

Letters

RESEARCH LETTER

Thirty-Year Outcomes of the National Hepatitis B Immunization Program in Taiwan

Hepatitis B virus (HBV) infection causes infant fulminant hepatitis (IFH), and chronic HBV infection may progress to chronic liver disease (CLD) and hepatocellular carcinoma (HCC). Taiwan launched a nationwide HBV immunization program for newborns in July 1984,¹ which has successfully lowered the prevalence of chronic HBV carriers, incidence of HCC, and mortality of IFH in vaccinated birth cohorts.²⁻⁴ The mortality of CLD before and after HBV immunization has never been examined. We assessed the 30-year outcomes of the immunization program.

Methods | From July 1984 to June 1986, the immunization program covered only newborns with high-risk mothers who were seropositive for HBV surface antigen. Coverage was extended to all newborns in July 1986, preschool children in July 1987, and primary school children in 1988-1990. Recombinant HBV vaccines replaced plasma-derived vaccines in 1992. The immunization coverage rates for birth cohorts from 1984 to 2010 was 88.8% to 96.9%.^{2,5}

The mortality of IFH, CLD, and HCC and the incidence of HCC were compared among birth cohorts born before and after the launch of the program. The National Death Certifi-

cates Database (1977-2011) was used to derive the mortality rates of IFH (*International Classification of Diseases, Ninth Revision [ICD-9]* code 570), CLD (*ICD-9* code 571), and HCC (*ICD-9* codes 1550 and 1552); the National Cancer Registry Database (1977-2009) was used to derive the incidence rates of HCC (*International Classification of Diseases for Oncology* code C220).⁶ Infant fulminant hepatitis was analyzed in birth cohorts to 2009-2011, whereas other outcomes were analyzed in birth cohorts to 2001-2004 (age range: 5-29 years in 2009). To control sex and duration of HBV infection, sex-adjusted or age- and sex-adjusted incidence and mortality rate ratios were calculated using Poisson regression models (SAS version 9.2; SAS Institute Inc). Two-sided $P < .05$ was considered statistically significant. This study was approved by the data release review board of the Bureau of Health Promotion, which waived the requirement for informed consent.

Results | Infant fulminant hepatitis mortality rates and sex-adjusted rate ratios declined significantly for infants born from 1977-1980 to 2009-2011 (Table). The decline was greatest from 1981-1984 to 1985-1988 and from 1989-1992 to 1993-1996, coincident with the launch of the national immunization program in 1984 and the change to recombinant vaccines in 1992. Compared with 1977-1980, the sex-adjusted rate ratio declined to 0.88 (95% CI, 0.65-1.21) in

Table. Mortality Rates of Infant Fulminant Hepatitis, Chronic Liver Diseases, and Hepatocellular Carcinoma and Incidence Rates of Hepatocellular Carcinoma of Birth Cohorts Born Before and After the Launch of Hepatitis B Immunization Program in 1984 in Taiwan

