Forecasting the Declining Rate of Chronic Hepatitis-B Carrier Status at a Taiwanese University: Twenty Years after Implementation of an Universal HBV Vaccination Program in Taiwan

Fu-Hsiung Su, BMBS; Hsiao-Yun Huang¹, PhD; Hong-Jer Chang³, PhD; Jin-Ju Jeng², BS; Yi-Hui Liu³, BA; Chih-Dao Chen, MD

Background: Prior to the introduction of universal hepatitis B virus (HBV) vaccination in Taiwan in 1984, 15-20% of the general population were chronic HBV carriers.

Methods: We forecasted and quantified the declining HBV carrier rate 20 years subsequent to the implementation of universal HBV vaccination in Taiwan. At a Taiwanese university, 28,763 freshmen tested for serum HBsAg level were divided into ten age cohorts by date of birth, from July 1976 to June 1986 inclusive. Comparisons of HBsAg carrier rates according to gender were examined with the Z test. Regression methods and a time series model were applied to our sample to forecast trends in changes to the HBsAg carrier rate for the next five years.

Results: Regression analysis demonstrated a trend toward declining HBsAg-positive carrier rates. The HBsAg carrier rate for male students decreased from 16.8% (for those born between July 1976 and June 1977) to 2.2% (for those born between July 1985 and June 1986). The carrier rate for their female counterparts over the same period declined from 12.2% to 2.4%. The HBsAg carrier rate for male participants was significantly greater than that of their female counterparts for certain years during the test period. The results of time series analysis suggests the HBsAg carrier status rate will approach zero for students born after July 1987 (expected to enrol in the university in 2006).

Conclusions: Our data demonstrate that in order for the HBV carrier rate to approximate zero, universal vaccination programs need to continue for at least 21 years. (Chang Gung Med J 2007;30:521-8)

Key words: HBV, Taiwan, epidemiology, vaccination program, hepatitis B vaccine

Hepatitis-B infection, a global health issue, is particularly prevalent in developing countries. Based on serological evidence, it has been estimated that each year, approximately two billion individuals...
worldwide succumb to hepatitis-B infections they contracted in the past.\(^1\) Of these, perhaps 350 million appear to be chronic carriers, of whom possibly one million die annually from cirrhosis and/or hepatocellular carcinoma.\(^2\)

Listed among the “hyperendemic countries,” Taiwan appears quite significant in that it features one of the highest HBsAg carrier rates in the world, with perhaps 15 to 20% of the general population being carriers.\(^3\) In 1984 Taiwan became one of the first countries to implement an universal hepatitis-B vaccination program for newborns.\(^4\) Vaccination for newborns of carrier mothers was implemented in July 1984 and was extended to include all neonates in 1986. The program reached somewhere between 84 and 94 percent of the population. At the commencement of the vaccination program, the HBV carrier rate among children was 9.8 percent.\(^5\) Five years later, the HBsAg seropositivity rate for children under five years of age had decreased to 2%.\(^6\) After ten years (1994), the HBV carrier rate among children had decreased to 1.3 percent.\(^7\) After sixteen years (the year 2000), a significant trend toward decreasing HBsAg carrier rates-from 20.3% (those born in 1976) to 3.4% (born in 1986)-was reported for high-school students in eastern Taiwan.\(^8\) Such studies show the HBV infection and carrier rates have been declining since the launch of this mass vaccination program,\(^6\) although the long-term efficacy of a mass HBV vaccination program such as this remains a question of great concern for public-health officials.

In this article, we report HBV infection trends for ten birth cohorts of Taiwanese university students, for the decades prior and subsequent to 1984, the year when Taiwan’s national hepatitis-B vaccination campaign for neonates commenced. The results of this study confirm that the effect remained significant 20 years after the first cohort received HBV vaccinations, which were ongoing thereafter. Furthermore, we observe that unvaccinated children have also benefited from the hepatitis-B vaccination program.

