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CONTENTS

This edition of *Viral Hepatitis* is based on material presented at the Viral Hepatitis Prevention Board meeting on **Burden and Prevention of Viral Hepatitis in Turkey**, Istanbul, Turkey, November 12-13, 2009

Editorial

This issue of *Viral Hepatitis* reviews topics covered at the VHPB's autumn meeting focusing on *Burden and Prevention of Viral Hepatitis in Turkey*, held on November 12-13, 2009 in Istanbul, Turkey.

This *country* meeting provided an update on the current status of viral hepatitis prevention in Turkey. The national surveillance and notification system for infectious diseases was presented by the Ministry of Health, with particular focus on significant improvements made since the system was revised in 2005. The specificities of hepatitis A, B, C and D (hereafter known as HAV, HBV, HCV and HDV) epidemiology in Turkey were reviewed, as well as molecular epidemiological approaches. Data were also presented for specific populations at risk, such as victims of human trafficking and health care workers. The management of patients chronically infected with HBV and HCV - including post-liver transplant patients - was also discussed, and an overview was provided of the current prevention and control measures with respect to viral hepatitis. In particular, the progress achieved in hepatitis prevention 10 years after the introduction of universal hepatitis B vaccination was assessed. Also, discussions took place on the introduction of a new preventive intervention such as hepatitis A vaccination and more effective use of existing control measures, strengthening of disease surveillance and coverage monitoring, and better use of data for planning and evaluation of prevention and control strategies. Overall, the meeting was an opportunity to discuss successes achieved in Turkey, problems and barriers still to be overcome, and the way forward.

Presentations and discussions during the meeting highlighted the aspect that Turkey is a large country with a young population that is epidemiologically, geographically and culturally heterogeneous. The epidemiological landscape of the country is characterized by pronounced contrasts between the East and the West, with higher incidences of HAV, HBV, HCV and HDV in the East and South-East.

The need for robust epidemiological data and improved surveillance was stressed, using the new system already in place, but enhancing its capacities in terms of closer monitoring, and identification of risk groups and risk factors. In particular, better access and reporting of collected data should be provided so that they can be used as a basis for the implementation of appropriate prevention strategies.

After 10 years of implementation, HBV vaccination policy has proven successful, with very high vaccine coverage among infants, in particular in the Western part of the country, and has led to significantly decreased HBV prevalence in children in the country. However, implementation of an HAV vaccination policy remains an important challenge, with social obstacles and misconceptions that still need to be overcome. The challenges for HAV are similar to those encountered in the past for HBV, that is, regional differences in seroprevalence. These lead some authorities to believe universal HAV vaccination is not essential whereas others think that improved hygiene and infrastructure in some regions is producing a shift in seropositivity towards older ages, which might indicate a need to switch to universal HAV vaccination in the future. It was recommended to prepare a comprehensive national strategy and plan of action for the prevention and control of viral hepatitis, including the goal of controlling hepatitis B, and implement the plan in coordination with all interested parties.

Proper studies evaluating prevention and control of viral hepatitis, including economic aspects, need to be conducted and could be used as the basis for national strategies.

The meeting also provided the opportunity to present an update on WHO strategies and recommendations for viral hepatitis prevention and control in WHO European Region, and in WHO Eastern Mediterranean Region.

Although the H1NI pandemic was at the time placing considerable demands upon clinicians, researchers, lab workers and policy makers, experts from these sectors were well represented at the meeting and participants valued the opportunity to meet and share ideas with workers from these different fields.

Selim Badur and Nedret Emiroğlu on behalf of the Viral Hepatitis Prevention Board

Breaking News

The 63rd World Health Assembly adopted the "Viral Hepatitis" resolution (WHA 63.18)

The World Health Assembly recognizes viral hepatitis as a global public health problem, and urges all Member States, supported by the WHO, to strengthen the preventive and control measures for viral hepatitis. July 28 has been established as World Hepatitis Day.

More details will be available on the news page of the VHPB website (www.VHPB.org) as of July 2010

Burden and Prevention of Viral Hepatitis in Turkey
Istanbul, Turkey, November 12-13, 2009

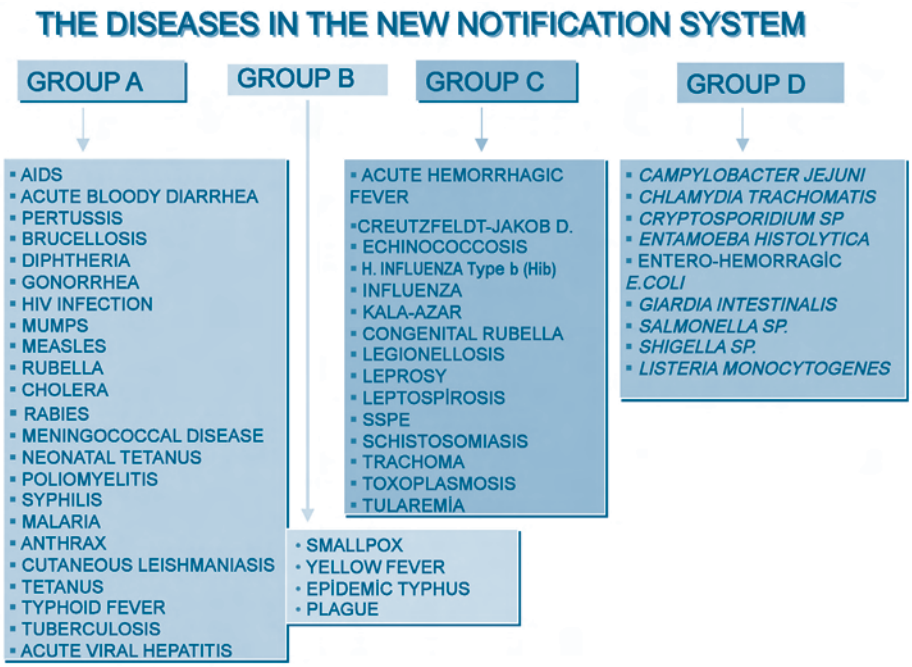
Viral hepatitis surveillance in Turkey

A notification system for communicable diseases has been in place in Turkey since the beginning of the Turkish Republic more than 80 years ago, but in 2005 the system was entirely reviewed with the support of EU and WHO funding, to comply with EU regulations.

Main changes in the Turkish notification system of communicable diseases in 2005 involved:

- a list updated from 39 to 51 mandatory communicable diseases;
- identification of a responsible officer/unit from each health facility;
- setting up of sentinel surveillance that did not previously exist for specific diseases, e.g. influenza;
- immediate reporting and notification determined for each disease;
- use of EU-compliant standard case definitions, with defined laboratory confirmation standards.

The updated list of 51 communicable diseases is divided into 4 groups from A (including acute viral hepatitis) to D, as illustrated below:



The respective roles of institutions in the new notification system are the following:

- collection by all healthcare institutions for Group A and B diseases;
- sentinel surveillance from inpatient institutions for Group C diseases; and
- laboratory diagnosis for selected exposures according to standard techniques in the case of Group D diseases.

For all disease groups, after case detection and classification, surveillance involves notification to the Ministry of Health (MOH) via the Provincial Health Directorate. For diseases where immediate reporting of each probable or confirmed case is required, either systematically or in case of epidemic, it should happen within 24 hours by phone.

Specific notification and investigation forms are used for some diseases, including vaccine preventable diseases.

For viral hepatitis, all probable and confirmed cases are notified by all healthcare institutions to the Provincial Health Directorate that will, in turn, inform the MOH when a case is confirmed, with immediate reporting (within 24 hours) required in case of epidemic. Data is collected separately for HAV, HBV, HCV, HDV and HEV but they only include acute cases.

The current collection system has been in place since 1997, and the efficiency of reporting tools was improved in 2005. It is entirely web-based and consists of standard electronic forms, entered on a monthly basis. Data are subsequently analyzed, using Oracle and Excel programmes.

Surveillance guidelines were issued in 2004 entitled *"Reporting and Notification System of Communicable Diseases. Standard Cases Definitions, Surveillance and Laboratory Guidelines"*, mainly to inform practitioners and physicians on notifiable diseases. The guidelines specifically explain appropriate case definitions, laboratory tests to be carried out for case confirmation, responsible notifying entities, appropriate timing of data collection, and mandatory reporting forms to be used. The rationale for surveillance of each disease is laid out, including general information about disease and implications of surveillance at national, WHO EURO, and global level. For each disease, the chronological steps of the surveillance process are described, as well as case definition parameters, i.e. clinical description, laboratory criteria for diagnosis and eventual case classification.

Overall, collection of data in Turkey is timely with the exception of one or two provinces, but the quality of surveillance results is not homogeneous across regions and types of diseases. In 2007-2008 research was done on cases which had to be notified in 2005 and 2006 from Ankara and Izmir, and it was found that only 1/3 of confirmed cases were reported, which may be explained by physicians only reporting probable cases after laboratory confirmation. On the other hand, duplication of data collection also occurred.

Incidence and prevalence analyses are conducted, based on data collected by the MOH and part of this information is integrated in the annual report available on the MOH website. However, there is no official MOH report or publication containing all diseases reported. The current surveillance system is a mere data collecting system, but it is neither a warning, nor even a consistent reporting system. Hence, the need for better definition of surveillance purposes and related actions (e.g. monitoring prevention programme) was stressed.

Although the updated surveillance system is functioning well in most parts of the country, detailed laboratory investigations are not currently part of MOH surveillance. Interaction between laboratory and epidemiological components need to be strengthened in the future in order to build a stronger surveillance system, with continuous training of staff, and focusing on sustainable diseases.

Based on a presentation by Ü. Özdemirer, Ministry of Health, Infectious Diseases and Outbreak Control Dept., Ankara, Turkey.

Epidemiology of viral hepatitis in Turkey

Several studies conducted between 1985-2000 in various regions of Turkey have indicated that HBV is the major cause of acute viral hepatitis. An average of 60% of the hospitalized acute viral hepatitis cases in adults (20-40 years of age) were due to HBV and among children this was only 22.4%. When considering 135 cases of fulminant hepatitis in Turkey, in around 40% of these cases the condition is virally induced and, among these, approximately 90% is HBV related.

HAV is the major cause of acute viral hepatitis in those under the age of 20 years [1-4] (see Table below).

Etiology of acute viral hepatitis in Turkey

REFERENCE	YEAR	N	HAV % MEAN AGE/ (AGE RANGE)	HBV % MEAN AGE/ (AGE RANGE)
KANDEMİR, 2007 [1]	1990 2004	561	48.2% 17 years	41.5% 28 years
YAMAZHAN T, 2001 [2]	1993 1997	246	43% (15-20 years)	45.9% (21-30 years)
ÇOLPAN, 2003 [3]	2001 2003	73	54.8% (20.4±6.1 years)	39.8% (30.9±12.5 years)
ERTUĞRUL, 2006 [4]	2004 2005	46	87% 12.35 years	13% 37.33 years

The aetiology of viral hepatitis and the prevalence of HAV infection in Turkey, compared to other countries, are presented in the Figures below [5].

Figure 1: Seroprevalence of viral hepatitis A in various countries (before 2000)

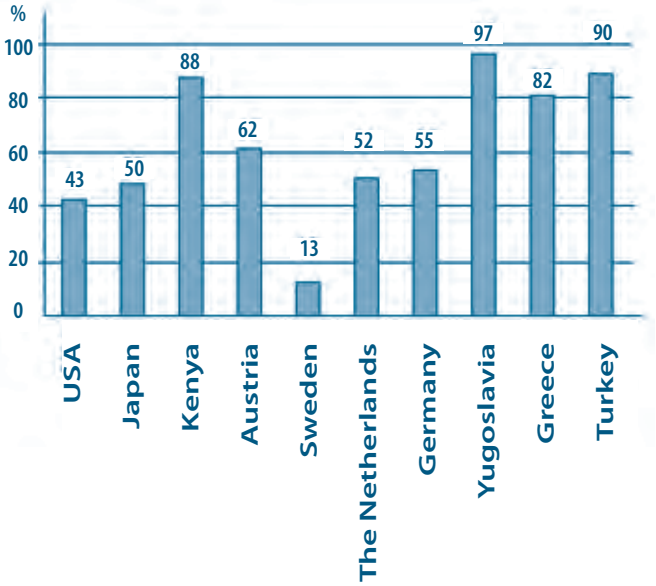
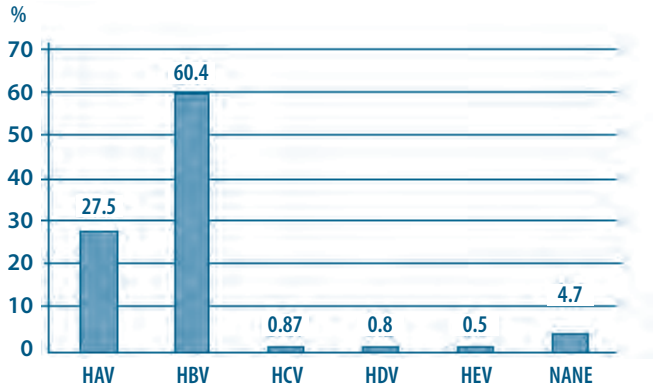


Figure 2: Aetiology of acute viral hepatitis in Turkey (pooled data of 4,471 cases)



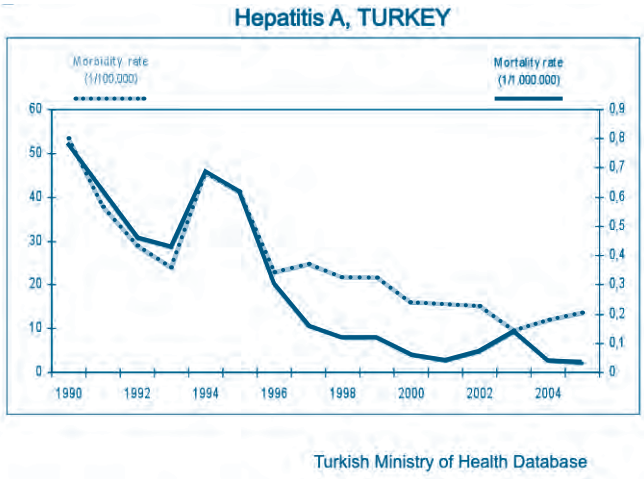
From the low proportion of acute viral hepatitis cases identified as being due to HCV (not higher than 3% before 2000 in Turkey) it appears that HCV only has a small contribution in the acute phase of viral hepatitis, due to the asymptomatic character of HCV infection.