Birth Years	Infant Fulminant Hepatitis				Mortality in Ages 5-29 y						Hepatocellular Carcinoma Incidence in Ages 5-29 y				
	PY Under Observation		No. of Cases		PY Under Observation		Chronic Liver Disease		Hepatocellular Carcinoma		PY Under Observation		No. of Cases	Age- and Sex-ARR (95% CI)	
	MR ^a	Sex-ARR (95% CI)	MR ^a	Sex-ARR (95% CI)	MR ^a	Sex-ARR (95% CI)	MR ^a	Sex-ARR (95% CI)	MR ^a	Sex-ARR (95% CI)	IR ^b	Age- and Sex-ARR (95% CI)			
1977-1980	1 492 223	86	5.76	1 [Reference]	39 962 223	260	0.65	1 [Reference]	325	0.81	1 [Reference]	39 962 223	454	1.14	1 [Reference]
1981-1984	1 433 854	73	5.09	0.88 (0.65-1.21)	37 443 552	147	0.39	0.65 (0.53-0.79) ^c	209	0.56	0.70 (0.59-0.83) ^c	36 301 908	278	0.77	0.73 (0.63-0.85) ^c
1985-1988	1 210 040	32	2.64	0.46 (0.31-0.69) ^c	26 428 945	35	0.13	0.40 (0.28-0.57) ^c	78	0.30	0.43 (0.33-0.55) ^c	25 146 138	94	0.37	0.48 (0.38-0.60) ^c
1989-1992	1 236 620	33	2.67	0.46 (0.31-0.69) ^c	21 172 702	5	0.02	0.12 (0.05-0.28) ^c	36	0.17	0.27 (0.19-0.39) ^c	19 895 132	46	0.23	0.37 (0.27-0.51) ^c
1993-1996	1 207 901	8	0.66	0.11 (0.06-0.24) ^c	16 201 336	11	0.07	0.39 (0.02-0.73) ^d	20	0.12	0.21 (0.13-0.34) ^c	14 908 280	33	0.22	0.43 (0.30-0.62) ^c
1997-2000	1 125 123	4	0.36	0.06 (0.02-0.17) ^c	10 046 542	3	0.03	0.16 (0.05-0.50) ^d	12	0.12	0.21 (0.12-0.38) ^c	8 867 241	15	0.17	0.37 (0.21-0.62) ^c
2001-2004	907 460	2	0.22	0.04 (0.01-0.16) ^c	4 084 224	1	0.02	0.11 (0.02-0.80) ^e	2	0.05	0.08 (0.02-0.34) ^c	3 391 623	3	0.09	0.20 (0.06-0.65) ^e
2005-2008	767 813	3	0.39	0.07 (0.02-0.21) ^c											
2009-2011	527 323	1	0.19	0.03 (0.01-0.24) ^d											

Abbreviations: ARR, adjusted rate ratio; PY, person-years.

^a Indicates mortality rate (MR) per 100 000 PY.

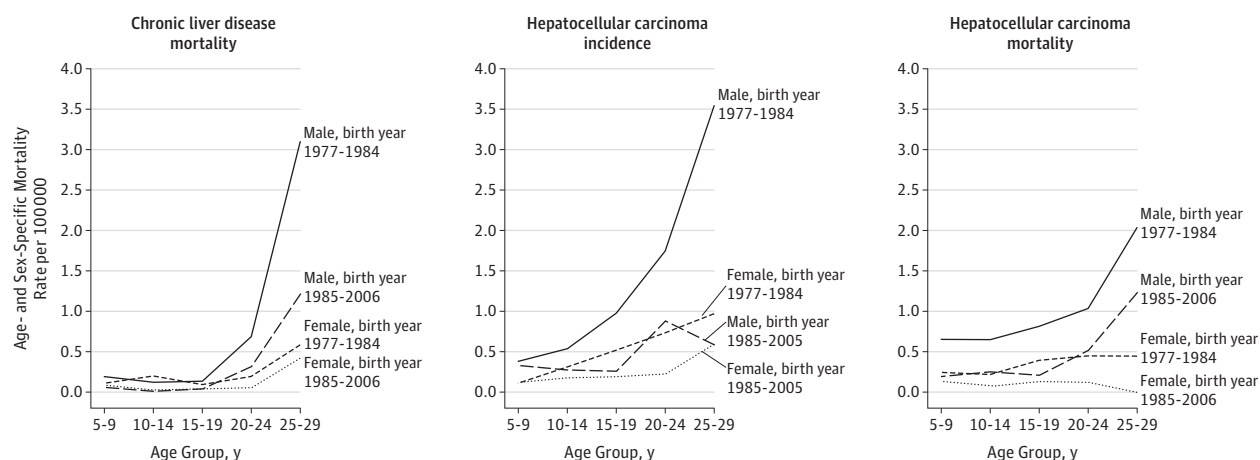
^b Indicates incidence rate (IR) per 100 000 PY.

