



Follow-up of Hepatitis B Vaccination Programs in Taiwan and Singapore

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Taiwan Experience

The 1st Nationwide Hepatitis B Vaccination Program

July 1984

Taiwan Launched
A Mass
HBV Vaccination Program for
Infants to **High-risk** Mothers
(HBsAg positive)

HB Vaccination Was
Extended to **All Newborns**
After July 1986

July 1986

UNIVERSAL HEPATITIS B VACCINATION IN TAIWAN

Infants of
HBeAg & HBsAg
Seropositive
Mothers



HBV Vaccines



HBIG*

* < 24 Hrs. after Birth

Infants of
HBeAg or HBsAg
Seronegative
Mothers



HBV Vaccines

**3 doses of recombinant vaccine
given in Month 0, 1, 6.**

UNIVERSAL HEPATITIS B VACCINATION IN U.S.A.

**Infants of HBsAg
Seropositive
Mothers**



**HBV Vaccines
+ HBIG***

**Infants of HBsAg
Seronegative
Mothers**



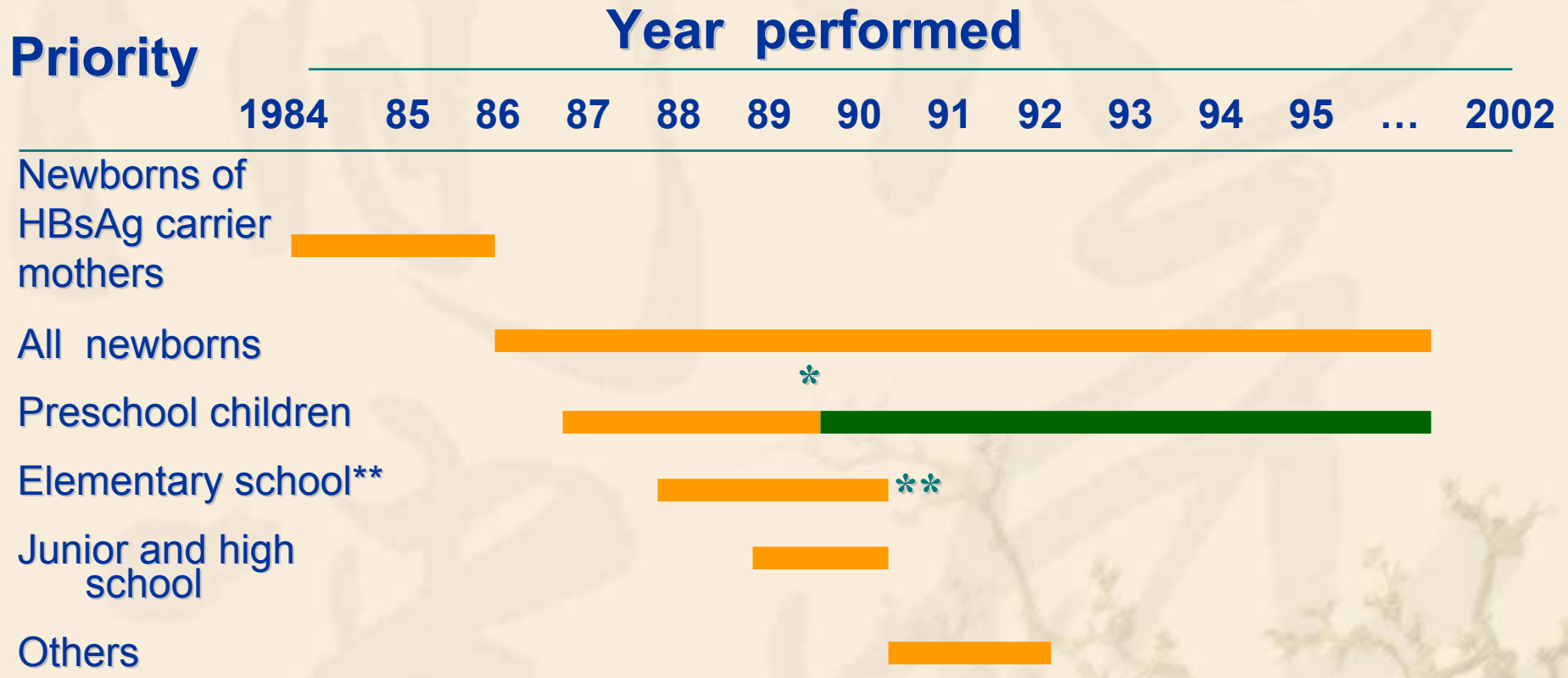
HBV Vaccines

* < 24 Hrs. after Birth

HBV VACCINATION PROGRAM IN SOUTHEAST ASIA

- ❖ **No Maternal Screening for HBsAg, HBeAg**
 - ❖ **No HBIG**
 - ❖ **All Infants Received HBV Vaccine 3 Doses**
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Priorities and Timetable of Hepatitis B Vaccine Program in Taiwan

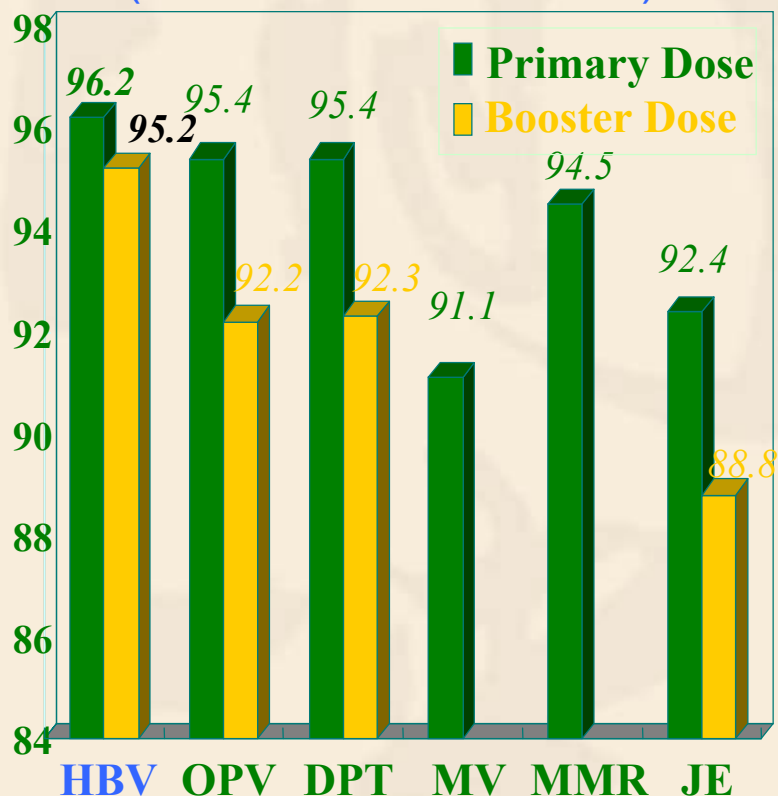


* July 1987 ~ Sep. 1990 : Vaccinate preschool on voluntary base with payment.
 After Oct. 1990 : Catch-up vaccination without charge for children up to 1st graders.