A population-based study on the prevalence of viral hepatitis in Turkey was launched in 2008, involving 5,250 individuals in 24 cities, screened for HAV, HBV (and HDV when HBV positive) and HCV, with expected results in November 2009. This study should bring reliable information on true prevalence in the country, allowing for public health actions and planning. In addition, it provides an opportunity for infected individuals to be referred to treatment.

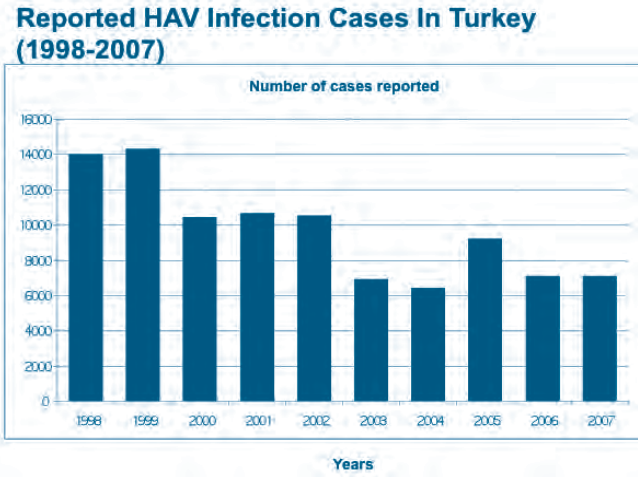
Epidemiology of hepatitis A in Turkey

As in many countries, HAV disease is the most common cause of acute viral hepatitis in Turkish children. Although HAV is generally perceived as a non-serious disease with low mortality rates in children, liver failure due to HAV occurs at all ages. Children are the main source of infection and represent an important risk for susceptible adults, who may go on to suffer from prolonged disease.

Before the 90's, HAV disease was highly endemic in Turkey, with seroprevalences above 80% in children and adults. Since then, morbidity and mortality due to HAV have been steadily decreasing (see Figure left below), due to improved hygiene and sanitary conditions.



There was a 50% fall in reported cases of HAV in Turkey over the last ten years, as seen in the Figure below:



Today, at national level, Turkey is a country of intermediate HAV endemicity. However, when considering regional incidences, a strong West/East gradient exists, with highly endemic regions in the Eastern and South-eastern parts of the country where incidences of up to 23.6/100,000 can be found, compared to intermediate Western regions with an average incidence rate of 10/100,000.

The seroprevalence rate among those under the age of 30 years is 71.3% and rates increase with age, from 42.7% among 1 year olds to 91.1% at 25-29 years of age. In the Western region large proportions, sometimes >50% of the population, are susceptible.

Reliable data on HAV incidence and outcome of fulminant HAV are currently missing for Turkey. HAV transmission does not seem to be restricted to toddlers. The pattern of HAV exposure in Turkey has been changing in recent years, due to altered eating habits (more fast food and exotic food consumption), increased day care attendance and changing migration patterns. More people originating from highly endemic regions in Eastern Turkey are moving to the Western part of the country, with susceptible second generations who lack anti-HAV antibodies, travelling back to the endemic home region during holidays. Also, issues such as recent cases caused by contaminated tap water emphasize the need for continuing improvements in sanitation and in public education on hygiene practices.

Molecular epidemiology of HAV

Serum samples from acute phase HAV patients, positive for anti-HAV IgM, collected in various areas in Turkey, were tested for viral RNA by reverse transcriptase polymerase chain reaction and PCR products underwent phylogenetic analyses [6]. All isolates belonged to genotype I, with a majority being of type IB, and most isolates were closely related to each other.

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1990-2004 yılları arasında yatırılarak izlenen akut viral hepatit olgularının değerlendirilmesi. Selçuk Üniversitesi Tıp Dergisi 2007;23(2):77-83.

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Based on presentations by

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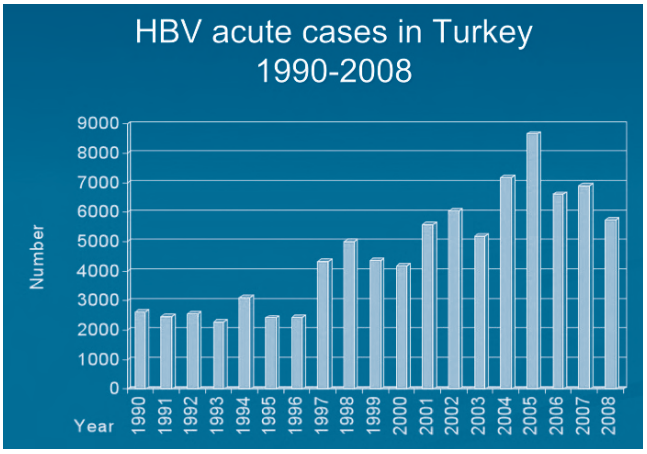
Epidemiology of hepatitis B in Turkey

Turkey is a country of intermediate/high HBV endemicity, with HBsAg prevalence in the general population ranging from 2.5% to 9.1%, depending on the region and the study. The number of acute HBV cases reported to MOH from 1990 up to 2008 is shown in the Figure below.



Further characterization of MOH HBV surveillance data shows that morbidity and mortality rates due to HBV are still high and even appear to have increased in recent years. The recent increase in morbidity and mortality was seen across all age groups. The number of HBV acute cases is highest in the young adults aged 20-40 years.

As shown in the Table right above, published data on HBsAg prevalences reported an average of 6.3% in healthy adults and 58% among patients with chronic liver disease in the period 1980-2000 (reviewed in [1], [2]).

Group (n)	Marker	1980 1990	1990 2000	p-value	Mean
"Healthy" adults (6,800,000)	HBsAg	6.8%	5.9%	p<0.05	6.3%
Health care workers (14,000)	HBsAg	5.8%	3.6%	p<0.05	4.7%
Chronic liver disease (5,000)	HBsAg	60%	56%	p< 0.05	58 %

Değertekin H. Hepatit B, 2003 [1]
Mıstık R, Balık İ. Viral Hepatit, 2001 [2]

However, as for HAV, higher HBV prevalence rates were reported in South-eastern and Eastern parts of the country, where mean prevalence before 2000 was 8.8% in adults and 68% among patients with chronic liver disease.

Based on published review articles and meta-analyses, the HBsAg prevalence rate for the general Turkish population over the years can be estimated to have been 6.8% in 1980-1990, 5.8% in 1990-2000, and 3.8% in 2000-2009 (2.2% when including blood donor data).

HBsAg prevalence increases with age among children and peaks are generally noted around the age of 10-20 years, such as in Western cities Istanbul and Izmir [3, 4], or between 5-15 years [1-8], depending on the study.

Studies conducted before 2000 (1990-2000) reported HBsAg prevalence rates in children aged 0 to 18 years in Western Turkey varying from 1.15% to 9.9% and in the Eastern region ranging from 3.1% to 13% (reviewed in [2]). One large, cross sectional study (N=2,683) covering 8 provinces over the country found an average of 5.4% HBsAg positive children, and 17% were anti-HBs positive [9].

After 2000 (2001-2008), HBsAg positivity among children was significantly lower, i.e. 1% in Istanbul among those aged 9 months up to 8 years and 2.7% in the area of Mardin in South-east Turkey among 6-17 year old school children [10]. Decreases in HBsAg positivity among children after 2000 are most likely due to prevention of perinatal and horizontal transmission by the vaccination programme.

Horizontal transmission is the major route of HBV transmission, especially among children. Particularly intra-familial transmission from parents to child or from sibling to sibling is common. A study among children with chronic HBV showed that the risk was 71.9% for intra-familial transmission and 23% for parenteral transmission. Transmission risk increases with the number of children in the family and when both parents are HbsAg positive.

After 2000 (2003-2007), a decrease in HBsAg positivity in the general adult population was reported in several field studies conducted across the country (Isparta, Bolu, Tokat, Erzurum, Diyarbakır, Urfa, Mardin and Batman provinces), with preva-

lences ranging from 2.5% to 9.1%. These studies found significant correlations between HbsAg positivity and low educational status, increasing age, male gender, living in rural area and family history of jaundice. In these studies, anti-HBs prevalences were 16.2%-47.4% [11, 12].

A significant decrease in HBsAg prevalence over several years has also been seen among blood donors, as reported by the Turkish Red Crescent [13], in line with a mean 1.8% HbsAg positivity rate based on several studies conducted across the country over the period 2000-2009.

The same decreasing trend was seen among healthcare workers (HCW), where HBsAg positivity rates decreased from 4.7% before 2000 to 2.9% after 2000 [14]. However, only 56.5% of HCW reported having been vaccinated and an important proportion of 25.2% remained anti-HBs seronegative and susceptible. Possible explanations for the lower HBsAg prevalence among HCW include better access to vaccines and good health care service and most HCW are better informed on the transmission routes and the risk factors of the disease.

In contrast, no significant decrease was observed over time among pregnant women: the mean HBsAg positivity observed from several studies was 4.2% before 2000 and 3.6% after 2000.

HBsAg seropositivity rates reported in other risk groups include 10.1% in hemodialysis patients, 9.6% in female sex workers, and 12.3% in barbers and hairdressers.

Molecular epidemiology of HBV

Numerous HBV genotyping studies have been conducted in Turkey and have been published. Like other Mediterranean countries, infection with HBV genotype D is predominant in Turkey [15, 16]. More than 90% of HBV cases are due to genotype D, with D1 being the most frequent, but other genotypes including A1 and B are also present. Recently, genotype A1 was isolated from three patients who were treated in the same hospital, hence these cases were possibly due to nosocomial infection [17].

Higher rates of HBV pre-core sequence variations are seen in Turkey (up to 12%) compared to other countries such as India, Pakistan, Bangladesh (e.g. only 3% recombinants in India). These data should be interpreted with caution because reported recombination rates in literature are confusing. The methodology of the reported studies should be evaluated properly before using the data reported.

In terms of serotyping, the serological HBsAg subtype ayw is dominant, mostly ayw2, while ayw3 and very rarely ayw4 also occur [18].

HBV mutant problems

Several reports of HBV mutants circulating in Turkey have been published and show that HBV mutation patterns and related issues in Turkey are not different from those reported in other countries.

Precore and core promoter mutations were identified in isolates from Turkish patients with stop codon mutation playing an essential role in the loss of HBeAg [19].

HBeAg negative infection represents an advanced stage of disease where mutations in HBV genome are more likely to be present. Therefore, prognosis and treatment response in HBeAg negative patients is poor with a mortality rate of 4% in 4 years and a risk of 14% to develop hepatocellular carcinoma (HCC). HBV genotype D, which is predominant in Turkey, is associated with a higher prevalence of HBeAg negative infection. In Turkey, 65%-80% of the patients with chronic HBV infection are HBeAg negative, which is a lower rate than in other Mediterranean countries (e.g. over 90% in Italy and Greece). This may be due to higher rates of perinatal transmission and the younger age of chronic HBV patients in Turkey. More than 10 years ago, the median age of treated chronic patients was 37 years while it is now 43 years.

Clinical consequences of S gene (coding for surface antigen) mutations include occurrence of HBV infection in postexposure prophylaxis or HBV recurrence in postransplant patients who received HBIG prophylaxis. Also, these mutations may be responsible for diagnostic inaccuracy in ELISA tests.

Naturally occuring variants at the level of the HBV surface antigen have been reported (27.7% in 81 Turkish patients), especially among chronic HBV patients (42.5%). Some of these variants may be detected at lower sensitivity in commercial HBsAg assays using monoclonal antibodies for capturing and detection [20].

Mutations of HBV polymerase, especially those occurring at the highly conserved YMDD region, exist as drug resistant mutations to Lamivudine. These mutations can also occur naturally. For instance, naturally occurring YMDD variants were detected at a high rate (18.3%) in a group of treatment-naïve inactive HBsAg carriers studied in Izmir [21]. Among treatment-naïve haemodialysis patients with occult HBV infection, the proportion with YMDD variants was as high as 50% [22], however the high rate of YMDD variants in this study could be linked to the use of assay pilot versions with questionable reliability.

Overall, drug resistant mutations in Turkish isolates are detected at the same rate and with the same type of mutations as in other countries. When looking specifically at Lamivudine resistant mutations, HBeAg negative patients were found to have a lower rate of biochemical breakthrough during Lamivudine therapy, comparing to HBeAg positive patients. However, this can be related to lower HBV DNA levels, compared to HBeAg positives.

The occurrence of vaccine escape mutants was occasionally reported, e.g. cases in a leukemia patient and in a renal transplant recipient [23, 24]. Such surface antigen mutants may result in HBsAg detection issues in commercial assays but do not represent an important public health problem.

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**Turkish reference*

Based on presentations by
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Epidemiology of hepatitis D in Turkey

Before 2000, the mean anti-HDV prevalence among Turkish asymptomatic HBsAg carriers at several centres across Turkey was 4.1%-5.4%, which decreased to 2.9% in 2000-2005 (reviewed in [1]). Since 2000, the rate of HDV infection has been decreasing in the country, but HDV prevalence is still high in East and South-East Turkey, with up to 6 % of HBsAg carriers being anti-HDV positive [1, 2].

In patients with HBV related chronic liver disease (CLD), anti-HDV positivity was significantly more common (30.6%) than in asymptomatic HBV carriers, in a region with a high prevalence of HBV infection [2, 3].

A correlation between the duration of HBsAg carrier status and anti-HDV positivity was found, whereas age, gender, and presence of HBeAg were not significantly associated with the development of anti-HDV positivity [2]. HDV is still an important issue despite its decreasing prevalence . Among patients with cirrhosis, HDV is more prevalent in the South-East of Turkey (46.3%), than in the West of Turkey (20.0%) although among HBV positive patients with HCC the proportion of HDV infected cases fell from 18% in 1994-1997 to 2% in 1994-2007 [3].

