ΕΛΛΗΝΙΚΗ ΓΑΣΤΡΕΝΤΕΡΟΛΟΓΙΑ 1993, 6(1):67–73
HELLENIC JOURNAL OF GASTROENTEROLOGY 1993, 6(1):67–73

Ανασκόπηση
Review

Epidemiology of hepatitis B virus infection

N.C. Tassopoulos,

Ο ιός της ηπατίτιδας Β (HBV) είναι σχετικά μικρός σε μέγεθος DNA ιός, με ευρύτατη όμως διασπορά. Υπολογίζεται ότι υπάρχουν περισσότεροι από 300.000.000 φορείς του HBV σε ολόκληρο τον κόσμο και ότι 250.000 περίπου άνθρωποι κάθε χρόνο πεθαίνουν από ηπατική ανεπάρκεια που οφείλεται σε οξεία ή χρόνια ηπατίτιδα Β. Η ενδημικότητα της HBV λοιμώξεως ποικίλλει ευρέως στα διάφορα μέρη του κόσμου. Στις χώρες με μεγάλη ενδημικότητα, όπου ο επιπολασμός του HBsAg ανέρχεται σε 8–15% επί του πληθυσμού, η μετάδοση του HBV είναι κυρίως κάθετη ή οριζόντια κατά τη διάρκεια των πρώτων 6 χρόνων της ζωής. Στις χώρες με ενδιάμεση ενδημικότητα, στις οποίες ανήκει και η χώρα μας, ο επιπολασμός του HBsAg κυμαίνεται σε 2–7% του πληθυσμού, η μετάδοση συμβαίνει κυρίως στα μεγαλύτερα παιδιά, στους εφήβους και τους νεαρούς ενηλίκους. Τέλος, στις χώρες με μικρή ενδημικότητα, στις οποίες ο επιπολασμός του HBsAg είναι μικρότερος του 1%, η μετάδοση συμβαίνει κυρίως μεταξύ ενηλίκων που ανήκουν σε ομάδες αυξημένου κινδύνου. Επιδημίες της ηπατίτιδας Β είναι ασυνήθιστες και οφείλονται συνήθως σε ιατρογενείς παράγοντες, ενώ επιδημίες βαριάς οξείας ηπατίτιδας Β έχουν περιγραφεί μεταξύ τοξικομανών, στους οποίους συνήθως συνυπάρχει λοίμωξη από τους ιούς ηπατίτιδας δέλτα και/ή C. Διάφοροι παράγοντες επηρεάζουν τη μετάπτωση της οξείας HBV λοιμώξεως σε χρονιότητα. Η ηλικία κατά τη λοίμωξη είναι ο σημαντικότερος από αυτούς και είναι αντίστροφα ανάλογη της συχνότητας μεταπτώσεως σε χρόνια HBsAg-αιμία. Η οξεία κλινική ηπατίτιδα Β στους ενηλίκους σπανιότατα (<1%) μεταπίπτει σε χρονιότητα. Ομάδες αυξημένου κινδύνου για HBV λοίμωξη είναι οι (α) ομοφυλόφιλοι, στους οποίους όμως παρατηρείται ελάττωση της επιπτώσεως μετά την εμφάνιση του ιού της ανοσοανεπάρκειας του ανθρώπου (HIV), (β) τοξικομανείς, (γ) ετεροφυλόφιλοι με πολλούς ερωτικούς συντρόφους ή με συντρόφους φορείς του HBsAg, στους οποίους ο κίνδυνος λοιμώξεως αυξάνεται με τον αριθμό των ερωτικών συντρόφων τη διάρκεια της γενετήσιας δραστηριότητας και το ιστορικό άλλων αφροδίσιων νοσημάτων, (δ) εργαζόμενοι σε επαγγέλματα υγείας, κυρίως οδοντίατροι, βιοχημικοί και αιματολόγοι, (ε) αιμοκαθαιρόμενοι, (στ) τρόφιμοι και προσωπικό ιδρυμάτων, (ζ) φυλακισμένοι και (η) πολυμεταγγιζόμενοι και αιμορροφιλικοί. Στον τόπο μας, αυξημένος επιπολασμός HBV λοιμώξεως παρατηρείται σε κοινότητες με κακές συνθήκες υγιεινής και χαμηλό κοινωνικοοικονομικό επίπεδο. Η οριζόντια μετάδοση μεταξύ των μελών της οικογένειας φαίνεται να είναι ο κύριος τρόπος διασποράς του ιού. Ο HBV ευθύνεται για τα 2/3 περίπου των οξειών κλινικών ηπατίτιδων, όπου η γενετήσια επαφή (ετεροφυλοφιλική ή ομοφυλοφιλική) και η τοξικομανία αποτελούν τους κύριους τρόπους μεταδόσεως. Επιπροσθέτως, ο HBV αποτελεί τον κύριο αιτιολογικό παράγοντα του ηπατοκυτταρικού καρκίνου. Επομένως, η HBV λοίμωξη αποτελεί σοβαρό πρόβλημα δημόσιας υγείας και, εκτός από τη σωστή ενημέρωση και προφύλαξη των ατόμων που ανήκουν στις ομάδες αυξημένου κινδύνου, τη βελτίωση των συνθηκών ατομικής υγιεινής και του κοινωνικοοικονομικού επιπέδου, απαραίτητη είναι η ανοσοπροφύλαξη των νεογνών των HBsAg θετικών μητέρων και ο εμβολιασμός όλων των εφήβων.