^c $P < .001$.

^d $P < .01$.

^e $P < .05$.

Figure. Age- and Sex-Specific Mortality and Incidence Rates of Chronic Liver Disease and Hepatocellular Carcinoma for Birth Cohorts Born Before and After the Launch of the Hepatitis B Immunization Program in 1984 in Taiwan



1981-1984, 0.46 (95% CI, 0.31-0.69) in 1985-1988, and 0.03 (95% CI, 0.01-0.24) in 2009-2011.

There was a continuous decline in age- and sex-adjusted rate ratios of CLD and HCC mortality and HCC incidence for birth cohorts born after implementation of the program. The birth cohort born in 1981-1984, which received HBV vaccines at preschool ages instead of early infancy, had significantly lower CLD and HCC mortality and HCC incidence than those born in 1977-1980. The age- and sex-adjusted rate ratio in 2001-2004 was 0.11 (95% CI, 0.02-0.80) for CLD mortality, 0.08 (95% CI, 0.02-0.34) for HCC mortality, and 0.20 (95% CI, 0.06-0.65) for HCC incidence.

Males had significantly higher CLD and HCC mortality and HCC incidence than females in most age groups (Figure). The 1985-2006 birth cohorts had significantly lower CLD and HCC mortality and HCC incidence rates than those born in 1977-1984 for both sexes.

Discussion | The mortality of IFH in vaccinated birth cohorts decreased by more than 90% from 1977-1980 to 2009-2011, which was greater than the previously reported reduction (approximately 70%) from 1975-1984 to 1985-1998.⁴ This long-term, high-coverage immunization program was associated with lower IFH mortality through increasing individual and herd immunity of vaccinated cohorts. From 1977-1980 to 2001-2004, the age- and sex-adjusted rate ratios for individuals aged 5 to 29 years decreased by more than 90% for CLD and HCC mortality and by more than 80% for HCC incidence, which were higher than the previously reported reduction (70%) in HCC incidence for youth aged 6 to 19 years.³

The national HBV therapy program launched in November 2003 may also be contributing to the reduction in risk of IFH, CLD, and HCC; however, this contribution is likely minimal because few members of the study cohorts were eligible for therapy. Hepatitis B virus immunization in infancy has been associated with a reduction in the risk of IFH, CLD, and HCC in Taiwan.

Chun-Ju Chiang, PhD

Ya-Wen Yang, MSc

San-Lin You, PhD

Mei-Shu Lai, MD, PhD

Chien-Jen Chen, ScD

Author Affiliations: Graduate Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei, Taiwan (Chiang, Lai); Taiwan Cancer Registry, Taipei, Taiwan (Yang); Genomics Research Center, Academia Sinica, Taipei, Taiwan (You, Chen).

Corresponding Author: Chien-Jen Chen, ScD, Genomics Research Center, Academia Sinica, 128 Academia Rd, Sec 2, Taipei 11529, Taiwan (chencj@gate.sinica.edu.tw).

Author Contributions: Drs Chiang and Chen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Chiang, You, Chen.

Acquisition of data: Chiang, Yang, You, Lai, Chen.

Analysis and interpretation of data: Chiang, Yang, You, Chen.

Drafting of the manuscript: Chiang, You.

Critical revision of the manuscript for important intellectual content: Chiang, Yang, You, Lai, Chen.

Statistical analysis: Chiang, Yang, You.

Administrative, technical, or material support: Chiang, You.

Study supervision: Lai, Chen.