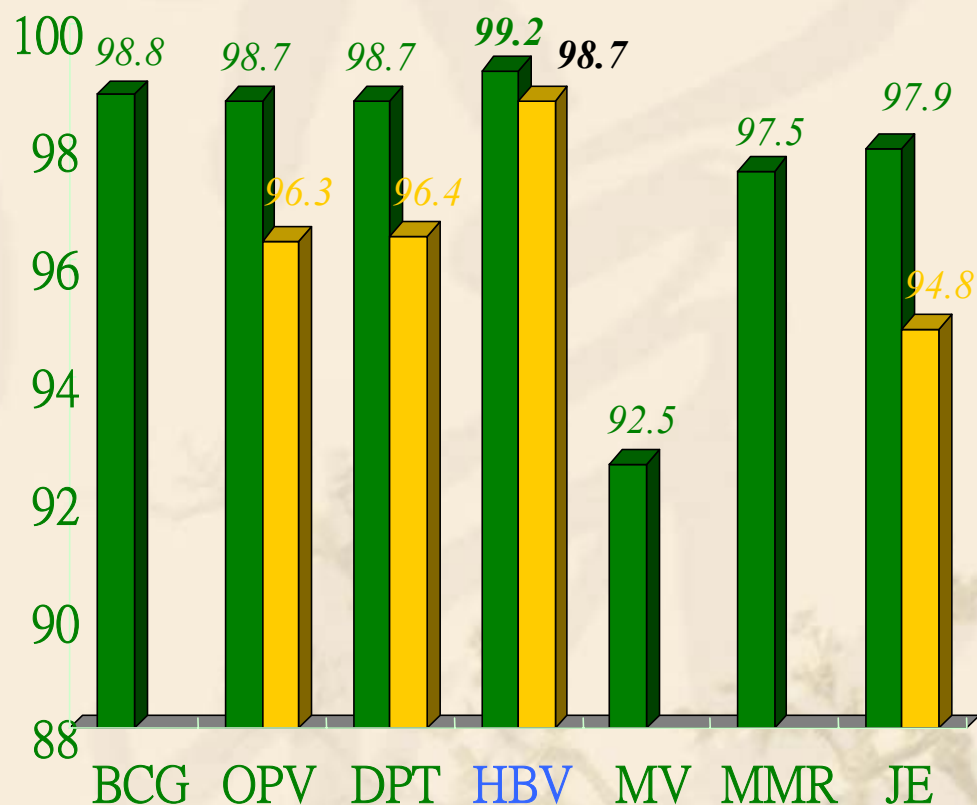
** After July 1991, all first graders were checked for their vaccination record.
 Non- or incompletely vaccinated pupils needed to be vaccinated.

Immunization Coverage

(1997-1999 Birth Cohort)



(Primary School Entrants, 2000)



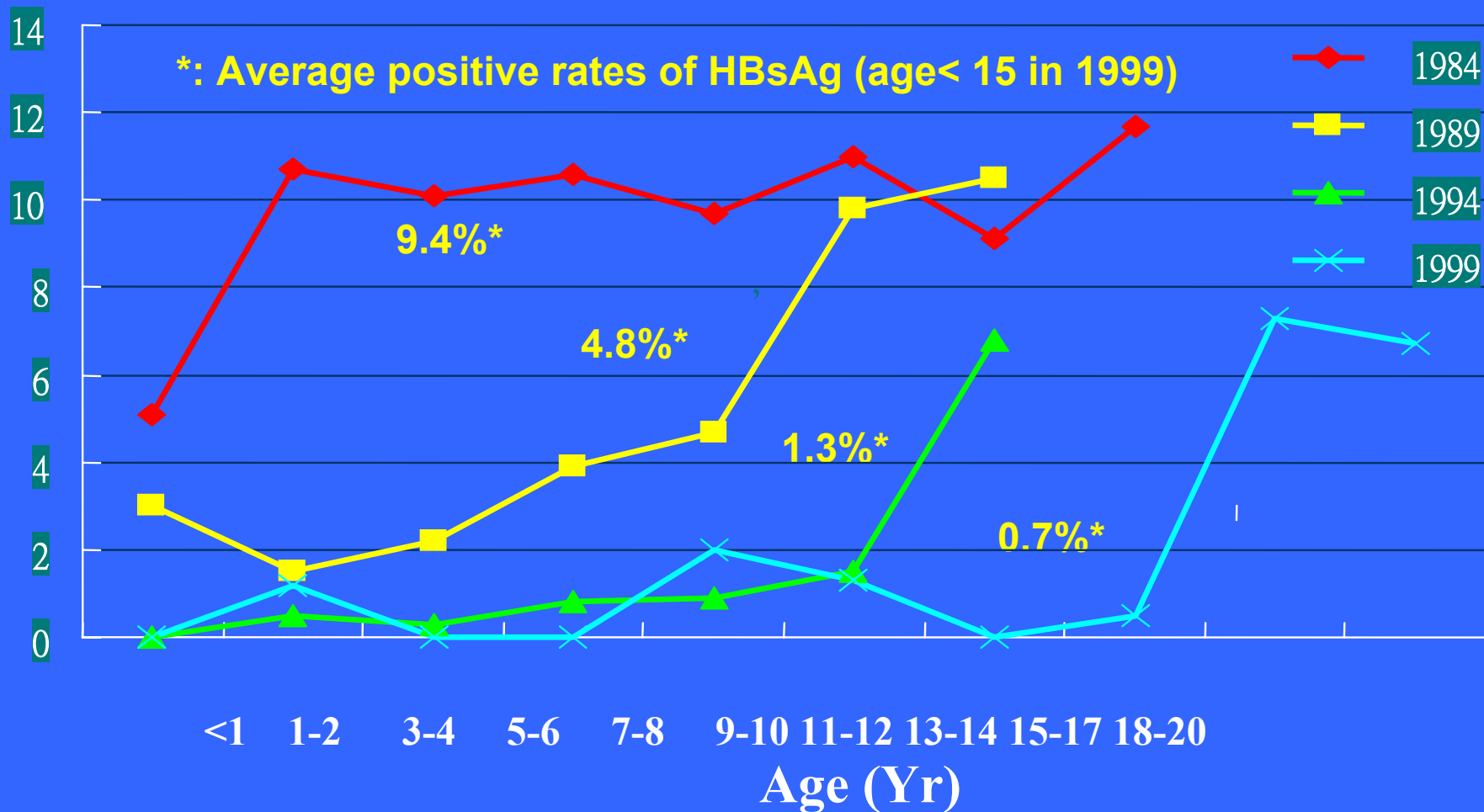
*Data of OPV,DPT,JE booster & MMR(99) is incomplete