Liver Unit, First Dept. of Medicine,
Western Attica General Hospital, 123 51 Athens

Hepatitis B virus (HBV) is a widely distributed pathogen that produces acute and chronic infection in man. Chronically infected individuals appear to be the only natural host for HBV and also are at high risk of death from chronic liver disease and hepatocellular carcinoma. However, several of the nonhuman primates (e.g. chimpanzee, gibbon, gorilla) have been shown to be susceptible to infection and could manifest a persistent HBV infection. Worldwide, it has been estimated that over 300 million persons are chronically infected with HBV, and over 250,000 peo-

ple die annually from hepatitis B associated acute and chronic liver disease.[1]

PATTERNS OF HBV ENDEMICITY

The patterns of the endemicity of HBV infection in various parts of the world vary greatly (table 1). It can be considered high in those areas of the world where the prevalence of HBsAg is 8% to 15% and where 70 to 90% of the population have serological evidence of previous HBV infection. In these areas (China, Southeast Asia, sub-Saharan Africa, Pacific Islands, the Arctic, parts of Middle East, the Amazon basin of South America) transmission is usually vertical from infected mother to the neonate or horizontal among children during the first 5 yearts of life. However, two distinct patterns of virus transmission are observed in high endemicity areas. In Asia, perinatal transmission predominates since 5% to 12% of women of the reproductive age are HBsAg-positive, and 30% to 50% of these women have high levels of circulating HBV indicated by the presence of HBeAg or HBV DNA.[3,4] Perinatal infections account for at least one fourth of chronic HBV infections in the adult population in this epidemiologic setting. In contrast, in other areas, such as Africa, the Middle East and the Arctic, horizontal transmission within families during the first 5 years of life is the predominant mode of HBV infection in children since fewer than 20% of HBsAg mothers are also HBeAg-positive.[5,6] Moreover, transmission of HBV infection can occur from sources outside of the family, and it may account for as much as 50% of all infections.

In intermediate areas of prevalence of HBV infection (India, parts of Middle East, Western Asia, Japan, Russia, eastern and southern Europe, most of South and Central America) the carrier rate of HBsAg ranges from 2% to 7% and 20% to 50% of the adult population have serologic markers of past infection. Although transmission occurs in all age groups (newborn, childhood, and adult), the highest rates of infection are probably among older children, adolescents and young adults. Wide variations in prevalence of infection occur in these areas, and racial, hygienic, cultural and socioeconomic factors may lead to differences in risk of infection. Improvements in socioeconomic conditions appear to correlate with significant declines in infection rates.[7]

In most developed countries (North America, Western Europe, Australia, temperate South America) the prevalence is low, with HBsAg carrier rates of less than 1% and overall infection rates of 5% to 7% (table 1). Within these populations, transmission occurs primarily among adults with life-styles or behaviours that place them at high risk of infection and these include homosexual men, intravenous drug abusers, health care workers, chronically transfused patients, residents of institutions for the mentally retarded and heterosexual contacts of acute hepatitis B cases or asymptomatic HBsAg carriers.