Molecular epidemiology of HDV

Genotyping in patients with chronic HDV in different parts of Turkey demonstrated that HDV genotype I is the only type determined so far [4, 5]. Divergence among isolated sequences can be up to 16%. Turkish HDV strains are related to Asian, Middle Eastern and European strains.

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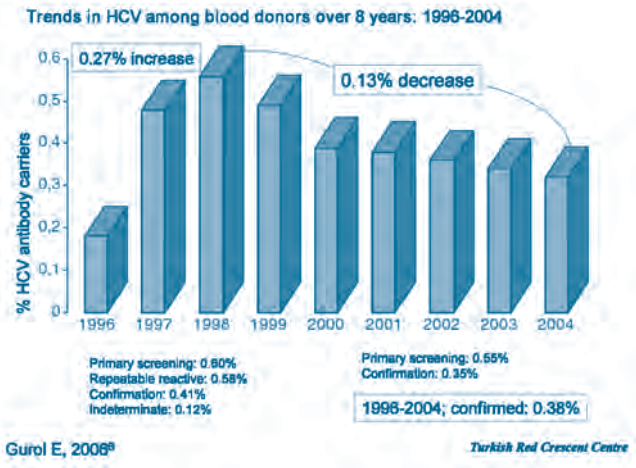
Epidemiology of hepatitis C in Turkey

General population

HCV epidemiological data for the general population in Turkey are only available from studies differing in sample size and sampling methodologies. Selected field studies including people attending outpatient clinics report anti-HCV rates varying from 0.17% to 2.8%, with highest rates in the Eastern part of the country. These HCV prevalence rates in the general population are similar to other European countries but lower than those reported in Eastern Mediterranean countries, e.g. Egypt. In Turkish children, HCV prevalences were lower than in adults, ranging from 0% to 0.56%, depending on the study and the region (1999, 2003). When considering anti-HCV rates by age, highest prevalences are generally seen in adults aged 35 years or older, i.e. between ~0.7% and 2.1% in Western cities Istanbul and Ankara [1, 2, 3], and 4.0%-7.1% in the Eastern region (Tokat and Van) [4, 5]. No significant difference in anti-HCV seroprevalence was noted between males and females. Income level appears to have an effect: higher anti-HCV prevalence (2.3%) is associated with low income.

Blood donors

Most epidemiological studies on HCV infection were conducted amongst blood donors. Routine screening of anti-HCV has been implemented in all blood centres in Turkey since 1997. An increase in blood donor seropositivity was seen in 1997 and can be related to the introduction of a better performing ELISA test (see figure left below). The overall prevalence among whole blood donors at 22 Red Crescent Centres was 0.38% for confirmed HCV antibody carriers during the study period between 1989 and 2004. The annual anti-HCV seroprevalence in these centres first gradually increased from 0.18% in 1996, to 0.56% in 1998, and then decreased to 0.34% in 2004 [6].



The mean anti-HCV seropositivity reported by several studies in blood donors in 1995-1999 was ~0.6%, and ~0.54% in 2000-2007. Overall, prevalence rates among blood donors in Western and Eastern parts of the country were similar and, although some regional variations were observed, regional prevalences never exceeded 1% over the period 1996-2004.

Health care workers

As for blood donors, the anti-HCV positivity in HCW was low and similar to rates in other countries. The average prevalence in HCW decreased from ~0.7% in 1992-1999 to ~0.4% (range 0-2.1%) in 2000-2004. Viral hepatitis in HCW is discussed further in the section on populations at risk.

Risk groups – risk factors

The average anti-HCV prevalence in haemodialysis patients, based on a number of small studies conducted across the country decreased from 41.5% during the period 1991-1999 to 27.4% between 2000 and 2006. These average rates are in agreement with data from larger multi-centre studies which reported 49.5% of haemodialysis patients to be anti-HCV positive in 1995 and 28% in 2005. At regional level, prevalence rates among these patients are highly variable, with levels of up to ~82%, both in Eastern and Western parts of the country.

Multiple transfusion appeared to have an impact on anti-HCV seroprevalence, especially when performed before 2000 and in older patients, leading to higher rates of 4.5% to 30% [7, 8]. Seroprevalence is also higher in patients with non-Hodgkin lymphoma (1.4%-22.5% anti-HCV positive) [9] and patients with liver disease such as chronic liver disease, hepatocellular carcinoma (HCC) and cryptogenic cirrhosis (11%-72% anti-HCV positive). The contribution of HCV in CLD was said to be comparable with other countries.

In female sex workers, the average anti-HCV seropositivity was ~4.5% over the period 1992-2000, and ranged between 2.3% and 12%, with higher rates in Eastern provinces.

Although multiple sex partners was identified as a risk factor [8], the prevalence among sexual partners of patients with chronic HCV (2%-5.5%) is not significantly higher than among the general population. Moreover, when excluding partners with other risk factors, HCV prevalence in this group is even lower [10]. Among children of chronic HCV patients the prevalence is 1.3%-2.2% [11].

Also, high anti-HCV seroprevalences (45-55%) were seen among intravenous drug users (IDU). The transmission of HCV

among IDU in Turkey has not been studied and further investigations in this risk group are needed.

Main routes of HCV transmission are healthcare related: history of blood transfusion (before the '90s, i.e. before implementation of the blood screening programme) and previous surgery (after the '90s), as well as a history of hospitalization for invasive procedures. Molecular studies investigating HCV transmission during surgery are still ongoing. Nosocomial HCV infection still happens in Turkey, the situation should improve with better prevention measures.

Most anti-HCV positive patients are HCV RNA positive (>50%). HBV/HCV coinfected patients are mainly renal transplant and haemodialysed patients. Among HIV positive individuals, the rate of HCV coinfection is 20-30%.

Molecular epidemiology of HCV

HCV genotype 1 is the predominant type in Turkey, with ~80% type 1b and ~9-20% type 1a, while HCV types 2, 3 and 4 viruses also circulate in the country at lower frequencies (1%-2%). The genotype distribution in the period before 2001 seems to be similar to the distribution post 2001 [12, 13], however, a systematic review is needed to confirm this. In some European countries and in Syria, pockets of HCV type 5 infection have been observed, but to date it is not reported in Turkey. More research on genotyping distribution in different risk groups was advised during the meeting.

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Chronic viral hepatitis and treatment strategies in Turkey

Epidemiology of chronic hepatitis and cirrhosis

HBV is still the leading cause of chronic hepatitis and hepatocellular carcinoma (HCC) in Turkey. According to the MOH, the incidence of HCC in Turkey was 0.83/100,000 and remained unchanged between 2000 and 2003. Over the period 1994-1997, 56% of HCC cases were due to HBV [1] and from 1994-2007 this was still 44.4% [2].

Etiology of Hepatocellular carcinoma (HCC) in Turkey according to geographical region

Region	Etiology		
	HBV	HCV	Alcohol
West Turkey	18/54 (33.3%)	20/54 (37%)	17/54 (31.5%)
Central Turkey	53/85 (62.4%)	21/85 (24.7%)	7/85 (8.3%)
South and Southeast Turkey	45/68 (66.2%)	7/68 (10.3%)	9/68 (13.2%)

Uzunalimoğlu et al, Dig Dis Sci 2001 [1]

Data on HCC etiology for the different geographical regions demonstrate that HBV is especially a problem in Central, South and South-East Turkey [1] (see Table left). In the East and South-East, HBV is responsible for 73% of liver cirrhosis cases versus only 8% related to HCV, and 2.5% due to alcohol [3].

In the Western part of the country, the contribution of HBV to chronic viral hepatitis slightly decreased over the last 15 years, from 63% in 1991-1994 to 51.3% in 2002-2005 whereas the

proportion of chronic cases attributable to HCV increased from 26% to 42%. Likewise, the role of HBV in liver cirrhosis declined (from 56% in 1990-1993 to 46% in 1998-2001) but HCV gained importance in liver cirrhosis etiology (from 25% to 31% in 1998-2001). Although the role of HBV in chronic viral hepatitis and liver cirrhosis declined, the overall impact of viral infections on liver cirrhosis slightly increased over time.

HDV prevalence is higher in East and South-East Turkey, with 23.5%-27.1% of chronic HBV patients being anti-HDV positive as compared to 4.8% in the West, and 12.1% in Central Turkey [4]. Also, among patients with cirrhosis, HDV prevalence is again higher in the South-East Turkey (46.3%), than in the West of Turkey (20.0%) [4]. However if we compare pre- with post- 1995 figures, anti-HDV prevalence has fallen in all the regions of Turkey measured (see Table below) [4].

Change in HDV prevalence among patients with chronic hepatitis B in different regions of Turkey

Region	Disease Group	< 1995 n (%)	>1995 n (%)	p value
Central	Chronic HBV	106/365 (29.0%)	20/166 (12.1%)	<0.001
Southeast	Chronic HBV	58/154 (37.7%)	78/288 (27.1%)	<0.001
Western	Liver cirrhosis	70/183 (38.3%)	113/564 (20.0%)	<0.001
Southeast	Liver cirrhosis	73/110 (66.4%)	83/179 (46.4%)	<0.001

Değertekin H et al.,Liver Int, 2008 [4]

A recent study found that among HBV positive patients with HCC, the proportion of HDV infected cases also fell from 18% in 1994-1997 to 2% in 1994-2007[4]. Overall, these figures show that, although its prevalence is decreasing, HDV remains an important problem, especially in Central and Southeast parts of the country with low socioeconomic level [4].

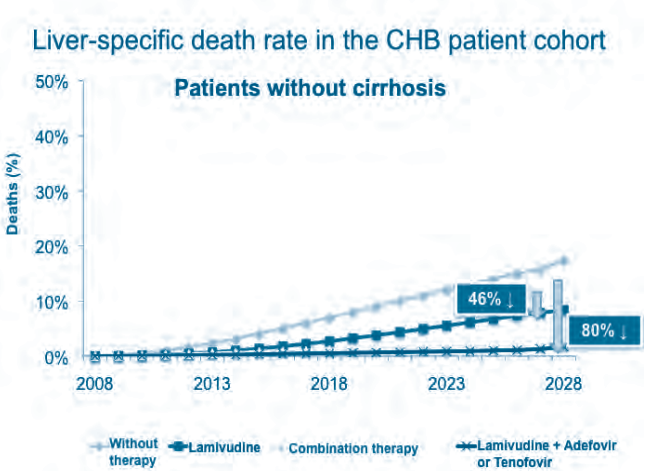
Mathematical modelling of chronic HBV burden

The potential burden of chronic HBV in terms of mortality and morbidity in Turkey was estimated using mathematical modelling [5]. To this end, age-specific HBsAg prevalence data obtained through extensive analyses of the Turkish HBV literature were compared with population statistics provided by the Turkish Statistics Institute. In addition, the databases of the gastroenterology departments of the University of Ankara and a state hospital in Ankara (Türkiye Yüksek İhtisas Hastanesi) were searched for age-specific HBV DNA level, HBeAg status and alanine aminotransferase ALT level. This resulted in a total cohort of 1453 Turkish patients, of which 24.5% had active hepatitis, which was then compared with an international patient cohort. Based on this model, a realistic estimate of 4.2-4.8% for the overall HBsAg prevalence for Turkey was made, ranging according to region from 2.5% (West Turkey) to 6.9% (East Turkey). For the 71 million total Turkish population, this would represent over 3 million HBsAg positives, approximately 890,000 individuals with active chronic HBV and, of these, around 107,000 with liver cirrhosis. Considering a conservative approach, 10% of HBsAg positives are estimated to have active chronic hepatitis (n=300,000). Based on sales data, it was roughly estimated that a large proportion (possibly as high as 90%) of patients with active chronic hepatitis are not being treated. Also, many of them probably do not even know that they have a disease.

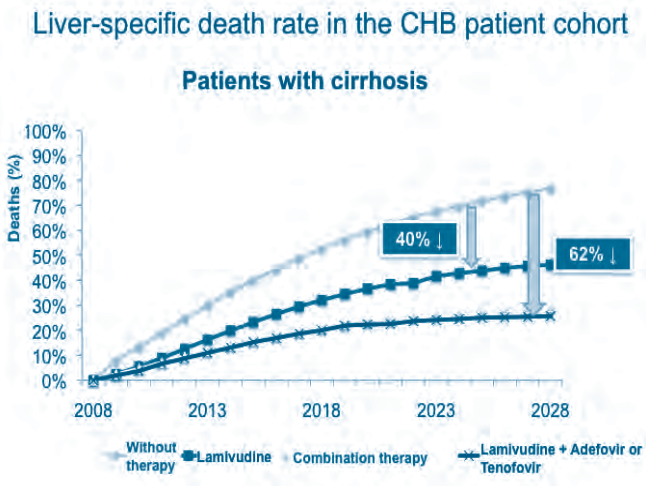
A dynamic mathematical model (Markov simulation) was used to predict the effect of treatment of chronic HBV. A 20-year projection of this dynamic model roughly predicted that out of approximately 858,000 patients with chronic HBV:

- 46% (394,000) would develop cirrhosis,
- 9% (77,000) would develop decompensated cirrhosis,
- 10% (85,000) would develop HCC,
- 4% (34,000) would need liver transplantation,
- 22% (188,000) would die.

Furthermore, it was predicted that almost 20% of patients without cirrhosis would die in 20 years if not treated (see Figure below). This mortality rate would be reduced by 46% if treated with Lamivudine, and by 80% if treated with Lamivudine, together with a drug effective in patients who develop resistance to Lamivudine, such as Adefovir or Tenofovir.



A worse outcome was predicted for patients with cirrhosis (see Figure below): 75% would die in 20 years if not treated but with appropriate treatment this mortality rate would be suppressed by more than 60%.



