



PATOLOGIE **E**MERGENTI E **R**IEMERGENTI

Globalizzazione e Salute: l'importanza della Vaccinazione

Martedì, 24 gennaio 2012

CAMERA DEI DEPUTATI
Palazzo Marini - Sala delle Colonne
Via Poli, 19 - Roma

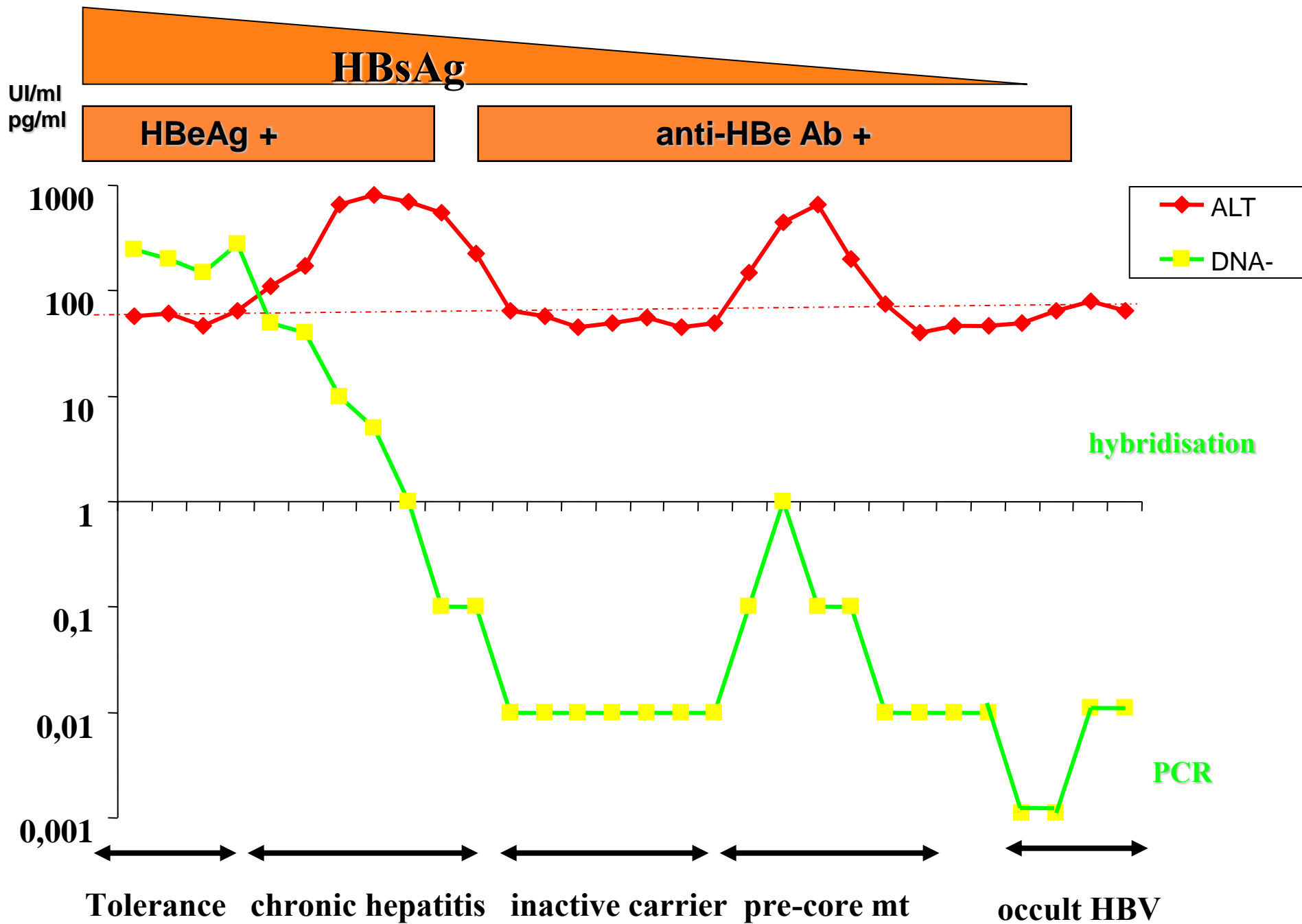
Alla ricerca del virus nascosto

(quando il virus dell'epatite B si "oculta")