GEOGRAPHIC DISTRIBUTION

The global distribution of HBV infection has been extensively elucidated in the past several years. Within

Table 1. Worldwide distribution of hepatitis B virus infection.*

	Endemicity		
	Low	**Intermediate**	**High**
Prevalence:			
HBsAg	<2%	2–7%	8–15%
Anti-HBs	<20%	20–60%	>60%
Distribution:	North America Western Europe Australia	Eastern Europe Mediterranean South America Middle East Russia	Southeast Asia China Tropical Africa Pacific Islands South America Middle East

* Adapted from Maynard[2]

areas of high prevalence of HBV infection there is usually little variation in disease prevalence. However, in areas of intermediate and low prevalence of HBV infection reside ethnic groups with HBV infection rates that are significantly higher than those of the general population and are considered highly endemic. Examples include Eskimo populations in both the United States and Canada[8] and immigrant population from high or intermediate endemicity areas of the world.[9]

EPIDEMICS

Outbreaks of hepatitis B are unusual and are usually attributed to direct parenteral exposures. Epidemics have occurred in the hospital setting through contaminated medical equipments that were not adequately sterilized or disinfected.[10–14] In addition, common-source outbreaks in which multidose medication vials or intravenous solution contaminated with HBV-infected blood have also been reported.[15–17] Transmission of HBV from health care workers who are HBsAg carriers to their patients during the course of surgical procedures, e.g. deep pelvic operations,[18] and among patients of oral surgeons and dentists have also been reported.[19,20]

Outbreaks of severe hepatitis B have also been reported among parenteral drug abusers; coinfection with hepatitis delta virus (HDV) explained the high mortality rate.[21]

HEPATITIS B CARRIERS

Several factors have been shown to influence the risk of a person becoming a chronic lifetime carrier of HBV, of which the most important is the age of infection. Infants born to HBsAg carrier mothers who are HBeAg positive have a 70% chance of becoming infected, with 90% of newborns becoming chronic HBV carriers.[22–24] In contrast, newborns of HBsAg carrier mothers who are HBeAg negative have a 5% to 10% chance of becoming infected at birth.[4,25] Children born into families with an HBsAg carrier have approximately a 30% risk whereas adolescents and adults have a 6% to 10% risk of becoming chronic HBsAg carriers.[26,27] Clinical expression of acute HBV infection is inversely related to the age; HBV infection tends to be symptomatic in 33% to 50% of the cases in adolescents and adults.[27] Symptomatic acute type B hepatitis in adults is a self-limited disease and rarely (0.2%) leads to the development of the carrier sta-

OCCUPATIONAL RISK

Hepatitis B has traditionally been a hazard of blood transfusion, the use of shared syringes, and exposure to infected blood. For these reasons high rates of infection occur in certain occupational groups such as dentists, staff and patients in dialysis units, biochemists and hematologists.[30,31] Serological surveys among physicians and dentists have shown a two to four fold higher infection rates than that in the general population;[32,33] risk of HBV infection increases with age and number of years in practice.[34] In this epidemiological setting the transmission of HBV appears to be through parenteral or inapparent parenteral contacts through breaks in the skin or contamination of mucous membranes with infectious secretions. Accidental needlestic exposure with HBeAg negative blood carriers a remarkably lower risk (14%).[35]

HBV INFECTIONS IN ADULTS

Homosexual men have been one of the highest risk groups for HBV infection and were responsible for one fifth of the cases of hepatitis B from 1980 to 1985 in the United States. However, a dramatic decline in the number and proportion (8%) of cases of hepatitis B had been observed in the '90s probably due to changes in high-risk sexual behavior to lessen the risk of human immunodeficiency virus infection.[36] HBV infection in homosexuals has been associated with receptive anal intercourse, increased numbers of sexual partners and duration of regular homosexual activity, so that 70% of men were infected after 5 years of sexual activity.[37,38]

Intravenous drug abusers have been also considered at high risk of HBV infection since prevalence of HBV serological markers has been found three-fold higher than that in the general population (77.1% vs. 22.5%).[39] In addition, HDV infection significantly increases the severity of acute hepatitis B leading to fulminant hepatic failure.[40,41] Recently, a retrospective serological analysis of 208 Greek drug abusers with acute hepatitis B revealed that fulminant hepatic failure was observed exclusively in 8 (18.2%) of the 44 patients with HBV and HDV coinfection superimposed on unrecognized HCV infection. This prevalence was statistically significant in comparison with the remaining 164 patients (8/44 or 18.2% vs. 0/164 or 0%, $p<0.00001$).[42]