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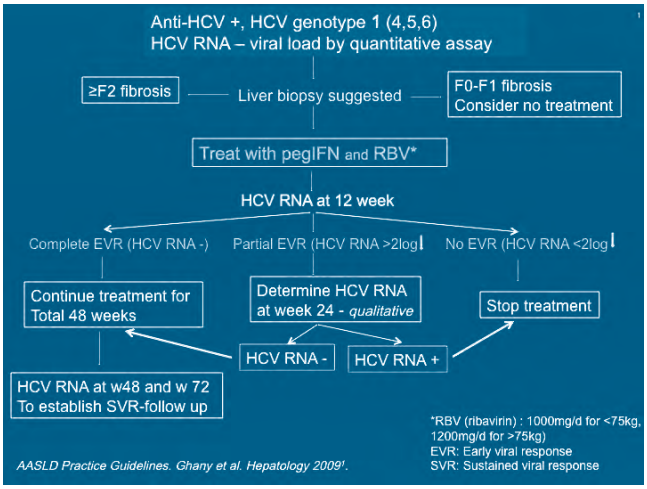
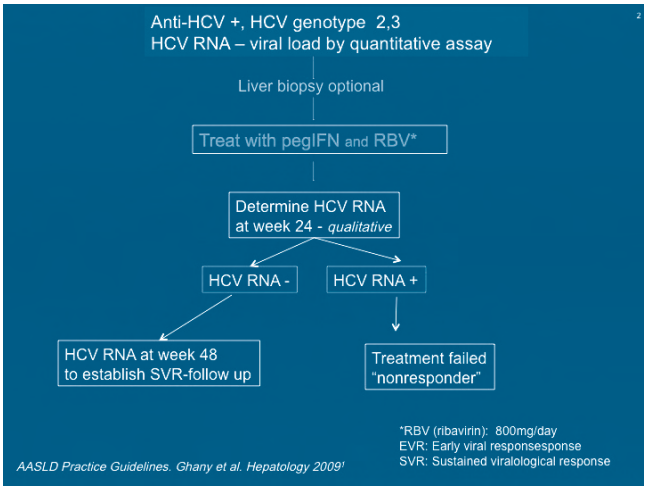
Treatment algorithms for chronic hepatitis

HCV

Treatment of chronic HCV has known a successful progress in the last decades, with an increase in sustained virological response (SVR) rate from 5-10% in the late '80s to approximately 70% in 2009. Moreover, patients achieving SVR can now be considered as 'cured'.





Generally, genotype 2 and 3 HCV infection is easier to treat, with higher SVR rates than genotype 1 HCV infection, hence the American Association for the Study of Liver Diseases (AASLD) recommends different treatment algorithms to be applied for these two patient categories, i.e. patients infected with genotype 2 or 3 versus those with genotype 1 (or 4, 5, 6) (see two Figures left below) [1].

According to this algorithm, treatment is only recommended in patients with genotype 1 HCV when they have marked fibrosis (≥F2). However, as proposed by the Turkish Association for the Study of the Liver (TASL) and as decided by the department within Turkish Health Authorities responsible for reimbursement decisions (SUT), biopsy is optional in Turkey and treatment can be initiated without biopsy if no contraindications exist. Clinical practice shows that SVR rates in patients with mild fibrosis (F0-F1) are around 76% and approximately twice as high as those in advanced fibrosis patients (F3-F4) [2].

Recently, a new rapid responder schedule was developed for HCV genotype 1 treatment with low initial viral load. In these cases, HCV RNA is checked after 4 weeks of treatment and those who test negative only need to be treated for 24 weeks, which generally results in very high SVR rates of 85-92%. This approach is adopted in some European countries whereas in Turkey, the 4-week check is performed but currently all genotype 1 patients are still treated for 48 weeks.

To date, there are no data available for Turkey on the proportion of HCV patients requiring treatment who are actually receiving therapy.

HBV

Treatment of chronic HBV is challenging and several international and national HBV treatment guidelines have been developed, which in most European countries are applied by more than 80% of the physicians. Treatment knowledge has significantly increased over time and recommendations have evolved accordingly, with most recent guidelines recognizing that many patients are at significant risk of disease progression. Quality of life and survival by preventing progression to (decompensated) cirrhosis, end-stage liver disease, HCC and death should be the goal of the recommended therapy. This can be achieved by suppressing HBV replication in a sustained manner, while acknowledging that HBV infection cannot be entirely eradicated due to intrahepatic covalently closed circular DNA(cccDNA) persistence. In Turkey it is estimated that only 10% of HBV patients are treated, but for those treated, treatment guidelines are generally well-followed.

The 2009 guideline issued by the European Association for the Study of the Liver (EASL) is the most recent and up-to-date recommendation providing clinicians with best practice on how to treat chronic HBV patients [3].

According to the EASL guideline, chronic HBV patients should be considered for treatment when HBV DNA levels are > 2,000 IU/mL (10,000 copies/mL) and/or serum ALT levels are above the upper limit of normal levels, and when liver biopsy shows

moderate to severe active necroinflammation and/or fibrosis [3]. Recommended therapies include treatment with PEG INFα or nucleotide/nucleoside analogues (Tenofovir or Entecavir).

In some well-defined patient subgroups (mainly HBeAg positive with greatest chance of seroconversion, with high ALT levels but relatively low viral load), the intention is to achieve sustained off-treatment virological response, therefore 48 week treatment with PEG IFN-α is advisable. If PEG INFα is not the first choice, the most potent agents with the highest genetic barrier to resistance are recommended for both HBeAg positive and HBeAg negative patients. Nucleotide/nucleoside analogue treatment can be stopped 24 to 48 weeks after HBe seroconversion, with follow-up check every 6 months. In case of long term or sustained therapy with nucleoside analogues, it was recommended that HBV DNA levels should be monitored to detect treatment failures. Ideally, HBV DNA reduction to undetectable levels (<10-15 IU/ml) needs to be achieved in 24-48 weeks to avoid development of resistance.

Compared to other frequently applied guidelines (such as AASLD [4]), the 2009 EASL recommendations apply the lowest viral load and ALT criteria for treatment initiation. The Turkish recommendations by TASL, published in 2007 [5], are in line with these EASL criteria, except that liver biopsy evidence is always required to start treatment in patients with no established cirrhosis. Importantly, a new modification issued in 2009 by SUT, following the suggestion of some hepatologists, states that Lamivudine should be the first line therapy in all patients with viral load lower than 107 copies/ml. The more potent antivirals can be used ("add-on" or "switch to") if there is PCR-detectable HBV DNA in blood at the end of 6 months of Lamivudine therapy. The recommendation to use Lamivudine as first line therapy is currently under discussion among Turkish hepatologists and was also questioned during the meeting with reference to the problem of resistance. It was suggested that decisions should be made by the hepatologist on an individual basis, taking into account the patient's history, clinical condition and resistance profile. However, it seems that the cost aspect is an important component of the current Turkish recommendation. Furthermore, TASL strongly advises that there should be no further limitation in the use of oral antivirals and PEG IFN therapy in chronic HBV patients with biopsy proven moderate to severe necroinflammation (and HBV DNA >2000 IU/ml and elevated ALT) .

In Turkey, the decision to start antiviral therapy can only be taken by gastroenterologists and infectious disease specialists and it was recommended during the meeting that antivirals should only be prescribed by these physicians based on a patient's history, the severity of liver disease and taking into account the risk of developing drug resistance.

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HBV and liver transplantation

In Western countries, up to 10% of liver transplant patients have HBV. The number of liver transplant patients in Turkey is 400-500 per year and this treatment is paid for by health insurance. At the largest liver transplantation centre in the country (Ege University Medical School Gastroenterology Department, Izmir), approximately 100 liver transplantations have been performed annually during the last decade. Since HBV is the leading cause of end stage liver disease in Turkey, an important proportion of HBV infected patients require transplantation. In the Ege University centre, 60-70% of transplant patients are infected with HBV/HDV. The number of patients with HCC is increasing at Ege University and recurrence of HBV and HCC after liver transplantation seems to be correlated. Liver donors are only vaccinated against HBV if there is enough time before transplantation.

Before the availability of prophylactic agents, HBV recurrence rate after transplantation was up to 100%. In the last two decades, recurrence rates have fallen with the introduction of hepatitis B immunoglobulin (HBIG) for post-transplantation prophylaxis (to 40% recurrence) and now with the use of Lamuvidine therapy combined with HBIG recurrence has again fallen and is now below 10%. Accordingly, post-transplantation survival rates for HBV patients are substantially improved thanks to the introduction of prohylaxis therapy and are at rates comparable to those for post-transplantation patients who have viral hepatitis resulting from other aetiologies [1].

In the pre-transplantation setting, the main objective is to suppress viral replication without acquiring drug resistance to undetectable HBV DNA levels in order to avoid post transplantation recurrence. With the new generation of antiviral agents, it is now possible to significantly delay or even avoid transplantation. A pre-transplantation HBV DNA threshold of 100,000 copies/ml can be considered predictive for the risk of developing recurrence after surgery [2].

In terms of post-transplantation prophylaxis therapy, HBIG combined with Lamivudine has become the standard of care in most centres worldwide, but there is no consensus on dosage,

duration and route of administration of HBIG. At the Ege University centre, low dose HBIG has shown to provide an acceptable 5% recurrence rate after a median follow up of 18 months [3]. The effectiveness of low dose HBIG on longer term, up to 5 years, was demonstrated in a recent study conducted in Australia/New Zealand [4]. However, additional studies are needed to investigate whether complete elimination of HBIG is feasible. Approaches that could be considered include:

- active immunoprophylaxis or vaccination;
- discontinuation of HBIG and continuing prophylaxis with nucleoside analogues.

The feasibility of the first approach was investigated at the Ege University centre, but HBV vaccination was found not to be an effective strategy for HBV prophylaxis after liver transplantation, since only one out of 14 patients seroconverted after having been administered with a double course of double dose HBV vaccine [5].

Treatment of post-transplantation recurrent HBV infection despite prophylaxis with HBIG and Lamivudine combination therapy is challenging. A study conducted at the Turkish Ege University centre showed that new nucleotide analogues (such as Adefovir and Tenofovir) can be an effective treatment option for post-transplant HBV recurrence, even among patients with Lamivudine resistant HBV [6].

HCV and liver transplantation

In Western countries, HCV represents a major problem in chronic liver disease with almost half of liver transplant recipients infected with HCV. In Turkey, however, the proportion of HCV in transplant patients is lower (10-20%) and, at the Ege University centre, fewer than 10% of transplant patients have HCV.

The majority of HCV patients continue to be HCV RNA positive after transplantation. About 75% of HCV patients experience acute hepatitis after surgery; the majority progress to chronic HCV and one third become cirrhotic after 5 years. Also, progression to decompensation is much faster in post-transplant HCV patients than in immunocompetent individuals. In addition, HCV is also the leading cause for graft loss. As a consequence, survival rates in post-transplant HCV patients is significantly lower than in patients undergoing liver transplantation for other indications. According to the European Liver Transplant Registry, no improvement in survival rates has been seen in HCV transplanted patients in the last 20 years, in contrast to the marked improvement noted among HBV patients.

In post-transplant patients with recurrent chronic HCV infection, end of treatment virologic responses are comparable to those in non-transplanted patients, but SVR is lower in the post-transplant setting, and almost half of the patients with end of therapy response experience relapse. Due to their immunocompromised status, an important proportion of transplant patients are slow or late responders to HCV treatment. A pilot study conducted at the Ege University centre showed that extending therapy in slow responders can effectively increase the SVR [7-8].

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Viral hepatitis in populations at risk

Victims of human trafficking (VOT)

Human trafficking is an old issue but changes have taken place since the Soviet Union separated into independent nations, which has had consequences for neighbouring regions, including Turkey.

In accordance with Article 3 of the Palermo Protocol from the 2000 United Nation's Convention against Transnational Organized Crime [1], human trafficking is defined as:

"the recruitment, transportation, transfer, harbouring or receipt of persons, by means of the threat or use of force or other forms of coercion, of abduction, of fraud, of deception, of the abuse of power or of a position of vulnerability or of the giving or receiving of payments or benefits to achieve the consent of a person having control over another person, for the purpose of exploitation."

According to the US State Department 600,000 to 800,000 individuals are trafficked across international borders every year. According to United Nations sources, traffickers earned 31 billion dollars, buying and selling human beings, in 2008. Turkey is an important destination country for human trafficking where 1,019 victims, representing only a small percentage of the total amount of affected individuals, were identified over the period 2004-2009.

Turkey is an important tourist destination with loose border controls and very close to countries of the former Soviet Union. As a consequence, Turkey has an important underground sector with a high demand for foreign sex workers. It is an attractive country for irregular migration (human smuggling) from countries such as Iran, Afghanistan, and Iraq to Western Europe. Although human trafficking is defined as a crime by the Turkish penal code, it is very hard to identify VOTs.

The Human Resource Development Foundation (HRDF) is a leading non-profit, non-governmental and autonomous organization that promotes reproductive health and family planning education, information, training and services in Turkey. HRDF is mainly active at the level of population and development and has been operating a shelter since 2004. HRDF provides support to more than 400 VOTs to date, particularly with regards to legal and health aspects linked to psychological trauma, and reproductive health problems including sexually transmitted diseases (STI).

STI services for VOTs in Turkey are problematical. All foreign sex workers are subject to compulsory controls for STIs, involving screening tests performed for syphilis, HIV, HCV and HBV. VOTs are only identified after this compulsory testing has taken place and subsequently referred to the HRDF shelter where they are offered a second opportunity to be tested against STIs. If they consent, they are sent to public hospitals and offered free medical services provided by MOH. However, due to their traumatic history, VOTs generally refuse this opportunity. Also, neither compulsory checks, nor voluntary checks at the shelter, include HBV vaccination.

To date, among 59 VOTs referred for STI testing in Istanbul 8% tested HBsAg positive, 10% tested anti-HCV positive and 2 victims (3%) were found to be HIV positive.

The evidence of this small cohort, which also includes sex workers, shows that viral hepatitis prevalence can be high among VOTs in Turkey, hence there is a need for prevention measures to be taken against both viral hepatitis and human trafficking. More support for human rights is needed, including the right for VOTs to have easy access to health services. Improved surveillance data, including transmission routes, is also needed to convince public health authorities to include irregular migrants in their STI prevention programmes.

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Health care workers (HCW)

There are approximately 150,000 HCW in Turkey, including doctors, nurses, and students at medical, dentistry and nursing schools, as well as laboratory and radiology technicians. These HCW are all at risk of infection with blood-borne pathogens, such as HBV, HCV and HIV.

