation by Y. Tountas, University of Athens, Athens, Greece.

MEETING NEWS

Viral hepatitis surveillance, prevention and control in Greece

National Program for Viral Hepatitis

The Hellenic Centre for Disease Control and Prevention (HCDCP/Keelpno) is an independent center responsible for the surveillance and control of infectious diseases in Greece, located in Athens. It functions under the supervision of the Ministry of Health, and in close collaboration with all public health authorities.

HCDCP was established in 1992 with the aim of developing activities on HIV/AIDS, including:

- support to specialist clinical infectious disease departments and reference laboratories
- provision of medicines to patients
- · epidemiological studies
- health education
- · psychosocial support

Today, HCDCP is responsible for a wider range of activities related to infectious diseases, including:

- public health support for immigrants, refugees and other minority groups
- · prevention and control of viral hepatitis
- · nosocomial infection research and control measures
- · travel medicine consultation and issuing of guidelines

Furthermore, the Department of Surveillance and Intervention within HCDCP is responsible for public health surveillance in Greece.

Within the HCDCP, the Office of Viral Hepatitis consists of 2 physicians, 1 nurse and 1 administrative employee working in collaboration with a Scientific Commission of Viral Hepatitis constituted of 25 members.

The objectives of the Office of Viral Hepatitis and the Scientific Commission are:

- Prevention
- Education
- Surveillance
- Improvement of medical care
- Coordination of the nationwide HepNet.Greece study

Prevention is the highest priority of the HCDCP. Recommended HBV vaccination for all infants was introduced in the Greek National Immunization Program (NIP) as of 1 January 1998 (see section on HBV immunization), with the aim of preventing acute and chronic HBV infection and achieve elimination of HBV transmission in all age groups.

The HCDCP is responsible for updating the recommendations for HAV and HBV vaccination and also supports implementation of management programs to prevent perinatal HBV infection through:

- testing of pregnant women for HBsAg as part of routine prenatal care
- recording of HBV vaccination and hepatitis B immune globulin (HBIG) administration for all neonates born from HBsAg-positive mothers.

Education and training are strategic priorities of the HCDCP in order to increase knowledge and awareness among health care professionals, high risk populations and the general public. The aim is to favor changes in attitude and practice that will result in improved prevention and control. Specifically for viral hepatitis, free educational material for HBV and HCV is provided in different languages. Recommendations on prevention of transmission of HBV and HCV are given to school teachers and an informative website is available (www.keelpno.gr). One-day meetings and conferences on HBV and HCV as well as training programs for intravenous drug user (IDU) community outreach are organized. Brochures and clinical guide-lines are also issued.

The following recommendations, guidelines and related updates are issued by the HCDCP:

- Updated recommendations for HAV and HBV prevention
- · Updated recommendations for HBV vaccination
- Recommendations for HBV and HCV treatment
- Recommendations for the management of Health Care Workers (HCWs), occupationally exposed to HBV and HCV
- Guidelines for prevention of HBV and HCV transmission from HCWs to patients

Besides prevention and education, HCDCP is also responsible for **medical management**. The overall goals of medical and case management of individuals infected with viral hepatitis are:

- · to reduce the incidence of new infections of hepatitis
- to limit the disease burden from chronic hepatitis
- to improve the quality of life of those chronically infected with HBV and HCV

Improvement of health care for HBV/HCV patients is ensured through optimized approaches to screening, diagnosis and management of HBV and HCV infection; protocol design for laboratory follow up; and through recommendations for the treatment of chronic HBV and HCV.

In Greece, treatment of patients with chronic HBV and HCV is free of charge since January 2007; molecular biological tests are also offered free of charge.

Finally, the HCDCP is also responsible for the **coordination** and sponsoring of the nationwide HepNet.Greece cohort study for HBV and HCV since 2003. The aim of this study is to evaluate the epidemiology and the course of chronic viral HBV and HCV infection in Greece and their longitudinal changes (see section on HBV-HCV cohort study in this report).

A national seroprevalence study, including all geographical parts of Greece, is planned in order to evaluate prevalence, risk factors and cost effectiveness of medical care of viral hepatitis patients.

Viral hepatitis surveillance in Greece

Infectious Disease (ID) Surveillance aims at the identification of new cases and management of outbreaks, as well as monitoring incidence trends and

transmission patterns of viral hepatitis. The collected surveillance data are used to organize, develop and evaluate the prevention management.

Surveillance of ID was established in Greece as early as 1950 by Royal law (code Φ EK: 262/1950), which made recording of new ID cases mandatory, but achieved poor compliance. In 1992, the HCDCP was established with the main aim of developing HIV and AIDS activities. The HCDCP started an initial attempt at ID surveillance in 1998.

On 19 March 2002, EU Decisions (2002/253/EC by EU Council and 2119/98/EC by EU Parliament) relating to surveillance came into force. In order to obtain comparative data and better coordination between the different EU countries, these decisions stated the case definition for 41 notifiable IDs under surveillance.

The current ID surveillance program in Greece was initiated in 2003 in preparation of the Olympic Games and is compliant with above EU decisions. Following Greek public law (code 3172/2003 ΦEK 197), epidemiological surveillance became the responsibility of the HCDCP.

Since 2003, HCDCP assignments include:

- Preparation of a new list of diseases for the mandatory notification system
- Preparation of a case definition for every notifiable ID, in compliance with EU decisions
- · Preparation of a standardized notification form
- Establishment of weekly reporting of cases (formerly done on a monthly basis)
- Set up of campaign to inform health professionals about new list of IDs, case definition and mandatory case notification

The standardized notification form documents information on demographics, risk factors, clinical characteristics and laboratory results. The flow chart on the top right illustrates the notification process.

Cases are notified by general practitioners, primary health care units and hospitals to the District Department of Public Health, which takes local control actions and notifies the HCDCP. In case of more serious cases, the



hospital can directly notify the HCDCP. The HCDCP initiates special interventions, as needed, and cooperates with the Ministry of Health and relevant Health Authorities in order to take necessary measures, especially in case national public health may be affected.

Currently the system faces difficulties caused by low compliance from physicians, who sometimes do not notify cases or provide notification forms with incomplete data. The involved health personnel often sees the notification system as an additional administrative task and/or is not aware of the value of the notification information in the process of disease control.

Surveillance of viral hepatitis is part of the mandatory notification system in Greece.

Clinical and laboratory criteria, as well as case classification for acute HAV, HBV and HCV are summarized in the Table below. Of note, since 2003, initial diagnosis of asymptomatic HCV confirmed by anti-HCV is also notifiable.

Unlike other diseases, there is currently no separate laboratory notification system for hepatitis cases. However, including hepatitis to the list of diseases to be notified by laboratories would help reducing underreporting by private physicians.

Clinical criteria, laboratory criteria and case definitions used in Greece for HAV, HBV and HCV

	Clinical criteria	Laboratory criteria	Case classification	Limitations
HAV, acute	An acute illness with discrete onset	IgM anti-HAV positive or HAV RNA positive or detec- tion of HAV antigen in stools	 Confirmed: meets clinical case definition and laboratory confirmed Probable: meets the clinical case definition and has epidemiologic link to a case of acute HAV 	Case definition does not include asymptomatic HAV cases which are IgM anti- HAV positive
HBV, acute	of symptoms (e.g. fatigue, abdomi- nal pain, loss of appetite, intermit- tent nausea, vomiting) and jaundice or elevated serum aminotransferase levels	IgM anti-HBc positive or HBV DNA positive	 Confirmed: meets clinical criteria and laboratory confir- med Probable: meets clinical criteria and positive HBsAg 	HBsAg+, asymptomatic infants <12 m/o: should be notified, other asymptoma- tic cases, anti-HBc IgM+ or HBsAg+: should not be notified
HCV, acute		Anti-HCV pos and IgM anti- HAV neg and IgM anti-HBc neg or HCV RNA pos	 Confirmed: meets clinical criteria and laboratory confir- med Probable: not applicable 	None
Newly diagnosed HCV, Asymptomatic (confirmed by anti-HCV, 1st diagnosis)	No clinical manifestations, may have chronic liver disease ranging from mild to severe (cirrhosis, cancer)	Anti-HCV pos (repeat reactive) by EIA and verified by additional assay (RIBA or RT-PCR) for HCV RNA OR HCV RNA pos	 Confirmed: asymptomatic case diagnosed for first time and laboratory confirmed Probable: not applicable 	None

Case definitions for acute HAV, HBV and HCV (except for newly diagnosed asymptomatic HCV cases) are in compliance with EU decisions (2002) and HCDCP (2003)

Different approaches to national seroprevalence study

Reliable surveillance data- preferably available by age, risk group and geographical region- are necessary to determine the prevalence of a disease. Several approaches exist for obtaining initial seroprevalence data, relying both on active and passive surveillance, such as the use of a prediction model through back calculation methods, based on current data; seroprevalence study, based on residual samples; population-based serosurvey, or national health survey.

Irrespective of the method used, national notification data are always involved. As mentioned earlier, the Greek surveillance system is still under evaluation and does not yet provide reliable viral hepatitis data, due to substantial underreporting. Even if the surveillance system is working properly, it can be considered that the cumulative hepatitis notification rate would be underestimated due to underreporting, low levels of testing in some risk populations, the asymptomatic nature of acute hepatitis, and the long latency period.

Back calculation method

This approach combines the use of existing statistics on the number of reported cases with a mathematical representation of the natural history of the infection.

In order to be able to run the back calculation method, an initial estimate of the overall prevalence is needed. In the case of HCV in Greece, results from several studies conducted in specific areas are currently available, however there are no reliable national data. As shown in Table below, population-based results are only available from 2 studies, but these were conducted in very restricted areas [1, 2] while remaining data are all related to specific groups.

HCV prevalence data are also available for specific risk groups, such as IDUs, however HCV rates are variable, depending on the program involved, i.e. substitution or drug-free program (see section on Epidemiology of HCV).

Population	Studies	Prevalence of HCV
A. General population -	eneral population - Gogos et al, 2003	
specific geographical areas	Goritsas et al, 2000	
B. Specific groups		
Blood Donors	Zervou et al, 2003	0.61%
Healthy Employees	Sypsa et al, 2001	0.5%
	Mazokopakis et al, 2000	0.4%
Hemodialysis patients	Stefanidis et al, 2004	23.6%
Women giving birth	Panagopoulos et al, 2004	0.8% (0.16-1.33)
Refugees	Roussos et al, 2003	2.3%
Prisoners	Giotakos et al, 2003	6.5%
Pregnant women	Raptopoulou et al, 2001	1.95%
General practitioners	Lionis et al, 2000	3.5%

Several groups in different countries used back calculation to estimate HCV disease burden, e.g. in the USA, Australia and the UK. The method was applied to Greek data to estimate disease burden and to evaluate the future effect of different treatment strategies [3]. Further details on the outcome of this study are provided in the section on Epidemiology of HCV of this report.

Several drawbacks are linked to back calculation methodology. Availability and accuracy of data for the relevant parameters are very important. Estimations heavily influence the validity of the model's assumptions.