Heterosexuals with multiple partners appeared to

in developed countries.[36] In Greece, an area of moderate HBV endemicity, it was found that 30% of adults with acute hepatitis B had habitual heterosexual partners who were asymptomatic HBsAg carriers and were the most probable source of infections for the patients.[43] The epidemiological evidence of heterosexual transmission of HBV correlated positively with seropositivity for HBV DNA of the carrier-partners (table 2).[44] Although two-thirds of these carrier-partners were anti-HBe positive, which is considered to be a marker of low or absent infectivity,[45] 69% of them were IgM anti-HBc positive. Consequently, IgM anti-HBc may identify anti-HBe positive carriers with a potentially higher risk of transmitting HBV to their heterosexual partners (table 3).[46] Mutations in the precore region of HBV DNA have been identified in patients with fulminant and non fulminant hepatitis and their heterosexual partners.[47–49] Data on the sexual transmission of the variant were inconclusive and it could be speculated that most acute infections in Greece arise as a result of transmission from anti-HBe positive carriers and the only anti-HBe positive carriers who are infectious are those with the precore mutation and high viral replication (I.V.D. Weller, N. Tassopoulos, unpublished data).

Risk of HBV infection in heterosexuals increases with number of sexual partners, number of years of sexual activity and history of other sexually transmitted diseases.[50–52] In particular, the risk of infection is strongly associated with serologic evidence of previous infection with syphilis.[52]

Other groups that are known to be at high risk of HBV infection but who are not represented in the overall community-based rates include clients and staff of institutions for mentally retarded subjects,[53] prisoners,[54] individuals receiving blood transfusions,[55] hemophiliacs and prostitutes.[56] An important feature of the epidemiology of hepatitis B is that 30% to 40% of patients have no known source of infection. These patients tend to belong to minority populations and have characteristics associated with low socioeconomic level.[36,51]

Table 2. Biochemical and serological characteristics of Greek HBsAg carriers whose sexual partners were infected or not infected with hepatitis B virus.

Criteria	Carriers with infected partners (N=96)		Carriers with non infected partners (N=86)	
	N	%	N	%
Elevated ALT	42	43.8*	9	10.5*
HBeAg positive	32	33.3*	3	3.5*
Anti-HBe positive	61	63.5	83	96.5
HBV DNA positive	57	59.4**	10	11.6**

*p<0.01, **p<0.001

Table 3. IgM anti-HBc and HBV DNA in Greek HBsAg carriers positive for anti-HBe whose sexual partners where infected or not infected with hepatitis B virus.

Serological markers	Carriers with infected partners (N=52)		Carriers with non infected partners (N=80)	
	N	%	N	%
IgM anti-HBc positive	36	69.2	25	31.2
HBV DNA positive	20	38.4	8	10.0
p	<0.001		<0.01	

EPIDEMIOLOGY OF HEPATITIS B IN GREECE

Seroepidemiological studies in Athens and rural areas of Greece have shown high prevalence of HBV infections in early adulthood. Infection rate is high in communities wth poor hygienic conditions and low socioeconomic level (figure 1).[7,57–60] Horizontal transmission among family members appears to be the principal route of transmission.

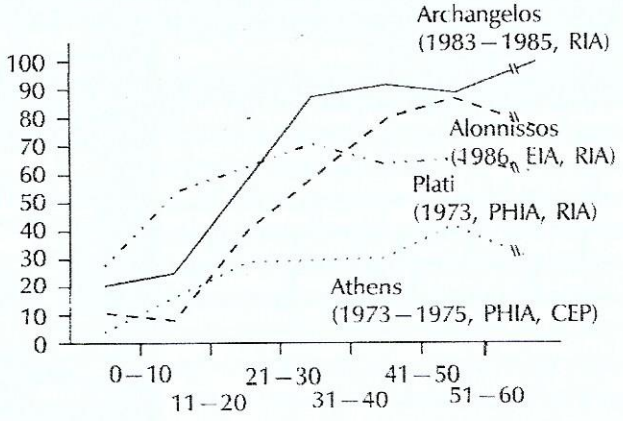

Figure 1. Age-specific seroprevalence of hepatitis B virus infection in selected Greek populations. Archangelos, Alonnissos and Plati are rural areas with a high endemicity of infection.[7,57–60]