**METHODS**

**National vaccination program**

Taiwan’s nationwide program of HBV vaccination started in July 1984 and for the first two years of the program, only newborns of HBsAg-positive mothers were immunized. From July 1986 onwards, all infants were immunized. The program was extended to preschool children in 1987-1990, to primary school children in 1988-1991, to teenagers in 1989-1991, and to adults in 1991-1994 on a fee-for-service basis. Beginning in October 1990, the free-of-charge HB vaccination program was expanded to include all children up to first grade. Since July 1991, the vaccine records of elementary-school entrants have been checked to confirm HB vaccination, and non- or incompletely vaccinated elementary school students have been monitored and given a full-cycle of catch-up vaccinations.

**Participants**

The study data were collected from Fu-Jen Catholic University, a private university located in northern Taiwan. Using birth place information available in university records, it was determined that the majority (72.6%) of the students in the study were from northern Taiwan (including 59.3% from the Greater Taipei Metropolitan Area) with only 13.2% from central Taiwan, 10.8% from southern Taiwan, and 3.4% from eastern Taiwan and the outlying islands. According to the university’s policy, all students were required to undergo a compulsory health screening examination prior to entering university. In total, 28,763 students (12,244 males and 16,519 females), including both graduate and undergraduate levels, completed the health check. Since the mass vaccination program was implemented in July 1984 and conducted in the same month each year, the students were grouped according to their date of birth, with groups stretching from July of a particular year to June of the subsequent year (Table 1). As a result, a total of ten birth cohorts over a period extending from July 1976 to June 1986 were included for analysis in this study.

Since the year 2000, an annual survey of serum HBsAg status has been conducted for members of the freshman class of Fu-Jen University in September of each year as part of a general youth cohort representative health check-up. All blood samples were transported in a refrigerator to a central laboratory for testing. The serum HBsAg level was determined using a commercially available enzyme immunoassay kit (Abbott Laboratories, North Chicago, IL, USA). A regression method was
applied to derived serum HBsAg data in order to evaluate any trends displayed in the rate of detected HBsAg positivity. Comparisons of HBsAg carrier rates by gender were performed by means of the Z test. Any difference between data sets was considered significant if the probability of difference was less than 0.05. A time series statistical method was applied to predict trends in HBV infection carrier rates in our sample population. Initially, HBsAg carrier rate trends among study participants were interpreted as a non-stationary time series. However, the data were also transformed to constitute a stationary time series by simple differencing. In the mathematical model, \( \{x_t\} \) was denoted as the HBsAg carrier time series. The simple differencing of \( \{x_t\} \) was denoted by \( \nabla x_t \) where \( \nabla x_t = x_t - x_{t-1} \). Thus, subsequent to performing model-building and model-searching procedures, the ARIMA(2,1,0) model as described by Shumway RH and colleagues was selected as best fitting the data elicited by the study.\(^{(11)}\)

### RESULTS

The data showed overall prevalence of HBsAg positivity among the students was 6.6% (95% CI: 6.3-6.9) [7.9% for males (95% CI: 7.4-8.4) and 5.6% (95% CI: 5.3-5.9) for females]. There was a significant trend \((p < 0.001)\) toward a decreasing HBsAg carrier rate among students at the study university from 14.6% (95% CI: 11.9-17.4) to 2.3% (95% CI: 1.8-2.8) over the ten-year study period (Table 1). For male students, the HBsAg carrier rate declined from 16.8% (95% CI: 12.8-20.9) in 1976 to 2.2% (95% CI: 1.4-3.0) in 1985; the corresponding figures for females declined from 12.2% (95% CI: 8.5-15.9) to 2.4% (95% CI: 1.7-3.1), respectively. The reduction was more obvious among male students (Fig. 1). The HBsAg carrier rate for male students was significantly greater than that of the female students in the 1977 cohort \((p = 0.035)\), the 1981 cohort \((p < 0.001)\) and the 1984 cohort \((p < 0.001)\) (Table 1).