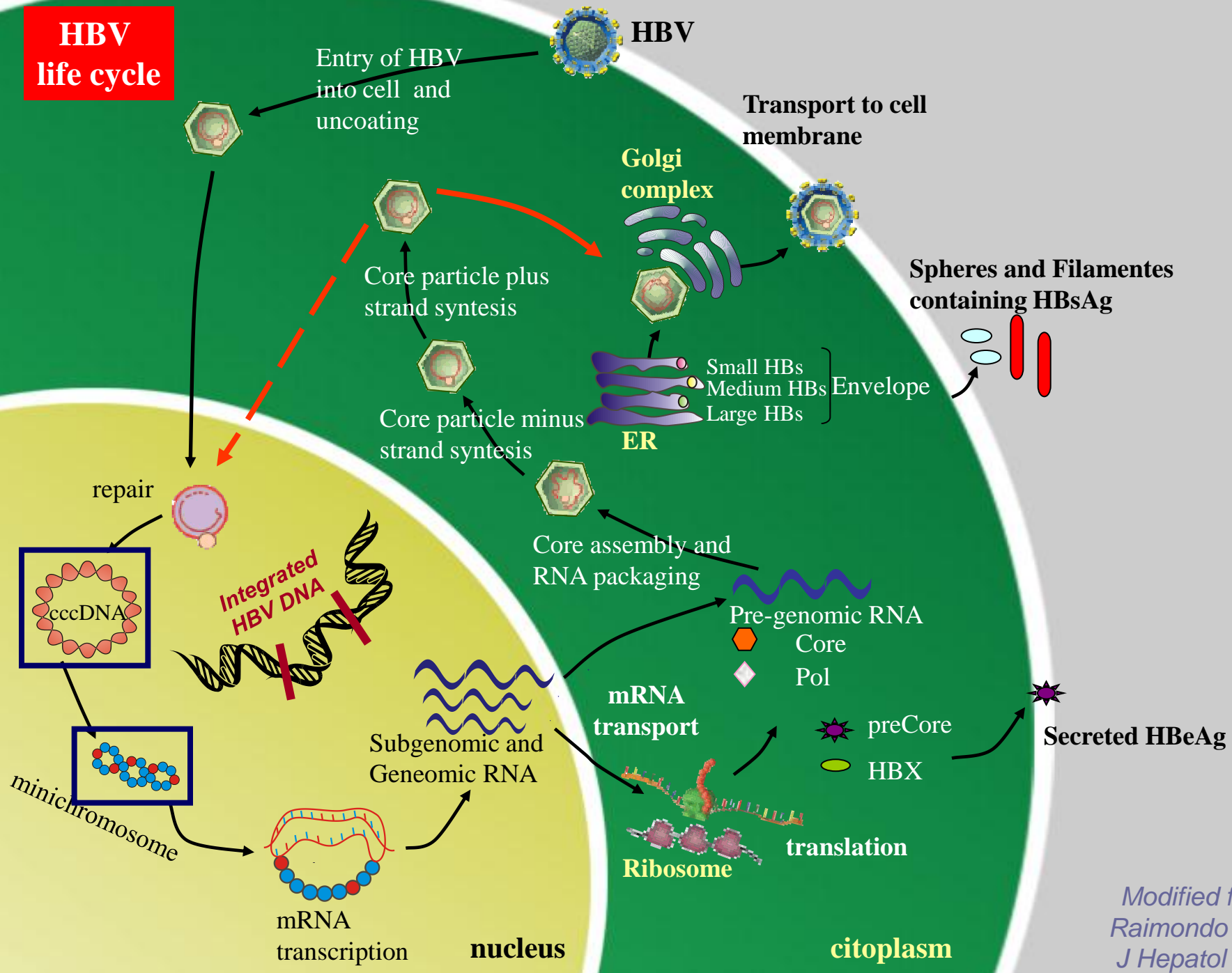
Giovanni Raimondo

Epatologia Clinica e Biomolecolare
Policlinico Universitario di Messina





**HBV
life cycle**



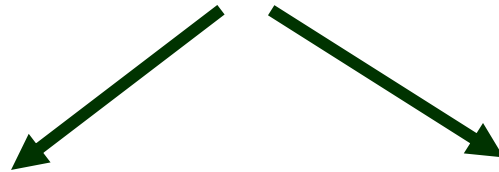
Modified from Raimondo et al, J Hepatol 2007

Occult HBV Infection (OBI)

*Presence of HBV DNA in the liver (\pm serum)
of individuals testing HBsAg negative by
currently available assays*