HBV still accounts for approximately two thirds of cases of acute hepatitis in the two referral hospitals in Athens and Macedonia (figure 2, table 4). A detailed questionnaire that provided clinical as well as epidemiological data showed that the source of HBV infections has changed and is similar to that of other developed countries (figure 3). Sexual contact, either heterosexual or homosexual and parenteral drug abuse are the principal routes of transmission. Heterosexual transmission is characterized by rapid clearance of HBsAg which is independent of sex.[61] This finding may explain the increase with age of the prevalence of serological markers of past HBV infection (figure 1). Unfortunately, the number of cases of hepatitis B attributable to parenteral drug abuse has dramatically increased since 1981.[43] Of equal concern is the increase in cases of hepatitis non-A, non-B associated with intravenous drug abuse[62] suggesting that hepatitis is a widespread problem in this epidemiologic setting.[63] In contrast, the number of cases of hepatitis B associated with blood transfusions has decreased during this decade. As a result, the incidence of fulminant hepatitis B declined from 4% to 2.7%.[64]

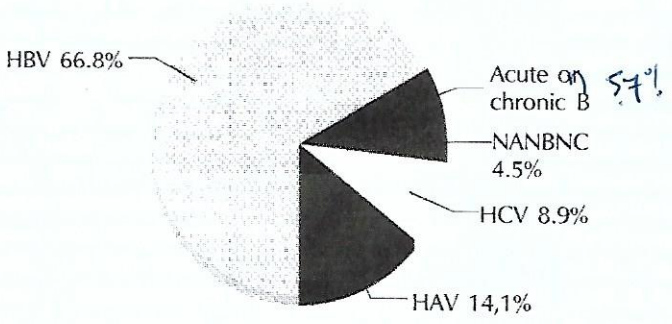

Figure 2. Etiology of acute viral hepatitis in Greek adults, Athens, 1986–1990.

Table 4. Etiology of acute viral hepatitis in Greek adults by type and referral center (1986–1990).

Type of hepatitis	Athens		Macedonia*	
	N	%	N	%
Hepatitis A	292	14.1	223	13.4
Hepatitis B	1387	66.8	1100	66.3
Hepatitis NANB	278	13.4	245	14.8
Hepatitis superimposed on HBsAg carriage	119	5.7		
Unclassified			92	5.5
Total	2076	100.0	1660	100.0

*A. Papachristou, personal communication.

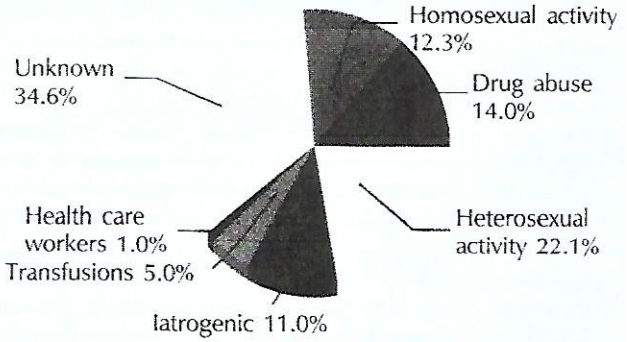

Figure 3. Risk factors associated with reported cases of hepatitis B, Greece 1986–1990. Heterosexual activity includes sexual contact with acute cases, asymptomatic HBsAg carriers and multiple partners (>3) (From the Western Attica General Hospital, Athens, unpublished data).

HBV is also the principal etiologic agent of hepatocellular carcinoma (HCC) (relative risk 13.7), particularly in Greek cirrhotic patients (relative risk 30.7 vs. 7.1 among HBsAg positive patients without cirrhosis).[65] Recently, the relative risk linking hepatitis C virus to HCC has been estimated 10.4, though it had been previously overestimated using first generation enzyme immunoassays in stored sera.[66]

CONCLUSIONS

HBV infections appear to remain stable at low levels in most developed countries and the infection rate is high in heterosexuals with multiple sexual partners, promiscuous homosexuals and parenteral drug abusers. Since 30% of cases of acute hepatitis B have no known source of infection, control and possible elimination of transmission of HBV infection is possible with immunoprophylaxis of infants born to HBsAg positive mothers and integration of hepatitis B vaccine into childhood immunization schedules.

REFERENCES

1. Maynard JE. Hepatitis B: global importance and need for control. Vaccine 1990, 8 (Suppl): 18–20
2. Maynard JE. Hepatitis B vaccine: Strategies for utilization. In: Maupas P, Quesry P (eds) Hepatitis B Vaccine. Elsevier/