With the application of the time series method, the ARIMA(2,1,0) model could be rewritten as

\[
X_t = 1.5X_{t-1} + 0.06X_{t-2} - 0.56X_{t-3} + W_t
\]

where \(X_t\) denoted the data value at time “t” and \(W_t\) denoted random “white noise.” Applying this model to predicting trends in the prevalence of HBsAg carrier status for this student population (Fig. 2), assuming that there were no interfering factors and that any trend was continuous, the positivity rate for HBsAg among students was projected to approach zero for the 1987 cohort, a group comprising students born between 07/01/1987 and 06/30/1988 and expected to enrol in the university in 2006 (Fig. 3).

A specific regression method was also applied to evaluate any trend in the HBsAg positivity rate with respect to time. Here, \(Y_t\) denoted the HBsAg

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Table 1. The HBsAg Carrier Rate for Taiwanese University Students Born between July 1976 and June 1986

<table>
<thead>
<tr>
<th>Birth cohort</th>
<th>Year of birth</th>
<th>Male % (N)</th>
<th>95% CI</th>
<th>Female % (N)</th>
<th>95% CI</th>
<th>All % (N)</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1976</td>
<td>0701/1976-0630/1977</td>
<td>16.8% (55)</td>
<td>12.8-20.9</td>
<td>12.2% (37)</td>
<td>8.5-15.9</td>
<td>14.6% (92)</td>
<td>11.9-17.4</td>
<td>0.105</td>
</tr>
<tr>
<td>1977</td>
<td>0701/1977-0630/1978</td>
<td>13.0% (51)</td>
<td>9.7-16.3</td>
<td>8.3% (31)</td>
<td>5.5-11.1</td>
<td>10.7% (82)</td>
<td>8.5-12.7</td>
<td>0.035</td>
</tr>
<tr>
<td>1978</td>
<td>0701/1978-0630/1979</td>
<td>12.5% (64)</td>
<td>9.6-15.4</td>
<td>10.6% (59)</td>
<td>8.0-13.2</td>
<td>11.5% (123)</td>
<td>9.6-13.4</td>
<td>0.334</td>
</tr>
<tr>
<td>1979</td>
<td>0701/1979-0630/1980</td>
<td>10.8% (84)</td>
<td>8.6-13.0</td>
<td>8.9% (69)</td>
<td>6.9-10.9</td>
<td>9.9% (153)</td>
<td>8.4-11.4</td>
<td>0.211</td>
</tr>
<tr>
<td>1980</td>
<td>0701/1980-0630/1981</td>
<td>10.4% (130)</td>
<td>8.7-12.1</td>
<td>8.5% (114)</td>
<td>7.0-10.0</td>
<td>9.4% (244)</td>
<td>8.3-10.5</td>
<td>0.095</td>
</tr>
<tr>
<td>1981</td>
<td>0701/1981-0630/1982</td>
<td>9.7% (197)</td>
<td>8.4-11.0</td>
<td>6.4% (175)</td>
<td>5.5-7.3</td>
<td>7.8% (372)</td>
<td>7.0-8.6</td>
<td>0.001</td>
</tr>
<tr>
<td>1982</td>
<td>0701/1982-0630/1983</td>
<td>8.6% (171)</td>
<td>7.4-9.8</td>
<td>5.9% (173)</td>
<td>5.1-6.8</td>
<td>7.0% (344)</td>
<td>6.3-7.7</td>
<td>0.001</td>
</tr>
<tr>
<td>1983</td>
<td>0701/1983-0630/1984</td>
<td>5.4% (101)</td>
<td>4.4-6.4</td>
<td>4.9% (133)</td>
<td>4.1-5.7</td>
<td>5.1% (234)</td>
<td>4.5-5.7</td>
<td>0.432</td>
</tr>
<tr>
<td>1984</td>
<td>0701/1984-0630/1985</td>
<td>4.7% (85)</td>
<td>3.7-5.7</td>
<td>2.9% (79)</td>
<td>2.4-3.4</td>
<td>3.6% (164)</td>
<td>3.1-4.1</td>
<td>0.001</td>
</tr>
<tr>
<td>1985</td>
<td>0701/1985-0630/1986</td>
<td>2.2% (29)</td>
<td>1.4-3.0</td>
<td>2.4% (49)</td>
<td>1.7-3.1</td>
<td>2.3% (78)</td>
<td>1.8-2.8</td>
<td>0.74</td>
</tr>
<tr>
<td>Total</td>
<td>28,763 students</td>
<td>7.9% (967)</td>
<td>7.4-8.4</td>
<td>5.6% (919)</td>
<td>5.3-5.9</td>
<td>6.6% (1886)</td>
<td>6.3-6.9</td>
<td></td>
</tr>
</tbody>
</table>
positivity rate and \( X_i \) denoted the year. The result showed that a simple linear regression line
\[
Y_i = 0.149 - 0.0012X_i
\]
could be fitted to the data. The regression coefficient associated with \( X_i \) proved to be negative, indicating that the HBsAg positivity rate was declining with time over the test period (Table 2).