In the particular case of Greece, there is no accurate estimate of prevalence by age and transmission group. The nationwide HepNet.Greece study provides data on age distribution, risk group, and disease progression but it does not allow for the calculation of a reliable estimate of viral hepatitis prevalence, because not all clinics in Greece participate in this study. Therefore, back calculation estimates may be even more biased than underreported notification data.

Residual sera

Seroprevalence studies using residual sera collected during routine laboratory testing represent a valid approach to assess disease burden, as illustrated from well-established studies conducted through the European Sero-Epidemiology Network (ESEN, www.hpa.org.uk/hpa/inter/esen2_menu.htm) or in Australia [4]. To this end, a national net of collaborating laboratories willing to provide residual sera needs to be established. The pre-specified number of sera to be tested each year, stratified by age and gender, has to be calculated, for instance according to ESEN methodology. Strengths of the residual sera approach are the easy accessibility of serum specimens and the low costs involved while a major drawback of using residual samples is that the population may not be representative.

Population-based survey

As a second option for the conduct of seroprevalence studies, specimens can be collected as part of a population-based survey, while ensuring population age and gender distribution are kept balanced. Sample weights can be adjusted for over-sampling of specific demographic groups or minorities, for non-response, or for differences between sample and population, as needed. Disadvantages of this method are linked to the difficulty of carrying out such complex and costly studies, and the scientific issue of nonresponse. Funding such a seroprevalence study remains an issue in Greece, but extending the study to other diseases, e.g. HIV seroprevalence, might make it a more feasible plan, in particular if seeking collaboration and support from experienced research teams, e.g. :

- National Health and Nutrition Examination Survey (NHANES, www.cdc.gov/nchs/nhanes.htm)
- Survey of Health, Ageing and Retirement in Europe (SHARE, www.share-project.org/)
- European Sero-Epidemiology Network (ESEN)

National health survey

In the particular case of Greece, a small national health survey study to estimate the prevalence of chronic conditions in the overall Greek population might offer a valid option, collecting information on:

- Demographics, socioeconomic status, general dietary habits and medical examination by trained medical personnel
- Identification of risk groups
- Data related to other diseases (anemia, cardiovascular disease, diabetes, infectious diseases, obesity) thereby creating the opportunity for collaboration with other scientific societies.

Should funding be made available for such a study to be conducted, this option could represent the best choice for Greece-on a cost-benefit basis- to provide a reliable estimate of the general health status of the population, with the possibility to project future disease burden, design public health actions, and calculate future costs related to health.

However, the importance of repeating such studies was underlined as a critical factor for the relevance of results yielded, as well as the need for clear objectives to be defined in relation to the choice of adapted methodology (e.g. different methodology is used to collect information on general population versus risk groups).

As an alternative to costly and complex NHANES-like studies, the conduct of demographic health survey (DHS) with biomarkers, using simpler methodology, was mentioned.

Experience gained from surveillance during the 2004 Olympics

During the Olympic Games in 2004, Greek surveillance systems of infectious diseases were enhanced. The surveillance aimed at recognizing and responding to potential outbreaks, bioterrorism events and single cases of infectious diseases requiring measures to prevent further spread. In addition, primary prevention measures were evaluated.

Enhanced routine surveillance system

During the Olympics, multiple surveillance systems were in operation, involving activities to be coordinated among 69 participating health units. Intensive training of health care staff, collaboration between regional health units as well as support from international cooperation was ensured. The reporting frequency was increased from monthly to daily during the Olympics period, and data were analyzed and reviewed on a daily basis. Standard operating procedures (SOPs) for interpreting data and deciding on measures to be implemented were developed. The statistical significance of the outcome was translated into public health actions, for which adequate capacity of specialists needed to be available. All these enhancements required a major reorganization of former routine surveillance.

Mandatory notification, laboratory reporting, and primary care sentinel physicians were part of this enhanced routine surveillance:

- EU-compliant case definitions were used, notification forms were revised and protocols for public health actions were established. Among notifiable diseases, HAV was to be reported within 24 hours. Acute HBV, HBsAg positivity in infants <12 months as well as acute HCV or anti-HCV-confirmed first diagnosis were to be reported within the first 3 days of the week following the week of diagnosis. Mobile health units were in charge of immediate health issues among mobile populations, immigrants or other refugees. The teams were trained for outbreak investigation and immediate response.
- In terms of laboratory reporting, 16 reference and satellite laboratories were set up, using protocols for an extensive list of selected pathogens and describing collection, transportation and laboratory processing.
- The primary care sentinel physician system used was the one in place for influenza and included approximately 200 primary care physicians across the country.

Syndromic surveillance

In addition to the above routine surveillance practices, a new syndromic surveillance system, adapted from the 2002 Winter Olympics in Utah, was implemented and is based on a predefined list of syndromes to be reported. The major objective was early detection of bioterrorism events and quick detection of potential disease outbreaks.

The system was first tested during a 2002-2003 pilot phase, with weekly data collection and retrospective analysis. During the Olympics period, the system was enhanced, with daily collection from 31 points across the country and daily analysis and reporting.

Surveillance results

Diseases reported most frequently by mandatory notification during the Olympics were Salmonellosis (54%) and Tuberculosis (17%). Based on laboratory notification, Salmonella was again notified most often (67%), followed by Campylobacter (19%).

Very few reports of hepatitis were received through the routine surveillance system: 4 cases (0.9%) of HAV, 20 cases (4.5%) of HBV and 11 cases (2.4%) of HCV. Based on syndrome surveillance, 68 cases (0.1%) of acute HAV were observed.

When looking at outbreaks during the Olympics period, 14 clusters of foodborne or waterborne disease, each with a small number of cases (2-5) usually among family members, and eight larger outbreaks of gastroenteritis (6-8 cases each) were notified.

The most challenging task was the comparison and interpretation of the numerous data collected. Daily data were compared with the previous 7 days for each disease or syndrome, according to district, and statistical signals from the enhanced surveillance were carefully processed.

In addition, specific operational procedures were followed to deal with single cases. All reported single cases of communicable diseases, related to the Olympics, underwent further epidemiological investigation to establish the risk of outbreak and to take control measures. Follow-up of single cases reported through the syndromic surveillance system was performed to exclude the possibility of a bioterrorism event.

Overall, no major public health event occurred during the Athens 2004 Olympic Games. Although the enhanced surveillance system was very demanding in terms of personnel workload, the daily reporting was well accepted. Importantly, the whole experience created significant expertise among the staff of the HCDCP and the same individuals and systems involved in routine public health surveillance activities were used in the surveillance systems aimed at the detection of potential bioterrorism events [5]. While daily reporting was only considered feasible on short term basis (e.g. for large scale gatherings), the enhanced surveillance system, including the newly implemented syndromic surveillance, could be maintained for ongoing routine surveillance by HCDCP.

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A. Konstantopoulos, University of Athens, Athens, Greece

[slides presented by V. Papaevangelou, A. Kyriakou Children's Hospital, University of Athens, Goudi, Greece];

- G. Nikolopoulou, HCDCP (Keelpno), Athens, Greece; G. Touloumi, University of Athens, Athens, Greece;
- S. Tsodrias, University of Athens, Athens, Greece and A. Zisouli, HCDCP (Keelpno), Athens, Greece.

HBV and HCV patient cohort study

In 2003 the HCDCP started a very extensive follow-up study of chronic HCV, HBV and HDV patients. This study called HepNet.Greece has received the financial support of the HCDCP to be conducted up to the year 2011 and is scientifically coordinated by the Viral Hepatitis section of the HCDCP. At study start in 2003, 30 hepatology centers were involved, mainly located in the metropolitan areas of Athens (60% of centers) and Piraeus (7%), and in Thessalonica, in Northern Greece (14%). By 2007, 20 hepatology centers were still participating and collaborating. The primary objective of the study is:

• to investigate the course and outcome of chronic HBV, HDV and HCV, with and without treatment, in this large cohort of Greek patients.

Secondary targets are:

- to obtain an indirect estimate of the incidence of chronic HBV, HDV and HCV infection in Greece from the number of newly diagnosed patients yearly;
- to introduce common standards of care among HBV and HCV patients; and
- to improve collaboration between Hepatology Centers in Greece.

The study is conducted according to a retrospective-prospective design and started in 2003 with the retrospective recording of all patients followed at each participating center since 1997. Data included demographic, clinical, biochemical and virological information available from patients' records.

Since 2005, patients already in the study as well as all new cases have been followed semi annually and new data has been reported centrally. Data recording was done manually in all centers while subsequently centrally evaluated and transferred to an electronic database. Since 2006 data entry and central reporting has been done electronically. The electronic data entry system ensures that critical information is provided before a case can be entered.

By October 2007, a large number of reports had already been analyzed: 3480 HBV cases and 2817 HCV cases, respectively. Of note, 538 cases of HBV and HCV co-infection were not included. Also, the analysis of HDV cases is currently pending.

HBV results

In the overall cohort of 3480 cases, the majority of HBV cases are adults (96%) with a mean age of 40.3 years at first diagnosis. Only 4% of reported HBV cases were children with a mean age of 6.6 years at first diagnosis. More HBV cases were observed in males than females in both adult (64%) and children (61%) groups.

Most HBV-infected adults were of native Greek origin (83%), with only 17% immigrants. However, as presented in upper right Table, a different distribution was observed among HBV-infected children, i.e. 57% were of immigrant origin (representing 12% of HBV-positive immigrant cohort) and 43%

were native Greeks (representing 2% of HBV-positive native Greek cohort). These results indicate that HBV disease initiates at an earlier age in immigrant populations who are thus more likely to become chronic carriers.

HBV results: Demographics by ethnic origin					
Status	Adults (N, %)	Children (N, %)			
Native Greeks	2,558 (83%)	53 (43%) (or 2% of natives)			
Immigrants	531 (17%)	69 (57%) (or 12% of immigrants)			

The higher proportion of children among HBV-infected immigrants is also reflected in the mean age at first diagnosis, which is lower among immigrant HBV cases (28.4 years) than among natives (41.4 years) (see Table below).

HBV results: Demographics by ethnic origin and age			
Parameter	Native Greeks	Immigrants	
Current Age (in years)	47.0±15.1	30.3±14.2	
Age (at 1 st diagnosis) (in years)	41.4±15.9	28.4±13.4	
Follow-up (at the time of study entry) (in years)	3.3±3.6	1.2±1.9	

Additional demographic data showed that HBV-infected immigrants originated mainly from Albania (74%) or other Eastern European countries (20%) while a smaller percentage came from Asian or African countries. The majority of immigrants in this HBV cohort live in rural areas of Greece (86.1%) whereas few live in urban or semi-urban regions (7.0% each). Among HBV-infected native Greeks, a majority of cases also live in rural areas (63.8%), followed by urban regions (25.7%) and semi-urban regions (10.5%).

The proportion of HBeAg-positive adults is low (8%) versus 62% of children. When considering origin, the percentage of HBeAg-positives is higher among immigrants (17%) as compared to native Greeks (8%).

As shown in Table below, at first visit, 7.4% of native HBV-infected cases reported cirrhosis. Although the immigrant subgroup in the cohort represents a younger population (approximately 30 years of age), already 3.3% had cirrhosis. The incidence of hepatocellular cancer (HCC) at first visit was 1.0% and 0.5% for natives and immigrants, respectively.