North Holland, Biomedical Press, Amsterdam, 1981: 13–19
3. Stevens CE, Neurath RA, Beasley RP et al. HBeAg and anti-HBe detection by radioimmunoassay. Correlation with vertical transmission of hepatitis B virus in Taiwan. J Med Virol 1979, 3:237–241
4. Xu Zu, Liu CB, Francis DP et al. Prevention of perinatal acquisition of hepatitis B virus carriage using vaccine: preliminary report of a randomized, double-blind placebo-controlled and comparative trial. Pediatrics 1985, 76:713–718
5. Marinier E, Barrois V, Larouze B et al. Lack of perinatal transmission of hepatitis B virus in Senegal, West Africa. J Pediatr 1985, 106:843–849
6. Hyams KC, Osman NM, Khaled EM et al. Maternal-infant transmission of hepatitis B in Egypt. J Med Virol 1988, 24:191–197
7. Tassopoulos NC, Kyriakis P, Saggana E, Limotirakis F, Papaioannou C, Hadziyannis S. Impact of socieconomic changes on the prevalence of HBV infection in an endemic area. J Hepatol 1987, 5 (Suppl 1):209
8. Schreeder MT, Bender TR, McMahon BJ et al. Prevalence of hepatitis B in selected Eskimo villages. Am J Epidemiol 1983, 118:544–549
9. Franks AL, Berg CJ, Kane MA et al. Hepatitis B infection among children born in the United States to Southeast Asian refugees. N Engl J Med 1989, 321:1301–1305
10. Canter J, Mackey K, Good LS et al. An outbreak of hepatitis B associated with jet injections in a weight reduction clinic. Arch Intern Med 1990, 150:1923–1927
11. Birnie GG, Quigley EM, Clements GB, Follet EAC, Watkinson G. Endoscopic transmission of hepatitis B virus. Gut 1983, 24:171–174
12. Kent GP, Brondum J, Keenlyside RA, Lafazia LM, Scott HD. A large outbreak of acupuncture-associated hepatitis B. Am J Epidemiol 1988, 127:591–598
13. Douvin C, Simon D, Zinelabidine H, Wirquin V, Perlemuter L, Dhumeaux D. An oubreak of hepatitis B in an endocrinology unit traced to a capillary-blood-sampling device. N Engl J Med 1990, 322:57
14. Polish LB, Shapiro CN, Bauer F et al. Nosocomial transmission of hepatitis B virus associated with the use of a spring-loaded finger-stick device. N Engl J Med 1992, 320:721–725
15. Alter MJ, Ahtone J, Maynard TE. Hepatitis B virus transmission associated with a multiple-dose vial in a hemodialysis unit. Ann Intern Med 1983, 99:330–333
16. Oren I, Hershow RC, Ben-Porath E et al. A common-source outbreak of fulminant hepatitis B in a hospital. Ann Intern Med 1989, 110:691–698
17. Carl M, Francis DP, Maynard JE. A common source outbreak of hepatitis B in a hemodialysis unit. Dialysis Transplant 1983, 12:222–229
18. Carl M, Blakey DL, Francis DP, Maynard JE. Interruption of hepatitis B transmission by modification of a gynecologist's surgical technique. Lancet 1982, i:731–733
19. Hadler SC, Sorley DL, Acree KH, et al. An outbreak of hepatitis B in a dental practice. Ann Intern Med 1981, 95:133–138
20. Shaw FE, Barrett CL, Hamm R et al. Lethal outbreak of hepatitis B in a dental practice. JAMA 1986, 255:3260–3264
21. Lettau LA, McCarthy JG, Smith MH et al. Outbreak of severe hepatitis due to delta and hepatitis B viruses in parenteral drug abusers and their contacts. N Engl J Med 1987, 317:1256–1262
22. Beasley RP, Huang LY, Stevens CE et al. Efficacy of hepatitis B immune globulin for prevention of perinatal transmission of the hepatitis B carrier state: Final report of a randomized double-blind placebo-controlled trial. Hepatology 1983, 3:135–141
23. Beasley RP, Tropo C, Stevens CE, Szmuness W. The e antigen in vertical transmission of hepatitis B surface antigen. Am J Epidemiol 1977, 105:94–98
24. Stevens CE, Neurath RA, Beasley RP, Szmuness W. HBeAg and anti-HBe detection by radioimmunoassay: correlation of vertical transmission of hepatitis B virus in Taiwan. J Med Virol 1979, 3:237–241
25. Wong VCW, Ip HMH, Reesing HW et al. Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis B vaccine and hepatitis B immunoglobulin. Double blind randomized placebo-controlled study. Lancet 1984, i:921–926
26. Beasley RP, Hurang L-Y. Postnatal infectivity of hepatitis B surface antigen carrier mothers. J Infect Dis 1983, 147:185–190
27. McMahon BJ, Alward WLM, Hall DB et al. Acute hepatitis B virus infection; relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis 1985, 151:599–603
28. Tassopoulos NC, Papaevangelou G, Sjogren MH, Roumeliotou-Karayiannis A, Gerin JL, Purcell RH. Natural history of acute hepatitis B surface antigen positive hepatitis in Greek adults. Gastroenterology 1987, 92:1844–1850
29. Seeff LB, Beebe GW, Hoofnagle JH et al. A serologic follow-up of the 1942 epidemic of post-vaccination hepatitis in the United States army. N Engl J Med 1987, 316:965–970
30. Hadler SC, Doto IL, Maynard JE et al. Occupational risk of hepatitis B infection in hospital workers. Infect Control 1985, 6:24–31
31. Osterholm MT, Garayalde SM. Clinical viral hepatitis B among Minnesota hospital personnel. Results of a 10 year statewide survey. JAMA 1985, 254:3207–3212
32. Smith JL, Maynard JE, Berquist KR, Doto IL, Webster HM, Sheller MJ. Comparative risk of hepatitis B among physicians and dentists. J Infect Dis 1976, 133:705–706
33. Gahl GM, Vogl E, Kraft G, Hess G, Arnold W. HBV markers among family contacts and medical personnel of 239 hemodialysis patients. Clin Nephrol 1980, 14:7
34. Danes AE, Smith JL, Maynard JE, Doto IL. Hepatitis B infection in physicians: results of a nationwide seroepidemiologic survey. JAMA 1978, 239:210–212
35. Alter HJ, Seeff LB, Kaplan PM et al. Type B hepatitis: the infectivity of blood positive for e antigen and DNA polymerase after accidental needdlestick exposure. N Engl J Med 1976, 295:909–913