**DISCUSSION**

From our observations, there appeared to be an abrupt decline in HBsAg carrier incidence from the 1976 cohort (14.6%) to the 1977 cohort (10.7%). Subsequently, a steady decline in the HBsAg carrier rate from the 1977 cohort to the 1984 cohort was observed. The students in these cohorts as much as seven years old at the time the HBV mass-vaccination program commenced. This finding is consistent with a previous study, which looked at children born up to 6 years before the start of the program.\(^{(10)}\)

Since vertical transmission (the perinatal route) was not modified for these students, the significant reduction in HB infection between the 1977 and the 1983 cohorts could be due to a decline in horizontal

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**Table 2.** Regression Model of HBsAg Carrier Rate for Taiwanese University Freshmen Born between July 1976 and June 1986

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized coefficients</th>
<th>Standardized coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>Standard error</td>
</tr>
<tr>
<td>1</td>
<td>(Constant)</td>
<td>.149</td>
</tr>
</tbody>
</table>

Dependent Variable: proportion (percentage) of population that is HBsAg (+)
transmission of the virus.\(^{(12)}\) We postulate that the obvious decline in the HBsAg carrier rate between the 1977 cohort and the 1983 cohort, particularly between the 1981 and 1983 cohorts, might reflect the impact of subsequent “catch-up” programs, e.g. in the period between 1987 and 1991 (children born between 1981 and 1991 had access to the self-pay preschool program) and the free-of-charge vaccination program for children under seven starting in 1990.

At the commencement of the national hepatitis-B vaccination program in 1984, the completion rate for the total 4-dose HBV vaccine was 81.6% for the infants of HBV carrier mothers and 9.5% for all newborns.\(^{(13)}\) In other words, some carrier mothers were not screened and some newborns of carrier mothers were not vaccinated. Furthermore, unvaccinated children born to non-carrier mothers still exhibited a chance of acquiring HBV infection in early childhood from older carriers.\(^{(10)}\) Hence the decline of the HBsAg positivity rate noted between the 1984 and 1985 cohorts should not only be attributed to the vertical (perinatal) effect of the mass vaccination program; consideration should also be given to the possible horizontal effect of the program as a cause for the decline. Our observations suggest the HBV mass-vaccination program successfully reduced horizontal transmission to older children up to age 7, in addition to contributing to the reduction in transmission of hepatitis B among children of the same age.\(^{(6)}\) Some previous studies have reported the blocking of both vertical and horizontal HBV transmission.\(^{(6,10)}\) We likewise conclude that twenty years subsequent to the commencement of Taiwan’s mass HBV vaccination program, the program’s effect of reducing horizontal and vertical transmission of HBV is still evident, thus the relative efficacy of the vaccination program would appear to have persisted for nearly twenty years.

Similar to results of previous studies,\(^{(3,5,10,14)}\) our study has revealed that the HBsAg carrier rate was higher among males than females. Furthermore, it has been reported that males were more likely to become HBsAg carriers following infection than their female counterparts.\(^{(3,10,14)}\) Fang JW and his colleagues have suggested that girls responded with a higher anti-HBs titre compared with boys after receiving the HBV vaccine.\(^{(15)}\) As infants and throughout early childhood, male toddlers are typically reported to be more active than their female counterparts and, thus may experience a greater number of opportunities for unwitting parenteral exposure than would appear to be the case for age-matched female individuals.\(^{(16)}\) These findings have demonstrated that universal vaccination can be used to control vertical and horizontal transmissions of HBV infection and the sequelae of chronic HBV infection.