Occult HBV Infection

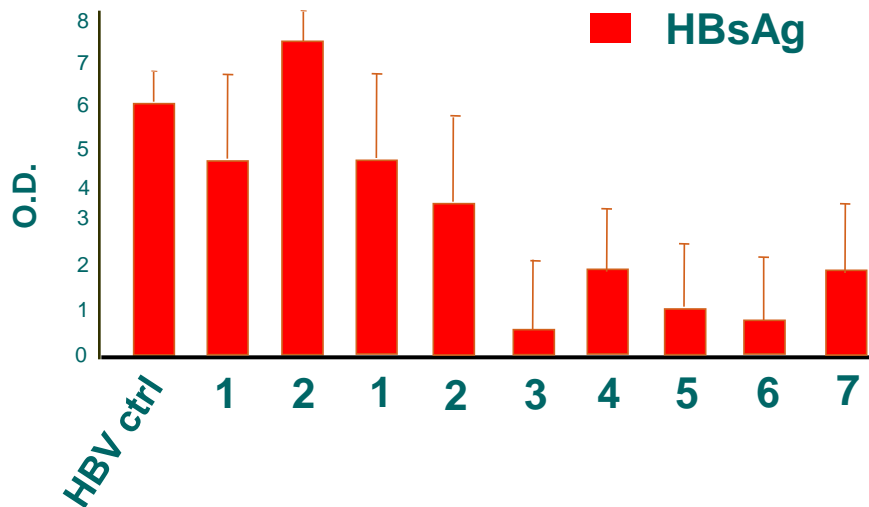
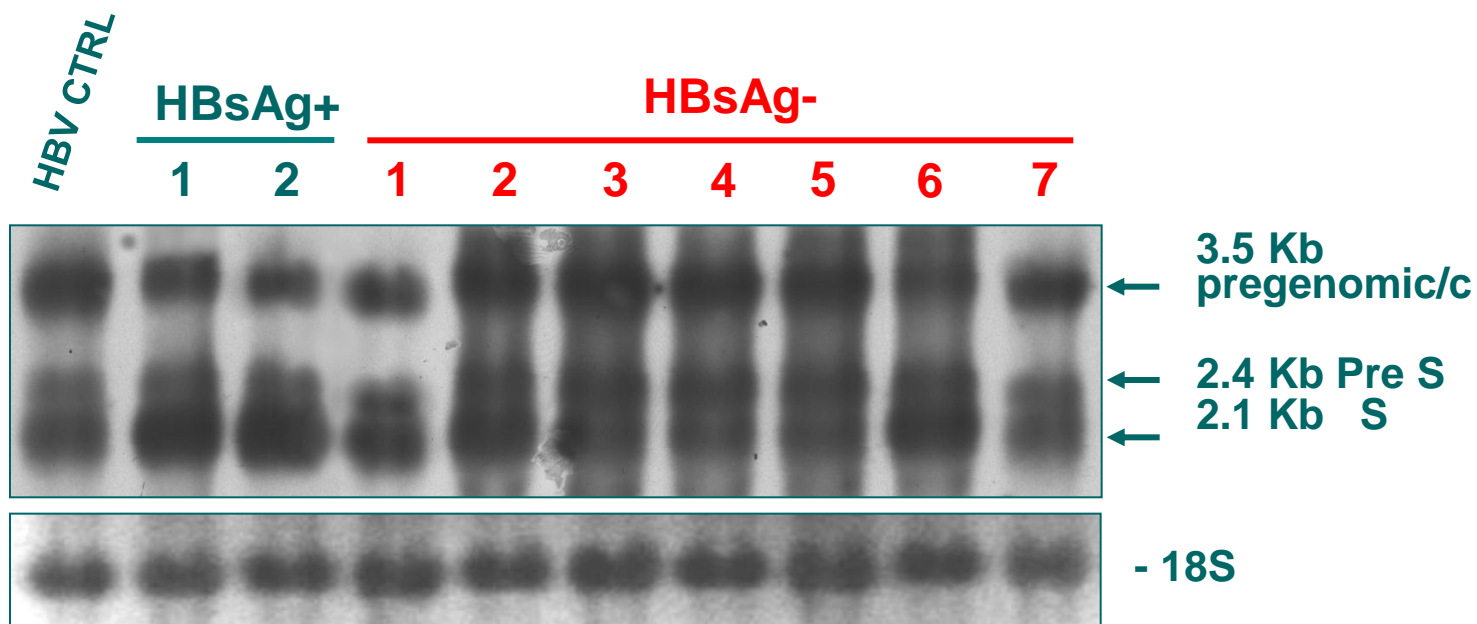
Cause(s) for the failure of HBsAg detection