Percutaneous or mucosal exposure of HCW with the blood or body fluids of infected patients is the main cause of blood borne pathogen transmission in Turkey. Several studies have shown that this type of exposure is frequent in Turkish hospitals (31%-68%), especially among doctors and nurses, mainly due to needle recapping (45%-55%) [1-3]. In a large study conducted among 988 HCW, approximately one third of the cases were shown not to have been vaccinated against HBV at the time of exposure, mainly because they reported to be unable to afford vaccination [1] - many HCW did not know the vaccine was free of charge. Most cases did not seek medical help after injury (67%). In another multicentred study conducted among 5,238 HCW, 50% of the participants reported at least one occupational exposure in the previous year, with identified predictive factors including working at a surgical site, being a doctor or a nurse, younger age, and low socio-economic status [4].

HBV in HCW

In Turkey, HCW (including health care students) are considered as a high risk group for whom the MOH recommends HBV vaccination, which is offered free of charge.

In attempting to assess HBV prevalence rates among HCW in Turkey, results are only available from several single centre studies conducted since the 1990s. These studies involved small numbers of subjects, heterogeneous for age and sex,

and generally no analysis was performed on demographics such as birth place, migration history or work experience. Hence, the results reported vary between different regions (1.3%-10%), with different prevalence rates reported even from the same region of the country.

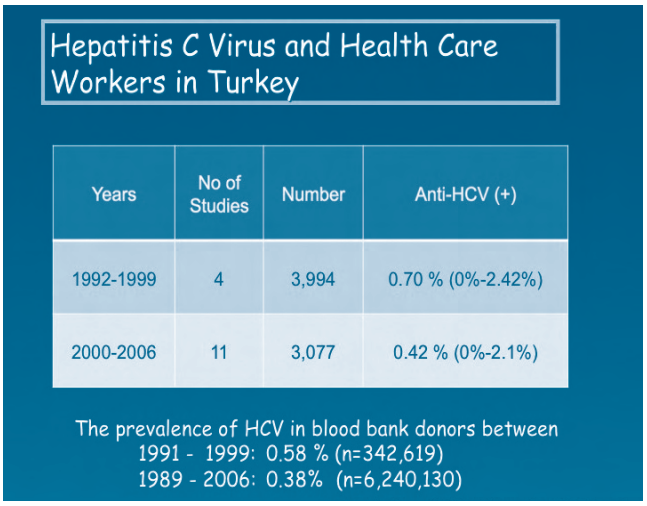
A meta-analysis performed on existing studies has shown that HBV prevalence is in fact lower among HCW than in the general population [5], and has decreased from 4.6% (1989-1999) to 2.6% (2000-2005) among HCW, and from 3.8% (1989-1990) to 1.8% (2000-2005) among health care students.

This decrease observed in HBV prevalence is probably also influenced by more effective vaccination of HCW (including health care students) at medical school or after starting work, which has increased from 25% in 1998 to 39% in 2006 [6].

However, although not investigated in HCW studies, several institutions check post-vaccination antibody levels and HCW are boosted if not protected. And although there are no protocols for compulsory vaccination, medical students at university are screened and vaccinated free of charge (but not recorded).

HCV in HCW

Several studies conducted between 1992 and 2006 have shown that prevalence of HCV among HCWs has fallen from 0.7% to 0.42% (see table below).This is probably due to increased risk awareness, as well as improved hygiene measures, including the promotion of safe disposables . However, the HCV prevalence rate remains higher in HCW than in the general population [6].



There are only a few case reports on transmission of HCV to HCW in Turkey, and in a recent study published in 2008 the risk of HCV infection after occupational exposure was investigated and transmission rates were reported as zero [7]. This finding conflicts with the high prevalence rates found in HCW in comparison with the general population.

Prevalence rates of other viruses were studied in the HCW population at the end of the 1990s, with the following reports: 76.3% anti-HAV positivity among 320 HCW [8]; 19.6% anti-HEV positivity among 102 HCW (compared to 8.03% in the general population) [9]; and 1.6% Hepatitis G virus (HGV) RNA-positivity among 120 HCW (against 3.3% in the general population) [10].

Enhanced preventive measures against blood borne pathogen transmission to HCW should be implemented in Turkey, such as education, screening and HBV vaccination of all medical students and individuals who start working in a HC setting. All HCW should be made aware of the importance of standard precautions, including hand washing, the use of protective barriers and care in the use and disposal of needles, and other sharp instruments. Written protocols for prompt reporting, evaluation, counselling, treatment and follow-up procedures should be implemented in all HC facilities.

In some countries such as the UK, Australia and the Netherlands guidelines or expert committees are in place to restrict HBV and HCV infected HCW from performing exposure prone procedures, based on either HBsAg or HBV DNA level, and HCV RNA level. Successfully treated HCW are subsequently allowed to resume work. In Turkey, such protocols and screening practices are still to be implemented and guidelines for the management of HBV and HCV infected HCW need to be developed. In spite of a Turkish law on occupational health and EASL 2003 guidelines, there is no occupational health system in place at national level, and measures are taken at institutional level only.

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** Turkish reference*

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Prevention and control of viral hepatitis in Turkey

HAV vaccination in Turkey

HAV infections cause considerable morbidity and mortality worldwide, with a large economic burden (e.g. adults missing 30 days of work due to HAV infection). Several studies conducted in risk groups and with routine immunization programmes have shown HAV vaccination to be cost-effective when disease prevalence is high.

Turkey is characterized by marked regional differences in HAV endemicity – levels are high in Eastern regions and rural areas, while Western Turkey and big cities show only intermediate endemicity. As a consequence, the population is at risk of HAV infection, mainly due to the significant amounts of migration from the East to the Western part of the country.

Given this particular HAV epidemiological pattern in Turkey, regional vaccination in the Western part of the country and big cities might be considered as an alternative prevention measure. However, it has been argued that including universal HAV vaccination in the Turkish National immunization programme (NIP) would be preferable to regional East-West programmes to ensure better protection, with fewer ethical and economical inequities.

Regional HAV vaccination as of 1996 in the Western states of the USA, targeting specific communities, resulted in dramatic declines in incidence, with only 50% vaccination coverage. Extending vaccination to all children in other US states resulted in a further dramatic decline in all age groups in spite of only 50% coverage in Western states and 20% in Eastern states.

Similarly, the toddler vaccination programme in Israel made it possible to almost eliminate HAV in the whole country with only 3% of the population immunized, proving the programme to be cost-effective in the long term.

However, when comparing such programmes with the situation in Turkey, one should consider that it is a heterogeneous country where health care priorities need to be established taking long term benefits into consideration.
The Turkish government's current HAV prevention policy is limited to improving hygiene status, and educating the public in hygienic practices, sanitation, and infection control. While several HAV vaccines are available on the private market, there is no immediate plan for Turkey to follow WHO recommendations for universal HAV vaccination in regions of intermediate endemicity.

The Turkish national immunization programme (NIP) has been significantly improved in the last five years, and its budget increased from ~10 to ~80 million EUR between 2002 and 2008. Vaccines currently included are shown in the upper section of table, below. Several other vaccines are currently available on the private market and optionally recommended for children in Turkey to protect them against HAV, varicella, rotavirus and seasonal influenza. Vaccines against HAV, varicella, rotavirus and meningococcal disease should be considered candidates for future inclusion into the NIP. But first retrospective and prospective cost-effectiveness studies need to be conducted in Turkey in order to justify introduction of this vaccine into the NIP, or alternatively start regional vaccination programmes.

National Immunization Program, Turkey, 2009

	Birth	1 m	2 m	4 m	6 m	9 m	12 m	16-24 m	1st cl	8th cl
Bacillus Calmette-Guérin (BCG)			I							
Diphtheria, Typhoid and Pertussis (DTaP)			I	II	III			IV		
Oral Polio Vaccine (OPV)/Inactivated Polio Vaccine (IPV)			I	II	III			IV	V	
Diphtheria and Tetanoids (dT)									I	II
Hepatitis B	I	II			III					I,II,III*
Measles, Mumps and Rubella (MMR)							I		II	
Haemophilus influenzae type B (Hib)			I	II	III			IV		
Pneumococcal vaccine			X	X	X		X			
Additional vaccines on market										
Varicella							X		?	
Hepatitis A							X	X		
Rotavirus			X	X	X					

Turkey has the following HAV epidemiological specificities, which should be taken into account:

- in the Eastern part of the country, all children are infected before the age of 1 year while the currently recommended age for vaccination is at least 12 months;
- HAV transmission is not restricted to toddlers;
- sanitation conditions need to be improved (e.g. contamination of tap water)

Potential interim solutions to address such specificities have been suggested, such as vaccination before the age of 12 months, or implementation of a one-dose programme as has been done in Argentina.

Based on presentations by M. Ceyhan and L. Akın, Hacettepe University, Faculty of Medicine, Ankara, Turkey.

HBV control programme in Turkey

The HBV immunization programme was started in Turkey in 1998 to comply with two regulations dating from 1998 and

2000, and consists of routine, free-of-charge vaccination of newborns and 0-11 month old infants as well as defined risk groups.

Defined high risk groups receiving free-of-charge HBV vaccination delivered by medical staff in all HC centres:

- HCW in contact with patients and patient-contaminated materials;
- Medical and dentistry students, as well as students at higher education colleges for health professionals
- Haemodialysis and CLD patients
- Patients requiring frequent use of blood and blood products
- Household contacts of infected individuals
- IDU
- Individuals with multiple sex partners
- Sex workers
- Men having sex with men (MSM)
- Prisoners (including those in juvenile detention centres)
- Travelers to areas where HBV is endemic
- Hairdressers and manicurists
- Staff from orphanages and institutions for the mentally retarded
- Firemen, policemen, soldiers, military recruits
- Emergency medical care staff (who have priority over other medical staff)

In addition, adolescent catch-up vaccination was approved by the immunization advisory board in 2004, starting from the 2005-2006 education year. As a result, all adolescents up to the age of 16 years had been vaccinated by the end of the 2007-2008 education year.

HBV infant vaccination is part of the Turkish NIP, with a recommended 3-dose schedule at 0, 1 and 6 months of age. The cost of a pediatric vaccine dose was 1.2$ (2.4$ for adult vaccine dose) at the last procurement in 2009 while the total cost of the 3-dose pediatric vaccination added up to 3.6$, and 7.3$ for risk group adult vaccination. In comparison, the costs of available commercial vaccines in the Turkish private sector range from 9-15$ per unit of pediatric vaccine dose, and 15-30$ for adult vaccine dose.

Overall, third-dose HBV coverage in 0-11 month old infants increased from 72% in 2002 to 94% in 2009. HBV birth dose coverage is 93% among 1.3 million newborns.

All coverage rates reported include private market vaccination (3.8% in 2009) while HBV coverage in high risk groups is not known.

Guidelines for complete adult immunization (see Table upper right), including 3-dose HBV vaccination schedule at 0, 1 and 6 months, are currently under development in Turkey, but not yet implemented. Vaccination schedule and implementation may vary according to the three age groups considered (18-49 years, 50-64 years, and >64 years of age) in accordance with international age group definitions. An adolescent vaccination schedule is not in place yet.

Adult vaccination schedule

Vaccine	Age 18-49	Age 50-64	Age ≥ 64
Tetanus, Diphtheria (Td)	Booster doses in every ten years		
Measles (M)/Measles Mumps, Rubella (MMR)	1 or 2 doses of vaccine		
Hepatitis B	3 doses of vaccine (at 0, 1, 6 months of age)		
Influenza	1 dose every year		1 dose in a year
Pneumococcus (polysaccharide)	1-2 doses of vaccine		1 dose of vaccine
Hepatitis A	2 doses of vaccine (at 0 and 6-18 months of age)		
Varicella	2 doses vaccine (at 0, 1 or 2 months of age)		
Meningococcus	1 or more doses of vaccine		

Individuals who have a risk factor and/or contraindications
Individuals who don't have any contraindications

Based on a presentation by Ü. Özdemirer, Ministry of Health, Infectious Diseases and Outbreak Control Department, Ankara, Turkey.

Results of blood bank screening in Turkey

There are more than 400 blood banks in Turkey, most of them small entities receiving fewer than 5,000 donations annually (of the remainder, 65 blood banks receive more than 5,000 donations a year; 27 over 10,000 a year and only 10 blood banks receive more than 20,000 donations/year). Blood collection in Turkey is organized around hospital blood banks (public, university, private and military) and Red Crescent blood banks. Until 2008, blood was mainly collected from hospitals (70-75%) but during that year the Red Crescent blood banks began to be organized as regional blood banks, accounting for 44% of blood collected.

In compliance with the new Blood Law of 2007, blood collection has been reorganized in Turkey, with:

- **Blood collection centres** collecting blood from donors and sending it to the regional blood banks.
- **Regional blood banks**, collecting blood, performing screening tests, preparing and storing all blood components to be systematically sent to transfusion centres.
- **Transfusion centres** in hospitals, storing only the amounts of blood components needed, and only performing cross-match and antiglobulin tests.

Classical measures are taken in blood banks to prevent transmission of infectious diseases such as HBV and HCV, and include donor assessment, screening tests, keeping collected blood in quarantine, and pathogen inactivation methods.

Donor assessment in Turkey consists of a standard questionnaire designed to eliminate high risk donors. It is implemented in all blood banks but 25-40% of the transmission routes for HBV and HCV are unknown and will not be eliminated simply by use of the questionnaire. Also, the truthfulness of donor declarations is questionable. Most donors in Turkey are first-time donors (mainly recruited among family members and friends of patients in hospital). The age of blood donors ranges from 25-45 years, with more young donors in recent years thanks to educational programmes on blood donation in schools and universities.

The quarantine method which can only be applied to fresh frozen plasma is currently not used in Turkey because it involves two-stage screening and since most donors are first-time donors, recall after several months is problematic. Pathogen inactivation, which is an expensive method, is also not yet used in Turkey.

Mandatory screening tests performed in all blood banks in Turkey include HBsAg (with a minimum sensitivity of 0.5 IU/ml); anti-HCV (± HCV core Ag); anti-HIV 1/2 ± HIV Ag (p24); and screening for syphilis. These tests are performed using highly sensitive 3rd generation immunoassays (EIA, chemiluminescent immunoassay). Quick tests used to be carried out only in emergency situations in very small blood banks, but these are now closed following the new 2007 Blood Law.