36. Alter MJ, Hadler SC, Margolis HS et al. The changing epidemiology of hepatitis B in the United States. Need for alternative vaccination strategies. JAMA 1990, 263:1218–1222
37. Schreeder MT, Thompson SE, Hadler SC et al. Hepatitis B in homosexual men: prevalence of infection and factors related to transmission. J Infect Dis 1982, 146:7–15
38. Dietzman DE, Harnisch HP, Ray CG et al. Hepatitis B surface antigen (HBsAg) and antibody to HBsAg: prevalence in homosexual and heterosexual men: JAMA 1977, 238:2625–2626
39. Roumeliotou-Karayannis A, Tassopoulos N, Karpodini E, Trichopoulou E, Kotsianopoulou M, Papaevangelou G. Prevalence of HBV, HDV and HIV infections among intravenous drug addicts in Greece. Eur J Epidemiol 1987, 3:143–146
40. Saracco G, Macagno S, Rosina F, Caredda F, Antinori S, Rizzetto M. Serological markers with fulminant hepatitis in persons positive for hepatitis B surface antigen. A worldwide epidemiologic and clinical survey. Ann Intern Med 1988, 108:380–383
41. Tassopoulos NC, Koutelou Mg, Macagno S, Zorbas P, Rizzetto M. Diagnostic significance of IgM antibody to hepatitis delta virus in fulminant hepatitis B. J Med Virol 1990, 30:174–177
42. Tassopoulos NC, Koutelou MG, Papatheodoridis GV, Kalantzakis YS, Hatzakis AE. Acute delta hepatitis in Greek parenteral drug abusers. In: Taylor J, Bonino F, Hadziyannis S (eds) Hepatitis Delta Virus: Molecular Biology, Pathogenesis and Clinical Aspects. Wiley-Liss, New York, 1993 (υπό δημοσίευση)
43. Papaevangelou G, Roumeliotou-Karayannis A, Tassopoulos N, Kolaitis N, Stathopoulou P. Source of infection due to hepatitis B virus in Greece. J Infect Dis 1983, 147:478–489
44. Tassopoulos NC, Papaevangelou GJ, Roumeliotou-Karayannis A, Ticehurst JR, Feinstone SM, Purcell RH. Detection of hepatitis B virus DNA in asymptomatic hepatitis B surface antigen carriers: relation to sexual transmission. Am J Epidemiol 1987, 126:587–591
45. Papaevangelou G, Tassopoulos NC, Roumeliotou-Karayannis A, Richardson C. Sexual transmission of hepatitis B virus. J Infect Dis 1985, 152:231
46. Tassopoulos NC, Papaevangelou GJ, Roumeliotou-Karayannis A. Heterosexual transmission of hepatitis B virus from symptomless HBsAg carriers positive for anti-HBe. Lancet 1986, ii:972
47. Omata M, Ehata T, Yokosuka O, Hosoda K, Ohto M. Mutations in the precore region of hepatitis B virus DNA in patients with fulminant and severe hepatitis. N Engl J Med 1991, 324:1699–1704
48. Carman WF, Fagan EA, Hadziyannis S et al. Association of a precore genomic variant of hepatitis B virus with fulminant hepatitis. Hepatology 1991, 14:219–222
49. Carman WF, Hadziyannis S, Karayiannis P et al. Association of the precore variant of HBV with acute and fulminant hepatitis B infection. In: Hollinger FB, Lemon SM, Margolis H (eds) Viral Hepatitis and Liver Disease: Contemporary Issues and Future Issues. Williams and Wilkins, Baltimore, 1991:216–219