Presence of cirrhosis and hepatocellular cancer at the first Visit			
Native Greeks Immigrants			
Cirrhosis	195/2625	20/598	
(N, %)	(7.4%)	(3.3%)	
HCC	25/2625	3/598	
(N, %)	(1.0%)	(0.5%)	

HCV results

Of the 2817 HCV cases, more males (59.3%) than females were HCV-positive. The mean age at first diagnosis was 41.5 years. Intravenous drug use

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(30.7%) was the most important known source of HCV infection, followed by blood transfusion (22.6%). A smaller proportion was due to hospital admission/operation (3.4%), professional exposure (1.1%) or other sources (5.6%). In a large percentage of HCV cases, the source of infection is unknown (36.6%), as shown in Figure below:



Half of the HCV-infected patients in this cohort have a normal BMI while 38% are overweight (BMI 25-30) and 12% are obese (BMI>30), which is often accompanied by a more rapid progress of the disease.

Recently, data on the change in the distribution of HCV genotypes in this Greek cohort study have become available. These are discussed in the section on HCV epidemiology.

In conclusion, the HepNet.Greece study follows a significant number of chronic HBV and HCV patients. The data from this nationwide cohort study may be used to improve prevention and control of HBV and HCV diseases and to achieve earlier diagnosis and more effective treatment through better screening and surveillance. It also allowed to improve collaboration between different hepatology centers and to introduce common standards of care.

New proposals for prospective studies to be conducted with centers are currently under discussion.

> Based on a presentation by E. Manesis, University of Athens, Athens, Greece

Surveillance in blood bank

The safety of blood supply remains a major concern of public health and requires continuous efforts to ideally reach zero-risk probability. The residual risk of transmitting blood-borne viruses through transfusion varies depending on the demographic and socio-economic conditions of each country.

The risk of transmitting viral infection to recipients of blood components has been significantly reduced over the last years owing to a combination of measures, including thorough donor selection, elimination of high-risk donors, appropriate use of blood and blood components, treatment of blood products, and implementation of advanced and highly sensitive screening assays.

Viral infections that can be transmitted through transfusion include HBV, HCV and HIV.

Serological detection of HBV infection is mainly based on detection of HBsAg by means of 3rd generation immunoassays (<0.1ng/ml). Detection of anti-HBc, used as surrogate marker in some countries, is optional in Greece. Detection of HCV infection is based on screening for antibodies against several HCV antigens by 3rd generation immunoassays, and/or HCV core detection. Western blot is used for confirmation. Detection of HIV infection is based on screening for antibodies against several HIV antigens, using 3rd generation immunoassays and screening for p24 antigen.

Greek serological data are available from the Hellenic Coordinating Haemovigilance Centre (SKAE, Athens) and are based on about 5.6 million blood units serologically screened in the period 1996-2006. Based on this screening, the prevalence of positive blood donors was shown to be 0.4% for HBsAg, 0.08% for HCV and 0.007% for HIV, respectively.

The implementation of Nucleic Acid Testing (NAT) technology in the blood bank setting was particularly significant, since it reinforced the safety of blood supply. Implementation of NAT technology was initially launched in Greece for HCV RNA/ HIV RNA in 2003 in a number of blood transfusion centers. HBV DNA testing was also included in 2005 and the number of blood transfusion centers performing NAT screening has gradually increased until the end of 2006.

Preliminary data of NAT screening over the period 2003-February 2007 (SKAE, Athens) are based on 348721 blood units: 169694 units (49%) were tested for both HCV RNA and HIV RNA and the remaining 179027 units (51%) were tested for the 3 viruses, HCV RNA, HIV RNA and HBV DNA.

Comparison of the Greek results with those from other EU countries has shown a higher incidence of NAT yield cases (samples identified as NATpositive but antibody-negative) for all three infections (1 HIV/133373; 1 HCV/50.015 and 1 HBV/6.080 blood units). These data emphasize the importance of establishing NAT as a routine screening test in the entire blood supply in Greece.

The 38 HBV NAT yield cases represent occult HBV infections (OBI, i.e. without detectable HBsAg) which were all positive for anti-HBc antibodies. Of these, 30 cases (80%) were consistently HBV DNA-positive at testing of follow-up samples. The other 8 cases were inconsistently positive, probably due to low viral load. Quantitative PCR, performed in 12 of these OBI cases, found viral load to be as low as 24-251 copies/ml.

Due to the high number of donors with OBI missed by HBsAg screening, the probability of having a potentially infectious donation released in the blood supply is higher for HBV than for HCV or HIV. The impact of HBV-NAT on the number of potential infectious units intercepted before donation is therefore significant. However, the benefit in terms of avoided morbidity and mortality should be further evaluated. In particular, the clinical significance of OBI and the impact on donor management are still under investigation.

> Based on a presentation by A. Varaklioti, Laiko General Hospital, Athens, Greece

Epidemiology of hepatitis A and E in Greece

Epidemiology of HAV in Greece

Greece is a country of intermediate HAV endemicity and travellers to Greece are not recommended to be vaccinated against HAV [1]. Although HAV is a notifiable disease in Greece, there is significant underreporting and no reliable national data on disease burden are available. Official reported data from the HCDCP on the annual incidence of acute

HAV over the period 1998-2006 are presented in the following Figure.



The incidence appears to be low (1.8-2/100,000) but low compliance and underreporting should be taken into account.

When analyzing annual HAV incidence by age, the highest incidence is observed in the age groups of 0-4 and 5-14 years respectively, i.e. age groups where the proportion of minorities and immigrants is highest.



When looking at the mean annual incidence by geographical region for this period (1998-2006), the highest incidence is observed in the regions of Thrace (3.2 /100,000) followed by Thessaly (2.7/100,000), Macedonia and Peloponese (both 2.3/100,000).



dervariability in seroprevalence, ranging from 1.6% to 52%. This might be attributed to the fact that most of these studies were conducted in small, non-representative samples; in addition changing HAV epidemiology over time (1978-1990) should be taken into consideration.

Prevalence of anti-HAV antibodies in					
Greek children and young adults					
Authors	Year	No of subjects	Age (y)	% anti-HAV (+)	
Papaevangelou and Frosner	1978	83	10-19	52	
Mavromichalis et al	1983	155	10-19	40	
Mavromichalis et al	1984	129	10-14	32	
Kremastinou et al.	1985	436	10-19	11	
Mavromichalis et al	1988	116	10-19	20	
Arvanitidou et al	1989	255	6-14	1.6	
Mamasi et al	1989	478	10-15	13.4	
Mamasi et al	1989	115	16-20	27.8	
Basoukou P. et al	1990	593	10-20	16.2	

A series of small studies on the prevalence of anti-HAV antibodies among

Greek children and young adults conducted over the years 1978 to 1990

were reviewed in 1990 [2]. As shown in Table below, there was a high

Basoukou P. et al. Acta Microbiol Hell 1990; 35:110-117

The most recent study (1990) listed in table above analyzed the anti-HAV prevalence in young individuals aged 10-20 years in Northern Greece, by residing area. Results show that seroprevalence in urban areas (11.9%) was lower than in rural areas, where seroprevalence reached 20.8%. Also, anti-HAV prevalence increased with age from 11.4% in those aged 10-15 years, to 15% in 13-15 year-olds and 27.8% in young 16-20 year-olds.

Evidence for changes in the epidemiology of acute HAV is also available from retrospective data collected at the large Infectious Disease Hospital of Salonica between 1985 and 1992 [3]. During this period, a total of 624 acute HAV admissions were recorded, of which 385 were in children. A significant decrease in the annual number of admissions was noted in the pediatric clinic, from 400-700 in 1970s to less than 50 in the late 1980s. Also, the mean age upon admission increased by 6.5 yrs over these years and the age at which most admissions occurred shifted from 1-5 year-olds in 1985 to 21-25 year-olds in 1992.

Another seroprevalence study was conducted in 2007 in children aged 0-14 years living in Greece. Demographic data and HAV vaccination status were collected and residual sera, stratified by geographical region, were tested for the presence of anti-HAV IgG antibodies (100 sera/year of age). Among children included in this study cohort, 32% had been vaccinated. A surprisingly high rate of natural immunity was found: up to 17.9% of unvaccinated children aged 1-14 years had evidence of a past natural infection in 2007 (see Figure below). In all age groups, the seroprevalence was higher than 10%.

Natural immunity against HAV in a cohort of unvaccinated children aged 1-14 years in Greece



When analyzing natural immunity by geographical region, HAV seroprevalence was found to be higher in the Northern part of Greece, as compared to the Central or Southern parts of the country. In the Greek population living in Attica, the metropolitan region of Athens, natural immunity was low (5.1%). There was no difference between natural immunity in urban or rural areas (16.5% and 18.1%, respectively), but vaccination coverage in urban areas was significantly higher (34.8% versus 26.8%, p=0.012).

Ethnicity was also a contributing factor. In immigrants, natural immunity was higher than in native Greek children (29.2% versus 16.0%) while immigrants had a lower vaccination coverage than native Greeks (16.4% versus 35.6%).

One limitation of this study was the use of residual serum samples from a public hospital, which caused a selection bias resulting in collecting data from an underserved population (approximately 18% of the study cohort were immigrant children). While acknowledging these limitations, the high prevalence of past natural infection has important implications for ongoing discussions on implementation of routine HAV vaccination in Greece.

Epidemiology of HEV in Greece

Few data are available on the epidemiology of HEV in Greece since only one center, the Salonica Infectious Disease hospital, performs anti-HEV antibody testing. Over the 3-year period 2004-2006, this center collected a total of 210 samples of acute non-A, non-B and non-C hepatitis. Of these, only 4 cases (2%) were positive for anti-HEV, i.e. 3 adults from India and one Greek adult without travel history [4].

Another study investigated the prevalence of anti-HEV in individuals at high risk of non-A, non-B hepatitis and sexually transmitted infection (STI), including healthy volunteers (mostly health care workers), IDUs, STI-infected individuals, thalassemia patients and HIV-positive men who have sex with men (MSM) (total N=1051) [5]. The prevalence varied between 1.5% and 2.4% and no association between anti-HEV and anti-HCV or anti-HBc was found.

The purpose of a third study was to estimate the prevalence of anti-HEV in various populations in North-Western Greece. A very low anti-HEV prevalence was found among 2636 healthy blood donors (0.23%). In contrast, a low but significantly higher prevalence of anti-HEV was found among 350

Albanian refugees (4.85%), 75 patients with chronic viral hepatitis (5.3%), and 149 hemodialysis patients (1.34%). In this study, anti-HEV was not detected in 165 children and 65 IDUs [6].

Additional data in at risk hemodialysis patients report high prevalences of 9.7% in the Agrinion unit (Western Greece) and 4.8% (range 1.8%-9.8%) in a unit in Central Greece [5,6]. Another multicenter hemodialysis cohort study found 6.4% patients positive for anti-HEV antibodies (N=420) versus 2.2% in younger healthy volunteers. Age and duration of hemodialysis appeared to be associated with higher risk. Further analysis revealed that the high prevalence of anti-HEV in these hemodialysis patients was due to the confounding effect of age and gender (higher prevalences were seen in older patients and females) [7]. The marginal association observed with the duration of hemodialysis in univariate analysis (p=0.07) was not confirmed in a multivariate analysis. No significant association was found between anti-HEV and anti-HEV or anti-HBC.