As a result of the donor selection procedure, the seroprevalence of infectious diseases reported in blood donors is lower than in the general population. This also reflects an overall decrease in HBsAg seroposivity observed through several studies conducted among blood donors in Turkey: from 5.6% in 1995 to 3.3% in 1999 in a study of more than 1,000,000 donors from 28 hospital blood banks [1] and from 4.8% in 1989 to 2.1% in 2004 in a study of over 6,000,000 donors from Red Crescent blood banks [2]. In contrast, there was no significant decrease observed in anti-HCV seropositivity rates in either study. The latter finding can be partially explained by the improvements in the HCV diagnostic detection assays used.

Further studies conducted in Bursa (200km South of Istanbul), Ankara, Izmir and Istanbul confirm these trends, although some regional differences are noted, as illustrated in the studies reported in the Table below:

Regional differences

Blood Bank / Region	Years	Number of donors (n)	HBsAg (%)	Anti-HCV (%)
Research and Teaching State Hospital Blood Bank / Trabzon-Black Sea Region	2004-2007	12.092	1,62 Decreased from 1,9 to 1,2	0,2 Decreased from 0,31 to 0,15
Süleyman Demirel University Blood Bank / Isparta-Mediterranean Region	2000-2007	51.361	1,09	0,44
Selçuk Meram University Blood Bank / Konya-Middle Anatolia	2006	54.266	0,6	0,1
Turkish Red Cresent Blood Banks / Middle Anatolia	2006	102.359	1,62	0,49
Turkish Red Cresent Blood Banks / Aegean Region	2004-2007	268.578	1,36 In Uşak-Kütahya 0,5	0,42

Possible explanations for the decrease observed in HBsAg seropositivity rates include advances in blood banking, with continuous educational programmes in place for the last ten years, and more attention paid to donor assessment. Positive-testing donors are followed up for the purpose of education and performance of confirmatory tests. Such follow-up services are offered by each blood bank separately, as there is no national donor organization. Increased public awareness about the risks of transfusion-transmitted diseases such as HBV and HCV, the need for preventive measures to be taken, and the availability of vaccination, are also believed to have played an important role. In particular, the effect of adult risk group vaccination is more likely to have had an impact while the effect of routine HBV infant vaccination since 1998 is expected to be visible in the next decades.

Additional screening methods which could lead to a further decrease of HBsAg and anti-HCV seropositivity rates among blood donors, including anti-HBc testing, nucleic acid testing (NAT) technology and HCV core Ag testing, are taken into consideration.

Anti-HBc screening is used in many countries to eliminate reactive donors. However, in Turkey this method is not implemented for fear that it might significantly reduce the numbers of donors. This was reflected in a study conducted among 9,282 HBsAg negative donors with anti-HBc positivity rates of 18% among HbsAg negative donors, and 2.7% among donors negative to both HBsAg and anti-HBs. Also, the limited risk of potentially infectious HBsAg negative but anti-HBc positive donors should be taken into consideration, as only one sample was found to be HBV DNA positive (0.45% among anti-HBc positive donors and 0.011% among HBsAg negative donors) [3].

A consecutive screening policy with initial HBsAg, followed by anti-HBs and anti-HBc testing would not be practical and cost-effective in Turkey, especially given the current majority of first time donors.

NAT is another technology which is increasingly used in blood banking screening policies in Europe and worldwide as it narrows the window period when compared to antibody testing, particularly for HCV but also HBV and HIV, with a detection limit that is very close to the infectivity threshold. However, NAT is not currently implemented in Turkey as it is difficult to estimate how many transfusion-transmitted HBV and HCV infections it could be expected to prevent. Other factors, such as viral load, quantity of infected product and immunocompetence of the recipient play a role in transfusion-transmitted infection. Also, a study conducted by the Turkish Red Crescent among 18,200 donors showed rates of positivity for HBV DNA and HCV RNA well above calculated estimates (1.72% and 0.34%, respectively) [4], suggesting the potential presence of false positives and the need for confirmation testing. In another study testing the presence of HBV DNA in 187 pooled samples from 4,484 donors, false positivity rates were found to be 1.6% for the mini pools and 0.04% for individual donors, while HBV DNA was ultimately not detected in repeated testing of donor samples [5]. Such results confirm the need for more studies as well as haemovigilance data in order to assess the number of blood

recipients who become infected with HBV or HCV in Turkey. More insight should be gained into these issues in the near future when blood banks from the Turkish Red Cresent initiate implementation of NAT testing in the regional blood banks.

On the other hand, implementing NAT technology was calculated to be cost-effective in at-risk populations with high prevalences of transfusion-transmitted infections, such as thalassaemia patients requiring multiple transfusions, with observed HCV infection rates at around 30% [6].

Additionally, HCV core Ag testing has been shown to be appropriate for use in blood banking screening, with results compatible with HCV NAT in reducing the window period. It is currently not used in Turkey but studies will begin shortly.

In conclusion, while HBsAg positivity rates are decreasing among blood donors in Turkey, the implementation of HCV blood screening policy has not led to a similar decrease in anti-HCV positivity rates. Some irregular variations observed at regional levels are not explained with, in some cases, levels higher than in other countries. In other cases, as a result of the implementation of improved anti-HCV tests, levels of recorded anti HCV positivity are even rising. Also, there has been no reduction in HCV infection rate since the '90s among patients needing frequent transfusions in fact it increased from 25% in 1994 to 28% in 2006.

Thanks to the recent reorganization of regional blood banks in Turkey, it would be hoped that there will now be significant changes in donor profile, with more regular voluntary donors, improved haemovigilance data, and enhanced screening policies involving NAT, HCV core Ag test, as well as pathogen inactivation technologies.

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* Turkish reference

Based on a presentation by
Y. Heper, Uludağ University Faculty of Medicine, Bursa, Turkey.

The role of NGOs in viral hepatitis prevention and control in Turkey

NGOs play an important role in supporting patients and their families, with a major responsibility for raising awareness concerning viral hepatitis and its related complications. Importantly, NGOs should act as a bridge between infected patients and national health organizations, a role which needs to be strengthened in Turkey.

Members of patient societies are also given opportunities to learn about their disease from educational speakers, facilitators and other patients. They develop and improve their coping skills and they also gain increased confidence and acceptance of their condition, which is essential for effective prevention and treatment. Several viral hepatitis associations and umbrella organizations exist at European level, such as the European Liver Patients Association (ELPA), which represents 20 patient advocacy groups from 17 European countries [1].

In Turkey, patient organizations exist for several diseases, including ankylosing spondilitis, haemophilia, autism, mental and physical handicaps, osteoporosis, coeliac disease, inflammatory bowel disease, multiple sclerosis, diabetes and obesity but until very recently there has been no patient society specifically for viral hepatitis. This may be explained by the strong presence of social stigma, in particular in the case of HCV, and the common misconception that hepatitis and immoral behavior are linked. Hepatitis patients might fear losing their jobs or positions even if they are inactive carriers. Isolation can also result from hepatitis patients being forbidden access to swimming pools, baths or other public places. There is a general lack of public understanding with respect to diseases associated with viral hepatitis and their transmission routes, while physicians remain indifferent to the problem. There is also a lack of interest from the media, who provide distorted information and underestimate the importance of the disease.

However, several organizations of medical professionals with an interest in viral hepatitis do exist in Turkey, as illustrated below:

Societies, foundations, advocacy groups and interest groups for viral hepatitis in Turkey

- Turkish Association for the Study of the Liver TASL (1992)
- Turkish Liver Foundation TKV (1992)
- Turkish Society of Gastroenterology TGD (1959)
- Society for the Fight against Viral Hepatitis VHSD (1989)
- Infectious Diseases and Clinical Microbiology Speciality Society ECMUD (2006)
- Turkish Liver Transplantation Society TKTD (2005)
- Liver Transplant Patients Society (2008)

A patient society was also recently established by the Turkish Liver Foundation. It is still at an early stage but has strong links with the Turkish Association for the Study of the Liver (TASL) and the Liver Transplant Patients Society.

Liver associations and viral hepatitis societies in Turkey are involved in educational programmes, the development and dissemination of educational materials to professionals and the public, as well as public awareness activities. Importantly, they also set up field studies including screening, testing, educating individuals and advising them to get vaccinated. However, this type of activity needs to be better organized with respect to Turkey's epidemiological situation if it is to yield results likely to benefit public health. NGOs also provide consultancy to the Turkish MOH for prevention, diagnosis and management of viral hepatitis.

Turkish Association for the Study of the Liver (TASL)

TASL is the oldest liver disease society in Turkey, currently with 390 members, and linked to international associations, such as the European (EASL) and Asian Pacific (APASL) Associations for the Study of the Liver, as well as membership of the Boards for Hepatology Education within Gastroenterology Training in Europe and Asia.

To date, TASL has been active in four main sectors, including research, scholarships, social responsibility projects and education. As well as offering grants and awards to young researchers, the organisation has developed educational materials for the public and professionals, including articles, leaflets, books, TV programmes and an active web page offering advice and information on liver disease and viral hepatitis. TASL organizes the National Hepatology Meeting and School of Hepatology every other year, as well as monthly post-graduate courses, panels and seminars focusing on viral hepatitis and related complications. It also publishes the journal Hepatology Forum and receives EU grants for viral hepatitis research.

At the policy level, TASL has collaborated with the publication of guidelines on HBV and HCV management, and provided consultancy to the MOH on the development of algorithms for HBV and HCV treatment.

TASL's vision:

- To become a major partner in health policies related to liver diseases, securing access to treatment for each patient.
- TASL's journal to be listed in the Science Citation Index.
- To contribute to HBV eradication thanks to HBV routine immunization campaigns led by MOH, together with NGOs.

Future projects include more effective awareness and educational campaigns and stronger collaboration between all stakeholders, including society members and other interest groups, health authorities and institutions, as well as the media. The importance of primary care centres and impact of advocacy groups should be enhanced. Efforts will be made to interest the Turkish government in implementing more effective policies against viral hepatitis. Continued research will require funds from internal and external resources, so there will be efforts to forge contacts at EU level and with the European Parliament.

Activities of other liver disease societies in Turkey

Other Turkish bodies initiated a 2-year ambulatory hepatitis screening project. It was organized by the Society for the Fight against Viral Hepatitis (VHSD) in collaboration with the MOH, via a "yellow bus" which has visited more than 10 cities in East and Southeast Anatolia to date. After testing, vaccination is recommended to citizens as appropriate. If needed, vaccines are provided by the MOH.

A less successful campaign sponsored by BMI (biomedical industry) was organized a couple of years ago in which HCV was represented by a "bug" on posters and billboards in public places, buses, TV shows, video clips, and short movies. Unfortunately, the visual seemed to have the effect of scaring people instead of prompting them to get tested.

However, this activity also called into question the role of patient organizations in implementing screening projects and the view was expressed that they would do better to focus on the support and follow up of all identified patients.

In summary, as well as supporting patients and their families, NGOs also offer their expertise to health authorities, helping to create the most effective prevention strategies against viral hepatitis. They also raise funds for research and disease management, educate professionals and the public, raise awareness of the condition, correct misconceptions and reduce stigma, as well as encouraging citizens to get tested and vaccinated. However, the majority of NGOs in Turkey and elsewhere lack funding and efficient communication networks, hence it will be vital to define their specific objectives and modes of action in order to make their efforts as effective as possible.

Reference

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Based on a presentation by
N. Tözün, Acıbadem University School of Medicine, Istanbul, Turkey.

Conclusions

Viral hepatitis surveillance in Turkey

A new notification system for communicable diseases was set up in 2005, built on the previously existing system of electronic collection of data. Since 2005 surveillance has been applicable to 51 diseases, including viral hepatitis (HAV, HBV, HCV, HDV and HEV), and sentinel surveillance was introduced for selected diseases. National case definitions are used, with laboratory confirmation criteria. An accompanying guidance was issued, including rationale and types of surveillance and for each disease a well defined reporting tree. Part of the collected data are included in the MOH annual report, however dissemination of findings could still be optimized.

Epidemiology of viral hepatitis in Turkey

Hepatitis A is the most common form of acute viral hepatitis in children. At national level, Turkey is a country of intermediate HAV endemicity; however, it is characterized by a strong West/East gradient, with high endemicity among young children in East and South-East. All circulating strains are of genotype 1, mostly 1B. In recent years, HAV has experienced a changing epidemiological pattern in Turkey due to improved infrastructure and hygiene. With the increasing numbers of susceptible individuals, outbreaks can occur, mainly due to evolving eating habits and migration. In spite of generally improved hygiene, poor sanitation remains an issue.

Hepatitis B: Turkey remains a country of intermediate/high endemicity with HBsAg prevalence ranging from 2.5% to 9.1%, in spite of a steady decline in prevalence observed over the last years. Indeed, reported HBsAg positivity decreases in children, blood donors and health care workers. One estimate indicates 3 million HBsAg positive individuals and 300,000 active chronic hepatitis cases of which only 30,000 are receiving treatment. Regional differences are characterized by West/East and South-East gradient. Most virus isolates are of genotype D1 but genotype A1 and B have also been reported. Despite the lack of well-designed studies investigating the etiology of HBV transmission in Turkey, in children horizontal transmission and in adults sexual transmission appears to be the main route.

Hepatitis D is still important although decreasing in prevalence in Turkey. Only genotype 1 has been detected so far but divergence exists in strains isolated. Treatment remains difficult.

Hepatitis C prevalence in Turkey is low (0.17- 2.8%) and has shown a gradual slow decrease in recent years, with a West/East gradient seen in the general population, but not in blood donors. A significant decrease was observed among haemodialysis patients. Most studies have been conducted on blood donors, showing that prevalence increases with age. Genotype distribution has remained unchanged over years with predominance of genotype 1, but type 2, 3 and 4 viruses are detected as well. Main risk factors for HCV are low socioeconomic status, history of multiple blood transfusions, hospitalization and surgery. Reliable data on HCV in IDU is lacking.

Management of chronic hepatitis in Turkey

HBV screening guidelines and policy should be put in place, provided that follow up can be guaranteed. To date, only 10% of HBV chronically infected patients are treated and the majority of HBsAg carriers are not aware of their disease. There is substantial knowledge base about viral mutants in chronic hepatitis patients but more information is needed about the impact of treatment. Guidelines are continually evolving for the treatment of chronic HBV but the controversy about first-line treatment with Lamivudine (drug with low resistance barrier) and whether to progress to more powerful drugs still needs to be resolved. Also, issues of drug resistance and cost of treatment should be considered.