**Infection by
S gene Variants**

**Suppression of
HBV replication and
gene expression**

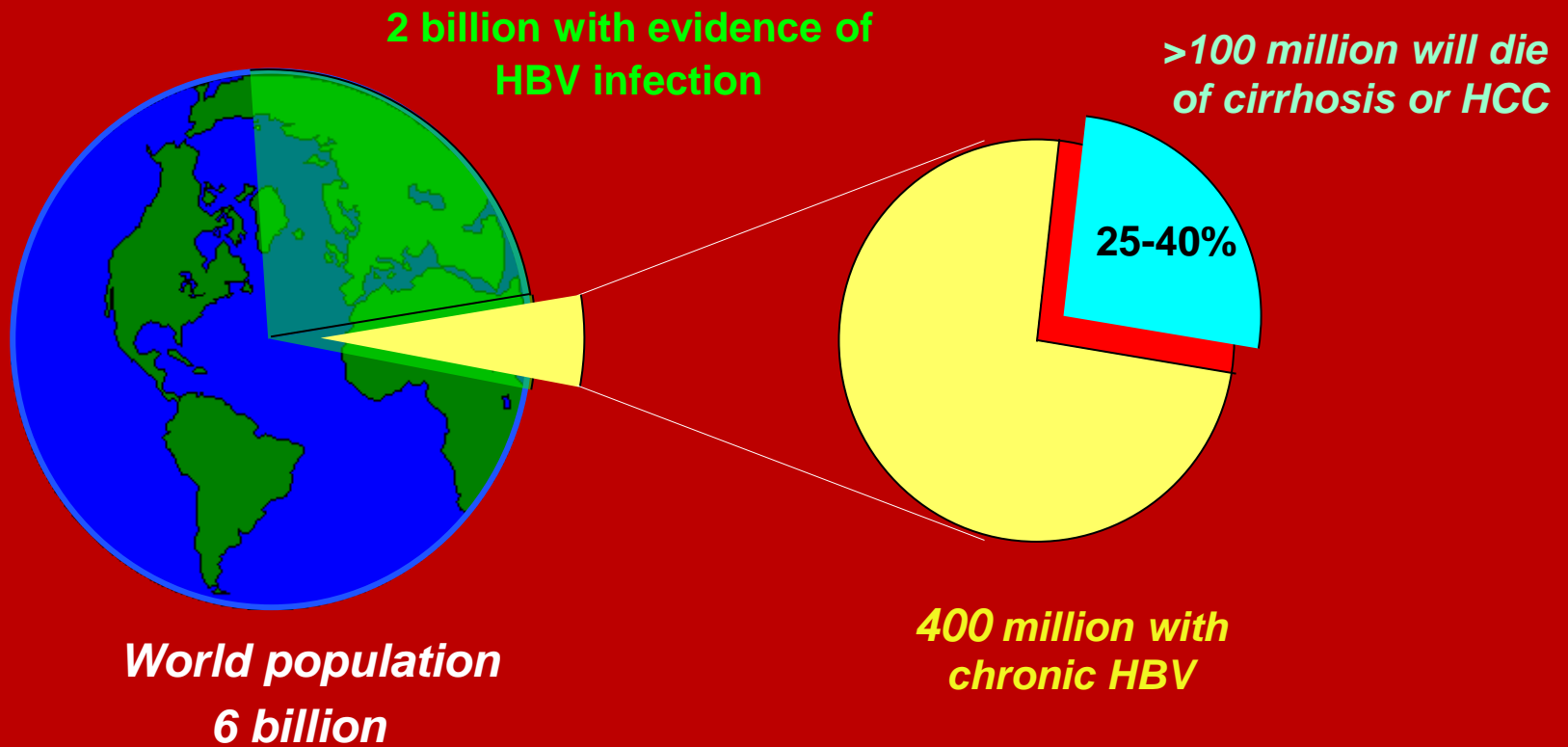
Molecular and functional analysis of occult hepatitis B virus isolates



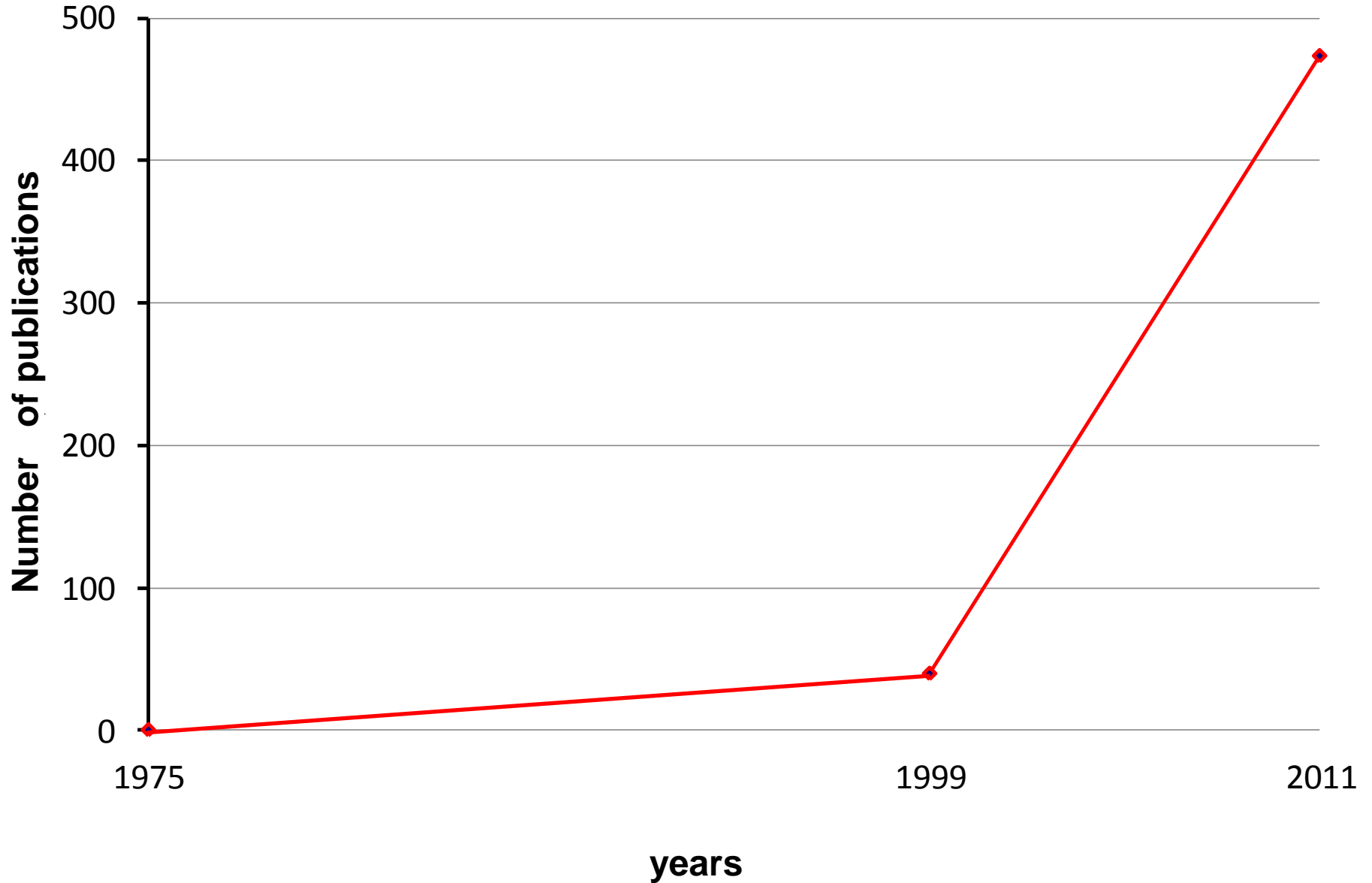
Factors possibly implied in HBV suppression and OBI development