Based on the limited data existing to date, there is no evidence of HEV endemicity in Greece. As no Greek data on environmental specimens are available, further research on the environmental spread and possible animal reservoirs might be considered.

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Based on presentations by

V. Papaevangelou, A. Kyriakou Children's Hospital, University of Athens, Athens, Greece and G. Nikolopoulou, HCDCP (Keelpno), Athens, Greece

Epidemiology of hepatitis B and D in Greece

Reliable epidemiological data of HBV and HDV infection based on representative samples of the general population in Greece are not available. Current information is based on selected low risk or high risk populations, or from specific areas.

It is known that during the last decades, the profile of the Greek population has changed significantly, with several factors affecting the epidemiology of viral hepatitis, including modes of transmission, frequent traveling and an increasing number of refugees and immigrants, in particular after 1990.

Epidemiology of HBV

Greece is a country of intermediate HBV endemicity (>2%). During the period 1970-1980, the estimated HBsAg prevalence was more than 3-5%. Annual incidence data of reported cases of acute HBV over the period 1998-2006 (HCDCP) are presented in the following Figure.



Following implementation of universal HBV vaccination in 1998, the HBV incidence has considerably decreased. A transient increase was noted in 2004 due to implementation of enhanced surveillance measures.

Incidence was highest among 15-24 year-olds, followed by 25-44 yearolds, as shown in Figure below.

Acute Hepatitis B: incidence / age group



Regions with highest incidences were Thrace and Macedonia (both 3.0 /100,000), followed by Attica (2.3/100,000) and Thessaly (2.0/100,000). Being a foreign citizen was shown to be a risk factor directly associated with acute HBV.

HBsAg prevalence already started to decline as early as the early 80s, far before vaccination was implemented, due to improvement of the socioeconomic situation and implementation of the health care system. Solid seroprevalence data representative for the general Greek population are not available, but recent estimates for HBsAg positivity vary between 2.1% and 2.7%, depending on the study and population investigated (e.g. general population, company employees, hospitalized patients in Crete).

Based on integrated data from a number of studies in the general population, blood donors and high risk groups, where a large number of individu-

als (N= 637920) were screened for HBsAg over many years (1971-2001), HBsAg prevalence in Greece is estimated to be 2.1%.

HBV prevalence in low risk groups

HBV screening of blood donors at Greek blood banks provides prevalence data over many years in this setting. For instance, this screening shows that the prevalence of HBsAg in blood donors in the Athens-Piraeus greater area declined from 4.9% in 1972 (N=6708) to less than 0.5% in 1995-1996 (N=45504) (see Figure below).



Epidemiological data from a coordinating center including 296012 blood units from 41 transfusion centers found that only 0.35% of blood donors were HBsAg-positive for the period 2000-2001. Other studies reported HBsAg-seropositivity rates among volunteer blood donors of 0.40-0.85%, depending on the region studied (Crete or Epiros) [1,2].

Young army recruits represent another setting providing data on HBV prevalence. In 1972, the national average of HBsAg carriage among army recruits was as high as 5.0% but after approximately 20 years this figure decreased to 1.27% in 1990, which represents a 75% reduction.

In agreement with these data, another study reported a 50-80% reduction in HBsAg prevalence over the period 1973-1999. It should be noted that this decline already started in the 80s, well before the introduction of the vaccine (see Figure below). Moreover, vaccination coverage was low, as in 1999 only 1/3 of army recruits had anti-HBs antibodies [3,4].



HBsAg prevalence is also well-documented in women at reproductive age. According to a report published in 2005, this was 1.15% in the overall cohort of women studied in 2003-2004 (N=13581), with a higher prevalence in Albanian (5.1%) and Asian (4.2%) women [5]. Although still high in Albanian women, this figure constitutes an important decrease as the prevalence in this subpopulation was as high as 13.4% according to a 1996 report [6]. Of note, in 2005, 71% of HBsAg-positive women were of Albanian origin.

HBV prevalence in high risk groups

Many studies have been conducted in IDUs since they represent an important high risk group for HBV infection.

In a selected cohort of anti-HCV-positive Greek IDUs, the observed HB-sAg prevalence was low (\leq 3%). Exposure to HBV in terms of anti-HBc antibody positivity dramatically decreased from 82.5% before 1992 (N=103) to 22% after 1992 (N=127). Based on the low percentage of anti-HBs-only-positive individuals (16.5% after 1992) and 61.5% HBV seronegative individuals, it can be concluded that only a small proportion of IDUs get vaccinated against HBV [7].



A larger epidemiological surveillance study conducted in a broader range of Greek IDUs (N=1094) reported 4.5% HBsAg-positive individuals in 2002. HBV infection data are also available from Greek prisons. Among prisoners, the HBsAg prevalence in 1994-1995 was 6.5% among IDUs versus 13% among non-IDUs [8]. This high prevalence was associated with a high proportion of immigrants among prisoners [8,9].

Among HIV-positive patients, 12-13% of patients were HBsAg-positive and 67.4%-78% were anti-HBc-positive. Importantly, the majority of HIVpositive individuals were HBeAg-positive (61%), which is in contrast with the low HBeAg prevalence among the Greek HIV-negative population.

Some specific regions and villages in Greece were known to have higher HBV prevalences of 10% or more 10-20 years ago. In some of these places, such as Thrace (North-Eastern Greece), a decreasing trend in HBV prevalence has also been noted over the last decade.

Modes of HBV transmission

The most important reported risk factors associated with acute HBV among Greek adults are heterosexual activity (22%) and IDU (22%). For 35% of acute cases, the source of infection is unknown (see first Figure next column).

Two thirds (64.6%) of chronic HBV infections in adult Greeks have an unknown cause. According to HCDCP data on the HBV cohort (N=3353), intrafamilial spread is the most common reported mode of transmission (16.9%) in Greeks with chronic HBV infection, followed by perinatal transmission (7.4%) (see second Figure next column). Another study showed





that between 1991 and 1999, 15.8% of family members of chronic HBV carriers (N=387) were HBsAg-positive [10].

HBV burden of disease

Over the years 1986-1990, HBV was responsible for 2/3 (67%) of acute viral hepatitis cases.

In the primary care setting, 76% of chronic HBV patients are HBeAg negative inactive carriers, therefore not requiring therapy but followed-up on a regular basis. 18.3% of the HBsAg positive patients were HBeAg-negative but had active liver disease [11]. In the setting of specialized hospitals, the situation is different, as shown at the Hippokration Hospital in Athens, where the proportion of inactive carriers between 2002 and 2006 was only (46%). In this hospital, 48% of the chronic hepatitis B patients were HBeAgnegative with active liver disease. Of the latter category, 1/6 presented with decompensated cirrhosis. The proportion of immigrants with chronic HBV infection in Greek hospitals over 1997-2006 was 19% (3234 cases), 17% of adult chronic patients (3112 patients) were adult immigrants and 57% of the hospitalized children were immigrants (122 patients). Among HBeAg-positive chronic cases, the proportion of immigrants was higher (41%), most likely due to infection by different genotypes and also because they were infected at younger age.

Molecular Epidemiology of HBV infection in Greece

As part of a study on drug resistance testing, HBV genotypes were determined in 64 patients living in Greece. Based on this small study, HBV genotype D appears as the most frequent clade (88% or 58 patients) in Greece, which was expected since HBV genotype D is the most prevalent type in South-Eastern Europe. Genotypes A and G were also detected, with the prevalence of genotype A (9.4% or 6 patients) being higher than genotype G (3% or 2 patients). Among the genotype D isolates, 23 out of 56 genotype D sequences (41%) fell within a monophyletic cluster, suggesting that HBV infection spreads within Greece. Overall, this small sample study indicates that the genotype distribution of HBV in Greece is in accordance with the distribution in other Mediterranean countries.

These results are also in accordance with previous findings relating HBV genotypes in patients with chronic HBV infection.

Epidemiology of HDV

Very few data exist for the prevalence of HDV in Greece. Overall, HDV infection was found mainly among IDUs or in specific areas, and is associated with more severe hepatitis disease.

A study investigating the role of HDV superinfection as a cause of acute hepatitis in chronic HBV patients in Greece showed that in non-IDU (N=77), HDV was responsible for only 10% of acute hepatitis episodes (9% HDV only, 1% HDV+HCV). In IDU chronic HBV cases (N=28), however, 80% of acute hepatitis cases (38% HDV only, 42% HDV+HCV) were found to be associated with HDV superinfection [12].

Among Greek IDUs with chronic HBV, HDV is responsible for 81% of acute hepatitis episodes. In contrast, in IDUs who are not chronic HBV carriers, significantly less (p<0.001) acute hepatitis cases (28%) are due to HDV [13].

Among patients with chronic HBV infection at the Hippokration hospital in Athens (2002-2006, N=655), only 3.5% were also infected with HDV, but these cases were associated with more severe disease and with a significantly higher proportion developing decompensated cirrhosis (48% versus 15% without HDV co-infection, p<0.001). In this hospital, the proportion of immigrants among chronic HBV cases was also significantly higher (p=0.005) if the patients were HDV co-infected (52%), as compared to those who were not HDV co-infected (24%).

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Based on presentations by

G. Nikolopoulou, HCDCP, Athens, Greece;

G. Papatheodoridis, Hippokration Hospital,

University of Athens, Athens, Greece

and D. Paraskevis, National Retrovirus Reference Centre, Medical School, Athens, Greece.

Epidemiology of hepatitis C in Greece

Epidemiology of HCV in Greece

Greece is a country of low HCV endemicity. However major regional differences have been reported. Epidemiological studies have focused on prevalence of HCV infection in subgroups of the general population, as well as in high risk groups.

Overall, HCDCP notification data indicate that HCV incidence is very low and decreasing over the last years, as shown in Figure below.



HCV incidence is highest among 15-24 and 25-44 year-olds over the period 1998-2006, as shown by the Figure below.



When analyzed by geographical region, the highest incidence was noted in the metropolitan region of Attica (mean annual incidence of 1.8/100,000), which is most likely attributed to the higher proportion of IDUs among inhabitants (see Figure below). The most important risk factor identified for HCV infection was foreign citizenship.



Prevalence of HCV in the general population

Based on integrated data from 5 studies (130,293 individuals in total), the anti-HCV prevalence in Greece over the period 1993-2001 was estimated to be 2.66%. Another study conducted in the general population reported a prevalence of anti-HCV over the period 1997 - 2001 of 1.94%, ranging from 0% to 7.8% depending on the group studied. Studies in volunteer blood donors in Crete or Epiros noted anti-HCV seropositivity rates of 0.38-0.61% [1,2].

Other studies with focus on selected age groups among the Greek population found that the prevalence of anti-HCV among adult employees in 1996-1997 was 0.5- 1.2%, while in Greek children or young adults, prevalence was close to zero (0% - 0.008%).