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COMMENT & RESPONSE

Genetic Variants Associated With Susceptibility to *Helicobacter pylori*

To the Editor The study by Dr Mayerle and colleagues¹ found a strong association between variants at the toll-like receptor 10, 1, and 6 (*TLR10/1/6*) locus on chromosome 4 and *Helicobacter pylori* serologic status, which contributes to the understanding of host susceptibility to a common infectious disease. During the process of evaluating the functional significance of their finding, the authors presented results that indicate that a single-nucleotide polymorphism within this locus (rs10004195), which was identified as having the strongest association with *H pylori* seroprevalence, may be an expression quantitative trait locus causing reduced expression of *TLR1*. They suggested that decreased *TLR1* messenger RNA expression or defective protein function, or both, might be responsible for the observed association with protection from the acquisition of *H pylori* seropositivity.

We would like to provide a modified interpretation of these findings given that prior studies have demonstrated that coding polymorphisms in the *TLR1* locus linked to rs10004195 are actually associated with increased leukocyte responses to *TLR1/TLR2* agonists. As the authors stated, there are 2 nonsynonymous variants within *TLR1* that are in almost perfect linkage disequilibrium with rs10004195, rs4833095 (Asn248Ser), and rs5743518 (Ser602Ile). These nonsynonymous polymorphisms are associated with changes in surface expression of the *TLR1* protein, but not with changes in messenger RNA or total cell protein levels.^{2,3}

In whites, the minor alleles of these coding variants (Ser and Ile) have been shown to be associated with surface expression of *TLR1* on monocytes, whereas cells from homozygotes for the common allele have no *TLR1* on their surface.^{2,3} Candidate gene and genome-wide association studies have shown that leukocytes carrying the minor alleles at rs4833095 and rs5743518 demonstrate increased responses to agonists for *TLR1/TLR2*,²⁻⁴ and patients carrying these alleles are at increased risk for several clinical phenotypes, including sepsis-related death³ and altered immune responses to the BCG vaccine.⁵

These functional effects do not correlate with *TLR1* messenger RNA expression and would not be detected with the cis-expression quantitative trait locus method used by

Mayerle et al.¹ Thus, we believe the literature supports that increased (not decreased) *TLR1/TLR2*-mediated responses could be the protective factor responsible for the decreased prevalence of *H pylori* serologic status in the study populations. This is a potentially important distinction as the implications for *H pylori*-related disease and other microbial infections are determined.

Mark M. Wurfel, MD, PhD
Thomas R. Hawn, MD, PhD

Author Affiliations: Division of Pulmonary and Critical Care Medicine, Harborview Medical Center, University of Washington, Seattle (Wurfel); Division of Allergy and Infectious Diseases, University of Washington, Seattle (Hawn).

Corresponding Author: Mark M. Wurfel, MD, PhD, Division of Pulmonary and Critical Care Medicine, Harborview Medical Center, 325 Ninth Ave, PO Box 359640, Seattle, WA 98104 (mmwurfel@uw.edu).

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In Reply The gram-negative pathogen *H pylori* is specifically adapted to colonize the mucus layer of the human gastric mucosa. It therefore differs from other gram-negative bacteria in several respects. First, despite the induction of a strong local immune response in the gastric mucosa of colonized individuals, the bacterium establishes chronic infection lasting up to several decades. Second, it persists strictly as an extracellular pathogen. Third, due to the different lipid A acetylation of its lipopolysaccharide, it induces 500- to 1000-fold lower endotoxic activity compared with bacteria such as *Salmonella typhimurium* or *Escherichia coli*. Fourth, even in strongly immunosuppressed patients, *H pylori* never causes septicemia. Therefore, the immune response to infection by *H pylori* maintains a balance between host and pathogen as well as the innate and the adaptive immune systems.

Although we are aware of the effect of the I602S polymorphism of *TLR1* and its effect on cell surface expression on monocytes,¹ we would like to stress that natural killer and T-helper 1 (Th1) cells are the driving force of *H pylori*-induced gastric disease. Even though our experimental approach could not eliminate the possibility that *TLR1* is translocated to the cell surface selectively on monocytes, we have no experimental indications for this. On the contrary, expression of *TLR1* in whole blood was decreased.