- **Immune surveillance**
- **Epigenetic mechanisms**

Global Impact of HBV Infection/Disease at the turn of the new Millennium



Occult HBV infection in literature over time



OCCULT HEPATITIS B VIRUS INFECTION IN PATIENTS WITH CHRONIC HEPATITIS C LIVER DISEASE

IRENE CACCIOLA, M.D., TERESA POLLICINO, M.D., GIOVANNI SQUADRITO, M.D., GIOVANNI CERENZIA, B.Sc., MARIA ELENA ORLANDO, B.Sc., AND GIOVANNI RAIMONDO, M.D.

ABSTRACT

Background Hepatitis B virus (HBV) infections in patients who lack detectable hepatitis B surface antigen (HBsAg) are called occult infections. Although such infections have been identified in patients with chronic hepatitis C liver disease, their prevalence and clinical significance are not known.

Methods With the polymerase chain reaction, we searched for HBV DNA in liver and serum samples from 200 HBsAg-negative patients with hepatitis C virus (HCV)-related liver disease (147 with chronic hepatitis, 48 with cirrhosis, and 5 with minimal histologic changes). One hundred of the patients had detectable antibodies to the HBV core antigen (anti-HBc); 100 were negative for all HBV markers. Eighty-three were treated with interferon alfa. We also studied 50 patients with liver disease who were negative both for HBsAg and for HCV markers. In six patients found to have occult HBV infection, we evaluated possible genomic rearrangements through cloning or direct sequencing procedures.

Results Sixty-six of the 200 patients with chronic hepatitis C liver disease (33 percent) had HBV sequences, as did 7 of the 50 patients with liver disease unrelated to hepatitis C (14 percent, $P=0.01$). Among the 66 patients, 46 were anti-HBc-positive and 20 were negative for all HBV markers ($P<0.001$). Twenty-two of these 66 patients (33 percent) had cirrhosis, as compared with 26 of the 134 patients with hepatitis C infection but no HBV sequences (19 percent, $P=0.04$). HBV sequences were detected in 26 of the 55 patients in whom interferon therapy was ineffective and 7 of the 28 patients in whom interferon therapy was effective ($P=0.06$). None of the sequenced HBV genomes had changes known to interfere with viral activity and gene expression.

Conclusions Occult hepatitis B infection occurs frequently in patients with chronic hepatitis C liver disease and may have clinical significance. (N Engl J Med 1999;341:22-6.)

Serial studies of hepatitis-associated antigen and antibody in patients receiving antitumor chemotherapy for myeloproliferative and lymphoproliferative disorders

Wands JR, Chura CM, Roll FJ, Maddrey WC. Gastroenterology, 1975

Type B hepatitis after transfusion with blood containing antibody to hepatitis B core antigen

Hoofnagle JH, Seeff LD, Bales ZB, Zimmerman HJ. N Engl J Med 1978

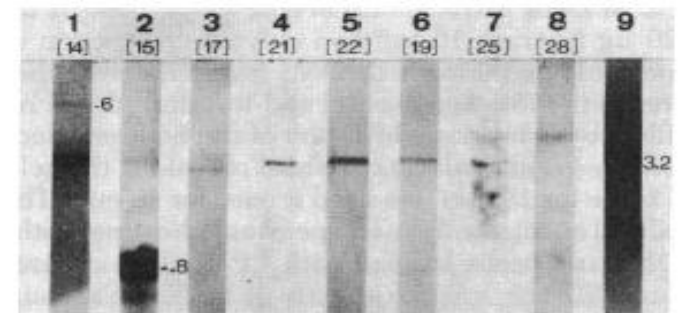
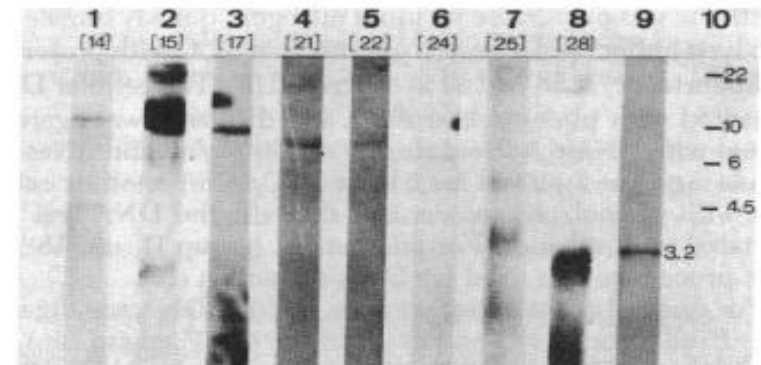
Integration of hepatitis B virus DNA into the genome of liver cells in chronic liver disease and hepatocellular carcinoma. Studies in percutaneous liver biopsies and post-mortem tissue specimens

Shafritz DA, Shouval D, Sherman HI, Hadziyannis SJ, Kew MC. *NEJM* 1981

State of hepatitis B virus DNA in hepatocytes of patients with hepatitis B surface antigen-positive and -negative liver diseases.