Given that the chronic HBV infection rate has declined in the years following the implementation of Taiwan’s mass HBV vaccination program, we wished to predict the approximate stage at which HBV infection can be virtually eradicated or reduced to a minimal level. The result of time-series analysis indicates that the HBV carrier rate will approach zero for the 1987 cohort (students born after 07/01/1987), should the current declining trend in HBV carrier rates continue unchanged. Lu SN and colleagues reported the prevalence of HBsAg decreased from 12.5% in 1984 to 5.4% in 1991 in one rural township in central Taiwan.\(^{(17)}\) In a small district of the Taipei metropolitan area, the HBsAg prevalence decreased from 7.3% in surveys done in 1982-1984, to 2% in 1990-1991.\(^{(18)}\) It is clear that the prevalence of HBsAg in rural areas was much higher than urban areas.\(^{(17)}\) In 1998, the Department of Health in Taiwan also forecast that if the HBV vaccination coverage rate of 90% of all newborns can be maintained, by the year 2010 the carrier rate in Taiwan could be expected to decline to < 0.1%.\(^{(19)}\) However, we predicted the carrier rate of HBsAg positivity among our student population would decline to a minimal level by the year 2006. The discrepancy between our findings and the data presented by the Department of Health might be due to the fact that the majority of our student population was from the greater Taipei metropolitan area and from more affluent families, which means that they likely had easier access to health resources than the general population. Another limitation of the present study is that this mathematical model does not take into account the subsequent catch-up programs and decline of vaccine induced immune memory. Some investigators have pointed out that the possible progressive decline of serum anti-HB levels for previously vaccinated individuals over the period following vaccination may be associated with increased likelihood of the developing new HB infections over
time, (20-22) McMahon BJ and colleagues also suggest that the decline of vaccine-induced memory was greatest for the group aged 0-4 years as compared with other age groups. (23) As a consequence, our results may underestimate the actual HBsAg carrier rate in the general population of young adults. Nevertheless, given the results of previous studies, (5-23) the rate in the group expected to be aged 0-4 years at the time of their births might also reduce the risk of horizontal transmission of HBV among children born after the program commenced, but that such vaccination might also reduce the risk of horizontal transmission of HBV to children born up to seven years prior to the commencement of the program. We also predict that the HBV infection rate can be reduced to a rather minimal level in 21 years (the 1987 birth cohort expected to enrol in 2006) following the implementation of an universal HBV vaccination program among the student population. Clearly, comprehensive, universal HBV vaccination programs should be launched in a number of other countries, especially for those for which this virus and associated infections are endemic.

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預測台灣某地區某大學 B 型肝炎帶原率下降趨勢：
台灣 B 型肝炎疫苗施打二十年

蘇富雄 黃孝雲^1 張宏哲^2 鄭津珠^2 劉懿慧^3 陳志道

背 景：台灣在 1984 年開始實施新生兒 B 型肝炎的預防接種之前，約有百分之 15 到 20 的民眾為 B 型肝炎帶原者。

方 法：我們預測和計算在實施全面性新生兒 B 型肝炎預防接種 20 年後的台灣，帶有 B 型肝炎病毒的人比率將會減少。本研究調查台灣某大學 28,763 位新生的 B 型肝炎表面抗原血清狀態，包含以出生日分為 10 年的組別，從 1976 年 7 月到 1986 年 6 月。根據性別以 Z 檢定來比較 B 型肝炎的帶原者的比率，並運用迴歸模式和時間序列模式預測接下來的五年 B 型肝炎帶原者比率的改變趨勢。


結 論：我們的資料顯示若欲使 B 型肝炎慢性帶原率降至零，新生兒 B 型肝炎預防接種計劃應至少持續 21 年。

（長庚醫學 2007;30:521-8）

關鍵詞：B 型肝炎，台灣，流行病學，預防接種方案，B 型肝炎疫苗