Long-term immunogenicity and efficacy of universal HB vaccination in Taiwan

- ❖ Hsu HY, Chang MH, Chen DS, et al. **Baseline** seroepidemiology of hepatitis B virus infection in children in Taipei, 1984: a study just before mass hepatitis B vaccination program in Taiwan. J Med Virol. 1986;18:301-7.
- ❖ Tsen YJ, Chang MH, Hsu HY, et al. Seroprevalence of hepatitis B virus infection in children in Taipei, 1989: **five years after** a mass hepatitis B vaccination program. J Med Virol. 1999;71:96-9.
- ❖ Chen HL, Chang MH, Ni YH, et al. Seroepidemiology of hepatitis B virus infection in children: **Ten years of** mass vaccination in Taiwan. JAMA 1996;276:906-8.
- ❖ Ni YH, Chang MH, Huang LM, et al. Hepatitis B virus infection in children and adolescents in a hyperendemic area: **15 years after** mass hepatitis B vaccination. Ann Intern Med. 2001;135:796-800.
- ❖ Shih HH, Chang MH, Hsu HY, et al. Long term immune response of universal hepatitis B vaccination in infancy: a community-based study in Taiwan. Pediatr Infect Dis J. 1999;18:427-32.
- ❖ Lin YC, Chang MH, Ni YH, et al. Long-term immunogenicity and efficacy of universal hepatitis B virus vaccination in Taiwan. J Infect Dis. 2003;187:134-8.

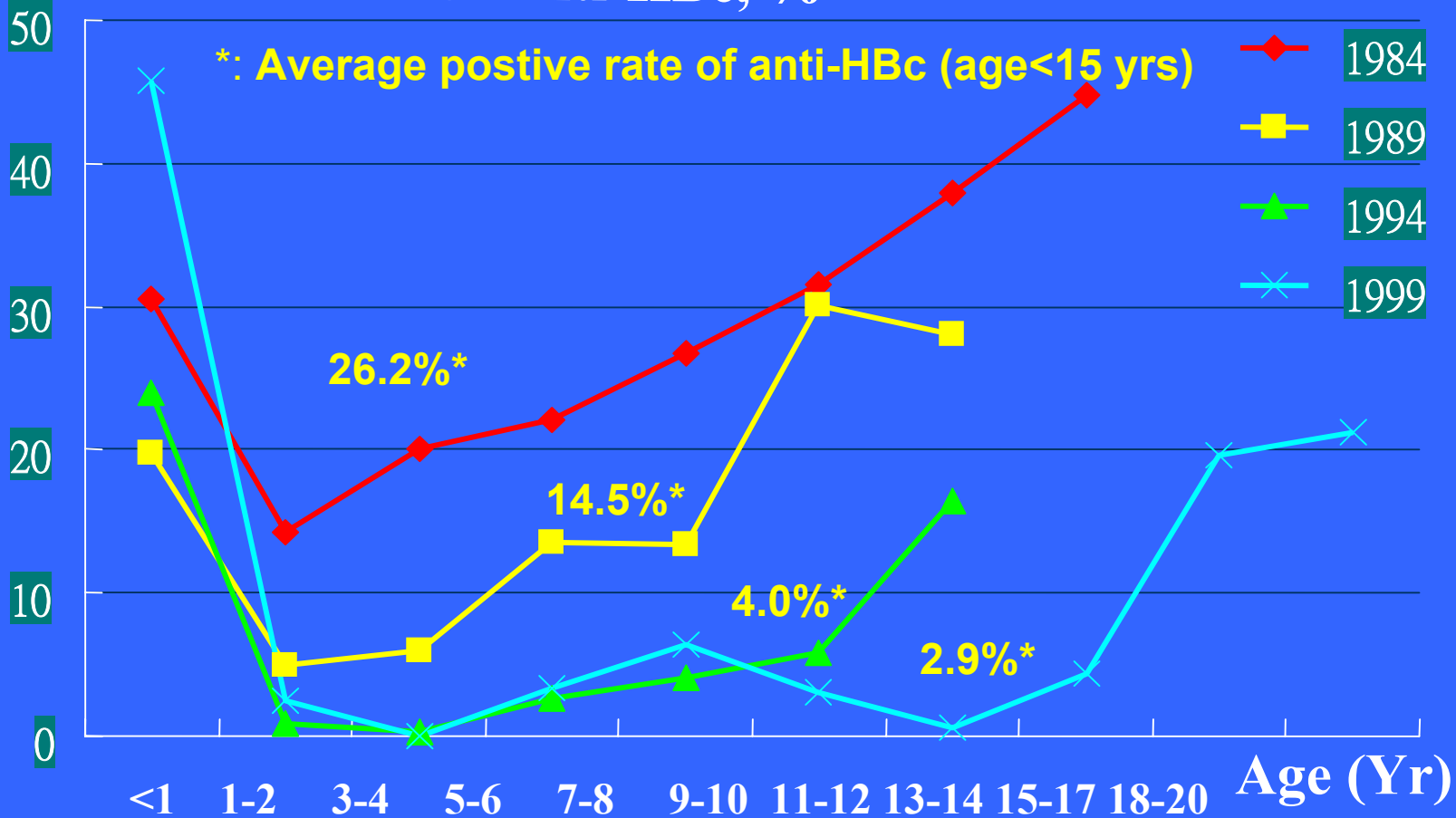
Seroprevalence of HBsAg

Positive rate of HBsAg, %



Seroprevalence of Anti-HBc

Positive rate of Anti-HBc, %



Hepatitis B vaccination and control of hepatitis B-related liver disease

[Decrease pediatric fulminant hepatic failure]

- ❖ Kao JH, Hsu HM, Shau WY, et al. Universal hepatitis B vaccination and the decreased mortality from fulminant hepatitis in infants in Taiwan. *J Pediatr*. 2001;139:349-52.
- ❖ Chen HL, Chang CJ, Kong MS, et al. Pediatric fulminant hepatic failure in endemic areas of hepatitis B infection: 15 years after universal hepatitis B vaccination. *Hepatology*. 2004;39:58-63.