Brechot C, Hadchouel M, Scotto J, Fonck M, Potet F, Vyas G, Tiollais P *PNAS* 1981

Proc. Natl. Acad. Sci. USA 78 (1981)



"Occult" hepatitis B virus as source of infection in liver transplant recipients

O. Chazouillères, D. Mamish, M. Kim, K. Carey, L. Ferrell.

J. P. Roberts N. L. Ascher, T. L Wright

The Lancet 1994

Clinical impact

Occult HBV infection may...

... be transmitted (*blood transfusion; organ transplantation*)

... reactivate

... contribute to liver fibrosis progression toward cirrhosis

... favour HCC development

Categories of occult HBV carriers known to be prone to viral reactivation

Patients with

Haematological malignancies

HIV infection

The list becomes longer day by day...

Liver transplantation

Kidney transplantation

Chemotherapy

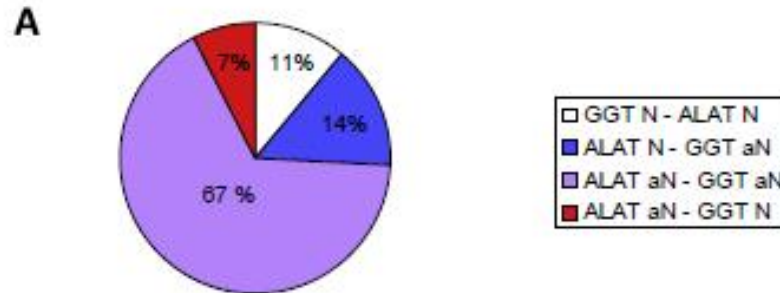
Treatment with anti-CD20 (Rituximab)

Treatment with anti-CD52 (Alemtuzumab)

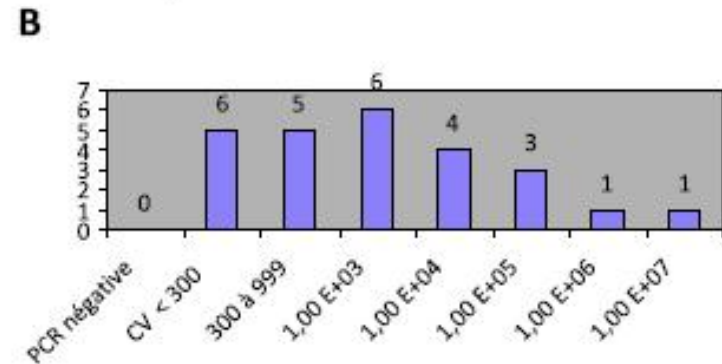
Treatment with anti-TNF (Infliximab)

Close monitoring of serum HBV DNA levels and liver enzymes levels is most useful in the management of patients with occult HBV infection

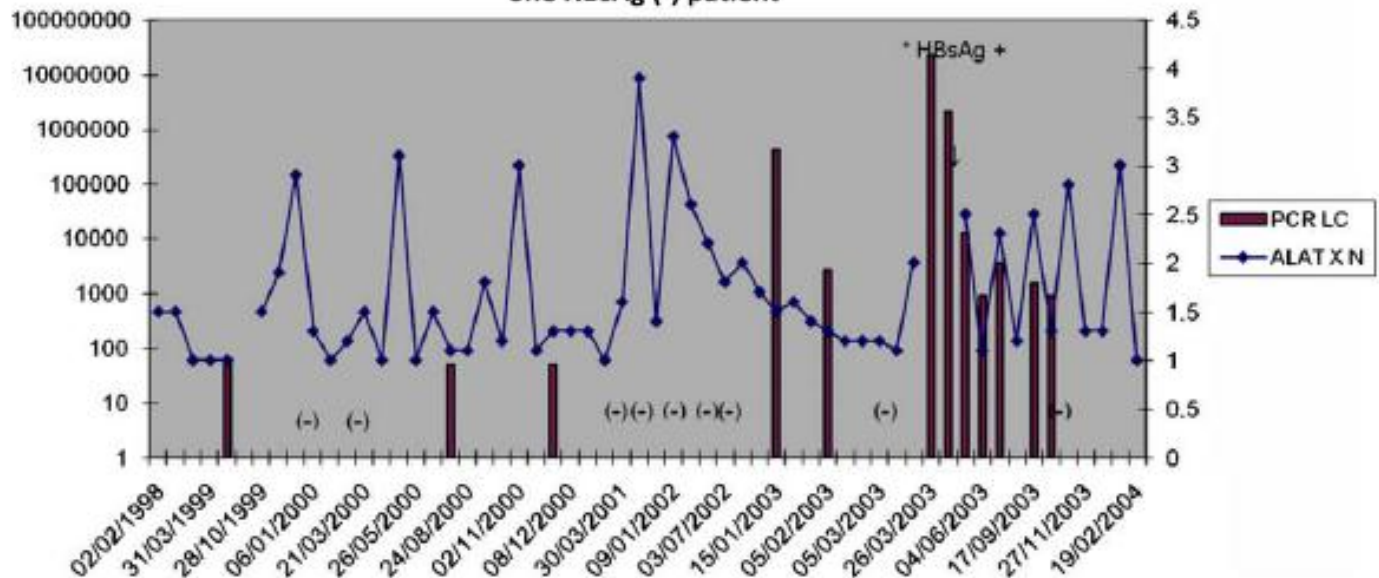
Liver enzymes level over time for all patients