In Achaia, a region in South-Western Greece, the anti-HCV positivity over the period 1997-1998 (N=1500) was 0.5%, which is lower than the rate reported in the Mediterranean region (1-2.9%) [3]. A study in the specific setting of pregnant women, conducted in Northern Greece, found 1.95% of pregnant women who attended prenatal clinics in 1996-1997 to be positive for anti-HCV [4]. Possibly, this higher rate of anti-HCV positivity can be attributed to the fact that 13% of the pregnant women were from former Eastern European countries, where disposable syringes were not used at the time, or that they were former IDUs. The risk of perinatal mother-to-child transmission of HCV appeared to be low and related to HCV RNA presence in the carrier mother.

Regions of Greece with high prevalence of HCV infection

There are several regions in Greece where seroepidemiology of hepatitis in well-defined populations seems to be different from other parts of Greece and Europe, with higher prevalence of HCV infection.

For instance, in 1997 on the Greek island of Zakinthos, the overall anti-HCV prevalence was 1.25%, while in small rural regions of the island significantly higher rates up to 6.8% were identified [5]. A high prevalence (10.9%) of anti-HCV was also observed in patients (N=257) visiting primary health services in 1993-1994 in the Spilli area, an area in rural Crete, compared to 3% in the neighboring villages (N=164) [6]. Another seroepidemiological study noted anti-HCV antibodies in 3.5% of 1961 patients who visited surgeries between July 1996 and February 1997 in primary health care centers located in rural Macedonia, Attika and Crete [7]. In this study, anti-HCV rates varied significantly between the different regions, with the highest prevalence of 4.8% identified in Crete. Other examples of elevated anti-HCV rates include the Island of Thasos (3.3%), Spilio (4.3-8.3%) and Katakolo Ilias (7.5%).

Overall, the widespread endemicity of HCV infection is the result of a combination of factors, including those related to the specific settings and behaviors facilitating transmission. The significant variation of HCV prevalence between different geographically well-defined areas confirms the hypothesis of a "pocket" model of HCV positivity in those regions of Greece. In addition to regional differences, some iatrogenic practices (prolonged hospital admission, history of blood transfusion or dental surgery, intramuscular injections including use of non-disposable needles and syringes or devices for various medical and paramedical practices) and IDU were associated with anti-HCV positivity [3,5,6,7]. Screening for these risk factors may enable to identify HCV-infected patients.

Prevalence of HCV in groups at risk

A higher HCV incidence is also observed in minorities and high risk groups. For instance, a study in 2 Greek correctional centers (533 subjects) found an overall anti-HCV positivity rate of 58.2% among prisoners [8]. For IDU prisoners only, the prevalence rate was as high as 80.6%, while in non-IDU 9.5% were positive. Multiple imprisonments, duration of incarceration, needle sharing and drug use in prison were identified as risk factors for HCV. Hence, the epidemic of HCV among imprisoned IDUs, as identified by this study, constitutes a major public health problem.

High HCV prevalence rates among Greek IDUs were confirmed by other studies. An epidemiological surveillance conducted by the Greek Reitox Focal (EKTEPN, 2002) [www.ektepn.gr] reported anti-HCV prevalences between 43.3% and 61.7% among Greek IDUs. Different profiles of drug users were screened by various programs, depending on the admission criteria used. In substitution programs (OKANA), the HCV positivity rate was 78.7% and in drug-free programs (KETHEA, 18 ANO) it was 44.1%. In general, an increase of anti-HCV rate was noted with age and years of injecting use.

Other risk groups identified with high HCV positivity are thalassemic patients (22.7%) and surgeons where one study reported a surprisingly high rate of HCV-positives (9.6%) in a single hospital (Vesiropoulos, Hippokratia, 2002).

Several studies have identified a strong association between HCV infection and the development of serious complications, such as cirrhosis and HCC. One study estimated the impact of primary prevention of HCV on the future burden of the disease in Greece and also predicted whether the recent decline in the incidence of HCV may affect the future occurrence of cirrhosis and HCC cases, using the back calculation methodology [9]. To this end, HCV epidemiological data coming from treatment studies from several clinical sites throughout Greece with enrolment over the period 1995-2000 were modeled. The model estimated that, under the assumption of a 20-100% decline in new HCV infections after 1990, the cumulative number of cirrhosis and HCC cases from 2002-2030 would be lower by 9.6-48.2% and 5.9-29.5%, respectively, than that estimated under the assumption of no decline in new HCV infections. However, the prevalent cirrhotic/HCC cases and HCV-related deaths were predicted to decline in the next 30 years only under the assumption of complete elimination of new HCV infections after 1990. Hence, despite the progress in the reduction of HCV transmission, primary prevention does not seem able to reverse the rise in the incidence of cirrhosis and HCC.

Molecular Epidemiology of HCV infection in Greece

A number of studies investigated the overall HCV genotype distribution and reconstructed the HCV genotype-specific incidence in Greece over the



past decades. In a first study, HCV genotypes were determined in 1585 HCV-chronically infected patients (sampled during 1987-2002) belonging to different risk groups. The following HCV genotypes were detected: genotype 1 was the most prevalent (47%) followed by genotype 3 (28%), 4 (13%), 2 (7%) and 5 (0.5%) [10] (See Figure left below).

A high prevalence of genotype 1 was particularly recorded in older individuals, including haemophilia (~66%) and hemodialysis patients (~52%), whereas HCV genotype 3 was found mainly among younger patients infected due to IDU (58%) [10] (See Figure below). Genotype 1b was found more frequently in older patients, suggesting that 1b was due to an older epidemic or introduced earlier in Greece compared to 1a.



In another study, the relative frequency of HCV genotypes was evaluated in a total of 434 unselected patients with chronic HCV infection, presenting during the period 1996-2000 at the Liver Unit of the Second Department of Medicine of Athens University [11]. The overall distribution of HCV genotypes 1, 2, 3 and 4 is presented in the Table below.

Frequency of HCV genotypes in 434 Greek patients

with chronic infection (1996-2000)				
	HCV Genotype (%)			
	1 2 3 4			
Overall	47	8.3	27	15.2
Post-transfusion hepatitis	57.5	10.2	18	12.5
IDU	17.5	1.2	65	15
Unknown route of transmission	50.3	9.6	18.7	17.7

Savvas SP, J Viral Hepat, 2005 [11]

Genotype 3 was again common in younger adults and IDUs, whereas genotype 1 predominated in older people and post-transfusion hepatitis patients. Infection acquired before 1981 was related to transfusion and genotype 1, while after 1981 it was due to IDU and genotype 3. The presence of cirrhosis was associated with the duration of infection while neither genotype nor age was related the development of cirrhosis. In contrast to HBV, the genotype distribution of HCV in Greece is different from that in other Mediterranean countries, such as Italy and Spain, but –surprisingly- is found to be closer to HCV genotype distribution in The Netherlands. The prevalence of genotype 4 in Greece is the highest percentage reported in all other European countries. Its putative origin in Greece was further investigated and molecular characterization of genotype 4 HCV isolates belonging to various risk groups revealed that the majority (78%) was of subtype 4a [10]. Most likely, genotype 4 was imported from Africa (probably Egypt) where this genotype is mainly present.

A change of HCV genotype distribution was observed in the last 20 years among Greek patients with chronic HCV infection as a result of epidemiological changes in HCV transmission [10]. As shown in the Figure below, there was a sharp (13-fold) increase for genotype 3 starting in the late 70s or early 80s, depending on the calculation methodology.



Estimated incidence of HCV infection (1950-1990) by genotype in Greece

Katsoulidou A J Viral Hepat 2006 [10]

The above molecular epidemiology data for HCV were recently confirmed by an initial report of the ongoing, nationwide HepNet.Greece study (see section on HBV and HCV patient cohort study for details on the design and objectives of this study). Initial data are available for 1518 anti-HCV positive patients presenting in different hepatology centers spread throughout Greece between 1997 and 2004. Similarly to the studies cited above, genotype 1 was predominant (44%), but this rate is relatively low as compared to other Northern European countries and North-America. About one third of the cohort was positive for HCV genotype 3 (32.8%). The remaining HCV cases were due to genotype 4 (15.3%) and genotype 2 (4.8%) [12].

In 620 patients with known infection duration and genotype, there was a reduction over time (before 1980 and after 1992) in the proportion of genotype 1 or genotype 4 cases and an important, gradual increase in the proportion of genotype 3 cases.

As shown in upper right Figure, older infections occurring before 1980 had a possibility of 55% that the HCV virus was of genotype 1 and this decreased to about 25% of new cases identified after 1992. Genotype 2 was stable throughout the years (5-10%), while genotype 4 slowly decreased (from 20% to ~7%). As in many European countries, genotype 3 became more important after 1980 due to the HCV epidemic among IDUs and was present in more than 60% of new HCV cases identified after 1992.

Distribution of genotypes by time of infection



The study also confirmed the change over time in source of infection, with transfusion as predominant source of infection before 1992 and IDU after 1992, paralleling the change in the distribution of the HCV genotype over time (See Figure below).



Distribution of sources of infection by time of infection

Thus, these nationwide data are in accordance with previous reports, demonstrating that epidemiology of chronic HCV infection in Greece has changed over the last decades, with a decrease of genotype 1 and possibly genotype 4, and an increase of genotype 3 infections. In the future, this nationwide cohort study will provide important data contributing to further understanding of the epidemiology and course of chronic HCV infection in Greece.

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Based on presentations by K. Manesis, University of Athens, Athens, Greece and President of the viral hepatitis office HCDCP; G. Nikolopoulou, HCDCP, Athens, Greece; D. Paraskevis, National Retrovirus Reference Centre, Medical School, Athens, Greece;

M. Raptopoulou, Aristotle University of Thessaloniki, Thessaloniki, Greece and G. Touloumi, University of Athens, Athens, Greece.

Migration and viral hepatitis

Greece has not had an elevated immigration rate until recently. Since the beginning of the 90s, following the dramatic political changes in the Balkans and Eastern European countries, people from Albania, other Balkan countries and Post-Soviet states have started to migrate to Greece, where endemicity for hepatitis viruses is low-to-intermediate. Immigrants reside in both urban and rural areas. According to the last official census in 2001, 7.2% of the Greek population consists of immigrants, mainly coming from Albania (65%), leading to a change in viral hepatitis epidemiology in Greece. Because not all immigrants are recorded in this census, the actual figure is estimated to be higher.

All immigrants and their families need to obtain a health certificate in order to receive legal documents. However, no routine serologic testing for viral hepatitis is required for those requesting a health certificate or living in refugee camps. As a consequence, limited available data on migration and viral hepatitis are derived from individual studies conducted in different areas of the country.

Immigrants and HAV

It is expected that people who grew up in an area with intermediate to high HAV endemicity developed natural immunity. In a study conducted in Epirus, a periphery in North-Western Greece, the anti-HAV antibody prevalence was found to be 98.2% in ~1000 immigrants from Albania who were 0-81 years old [1]. Among pregnant Albanian women the HAV prevalence

was 96.2% [2]. Sporadic HAV cases are also reported in immigrant children post-vacation after visiting their home country.

Immigrants and HBV

Many small studies provide local data on immigration and HBV infection rates. One older study conducted in Epirus found a very high prevalence of HBV markers among Albanian immigrants, i.e. 22.2% HBsAg (21.1%HBeAg), 70.6% anti-HBc, respectively while 12.7% were anti-HDV-positive [1].

The high HBV infection rates in immigrants were confirmed by a more recent study (reported in 2003) which was conducted in the Athens area and included 130 refugees originating from different areas of the world [3], as presented in the Table below.