[Decrease pediatric Hepatocellular carcinoma]

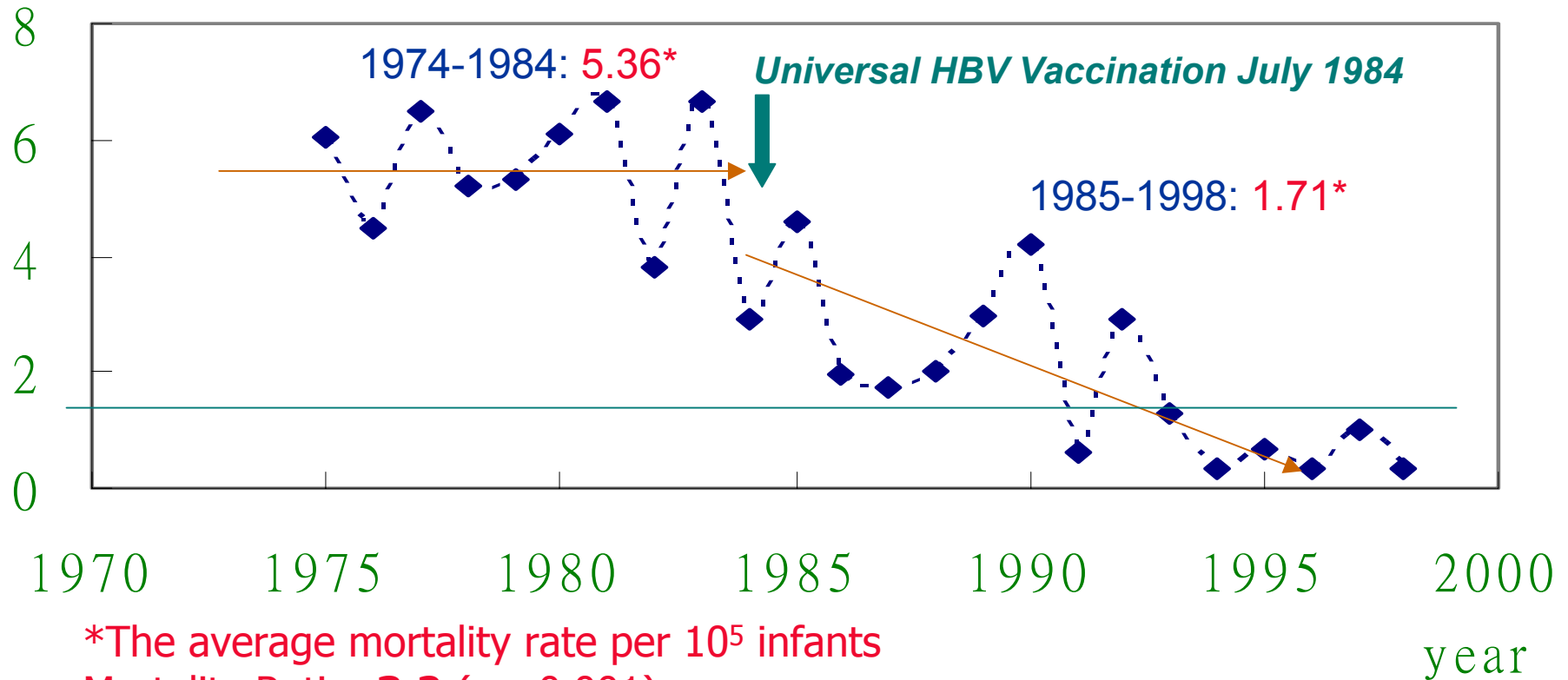
- ❖ Chang MH, Shau WY, Chen CJ, et al; Taiwan Childhood Hepatoma Study Group. Hepatitis B vaccination and hepatocellular carcinoma rates in boys and girls. *JAMA*. 2000;284:3040-2.
- ❖ Chang MH, Chen CJ, Lai MS, et al. Universal hepatitis B vaccination in Taiwan and the incidence of hepatocellular carcinoma in children. Taiwan Childhood Hepatoma Study Group. *N Engl J Med*. 1997;336:1855-9.

[Review]

- ❖ Chang MH. Decreasing incidence of hepatocellular carcinoma among children following universal hepatitis B immunization. *Liver Int*. 2003;23:309-14.
- ❖ Chang MH. Hepatitis B vaccination and control of hepatitis B-related liver disease. *J Pediatr Gastroenterol Nutr*. 2000;31:112-7.
- ❖ Chang MH, Chen DS. Prospects for hepatitis B virus eradication and control of hepatocellular carcinoma. *Baillieres Best Pract Res Clin Gastroenterol*. 1999;13:511-7.
- ❖ Chang MH. Hepatitis B: long-term outcome and benefits from mass vaccination in children. *Acta Gastroenterol Belg*. 1998; 61:210-3.

Universal HBV Vaccination and Decreased Mortality from Fulminant Hepatitis in Infants in Taiwan

Annual mortality rate of fulminant hepatitis per 100,000 infants in Taiwan



*The average mortality rate per 10^5 infants
Mortality Ratio: **3.2** ($p < 0.001$)

Incidence Rates Ratios of HBV-Positive v.s. HBV-Negative FHF within 15 Years of the Universal Vaccination Program

	Year 1985~1999 Case no. (per 10 ⁵)	IRR(<1Y Vs 1~15 Yrs)	<i>P</i> - value
HBV (+) FHF	43		
<1 yr	33(0.74)	54.2 [26.1, 123.2]	<0.01
1-15 yr	10(0.014)		
HBV (-) FHF	52		
<1 yr	25(0.56)	15.2 [8.5, 27.2]	<0.01
1-15 yr	27(0.039)		

IRR: incidence rate ratio ; [95%C.I.] ;