Nb of patients for each viral max viral load



C Transaminases and HBV viral load sequential measurement over time for one HBsAg (-) patient



Prevalence of occult HBV infection in HCC and chronic hepatitis (CH) patients

No. of Cases HBV + (%)		
HCC	107	68 (63,5)
CH	192	63 (32,8)

p < 0.0001

O.R. = 3.6 (95% CI, 2.2 – 5.9)



UNIVERSAL HEPATITIS B VACCINATION IN TAIWAN AND THE INCIDENCE OF HEPATOCELLULAR CARCINOMA IN CHILDREN

MEI-HWEI CHANG, M.D., CHIEN-JEN CHEN, Sc.D., MEI-SHU LAI, M.D., HSU-MEI HSU, M.P.H., TZEE-CHUNG WU, M.D.,
MAN-SHAN KONG, M.D., DER-CHERNG LIANG, M.D., WEN-YI SHAU, M.D., AND DING-SHINN CHEN, M.D.,
FOR THE TAIWAN CHILDHOOD HEPATOMA STUDY GROUP*

Background A nationwide hepatitis B vaccination program was implemented in Taiwan in July 1984. To assess the effect of the program on the development of hepatocellular carcinoma, we studied the incidence of this cancer in children in Taiwan from 1981 to 1994.

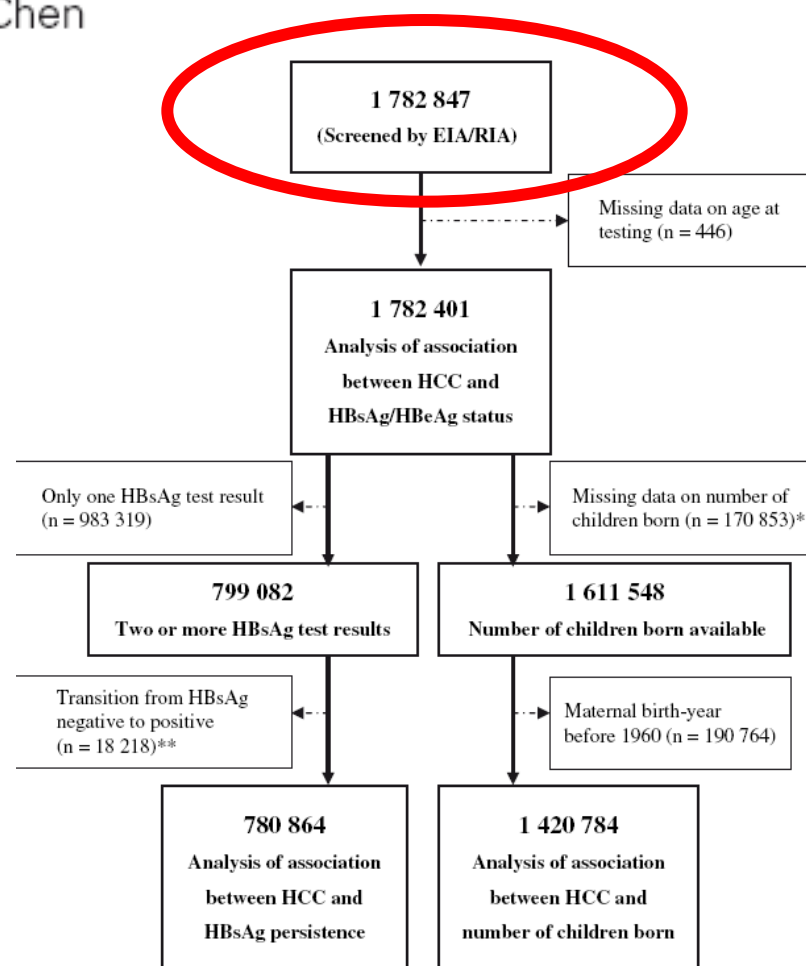
Methods We collected data on liver cancer in children from Taiwan's National Cancer Registry, which receives reports from each of the country's 142 hospitals with more than 50 beds. Data on childhood liver cancer were also obtained from Taiwan's 17 major medical centers. To prevent the inclusion of cases of hepatoblastoma, the primary analysis was confined to liver cancers in children six years of age or older. Data were also obtained on mortality from liver cancer among children.