50. Alter MJ, Ahtone J, Weisfuse I, Starko K, Vacalis TD, Maynard JE. Hepatitis B virus transmission between heterosexuals. JAMA 1986, 256:1307–1310
51. Alter MJ, Coleman PJ, Alexander WJ et al. Importance of heterosexual activity in the transmission of hepatitis B and non-A, non-B hepatitis. JAMA 1990, 262:1201–1205
52. Rosenblum LS, Hadler SC, Castro KQ et al. Heterosexual transmission of hepatitis B virus in Belle Glade, Florida. J Infect Dis 1990, 161:407–411
53. Cancio-Bello TP, Medina M, Shorey J, Valledor MD, Schiff ER. An institutional outbreak of hepatitis B related to a human bitting carrier. J Infect Dis 1982, 146:652–656
54. Decker MD, Vaughn WK, Brodie JS, Hutcheson RH, Schaffner W. Seroepidemiology of hepatitis B in Tenessee prisoners. J Infect Dis 1984, 150:450–459
55. Papaevangelou G, Roumeliotou-Karayannis A, Tassopoulos NC et al. Evaluation of methods of pre-vaccination screening for markers of hepatitis B infection. Eur J Epidemiol 1985, 1:100–103
56. Papaevangelou G, Trichopoulos D, Kremastinou T, Papoutsakis G. Prevalence of hepatitis B antigen and antibody in prostitutes. Br Med J 1974, 2:256–258
57. Blumberg BS, Hesser JE, Economidou I et al. The variety of responses within a community to infection with Australia (hepatitis B) antigen. In: International Symposium on Viral Hepatitis, Milan 1974. Develop Biol Standard, Karger, Basel, 1975, 30:270–283
58. Papaevangelou G, Kyriakidou A, Vissoulis L, Trichopoulos D. Seroepidemiological study of HBV infections in Athens, Greece. J Hyg Camb 1976, 76:229–234
59. Livadas DP, Koutras DA, Gatsios D et al. Some epidemiologic studies of HBsAg in Greece. Hepato-Gastroenterol 1981, 28:77–80
60. Hadziyannis SJ, Hatzakis A, Papaioannou C, Anastassakos C, Vassiliadis E. In: Rizzetto M, Gerin JL, Purcell RH (eds) Endemic Hepatitis Delta Virus and its Infection. Alan R. Liss, New York, 1987:181–202
61. Tassopoulos NC, Papaevangelou GJ. Correlation of hepatitis B surface antigen clearance with the route of hepatitis B infection. J Gastroenterol Hepatol 1990, 5:252–255
62. Tassopoulos NC, Paraloglou-Ioannides M, Halatsis K et al. Changing characteristics of acute hepatitis associated with parenteral drug abuse in Greece. Acta Microbiologica Hellenica 1987, 32:132–140
63. Alter MJ, Hadler SC, Judson FN et al. Risk factors for acute non-A non-B hepatitis in the United States and association with hepatitis C virus infection. JAMA 1990, 264:2231–2235
64. Papaevangelou G, Tassopoulos NC, Roumeliotou-Karayannis A, Richardson C. Etiology of fulminant viral hepatitis in Greece. Hepatology 1984, 4:369–372
65. Trichopoulos D, Day NE, Kaklamani E et al. Hepatitis B virus tobacco smoking and ethanol consumption in the etiology of hepatocellular carcinoma. Int J Cancer 1987 39:45–49
66. Zavitsanos X, Hatzakis A, Kaklamani E et al. Association between hepatitis C virus and hepatocellular carcinoma using assays based on structural and non structural hepatitis C virus peptides. Cancer Res 1992, 52:5364–5367