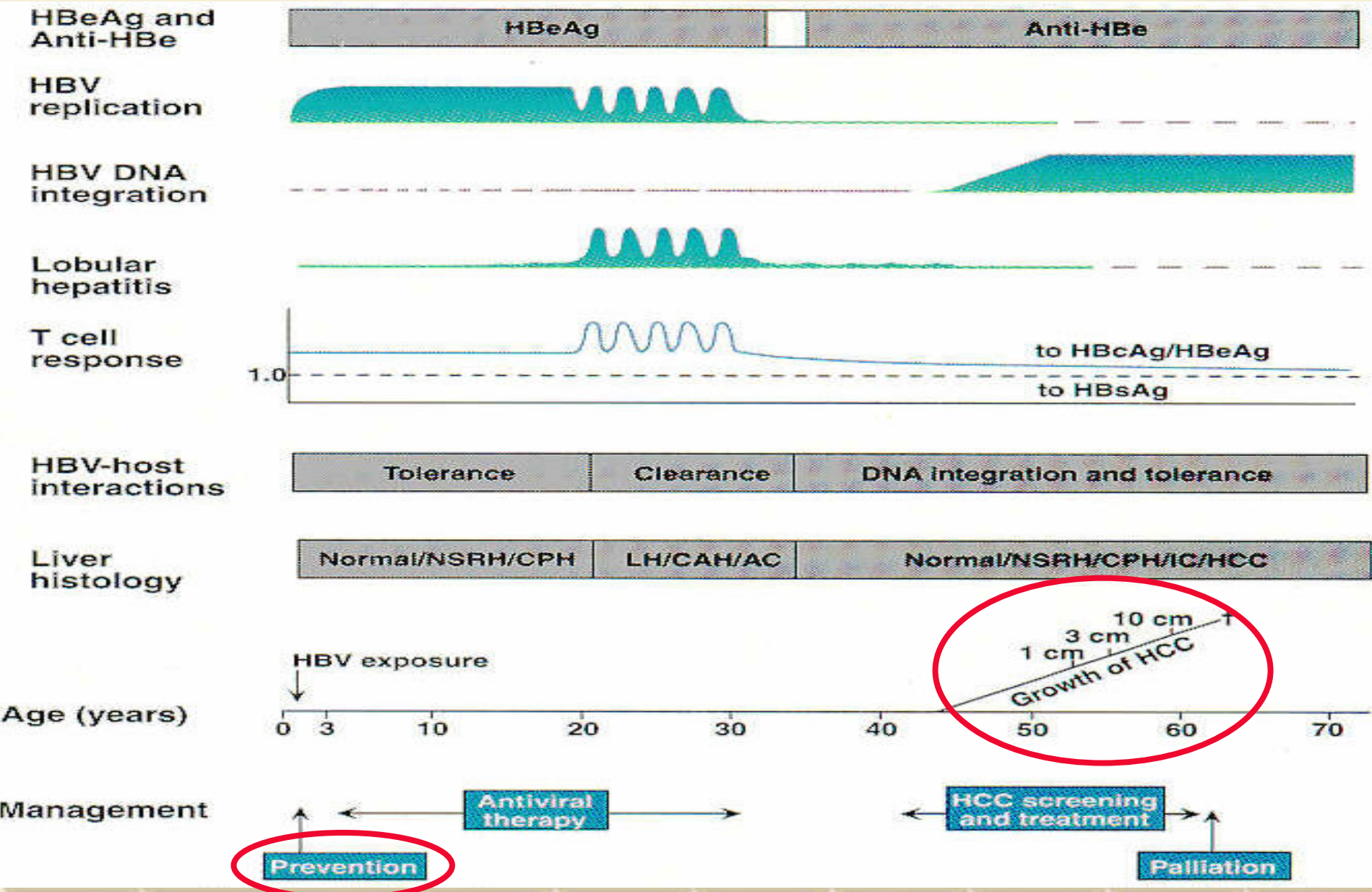
Infantile HBV-positive FHF related to HBsAg(+)/HBeAg(-) mothers

- ❖ Maternal **HBsAg** was found to be **positive** in **97%** of the infants with HBV-positive FHF, and **HBeAg** was found to be **negative** in **84%** of these infants.
- ❖ **74%** of all HBV-positive FHF patients had been **vaccinated**.
- ❖ HBV-positive FHF was prone to develop in infants born to HBeAg-negative, HBsAg-carrier mothers; **these infants had not received HBIG according to the vaccination program in place**



**A Vaccination Program
to Prevent A Virus
Infection Can Prevent
Its Related Cancer**





EVALUATION OF THE EFFECT OF UNIVERSAL HEPATITIS B VACCINATION ON HEPATOMA

- ❖ **Peak Age of Hepatoma :
40-60 Years of Age**
- ❖ **It May Take > 40 Years (Year 2024
or later) to See A Substantial
Decrease of Hepatoma in Adults**

Childhood Hepatoma in Taiwan

- ❖ Incidence (/10⁵) & HB/HCC ratio
 - ☞ Taiwan : HB 0.37, HCC 0.70 ; HB/HCC:1:2
 - ☞ U.S. : Total: 0.02-0.2; HB/HCC: 3.5:1
(HB: hepatoblastoma; HCC: hepatocellular carcinoma)
- ❖ Childhood HCC
 - ☞ Nearly 100% HBsAg positive; 86% HBeAg negative
 - ☞ Histology:
 - ❖ Tumor Portion : Similar to Adult Hepatoma
 - ❖ Non-tumorous Portion : Liver Cirrhosis 81% (21/26)
 - ❖ HBV genome integration into host genome

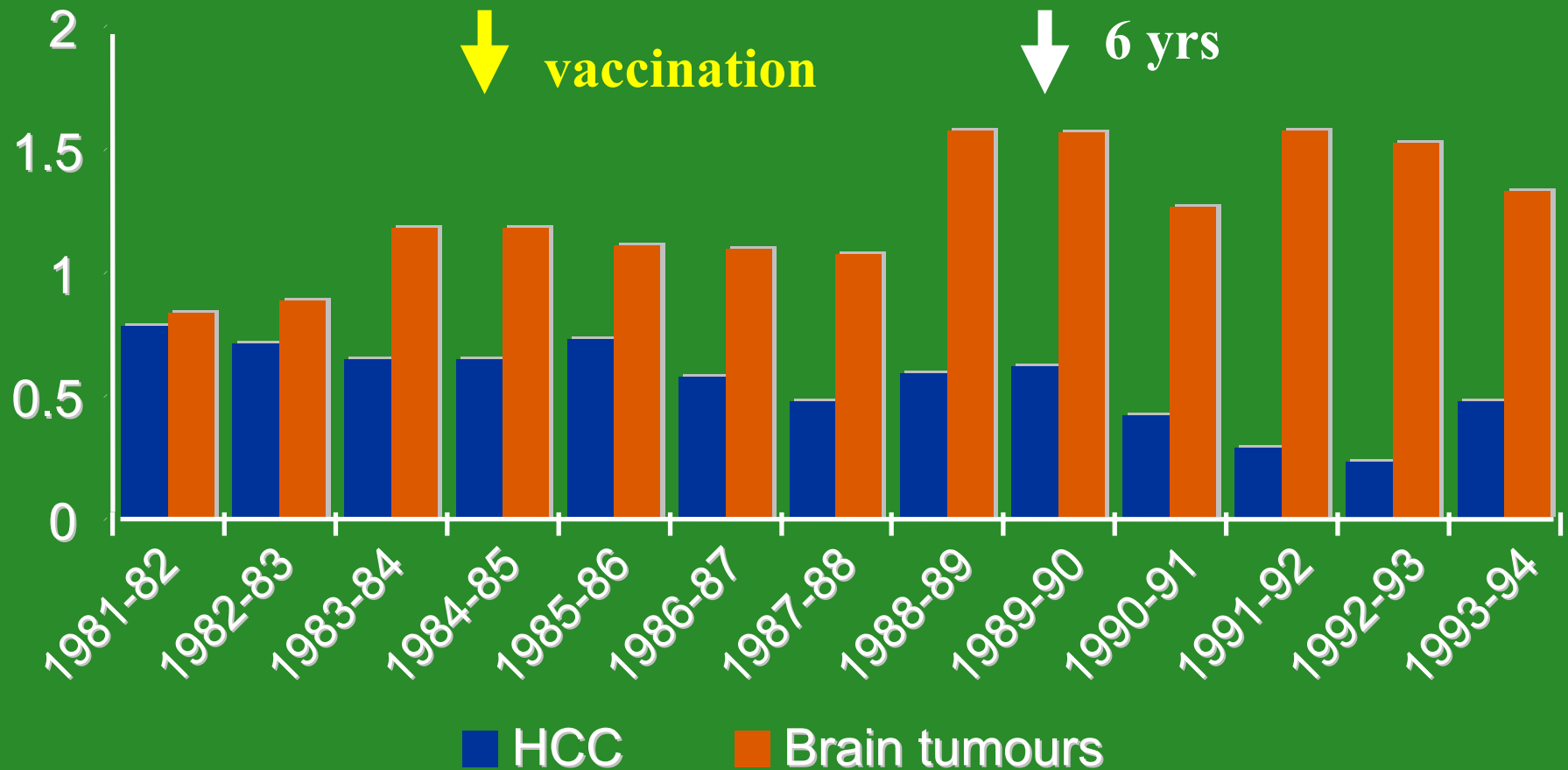
Is HCC in Children Closely Related to HBV and Similar to HCC in Adults ? (Yes)