Prevalence of HBV markers in immigrants residing in Athens

Ethnicity	N	HBsAg (+)	Anti-HBc (+)
Albania	76	17 (22.4%) ^a	54 (71%) ^a
Eastern Europe	35	0 (0%)	8 (23%)
Asia	11	3 (27.3%) ^b	5 (45%) ^b
Africa	5	0 (0%)	2 (25%)
Total	130	20 (13.4%)	69 (53.1%)

^a P<0.008, ^b P<0.001

Several studies investigating immigration and HBV in the specific setting of pregnant women (see Table below) indicate a clear need for further evaluation and follow-up of HBV prevalence among immigrants.

Author, year of publication	Data collection	HBsAg (+)
Malamitsi-Puchner A, et al. 1996 [2]	Retrospective data, 500 Albanian women, one center	13.4% HBeAg(+): 7.5%
Panagopoulos P, et al. 2004 [4]	Retrospective data; 5,497 women over 8 years; one center	Immigrants: 4.67% Greek: 2.9%
Papaevangelou V, et al. 2006 [5]	Prospective data; 3,760 women over 2 weeks, whole country	Immigrants: 5.7 % Albanian: 9.8% Greek: 1.7%
Elefsiniotis L, et al. 2007 [6]	Prospective data; 26,746 women over 2 years, one center	Albanian:4.9% E.Europe: 1.29% Asian: 5.6% Greek: 0.57% <i>HBeAg(+):</i> 2.67%

Immigrants and HCV

Significantly higher HCV rates are observed in immigrant populations (1.75-2.3%), as compared to native Greeks (0.4-0.8%) [1,3], with high variability depending on ethnicity (see Table below).

Prevalence of HCV antibodies in immigrants residing in Athens [3]

Ethnicity	% Anti-HCV (+)
Albania	1.9
Eastern Europe	2.8
Asia	0
Africa	12.5
Total (N=130)	2.3

The above higher rates of HCV infection among immigrants are confirmed by the following studies conducted in immigrant pregnant women:

- Retrospective study over 8 years from one center (N=5497): 1.33% (versus 0.16% in Greek controls) [4]
- Prospective study across the country over 2 weeks (N=3760): 0.8% [5]
- Prospective study in one center during one year (N=2408): 4.82%* [7]

Based on the above fragmented data, it can be concluded that viral hepatitis epidemiology has changed over the last 15 years with the increased number of immigrants. The increased number of acute HAV cases in susceptible children of immigrant families traveling back to their home country for vacation emphasizes the need for reinforced vaccination of this high risk group. The increasing number of immigrants with chronic HBV infection is also expected to have implications for the health care burden in Greece over the next decades. Early HBV vaccination of infants and catch-up vaccination of children and adolescents of chronically infected immigrant parents is therefore warranted.

Furthermore, it should be noted that currently available prevalence data for immigrants are underreported because they pertain to legal individuals only, with access to official health care services. It can be expected that recent immigrants might have higher prevalence rates of viral hepatitis, with an increased risk of infection and transmission.

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Based on a presentation by

V.A. Vasilopoulou, Aghia Sofia Children's Hospital, University of Athens, Greece and C. Hadjichristodoulou, University of Thessaly, Larissa, Greece

^{*} women originating from Eastern European countries where use of non-disposable syringes/needles was common until recently.

HIV and viral hepatitis coinfection in Greece

In Greece, all HIV infection cases are reported to the HCDCP. The majority (60%) of HIV-positive individuals are MSM while 30% are heterosexuals. IDUs constitute only 4.7% of the HIV-positive population, which may explain the low percentage of HIV-HCV coinfection in Greece.

Epidemiological data of HIV and viral hepatitis coinfection in Greece are available through a number of published studies:

- According to a report published in 1987, the prevalence of HBV serologic markers in 288 imprisoned IDUs was as high as 77% and 6.9% were HBsAg carriers. In this cohort of IDUs, 2.1% were HIV-positive [1].
- In a study of 181 HIV-positive individuals between 1986 and 1997, the prevalence of HBV markers was 67.4% and the prevalence of HCV antibodies was 13.8% [2].
- Among 194 male prisoners in 2000-2001, 13% were HBs-Ag-positive, 49% were anti-HBc- positive and 6.5% had anti-HCV antibodies. None of them were positive for HIV [3].
- A large study in a cohort of 6696 blood donors (1995-1997) showed that 0.61% were anti-HCV positive and none were HIV-positive [4].
- In a recent study of 737 HIV-positive individuals, published in 2006, 12% were HBsAg-positive and, of those, 61% were HBeAg-positive and 48% were positive for anti-HBc. The prevalence of anti-HCV antibodies was 8.2% [5].

To date, limited data on the long-term follow-up of coinfected patients in Greece are available. In one study, HBeAg-positive chronic HBV appeared to be very common in HIV-HBV coinfected patients in contrast to the general Greek population, where HBeAg seroprevalence appeared to be low (see section of this report on Epidemiology of HBV) [6].

Another long-term prospective study of haemophiliac men (N=1258) followed for a median time of 12 and 5.7 years in the pre- (1980-96) and post-HAART period (1997-2003) respectively, revealed that the probability for non-AIDS deaths was fourfold increased post-HAART and end-stage liver disease was the predominant cause of non-AIDS mortality in both periods [7].

Additional information on the current situation of HBV or HCV coinfection among HIV-infected individuals is available from three HIV hospital units. In the HIV unit of the Evaggelismos general hospital (495 HIV-positive patients), rates of coinfection were 4% for HCV and 2% for chronic HBV (mean duration 5 years) for the period 2006-2007. Among the 20 HCV-coinfected cases, 4 received treatment for HCV and liver biopsy was only performed in 2 patients. Two patients presented with known cirrhosis and 4 patients died (2 due to cirrhosis). None of them reported HCC. Among the 10 HBVcoinfected cases, 4 were HBeAg-positive and 3 seroconverted. Eight patients received treatment for HBV and none of them had a liver biopsy. One patient died from HCC, however, none of the patients had liver cirrhosis.

In the HIV unit of the AHEPA general hospital in Thessaloniki (551 patients), the second largest HIV unit in Greece, rates of coinfection were 7.6% for HCV and 4.4% for HBV [8]. In this unit, a better follow-up through liver biopsy was performed, i.e. in 23/42 HCV-coinfected and in 8/24 HBV-coinfected patients. Anti-HCV treatment was administered to 32/42 patients and the majority received treatment for HBV. None of the HBV or HCV coinfected cases reported HCC.

A recent report (2007) on HBV-coinfection from a third HIV unit in the University of Patras Hospital reported 33% of HIV patients to be exposed to HBV and 6.95% (6/92) to be chronic HBV carriers. In this HIV unit, the rate of HBV immunization was low (41%), (81% in males, 19% in females). Only 64% of HBV immunizations were successful [9].

These data show that in coinfected patients, HIV treatment is prioritized while treatment of chronic HBV or HCV is only of secondary priority, as seen from the low number of biopsies performed. In addition, coverage of HBV immunization is low. However, it has been demonstrated that HIV infection increases the need for liver biopsies, especially in patients coinfected with HCV [10]. Therefore, diagnosis and treatment of viral hepatitis as well as careful monitoring for evidence of progression of liver disease needs more emphasis in this population of coinfected HIV patients.

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Based on a presentation by

I.G. Baraboutis, Evaggelismos General Hospital, Athens, Greece.

Hepatitis A and B immunization programs in Greece

National Board of Immunization

The Greek National Board of Immunization (NBI) operates since 1982 and assembles 3-4 times/year. In March 2007, the eleven members composing this board were appointed for 3 years by the Minister of Health and include mainly pediatricians and representatives from the Ministry of Health.

The NBI is an advisory committee to the Greek Ministry of Health, responsible for the following tasks:

- Review of the National Immunization Program and update according to WHO and EU guidelines
- Review of the Immunization program for targeted patient groups
- Ensuring availability of vaccines and immunoglobulin G (IgG)
- Ensuring distribution and preservation of the cold chain (electronic follow-up)
- Introduction of new vaccines (e.g. varicella, combined meningococcal and pneumococcal, and human papillomavirus vaccines)
- · Report of vaccine related-safety issues

Hepatitis B immunization program in Greece

In 1982, Greece implemented a HBV vaccination program aimed at high risk groups, including HCW, IDU, sex workers, haemophiliacs and dialysis patients. Unfortunately, as in many other countries, this strategy had little impact on disease incidence or prevalence [1,2] and among the reasons for failure were: fear of emerging HIV epidemic, high cost of the vaccine and particularly the difficulty in accessing and targeting individuals at high risk. No risk factor for HBV infection could be identified in 35% of acute HBV infections [2] (see Table below).

Source	Frequency %
Heterosexual	22
Homosexual	12
IDU	14
Iatrogenic	12
Post transfusion	5
Unknown	35

Sources	of acu	te HRV	infection	in	Greece	1998
Sources	or acu	IC IID V	mection	ш	GIECCE,	1770

Papaevangelou G, Vaccine. 1998

After several scientific and medical associations jointly started a campaign for universal HBV vaccination of infants and adolescents in Greece in 1993, the government declared its intention to integrate the HBV vaccine into the National Immunization Program and private pediatricians started vaccination. Subsequently, between 1995 and 1997, the uptake of HBV vaccine among children entering primary school increased from 36.3% to 56.9%. Vaccinations were mainly performed by private pediatricians (62%), while only 29% were carried out by public health services.

The Greek national HBV prevention program, effective as of early 1998, includes universal screening for HBsAg of pregnant women and universal vaccination of infants. Monovalent as well as combined vaccines are available in Greece.

The Greek vaccination schedule recommends HBV vaccination at 2, 4 and at 6-18 months of age (see below, as presented on www.euvac.net). A birth dose is only given to newborns from HBsAg-positive mothers and is followed by two subsequent doses at 1-2 and 6-18 months.



As seen from Figure below, there was a substantial initial demand for HBV vaccine after it became available on the Greek market in 1992. A second peak in the number of doses distributed was observed in 1998, when the vaccine was incorporated into the National Immunization Program.





A national vaccination coverage survey was conducted in 2006 to assess immunization coverage by vaccine/dose of 6-year-old 1st grade children (both at national and regional level), and of 14-year-old 9th grade children (at national level), i.e. during the last year of compulsory school attendance. The sampling design included stratification by geographical region and type of area (urban/rural) and random cluster sampling (school classes). Some regions were combined in order to have at least 600 children/region. In Greece, the Child Health Booklet is a unique source of data on immunization status of children, which is very well kept and completed by almost 100% of the parents. As a result, the survey response rate was high: 88.3% in 6-year-olds (n=3878) and 71.6% in 14-year-olds (n=923).

The survey sample included 6-year-olds and 14-year-olds attending school in urban areas (76.8% and 87.1%, respectively) as well as children attending school in rural areas (23.3% and 12.9%, respectively). Minorities included immigrants (7.8%), Greek Muslims (7.5%) and Greek Roma (1.3%). HBV vaccination coverage rates observed during this survey were high, as illustrated in the Figure next page.