HCV treatment is most successful in patients with mild fibrosis but to date biopsy is not required to start treatment. The issue of whether the decision to treat HCV should depend on the degree of fibrosis is still under discussion.

Liver transplants HBV is the leading cause of chronic hepatitis and hepatocellular carcinoma. Between them, HBV and HDV account for two-thirds of liver transplants. Post-transplant survival is greatly improved for HBV infected patients, with HBIG and Lamivudine prophylaxis, but there is still no consensus on dose or duration of treatment. For HCV that represents the major problem in chronic liver patients, the outcome of transplanted patients is even more problematic. No major improvement has been observed in post-transplant survival of HCV-infected patients. Possible advances in treatment have been reported with the introduction of new antiviral agents but more studies are still needed.

Viral hepatitis in populations at risk

Health care workers: HBV and HCV seroprevalence rates among HCW are comparable to those in the general population of Turkey; they have been decreasing over the years, while HBV vaccination rate has been increasing. However, there are still high exposure rates and risks for doctors and nurses, justifying the need for reinforced education, training in universal precautions, and vaccination programmes. Despite laws and international guidelines, there is no overall responsibility at national level for occupational health, hence the need for decisions to be taken at ministry level. Consideration should be given to screening and vaccination of all HCW, starting with students. Increased resources are also needed to apply safe injection practices (i.e. WHO Safe Injection Global Network).

Victims of human trafficking (VOT): This represents a high risk population, deserving particular attention in Turkey, which is an important route for trafficking and drug transit. High HBsAg and anti-HCV rates reported among VOTs warrant implementation of identification methods and appropriate preventive measures to protect them both against viral hepatitis and human trafficking.

Prevention and control of viral hepatitis in Turkey

Hepatitis A: HAV is generally perceived as a non-serious problem, although it is the most common cause of acute hepatitis in children. However there is currently no HAV vaccination policy in Turkey, and no immediate plans by the MOH to implement HAV in the routine vaccination programme. Prevention is limited to improvement of the hygiene status. Vaccination of selected risk groups, and on the basis of geographical distribution, is being considered. HAV disease modeling studies are needed, assessing if HAV vaccination would be cost-effective, particularly in the context of competing priorities with other vaccine-preventable diseases.

Hepatitis B routine vaccination was successfully introduced in 1998 in Turkey and the policy was revised in 2000, targeting newborns and infants 0-11 months (including birth dose), at-risk groups, as well as catch up for adolescents. HBV vaccination is free for infants and at-risk groups, with good prices negotiated with manufacturers, and a considerably expanded MOH budget for vaccination over the years. Vaccine coverage among infants is high (>90%) but data is needed for birth dose, adolescents and adults at risk.

In compliance with a new law from 2007, the ***blood banking system*** in Turkey is being reorganized into blood collection centres, regional blood banks and transfusion centres in hospitals. This new structure should facilitate the implementation of standardized donor assessment, by considering the use of improved screening tests, such as nucleic acid testing (NAT). Also, it should help establish a more organized donor recruitment policy and reduce the number of first time (high risk) donors, which still constitute the majority of donors to date. Decreasing rates of HBsAg have been observed among blood donors over the years, versus steady anti-HCV rates.

Lessons learnt, challenges and recommendations

Epidemiology and Surveillance

- Published literature on incidence or prevalence of viral hepatitis is not representative at the national level, hence epidemiological, population-based studies and standardized surveillance data are needed.
- Epidemiological data need to be strengthened and validated in order to be representative and form the basis for public health actions relating to disease burden and risk factors, modeling results, and monitored disease trends over time.
- In particular, epidemiological data are needed for HBV and HCV risk populations, such as HCW, IDU, sex workers and MSM in order to establish the proportion and impact of sexual, nosocomial, perinatal and occupational transmission.
- Reliable HAV incidence data is also lacking, as well as the burden of disease, especially concerning the outcome of fulminant HAV.
- The use of reliable molecular epidemiology assays should be increased and standardized. Interaction between laboratory and epidemiological components should be improved in order to build a stronger surveillance system that needs to be evaluated regularly and adjusted as necessary.
- Access to currently collected data and results of analyses should be improved, with dissemination provided to field workers and the public.
- Chronic viral hepatitis, with appropriate case definition, should be included as a separate entity for surveillance.

Control & Prevention

- Excellent progress has been made in prevention and control of viral hepatitis with expertise, tools and networks available in islands of excellence but communication and collaboration between MOH, NGOs,

academics and hospital-based researchers need to be strengthened.
- Build up of public health aspects is needed, with a focus on control, including NGO-government liaison. Particular attention should be paid in the area of work against human trafficking and other risk groups.
- Capacity building needs to be developed for surveillance, care, treatment, occupational health, and other areas.
- Effectiveness of public health interventions (such as vaccination, screening, injection safety, infection control, promotion of safer sex, improvements in hygienic situation, counseling and treatment) needs to be assessed and programmes revised accordingly.
- High-level coordination of programmes and projects should be put in place to prevent and control viral hepatitis, such as, for example, a task force at ministry level, composed of all national stakeholders.
- There should be a comprehensive national strategy and plan for the prevention and control of all forms of viral hepatitis occurring in Turkey, including the goal of controlling hepatitis B, in coordination with all interested parties.

Based on a presentation by D. FitzSimons, WHO.

Evaluation of global viral hepatitis prevention and control measures

Global HCV prevention and control measures: lessons learnt and opportunities

HCV has become a global public health problem. The WHO estimates that there are between 2.3 and 4.7 million new HCV infections each year and 300,000 deaths annually. Between 130 and 170 million people worldwide are chronically infected and, if not treated, 14-45% of patients will develop chronic liver disease and cirrhosis within 20 years of becoming infected.

New viral hepatitis infections continue to occur due to:
- unscreened blood transfusions or blood products;
- failure to sterilize medical equipment and unsafe injections;
- dental and "traditional" medicine;
- IDU; and
- haemodialysis.

End stage liver disease accounts for 1 out of every 40 deaths worldwide. However, no good breakdown according to aetiology exists. Worldwide liver cirrhosis accounts for over 783,000 deaths/year and 619,000 deaths/year are due to liver cancer.

To tackle this world health problem a comprehensive HCV prevention strategy should be implemented, including:
- Primary prevention of new infections – best accomplished with a vaccine. Several companies had a vaccine in the pipeline (e.g.Novartis are investigating E1E2/MF59 HCV vaccine), but due to the lack of convincing market information most companies have frozen the development. A prevention plan on different levels should focus on transmission of the virus via blood or blood components, organs, tissue and semen.
- Secondary prevention of person to person transmission – via infection control practices. Safe injection programmes on national level, promoting single use equipment, sharps waste management and a reduction in the number of injections are already successful but could be adopted in more countries. Target groups for these prevention programmes should be haemodialysis patients, prisoners and IDU who are more at risk of this type of transmission.
- Tertiary prevention of the pathological consequences of chronic infection in those persistently infected with the virus. Early treatment of acute and new infections is important, because it interrupts the transmission dynamics and diminishes the severity of the disease. However, IDU, who represent the main HCV risk group, are difficult to treat, with 25% becoming reinfected after they have cleared the virus. HCV treatment is expensive and monitoring is demanding, which leads to the dilemma of who should be treated. In addition, treatment may not actually change the HCV public health problem drastically, since it does not guarantee a cure and does not prevent reinfection. Hence, primary and secondary prevention measures remain important.

It is essential that HCV is recognized as an important public health issue. Comprehensive government-led national programmes for prevention, control and management of HAV, HBV, HCV and HEV should be implemented to raise awareness about screening, diagnosis, referral and treatment. It is important within this strategy to involve advocacy groups (including religious groups), professional and scientific societies. It is also recommended that clear, quantifiable targets for reducing incidence and prevalence, and reducing morbidity and mortality, are set. Dissemination of the lessons learnt from existing prevention programmes is necessary to improve public health and reduce the impact of hepatitis.

Within countries it is more cost effective to use existing structures. For instance, the established testing services for HIV/AIDS and STDs can be adapted for HCV testing. In addition to this, as the work dedicated to H1N1 influenza virus decreases, there will be an opportunity to use the diagnostic and logistic tools that are currently being installed for influenza surveillance.

Epidemiological studies and standardized surveillance data are necessary and they should:

- Avoid heterogeneity in availability/quality of data;
- Detect outbreaks of HCV infection;
- Identify risk factors;
- Monitor chronic liver disease;
- Monitor disease trends. Identify and follow-up infected persons;
- Develop, implement and evaluate national prevention programmes;
- Evaluate the effectiveness of activities such as vaccination, screening, injection safety, infection control, safe sex, counseling and treatment; and
- Provide guidance for the allocation of resources and decision making.

However, past experiences warn of the challenges ahead. Detection and monitoring of chronic liver disease is unspectacular and therefore difficult to sell. Decision making is hampered by heterogeneity in the availability and quality of data, and evaluation of the effectiveness of past activities is all too often "forgotten".

The opportunities for the future include a resolution taken up by the WHO Regional Office for the Eastern Mediterranean (EMRO) in October 2009, which will be an important political tool, putting HCV on the public health agenda for governments to consider.

In May 2010, the World Health Assembly recognized viral hepatitis as a global public health problem with the announcement of its "Viral Hepatitis" resolution, urging all Member States, supported by WHO, to strengthen preventive and control measures for viral hepatitis (see breaking news first page).

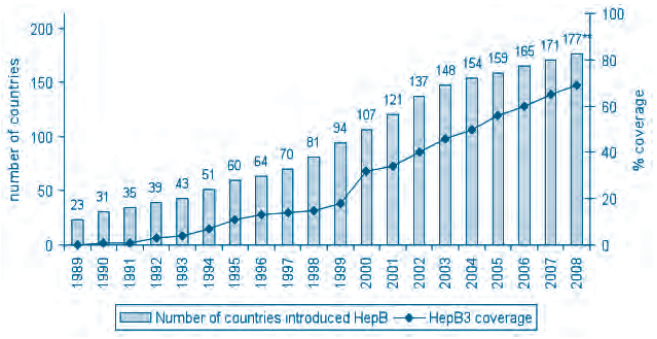
Based on a presentation by
D. Lavanchy, WHO, Epidemic and Pandemic Alert and Response (EPR), Geneva, Switzerland

HBV prevention and control programmes in the WHO European Region

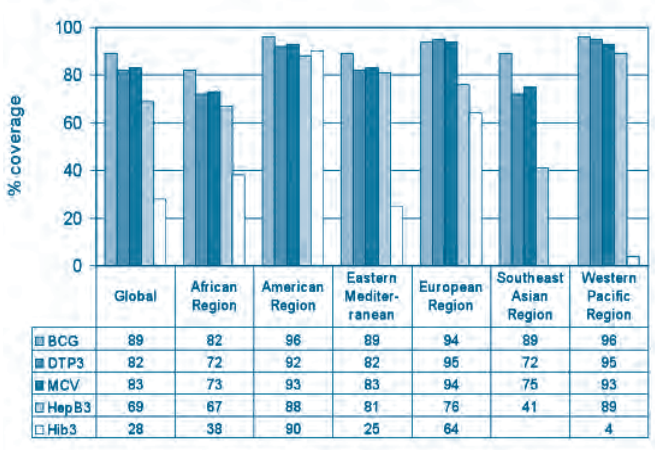
Situation analysis at global and regional level

Universal HBV vaccination has been integrated into routine immunization programmes in most countries in the WHO European Region. The situation in 2009 is that 46 out of the 53 countries in the region have introduced universal HBV immunization programmes, but 7 countries in Western Europe only selectively cover newborns and/or high risk groups.

With the help of the Global Alliance for Vaccines and Immunisation (GAVI), the poorest countries have successfully introduced HBV vaccine. All countries with high endemic HBV provide birth dose vaccination, catch-up vaccination, and vaccination of risk groups is being implemented. Globally, there are only 16 countries not using universal HBV vaccination and most of them are in Europe. Data shows that as the number of countries introducing the routine vaccination has increased, from 23 countries in 1989 to 177 countries in 2008, global infant coverage has also increased (see Figure below).



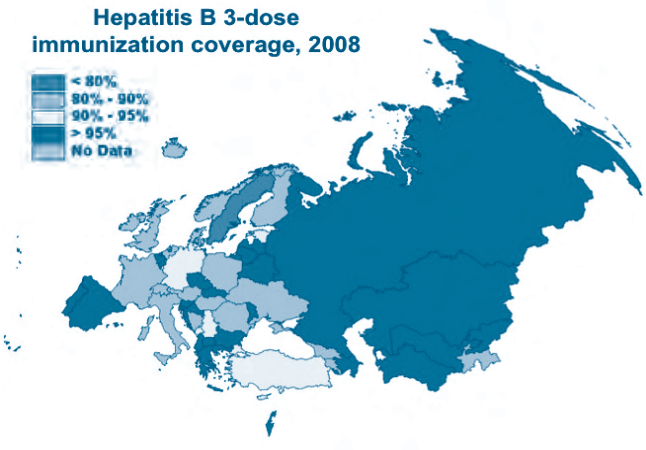
Although global coverage has increased over the years, the protection of the global population against HBV is not at the desired level. Global and European coverage estimates in 2008 for the third dose of HBV vaccine are still not at the level of other traditional, more established vaccines, as shown in the figure below.



	Global	African Region	American Region	Eastern Mediterranean	European Region	Southeast Asian Region	Western Pacific Region
BCG	89	82	96	89	94	89	96
DTP3	82	72	92	82	95	72	95
MCV	83	73	93	83	94	75	93
HepB3	69	67	88	81	76	41	89
Hib3	28	38	90	25	64		4

Source: WHO/UNICEF coverage estimates 1980-2008, July 2009, for 193 WHO Member States.