Can the Incidence of HCC in Children Reflect the Effect of HBV Vaccination on HCC ?

HB Vaccination Reduces the Incidence of Hepatocellular Carcinoma in 6-14 Yrs Old

Incidence per 100,000



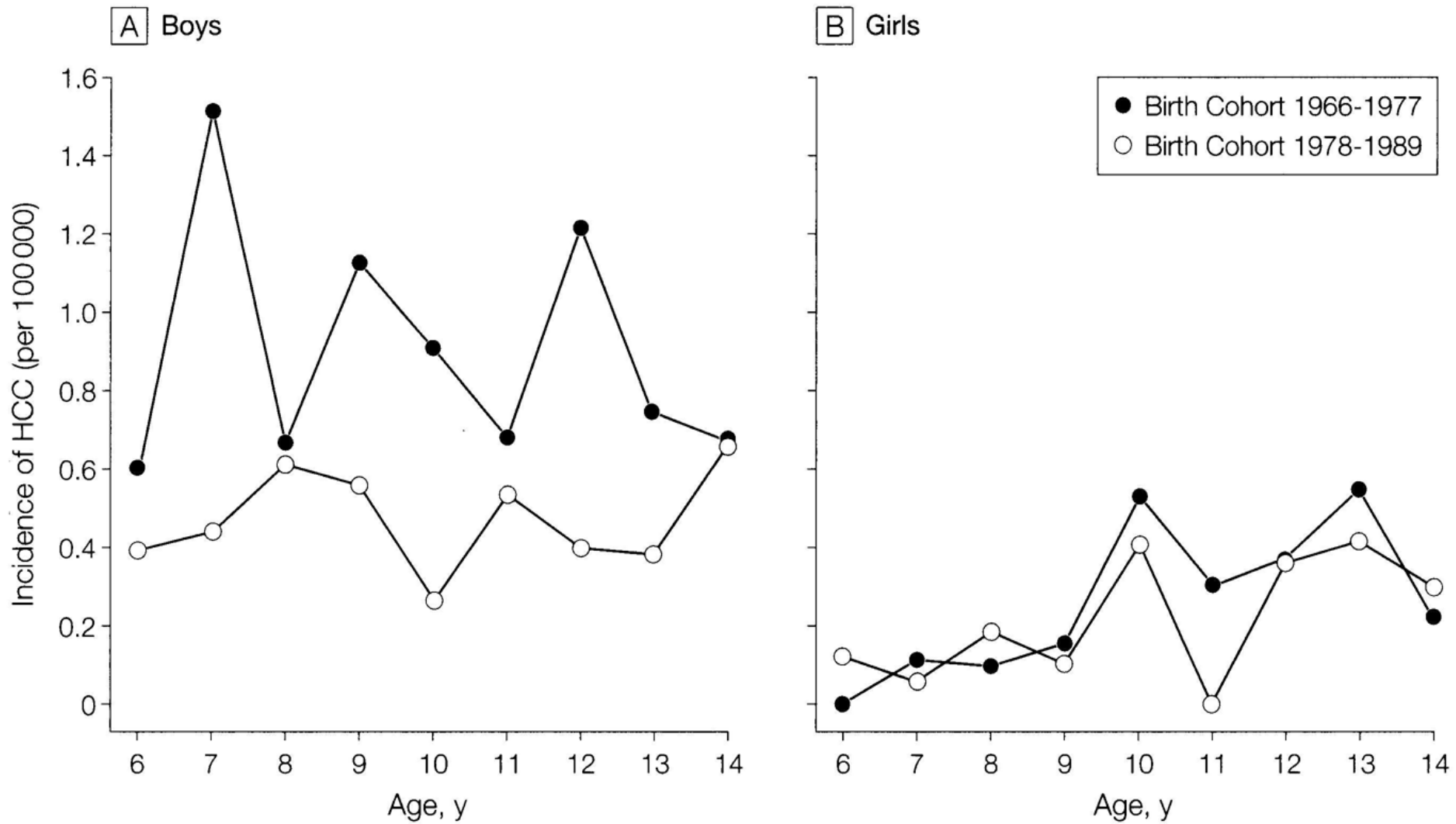
EFFECT OF UNIVERSAL HEPATITIS B VACCINATION ON HCC IN TAIWAN

Birth Year	HCC Incidence in Children
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1974-84	0.52/10 ⁵
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1984-86	0.13/10 ⁵
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Figure. Incidence of Hepatocellular Carcinoma (HCC) in Boys and Girls Aged 6 to 14 Years



Problems in Hepatoma Prevention by Vaccination

❖ NO VACCINATION PROGRAM

HBV :

- ❧ Inadequate Resources : Asia, Africa
- ❧ Anxiety to the Safety of Vaccine : Low Prevalence Areas
- ❧ Ignorance

HCV : No Available Vaccine

❖ POOR COMPLIANCE TO THE VACCINATION PROGRAM

- ❧ Cost Not Covered by the Government (Poor Compliance if Self-paid)
- ❧ Anxiety to the Safety of Vaccine : Low Prevalence Areas
- ❧ Ignorance

❖ VACCINE FAILURE


- ❧ Intrauterine Infection
- ❧ High Viral Load
- ❧ Vaccine Escape Mutant
- ❧ Genetic Hyporesponsiveness
- ❧ Immune Compromized Host

The importance of chronic HCV infection in Taiwan

- ❖ Even HBV infection controlled by vaccination, HBsAg-negative HCC should be another problem.
- ❖ Besides of HBV, HCV infection is the major etiology of HCC in Taiwan.