MEETING NEWS



When looking at 3-dose coverage by region (analyzed in 6-year-old children), the data were quite evenly distributed, ranging between 92% and 97%. Coverage in urban areas was not different from that observed in rural areas (95% for both). A high level of coverage was also reached in minorities (91-96%), except for Greek Roma where only 59% of 6-year-old children received all 3 HBV vaccine doses.

When analyzing the timing of HBV vaccine dose uptake in a group of 6year-olds, it appeared that for the majority of children, HBV vaccination only started in the second half of their first year of life (see Figure below). Although the HBV vaccination schedule recommends the first dose to be



administrated at 2 months of age, only 19.2% of children had received the first dose by 6 months and only 64.6% by the age of 12 months. The 3-dose primary vaccination course was therefore completed at 12 months for 15.8% of children only, and at 18 months for 53.2% of them. Results also show that once the first HBV vaccine dose was administrated, the second dose followed shortly after, however, there is a clear need in Greece to emphasize the rationale for starting HBV vaccination as early as possible in order to reduce the risk for chronic carriage caused by delay of the first

Finally, the survey results indicate that vaccination was mainly carried out in the private sector (approximately 2/3 of vaccinations).

Hepatitis A immunization program in Greece

HBV dose and risk of infection early in life.

HAV vaccine has been widely available in Greece since 1995 and several monovalent HAV vaccines are currently available in the country. It is recommended for use in high risk groups but it is not included in the National Immunization Program.

Results from the national vaccination coverage survey conducted in 2006 (also discussed in section of this report relating to HBV immunization)

show that 36.9% of 6-year-old children and 21.8% of 14-year-olds received two doses of HAV vaccine (see Figure below).



As HAV vaccination is not part of the Greek National Immunization Program, most vaccinations (88%) are performed by private pediatricians, often at entrance in day care center.

When looking at vaccine uptake by region (analyzed in 6-year-olds), important differences were noted, ranging from 12.4% in Thrace (North-Eastern Greece) up to 49.4% in Attiki (Athens region) for the 2-dose course. It was also noted that coverage in urban areas (39.8%) was higher than in rural areas (24.6%). Coverage level reached in minorities included in the survey was substantially lower than in the rest of the population, where coverage was 40.0%. Only 14.7% of immigrant children, 10.8% of Greek Muslims and none of the Greek Roma children included in the survey received 2 HAV vaccine doses. Based on the 2006 national survey, it can be concluded that HAV vaccine is widely used in Greece, but large differences in coverage are observed between social groups.

The HAV disease burden in Greece is very difficult to estimate, because:

- The existing surveillance system provides unreliable data due to significant underreporting;
- Less than 10% of children have symptomatic disease;
- No data on duration of hospitalization complications or societal costs have been collected.

Recent Greek seroprevalence data show that the virus is indeed circulating (as discussed in the section of this report devoted to the epidemiology of HAV).

Vaccination coverage data collected by the University of Athens, Department of Pediatrics in 2007, show that the overall coverage rate for HAV vaccination is 32.7% (see Figure on page 23), which is in close agreement with the vaccine uptake observed during the 2006 national vaccination coverage survey.

In general, when looking at HAV vaccination coverage by geographical region, coverage rate and natural immunity are inversely related (see Figure on page 23). Vaccination coverage is higher in the Central and Southern parts of Greece where natural immunity is lowest, for instance in the region of Athens (36% HAV vaccine coverage and 10% natural immunity). On the other hand, in those parts where coverage is lowest (mainly in the Northern part), natural immunity is highest.

HBV vaccine uptake by age





Natural immunity and vaccination coverage by geographic area



A similar trend was observed when analyzing coverage by ethnicity. Immigrant children were less likely to be vaccinated than native Greek children (16.4% versus 35.5% coverage), while natural immunity was significantly higher among immigrants (29.2% versus 16.0%). Also, children living in urban areas had significantly higher vaccination coverage rates than those in rural areas.

In conclusion, these data indicate that those at higher risk of HAV infection appear to be vaccinated less, thereby revealing the inequities of the Greek health care system.

A cost-effectiveness study on HAV vaccination was conducted by the Pediatric Infectious Disease Clinic in Athens, based on data obtained from 161 children hospitalized between 1990-1995 [3]. The study concluded that HAV vaccination is cost-effective only in high-risk groups with a seroprevalence above 10% and that among low risk groups, only adolescents should be immunized. Based on the fact that results from this study might be outdated and, particularly, that the conclusion of the cost-effectiveness analysis may be different when taking into account the recently observed 17.9% of unvaccinated Greek children with serologic evidence of past natural infection, the time seems appropriate to revise and re- discuss HAV immunization policy in Greece and to re-evaluate the need for routine vaccination.

Considerations for the future could include new cost-effectiveness studies to assist the decision-making process, including assessment of factors such as indirect costs, herd immunity effects, etc. However, it should be noted that the timing of HAV vaccine introduction into the Greek National Immunization Program will be influenced by competition with introduction of other (expensive) vaccines, such as recently introduced varicella, conjugated pneumococcal and rotavirus vaccines, as well as the planned Human Papillomavirus vaccine. As an alternative, extending the targeted policy to other risk groups, such as immigrant children, could be considered.

HAV immunization experience in Israel

As an illustration of the decision-making process on implementation of HAV routine vaccination, the recent experience in Israel was presented at the meeting as a relevant example for countries with similar HAV epidemiology of intermediate endemicity in transition, including Greece.

The mean annual incidence of HAV disease in Israel was 50.4 per 100,000 over the period 1993-1998. Israel has a heterogeneous population with high contact rates between high and low socio-economic groups. The highest HAV attack rate was seen in 5-9-year-old children. Maternal anti-HAV IgG is usually cleared in babies by the age of 18 months and the disease was rarely observed before this age. Toddlers seemed to be the main vehicle for HAV transmission.

There were several arguments in favor of routine vaccination for HAV:

- Israel is an area of intermediate endemicity in transition
- · Contact between populations with high and low risk
- The true HAV incidence is >5x higher than reported cases/ year through passive surveillance
- Although HAV in children is generally seen as a benign disease, a surprising increase in the number of fulminant HAV cases among Israeli children was noted
- The most convincing argument was a favorable cost-benefit analysis [4]
- High acceptance rate by population

As a consequence, a 2-dose universal HAV immunization program, aimed at children aged between 18 and 24 months without a catch-up program beyond toddlers, was started in 1999.

Vaccine coverage in 2001-2002 was 90% and 85% for first and second doses, respectively, indicating that the vaccine was very well accepted by the population. After initiation of the program, a sharp decrease in disease rate was observed in both Jewish and non-Jewish populations. For those aged 1-4 years, a reduction of ~99% in disease was observed from 2002 through 2004, compared to pre-vaccination. A sharp decline was also observed in all other (non-vaccinated) age groups, ranging from ~75% to 97% reduction, depending on the age group, demonstrating the high efficacy of this toddler-only routine HAV immunization program in Israel, achieving a dramatic reduction of HAV circulation and disease in all ages, with induction of marked herd protection [5].

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The experience gained in Israel raises two important questions:

- The results challenge the need for catch-up HAV vaccination programs if the toddler-only approach is adopted;
- Cost-benefit studies must take into account that vaccination programs aimed at only a small fraction of the population (in the present case <3%) can substantially reduce disease in the entire population.

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Based on presentations by

A. Konstantopoulos, University of Athens, Athens, Greece;

T. Panagiatopoulos, National School of Public Health, Athens, Greece; V. Papaevangelou, University of Athens,

A. Kyriakou Childrens Hospital, Athens, Greece

and D. Shouval, Hadassah-Hebrew University, Jerusalem, Israel.

Conclusions

This section provides highlights of meeting sessions and is concluded with lessons learnt and recommendations for future actions.

Organization of health care (HC) system in Greece

- The Greek HC system is a complex mixed system, with health services organized in 3 sectors including the NHS (mainly funded by state taxes), Social Insurance Services (funded by social insurances) and the private Sector.
- Primary HC centers are developed mostly in rural areas, as part of NHS, while in urban areas, IKA- funded services and the private sector – with a high number of private doctors and diagnostic centers – are mainly used.
- 44% of hospitals are public, large capacity, structures while 54% are private smaller entities; 69% of hospital beds belong to the public sector and 28% to the private sector, Greece meets the WHO requirement for beds/population ratio.
- The ratio of public/private health expenditure in Greece has evolved to approximately 50/50, with public expenditure mainly devoted to hospitals and private expenditure mainly spent on primary HC. Greece has the lowest level of public health expenditure in Europe, leading to:

- social inequities in the access to health services
- fragmented responsibilities between ministries and related lack of organized prevention health promotion
- inadequate management of HC resources
- poorly regulated private sector.

Viral hepatitis surveillance, prevention and control in Greece

- Viral hepatitis surveillance conducted by the HCDCP in Greece aims at disease identification, monitoring and prevention. Within the HCDCP, the Office of Viral Hepatitis works in collaboration with a Scientific Commission of Viral Hepatitis whose objectives consist in prevention, education, surveillance, improvement of medical care and coordination of the nationwide HepNet.Greece study.
- The current ID surveillance programme is based on a mandatory weekly notification system for selected diseases, based on EU case definition and standardized notification form, and is compliant with the EU decisions relating to surveillance. Notification is mainly done by hospitals but considerable non-compliance from physicians leads to major underreporting. Introduction of a separate laboratory notification system for viral hepatitis infections (asymptomatic versus symptomatic) might be considered in order to improve current surveillance of viral hepatitis in Greece and to reduce underreporting by private physicians.

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- Awareness and recognition of the limitations of existing surveillance data have led to initiatives such as the design and conduct of additional epidemiological studies, as well as issuing and updating guidance and recommendations by the HCDCP.
- Different approaches to study national seroprevalence were presented and discussed to document age-specific prevalence at national level, burden of disease and impact of prevention interventions, including:
 - Prediction model through back calculation methods, based on current data
 - Seroprevalence study based on residual samples (ESEN-like)
 - Population-based serosurvey
 - National health survey.
- HCDCP is responsible for the coordination of HepNet.Greece, a large nationwide retrospective-prospective study that started in 2003 and involves chronic HBV and HCV patients. The primary objective is to investigate the course and outcome of chronic HBV, HDV and HCV. Secondary targets are to obtain an indirect estimate of the incidence of chronic HBV, HDV and HCV infection from the yearly number of newly diagnosed patients; to achieve early diagnosis through better screening and surveillance; to introduce common standards of care and more effective treatment of HBV and HCV patients; and to improve collaboration between Hepatology Centers in Greece. This ongoing Hepnet.Greece study provides opportunities for planned research.

Experience from surveillance of infectious diseases during the 2004 Olympics

Enhanced surveillance systems (in particular, daily reporting) and new syndromic surveillance system were implemented during the 2004 Olympics in Greece. New SOPs for data interpretation were developed and significant expertise was built among HCDCP staff.

Surveillance in blood bank

Implementation of NAT technology in individual blood donations, in addition to serological screening, reinforces the safety of blood supply, supporting the value of establishing NAT as a routine screening test which is particularly relevant for the detection of occult blood infection (OBI) cases missed by HBsAg screening. However, the clinical significance of OBI and the impact on donor management should be further studied in order to fully assess the benefit of NAT-testing in terms of reduced morbidity and mortality.