At less than 80% coverage, 5 years ago, Turkey had been among the countries with the lowest coverage in the WHO European region. However, through emphasis on its immunization programme and recently introducing a new antigen, outreach clinics and incentives for HCW to provide immunization, Turkey has managed to increase its national coverage to 90-95%. HBV 3-dose immunization coverage in the WHO European Region in 2008 is shown below:



Global and regional policy recommendations

The WHO position paper of 2004 [1] recommended that routine HBV vaccination of all infants should become an integral part of national immunization schedules worldwide. High coverage of infant vaccination has the greatest overall impact on the prevalence of chronic HBV infection and should be the highest priority. Catch-up strategies targeted at older age groups or groups with risk factors should be considered as a supplement to routine infant vaccination in countries of intermediate or low HBV endemicity.

The Scientific Advisory Group of Experts (SAGE) discussed HBV in 2008 and proposed clear changes, which were detailed in a WHO position paper in 2009 [2]. When HBV vaccine is given at birth, there is a 3.5 times lower risk of becoming infected with HBV, whereas delaying the first dose to 7 days after birth significantly increases risk of HBV infection. Therefore, the 2009 position paper recommends that all infants should receive their first dose of HBV vaccine as soon as possible after birth, preferably within 24 hours. Delivery of HBV vaccine within 24 hours of birth should be a performance measure for all immunization programmes. The WHO Regional Office for Europe will further discuss the implementation of a universal birth dose of HBV vaccine at the upcoming European Technical Advisory Group of Experts on Immunization (ETAGE) meeting. The birth dose is crucial in areas of high HBV endemicity, but important even in intermediate and low endemicity areas, and should be promoted through collaboration with maternal and child health programmes. The timeliness of birth dose administration deserves special attention, as it may pose particular difficulties in countries where a high proportion of women deliver their babies at home. Also, a reporting system to monitor birth dose coverage should be in place.

There is no evidence to support the need for a booster dose following 3 (or 4) doses of HBV vaccine in routine immunization programmes. Catch-up vaccination for older age groups should be considered for cohorts with low coverage and should be determined by the baseline epidemiology of HBV infection in the country.

The WHO position paper of 2009 also supports the determination of high risk groups through seroprevalence studies on HBV infection. A comprehensive approach to eliminating HBV transmission must address infections acquired perinatally and during early childhood, as well as those acquired by teenagers and adults. The WHO strongly recommends that all regions and associated countries develop goals for HBV control appropriate to their epidemiological situation. Serological surveys of HBsAg prevalence, supplemented by surveillance for acute disease and collection of burden of diseased data, will serve as tools to measure the impact of vaccination.

Summary and way forward

The routine viral hepatitis surveillance that has been introduced into most countries recently is of varying quality, even in the EU. There is a lack of standardization of surveillance in the following: populations being tested; mandatory or voluntary reporting; case definition (varies within the region); case reporting (differs in acute and/or chronic, confirmed or unconfirmed); and sources of case reports differ or are unclear (clinics and/or laboratories, government and/or private sector or other). There are inadequate data to describe the true infection trends and disease burden, for example, data about risk groups and sub national and geographical distribution.

One of the challenges in controlling HBV is that many infants are not immunized with 3 doses of HBV vaccine. Globally in 2007, over 44 million infants did not receive these 3 doses.

In March 2009, the ETAGE recommended that the WHO Regional Office for Europe should develop a regional strategy on prevention and control of viral hepatitis. Process indicators will continue to be based on HBV 3-dose coverage and HBV birth dose (with improved birth dose definition and monitoring). However, the use of serological and clinical outcome measures is critical to verify if such goals are achieved. Serologic surveys of HBsAg prevalence, representative of the target population, will serve as the primary tool to measure the impact of immunization and achievement of the control goals, supplemented by acute disease surveillance and mortality data. Among Member States of the WHO European region not implementing HBV routine vaccination, Greenland poses a particular problem because it is highly endemic, but has no resources available. The WHO Regional Office for Europe is aware of the situation in Greenland and is trying to address the problem.

The way forward should involve strengthening routine immunization with innovative approaches, political commitment, and societal support; strengthening routine immunization through optimized mix of service delivery strategies that could be successful in reaching the "hard to reach" groups; strengthening evidence based decision making and communication through National Immunization Technical Advisory groups (NITAGs); ensuring health care staff are trained with the right mix of skill sets and knowledge to deliver immunizations; and increasing ability of countries to mobilize and efficiently use domestic and supplemental external resources.

For the verification of control and immunization goals the viral hepatitis surveillance system needs to be strengthened and should investigate both acute and chronic cases, as well as behavioural and risk factor surveillance. Intensive collaboration exists between the WHO Regional Office for Europe and the European Centre for Disease Prevention and Control (ECDC), with a mutual presence on technical and advisory bodies, but issues still need to be resolved such as the use of different case definitions. The system should also investigate laboratory networks and testing strategies. Viral hepatitis surveillance would be strengthened by the establishment of an expert advisory group. Support should be given to the countries to strengthen surveillance at national and regional levels for viral hepatitis related burden of disease, including morbidity and mortality.

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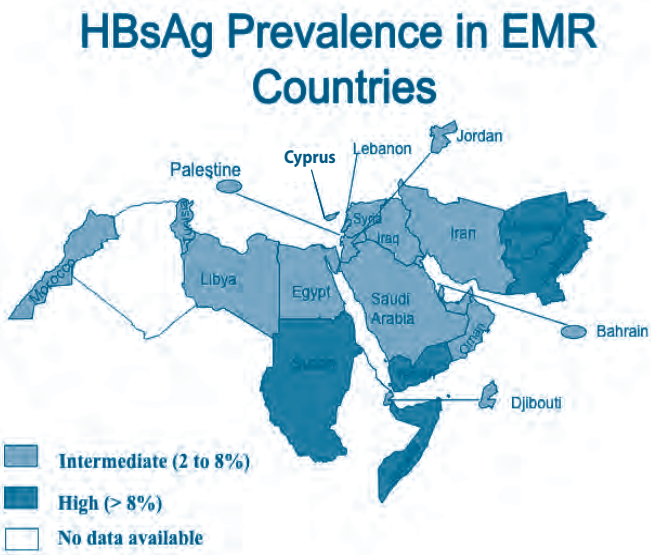
Based on a presentation by
N. Emiroğlu, WHO Regional Office for Europe (EURO), Division of Health Programmes, Copenhagen, Denmark.

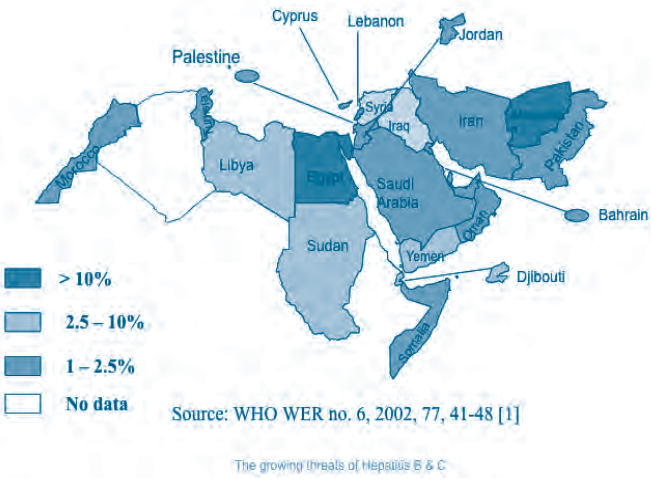
HBV and HCV Control in the WHO Eastern Mediterranean Region (WHO EMR)

In the WHO Eastern Mediterranean Region (EMR) there are an estimated 170 million people with serological evidence of HBV infection. The prevalence of HBsAg in the region is shown below.



There are approximately 4.3 million new HBV infections in the WHO EMR every year. In the absence of immunization, approximately 100,000 people from each annual birth cohort will die from HBV-related liver diseases and HCC during their lifetime.

In the Eastern Mediterranean Region 800,000 new HCV infections occur every year. It is estimated that 17 million people have chronic HCV infection in the region, with a prevalence of 1% to >10% and up to 20% in some parts of Egypt, as shown below:



The growing threats of Hepatitis B & C

If untreated, 14%-45% of HCV patients will develop chronic liver disease and cirrhosis 20 years after acquisition of the disease. The proportion of HCC patients and cirrhosis patients with HBV and/or HCV infection in the WHO EMR is shown in the Table right above:

Country	Year	Number of patients	% of HCC patients with:		
			HBs Ag only	anti-HCV only	HBs Ag and anti-HCV
Islamic Republic of Iran	1999 2004	71	52	8	0
Saudi Arabia	1995 1996	118	64	9	3
Tunisia	1994	31	55	16	10
Egypt	1998 2002	750	10	77	11

Country	Year	Number of patients	% of cirrhosis patients with:		
			HBs Ag only	anti-HCV only	HBs Ag and anti-HCV
Saudi Arabia	1989 1990	28	39	29	7
Tunisia	1994	168	30	40	5
Egypt	1992	39	13	59	23
Pakistan	1999 2000	72	14	58	10
Somalia	1988 1990	30	47	7	3

Hepatitis C is a curable disease, but the treatment cost is very high. We estimated the cost to treat 50% of potential candidates for therapy in the WHO EMR to be more than $125 billion (going from $26 million in Djibouti, to more than $40 billion in Pakistan, and $53 billion in Egypt), which is much higher than the cost of implementing the recommended preventive/control measures.

The key modes of HBV and HCV virus transmission vary according to the country and the virus. Health care associated transmission is currently the predominant transmission mode for both viruses in most countries of the WHO EMR. There are weak infection control programmes, due to fast and intensive introduction of new technologies and invasive procedures and a lack of adequate accompanying measures. In particular, this is the case in countries with weak health care systems, where health care workers are not well trained, there is a rapid turnover of staff, and there is poor knowledge and education on blood-borne pathogen transmission and infection control.

The modes of health care associated transmission include:

- Invasive procedures;
- Equipment reuse;
- Unsafe injections: although 17 countries currently use disposable syringes in the EPI programme, injection safety in the health system is not well developed, especially in

the curative and the private sector. In 2000 in the WHO EMR, there were an estimated 2,500,000 HBV infections and 600,000 HCV infections due to unsafe injections;

- Unsafe transfusions: a comprehensive screening of blood has not been achieved. In a study of 55 blood banks in Pakistan, only 30% had the capacity to screen for HCV. Many countries continue to use paid donors and several countries do not conduct ongoing monitoring; and
- Occupational exposures: which are exacerbated by problems with screening patients in several countries. The WHO estimates that there are 10,000 HBV infections and 3,500 HCV infections per year among HCW in this region. Eleven countries reported implementation of HCW vaccination programmes, but there is little information on regularity, targeted population and especially on the coverage. The frequency of needlestick injuries amongst workers is high and will not improve as long as there is a lack of educational programmes that could lead to the change in behaviour of HCW.

IDU, playing a role in the spread of both HBV and HCV, are a growing phenomenon in the region, currently numbering around 1 million. In 2005, the Regional Committee for the WHO EMR (RC52) urged Member States to make available a wide range of interventions for drug users including harm reduction (opioid substitution therapy and needle and syringe programmes), however many countries have not introduced these interventions. Prevention programmes addressing IDU often have low coverage and some countries' national policies and drug control laws and regulations are not conducive to harm reduction. Iran is the only country to have introduced a harm reduction programme successfully.

Other modes of transmission, particularly of HBV, include: perinatal transmission which is responsible for a high proportion of chronic HBV infection; transmission during early childhood due to the close contact of children; and sexual transmission.

Between 1989 and 2007, the HBV vaccine was introduced into 21 countries out of the 22 countries in the WHO EMR. The only country that has not been able to introduce the vaccine yet is Somalia, because it was not eligible for GAVI support during the new vaccines introduction window. Thirteen countries give a birth dose (33% of birth cohort) and four countries report having implemented catch-up campaigns. In terms of monitoring HBV vaccination impact, routine disease surveillance is not appropriate, since HBV infections in infants and children are asymptomatic. Therefore specific studies based on the disease reduction goal are needed to demonstrate the impact on HBsAg prevalence. Studies monitoring the impact of HBV vaccination on prevalence of chronic HBV infection among children born after the vaccine's introduction were only reported in Egypt, Saudi Arabia and Oman.

To adapt and control the prevention strategies, there is an urgent need for specialized studies and enhanced surveillance in the region. It was concluded that HBV and HCV are a growing threat in the eastern Mediterranean region and, to speed up prevention and control, the regional committee issued a resolution (RC56).

At the 56th Session of the Regional Committee for the Eastern Mediterranean Region (RC 56), on 5-8 October 2009, the Committee urged Member States to:

- Develop a national strategy to reach the regional target related to reducing the prevalence of chronic HBV infection to less than 1% among children below 5 years of age by 2015, if they have not yet done so;
- Develop and implement a comprehensive national strategy for prevention and control of blood borne pathogens, supported by necessary legislation and regulation;
- Expand HBV vaccination programmes with a birth dose to all infants within the first 24 hours of life; vaccination of all persons with occupational exposure to blood and body fluids and vaccination of other high risk populations, including IDU;
- Promote infection control through adoption of national guidelines and an accreditation process to monitor compliance, and ensure that all injections are given safely;
- Ensure transfusion safety by promoting safe blood donation, strengthening national regulatory activities related to quality assurance of safe blood and blood products and related in-vitro procedures;
- Establish education and communication programmes to increase awareness among the public and health care workers on the mode of transmission and opportunities to prevent viral hepatitis;
- Rapidly scale up harm reduction services for IDU;
- Expand treatment services for the chronically infected; and
- Improve epidemiological surveillance systems, develop a hepatitis registry and implement serosurveys in order to produce reliable data to guide prevention and control measures and monitor impact of preventive strategies.

In RC 56 the Regional Committee asked the Regional Director to:

- Continue providing technical support to Member States to develop national strategies and plans of action to reach the regional target of reducing prevalence of chronic HBV infection to less than 1% among children below 5 years of age by 2015, and for prevention and control of transmission of blood-borne pathogens;
- Facilitate transfer of technology to support local production of necessary medicines and vaccines, where appropriate;
- Support national studies/surveillance activities in order to better understand the epidemiology of HCV in selected countries; and
- Assist Member States to secure needed medicines at affordable prices.

References

[1] WHO. Global distribution of hepatitis A, B and C, 2001. Weekly Epidemiological Report 2002;77(6):41-48.

Based on a presentation by
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