Prevention and control of HBV infection in Singapore

- ❖ **Epidemiological News Bulletin. June, 2002; 28 (6)**
(http://www.env.gov.sg/cop/qed2/enb_news.htm)
- ❖ ***The Hepatitis B Info-Page***
(<http://www.geocities.com/hbvinfo>)
- ❖ **Health Promotion Board: The hepatitis B immunisation programme**
(<http://www.hpb.gov.sg/hpb/pro/pro0902.asp#3doses>)
- ❖ **Guan R. Gut. 1996;38 Suppl 2:S13-7, 1996.**
- ❖ **Goh KT. Ann Acad Med Singapore 26:671-81 1997.**
- ❖ **James L, et al. Singapore Med J 2001; 42: 420-4.**



Singapore Experience

Nationwide Hepatitis B Vaccination Program

Oct. 1985

A Mass
HBV Vaccination Program for
Infants to **High-risk** Mothers
(HBsAg positive)

HB Vaccination Was
Extended to **All Newborns**

Sep 1987

UNIVERSAL HEPATITIS B VACCINATION IN SINGAPORE

Infants of
HBsAg & HBeAg
Seropositive
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HBV Vaccines



HBIG*

* < 24 Hrs. after Birth

Infants of
HBsAg or HBeAg
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HBV Vaccines

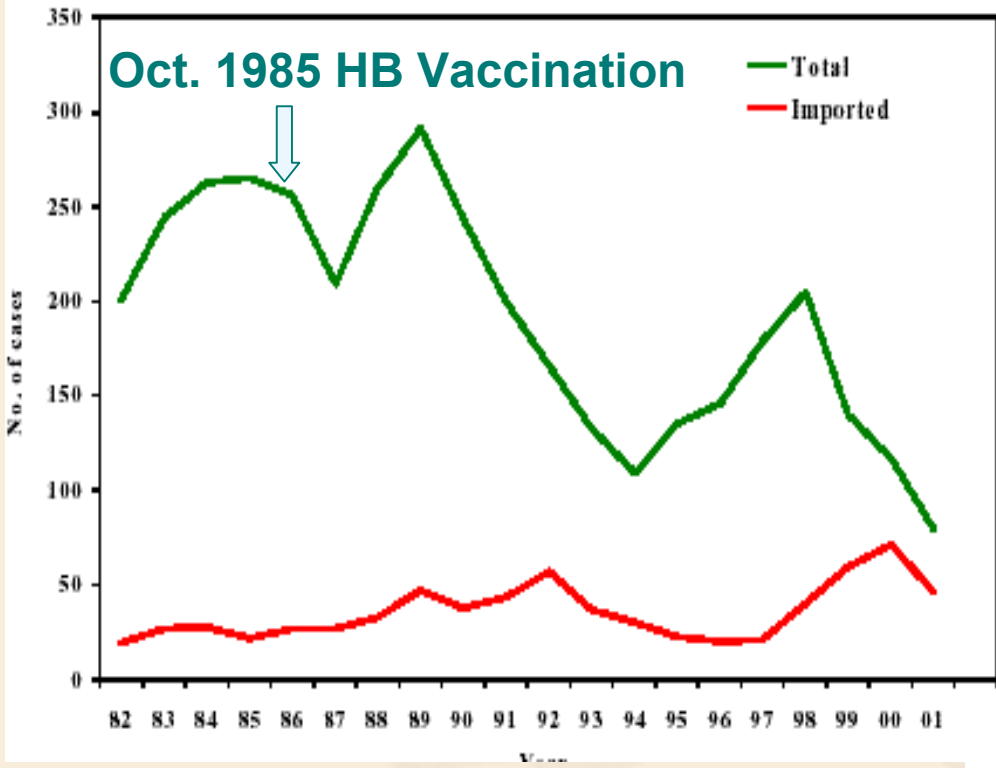
3 doses of recombinant vaccine
given in Month 0, 1, 6.

**Infants born to HBsAg carrier mothers should
receive another booster dose in month 12.**

Hepatitis B carrier status after vaccination

- ❖ Coverage: 85% in 1993, 91% in 1994, 94% in 1995
- ❖ For vaccinated babies born to carrier mothers, perinatal transmission has been reduced by 80% - 100%, with **no carriers detected among newborns of HBeAg-negative mothers.**
- ❖ In primary school children, HBsAg prevalence has dropped from 4% in 1987 to 0% in 1996.
- ❖ In secondary school children, the prevalence rate was <1% in 2001.
- ❖ Serological surveys in 1993 and 1998 showed that **none of the vaccinated persons were HBsAg positive,** whereas the antigen was detected in 4-5% of unvaccinated persons.

Decrease of acute hepatitis B



Year	No. of cases	Mean annual rate per 100,000*
1983-85	27	1.44
1986-88	13	0.71
1989-91	8	0.43
1992-94	7	0.35
1995-97	3	0.14
1998-2001	0	0

Incidence report of total and imported acute hepatitis B, 1982~2001

Age < 15 yrs

Age-gender distribution and age-specific incidence rates of acute hepatitis B, 2001

Age group	Hepatitis B			Incidence rate per 100,000*
	Male	Female	Both (%)	
0 – 4	0	0	0	0
5 – 14	0	0	0	0
15 – 24	7	7	14 (17.5)	2.8
25 – 34	36	6	42 (52.5)	7.6
35 – 44	4	2	6 (7.5)	0.9
45 – 54	11	2	13 (16.3)	2.6
55+	4	1	5 (6.3)	1.0
Total	62	18	80 (100.0)	2.4

Singapore integrated HBV vaccine administration into existing expanded childhood primary immunization program
about 62% of 15 – 24 year olds will require immunisation

- ❖ A four-year immunisation programme in February 2001.
- ❖ Students (~14 yr-old, born after HB vaccination program): Secondary 3, Junior college 2 and centralised institute 3 in 2001, every year for 4 yrs.
- ❖ Polytechnic, university and Institute of Technical Education students (born before HB vaccination program) will be offered the program in 2001-2002.
- ❖ **free blood screening** and a **three-dose vaccination course for \$25**. (~12 EURO).
- ❖ Students who have already received 3 doses of hepatitis B immunisation previously will not be given further immunisation or booster doses