Results The average annual incidence of hepatocellular carcinoma in children 6 to 14 years of age declined from 0.70 per 100,000 children between 1981 and 1986 to 0.57 between 1986 and 1990, and to 0.36 between 1990 and 1994 ($P < 0.01$). The corresponding rates of mortality from hepatocellular carcinoma also decreased. The incidence of hepatocellular carcinoma in children 6 to 9 years of age declined from 0.52 for those born between 1974 and 1984 to 0.13 for those born between 1984 and 1986 ($P < 0.001$).

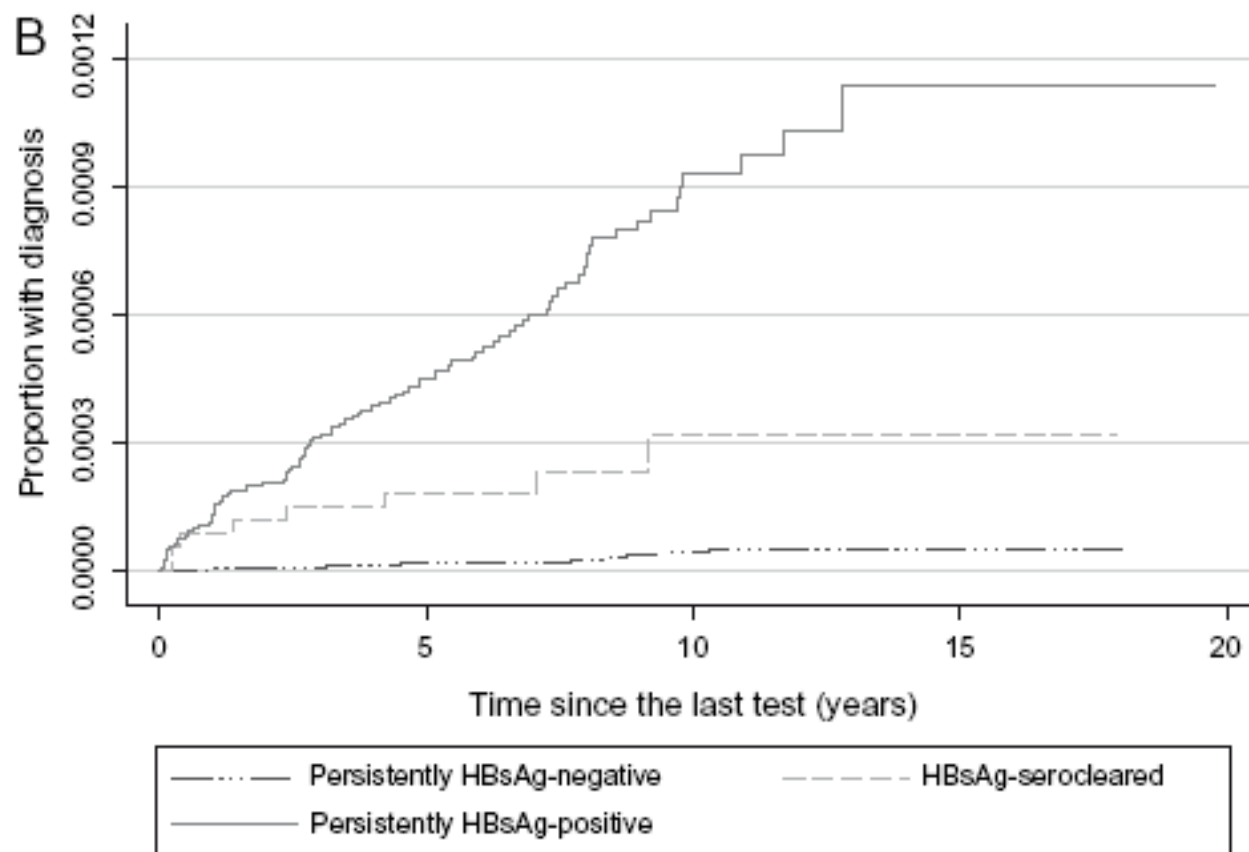
Conclusions Since the institution of Taiwan's program of universal hepatitis B vaccination, the incidence of hepatocellular carcinoma in children has declined. (N Engl J Med 1997;336:1855-9.)

Hepatitis B Virus Infection and Hepatocellular Carcinoma Among Parous Taiwanese Women: Nationwide Cohort Study

Chyng-Wen Fwu, Yin-Chu Chien, Gregory D. Kirk, Kenrad E. Nelson, San-Lin You, Hsu-Sung Kuo, Manning Feinleib, Chien-Jen Chen



Hepatitis B Virus Infection and Hepatocellular Carcinoma Among Parous Taiwanese Women: Nationwide Cohort Study



Incidence rates were 0.39, 3.10, and 9.01 per 100 000 person-years, respectively, among persistent noncarriers, HBsAg-serocleared carriers, and persistent HBsAg carriers

Development of an efficacious anti-HBV vaccine has been one of the most important goals achieved by medical science in the last decades, and we might suppose that in countries like Italy, where anti-HBV vaccination has been extended to the general population, a more relevant reduction of cases of severe liver disease and hepatocellular carcinoma than is currently expected will be observed in the future.