Epidemiology of HAV in Greece

- No reliable national data on HAV disease burden are available: results are only available from small studies with high variability and significant underreporting is anticipated.
- Overall, Greece is a country of intermediate HAV endemicity. HAV incidence has decreased over the last years and changing epidemiology is related to migration, with well-known risk factors. Higher incidence is observed in the Northern part of the country, among

rural populations, and in minorities. Surveillance data have shown that highest HAV incidence has shifted towards older age.

• Results from a study conducted in 2007 among unvaccinated children 1-14 yrs reported that 17.9% had serologic evidence of past natural infection. This finding warrants consideration of implementation of routine vaccination against HAV in Greece.

Epidemiology of HEV in Greece

- Little data are available on HEV epidemiology in Greece except for prevalence estimates available from healthy blood donors (0.23%), healthy workers (2.2%) and hemodialysis patients, for whom higher HEV prevalence was noted (up to 9.7%).
- Based on the few existing data, there appears to be no evidence of HEV endemicity in Greece. However, further research might be considered on environmental spread and potential animal reservoirs.

Epidemiology of HBV in Greece

- Greece is a country of intermediate HBV endemicity (HBsAg prevalence >2%) with higher incidence in the Northern part of the country, in minorities, and high risk groups. HBV incidence is highest among 15-24 year-olds.
- Over time, HBV incidence has decreased due to the impact of immunization, as well as improvements in socio-economic status and HC system. However, changing epidemiology is also related to migration, with residual reservoirs of carriers and documented intrafamilial spread of HBV.
- Factors influencing current HBV epidemiology include modes of transmission, travelling habits, and immigrants with high HBsAgand HBeAg-positivity rates.

Epidemiology of HCV in Greece

- Greece is a country of low HCV endemicity (<2%) with overall HCV incidence decreasing over time and highest incidence observed in the region of Athens (linked to IDU). The importance of genotype 3 is increasing over time.
- A higher HCV incidence is observed in minorities and high risk groups (blood transfusion, IDU, etc). Some groups with higher HCV rates need better understanding and follow-up actions.
- Risk factors remain through failure of prevention in medical practice and nosocomial risk. As higher HCV prevalence was reported to be associated with some iatrogenic practices (use of glass syringes, non-disposable material, dental practices, surgery, hospitalisation, etc), control and standard precaution measures should be implemented and their importance should be emphasized in (para)medical education. More specifically, the need for further research on the potential implications of high HCV in HCW in some hospitals was identified, since this could represent a risk of further spread as well as an issue of exposure and universal precautions.

Epidemiology of HDV in Greece

No HDV data representative of the general population in Greece are available. HDV infection mainly occurs in IDU or in specific areas, while higher rates are also noted in immigrants (study in Albanians: 12.7%). High risk groups include IDU, prisoners, HIV-positive individuals, sex workers and minorities.

Molecular epidemiology of HBV and HCV

- In accordance with HBV genotype distribution observed in other Mediterranean countries, HBV genotype D is the most frequent in Greece, followed by genotypes A and G.
- The distribution of HCV genotypes in Greece is different from other Mediterranean countries. Several HCV genotypes are detected with a predominance of genotype 1 (particularly in older individuals) and a fast increase in prevalence of genotype 3 since the 1970s (especially in younger individuals).

Migration and viral hepatitis

- Immigrants account for 7-10% of the Greek population, mainly from Albania, other Balkan countries and Post-Soviet countries, leading to changes in HBV and HAV epidemiology in Greece. No routine serological testing is performed in the immigrant population. Health issues in migrant populations need to be documented since they have implications for immigrants as well as for the Greek population.
- High prevalence levels are observed, e.g. up to 22% HBsAg-positivity in Albanian immigrants, 96% anti-HAV-positivity among Albanian pregnant women, and up to 2.3% anti-HCV-positivity in immigrants living in Athens.
- Prevalence data among immigrants, only available in a fragmented way, are based on legal individuals only and can therefore be considered as underreported.

HIV and HBV/HCV coinfection

The prevalence of HCV coinfection among HIV patients in Greece is relatively low. Unlike patients infected with HBV but who are HIVnegative, the incidence of HBeAg-positivity is high in coinfected HIV patients in Greece.

National Board of Immunization (NBI)

- NBI is an Advisory Committee to the Greek MOH; members are mainly pediatricians although the board is also responsible for adult immunization recommendations.
- NBI reviews immunization programs, including the introduction of new vaccines, and makes recommendations for targeted patient groups. NBI also ensures the availability and distribution of vaccines and is responsible for reporting vaccine-related safety issues.

Overview of HBV Immunization program in Greece

• 1982: risk group vaccination was introduced

- 1993: start campaign for routine immunization
- 1998: HBV vaccine was included in the National Immunization Program (2, 4, 6-18 month schedule; for infants of HBsAg-positive mothers: birth dose + 1-2, 6-18 month schedule)
- 2006 national coverage survey has shown that 67% of vaccinations are carried out by the private sector. Vaccination coverage in young school children is 95% versus 85% in adolescents; it is evenly distributed among regions with good coverage of immigrants (except Greek Roma children coverage of only 59%). The observed delayed start of HBV vaccination and delayed completion of the primary course increases the risk for chronic carriage.

Overview of HAV Immunization program in Greece

- HAV vaccine is available since 1995 and recommended for risk groups but not included in the National Immunization Program.
- 1/3 of children are vaccinated, mainly by private pediatricians at entrance in day care centre. HAV vaccination coverage is higher in Central and Southern Greece where natural immunity is lower than in the North.
- HAV vaccine is widely used but not necessarily for those who need it most (e.g. immigrant children). As >60% of immunization practices are being performed by the private sector, this may leave unprotected population unvaccinated and contribute to shifting HAV incidence to older age groups.
- Results from a 2006 national coverage survey have shown that 88% of vaccinations are carried out by the private sector. Vaccination coverage in young school children is 37% versus 22% in adolescents. Large differences in coverage were noted between regions and social groups, with high risk groups (minorities) vaccinated less.
- New cost-effectiveness studies are needed to assist decisionmaking process on HAV vaccination policy, taking into account indirect costs, herd immunity effects, etc.
- Feasibility and timing of HAV vaccine introduction into the National Immunization Program depend on the competition with other vaccines, such as HPV, varicella, rotavirus and pneumococcal vaccines. There is a need to reevaluate routine HAV vaccination or more extended targeted HAV vaccination including other risk groups, in particular immigrant children.

Lessons learnt and challenges

- Prevention and control of viral hepatitis in Greece is the responsibility of a group of remarkable scientists, doctors and public health experts, with a large research output, based on the recognition of viral hepatitis as a well-known public health burden.
- As epidemiological data are often fragmented and not based on representative samples, figures are sometimes surprising. Hence, there is a need for validation in larger representative cohorts: national

hepatitis seroprevalence and incidence data as well as reliable surveillance systems are needed. Funding of a national seroprevalence study is a major issue but linking with HIV seroprevalence might increase feasibility.

- Child Health Booklet is a unique source of data on immunization status of children in Greece and is very well kept by the parents.
- The high involvement of the private sector in Greek HC services leads to social inequities. Although the strong involvement of the private sector allows for rapid introduction of new vaccines, it provides no guarantee to cover the whole country, in particular immigrant (7-10%) and lower socio-economic populations. However, the higher HAV, HBV and HCV incidence in immigrants deserves special attention in terms of immunization policy for this population.
- The expertise gained during the 2004 Olympics may be used for the benefit of current surveillance systems and enhanced surveillance could be maintained for routine surveillance by HCDCP.
- Although increasing experience with treatment of HIV-HBV and HIV-HCV co-infected patients exists, there is a further need for long-term follow-up of this population. In these patients, attention should be paid to strengthen primary prevention programs, including harm reduction measures and needle exchange programs. Data relating to preventive measures taken to reduce HIV/HBV/HCV infections in IDUs should be made available. In addition, HBV vaccination policy as well as HBV and HCV

treatment in HIV-positive patients should be enhanced.

Recommendations for future actions

- Representative cohort studies should be designed and conducted in order to obtain national hepatitis seroprevalence data.
- Future vaccination coverage studies should be conducted, with inclusion of younger age groups, as feasible.
- Campaigns should be set up to stress the importance of timely HBV vaccination and the use of combined vaccines could be promoted, while paying specific attention to related financial issues.
- Early HBV vaccination of infants and catch-up of children and adolescents of immigrant parents with chronic HBV infection should be implemented.
- HAV vaccination programs should be set up for susceptible immigrant children before visiting their endemic home country.
- Greece should make a decision on the introduction of routine HAV vaccination, taking into account elements of the Israelian experience, such as pros and cons of routine vaccination, parameters of the decision-making process involved, context of an area of endemicity in transition, level of contact between high and low socioeconomic groups and the risk for outbreaks, numbers of fulminant HAV cases, in order to set priorities on the basis of cost-benefit analyses and achieve long-term policies.

Based on a presentation by

P. Van Damme, Centre for the Evaluation of Vaccination, Vaccine and Infectious Disease Institute, University of Antwerp, Belgium.

Dr Badur S	Turkey	Dr Panagiotopoulos T	Greece
Dr Baraboutis I	Greece	Dr Papaevangelou V	Greece
Dr Blystad H	Norway	Dr Papatheodoridis G	Greece
Dr Bonanni P	Italy	Dr Paraskevis D	Greece
Dr Delpire V	Belgium	Dr Pierroutsakos J	Greece
Dr Elefsiniotis I	Greece	Dr Raptopoulou-Gigi M	Greece
Ms Engelen E	Belgium	Dr Roudot-Thoraval F	France
Dr Goldberg D	Scotland, UK	Dr Shouval D	Israel
Dr Guérin N	France	Dr Stavrou T	Greece
Dr Hadjichristodoulou C	Greece	Dr Touloumi G	Greece
Dr Hadziyannis S	Greece	Dr Tountas Y	Greece
Ms Hendrickx G	Belgium	Dr Trimis C	Greece
Dr Jilg W	Germany	DI TIIIIIS G	Greece
Dr Kitis G	Greece	Dr Tsiodras S	Greece
Dr Konstantopoulos A	Greece	Dr Vafiadou I	Greece
Dr Kottakis I	Greece	Dr Van Damme P	Belgium
Dr Kyrlesi A	Greece	Dr Vanderpooten A	Belgium
Dr Lavanchy D	Switzerland	Dr Varaklioti A	Greece
Dr Manesis E	Greece	Dr Vassliadis T	Greece
Dr Manolaki N	Greece	Mr Vorsters A	Belgium
Dr Muscat M	Denmark	Dr Wiersma S	USA
Dr Nikolopoulou G	Greece	Dr Zissouli A	Greece

List of Participants

www.vhpb.org

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For further information, please contact: VHPB Executive Secretariat Centre for the Evaluation of Vaccination WHO Collaborating Centre for Prevention and Control of Viral Hepatitis Vaccine and Infectious Disease Institute Faculty of Medicine University of Antwerpen (Campus 'Drie Eiken') Universiteitsplein 1, B-2610 Antwerpen, Belgium Tel +32 (0)3 820 25 23 Fax +32 (0)3 820 26 40 E-mail: info@vhpb.org