Decrease of HBsAg carrier rates and HCC incidence in non-vaccinated population

- ❖ Among national servicemen, the HBsAg-positive rate has also declined from 8.1% in 1984 to 4.4% in 1998.
- ❖ For antenatal women, the overall HBsAg prevalence was 4.4% in 1980-1981, 4.1% in 1983-1985, 2.9% in 1996, and 2.3% in 2000.
- ❖ **The age-standardised incidence rate of HCC among males had also dropped from 27.8/10⁵ per year during 1978 to 1982 to 19.0 /10⁵ per year during 1988 to 1992.**

4 Issues of this 24th VHPB meeting

- ❖ **Long-term efficacy of hepatitis B vaccine and effectiveness of hepatitis B vaccination**
- ❖ Immune memory induced by hepatitis B vaccine
- ❖ Current hepatitis B booster vaccination recommendations
- ❖ Potential impact of HBV mutants on hepatitis B vaccination programmes

Long term Immunogenicity and Efficacy of HBV Vaccination

- ❖ 1200 vaccinated school children, 7 years old, recruited one decade after the launch of universal HBV vaccination program.
- ❖ Determined HBsAg, anti-HBs, and anti-HBc.
- ❖ 200 of the 504 vaccinated non-carrier children with undetectable or low anti-HBs received booster vaccination at 7 years of age.
- ❖ They were observed annually until 14 years old.


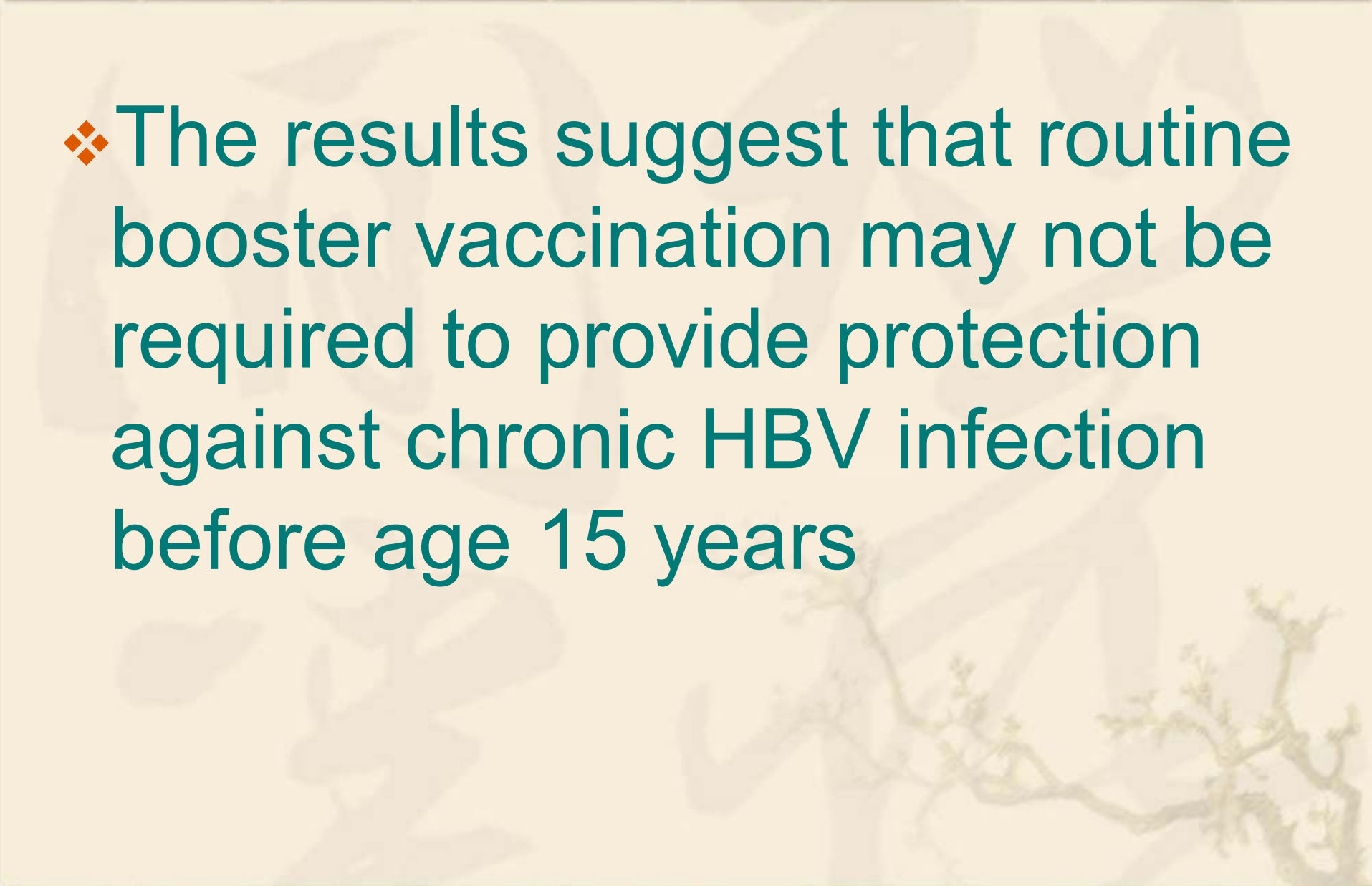
Long-term immunogenicity and efficacy of universal hepatitis B virus vaccination in Taiwan

- ❖ HBsAg positive rate was 0.7%. No new HBsAg carrier was observed.
- ❖ The percentage of protective anti-HBs in 951 children without booster vaccination gradually decreased from 71.1% at age 7 years to 37.4% at age 12 years.
- ❖ Eleven children had new HBV infections with anti-HBc positivity as the only marker. (9/11 at *t* least anti-HBc positive twice one year apart).
- ❖ None became positive for HBsAg or had detectable HBV DNA by polymerase chain reaction.
- ❖ Only 1 of the 200 children in the booster group and 2 of the 258 children in the nonbooster group developed new anti-HBc (+).

New Annual anti-HBc Seropositive Rate*

*0.3% (N=3/1108) at Age 8,
0.1% (N=1/1020) at Age 9 ,
0.1% (N=1/958) at Age 10,
0% (N=0/925) at Age 11,
0.1% (N=1/914) at Age 12,
0.4% (N=3/769) at Age 13*

** At least anti-HBc positive twice one year apart*

- 
- 
- ❖ The results suggest that routine booster vaccination may not be required to provide protection against chronic HBV infection before age 15 years

Changes of hepatitis B surface antigen variants in carrier children before and after universal vaccination in Taiwan

- ❖ **Rate of hepatitis B surface mutant at the “a” determinant site (target of HBV neutralization antibody) in children:**
 - ↪ **7.8% (8/103) in those born before the vaccination program**
 - ↪ **28.1% (9/32) in those born after the program**
- ❖ **Currently it is not a major problem in the HBV immunoprophylaxis.**



謝謝您！

Thank you for your attention!