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Pediatrics 2011;128;e530; originally published online August 28, 2011;
DOI: 10.1542/peds.2011-0742

Decreasing Rate of Biliary Atresia in Taiwan: A Survey, 2004–2009

WHAT'S KNOWN ON THIS SUBJECT: Biliary atresia (BA) is the leading cause of liver death and liver transplantation in the pediatric age group. The pathogenesis of BA remains unclear, but epidemiological studies may enhance our understanding of the possible causes.

WHAT THIS STUDY ADDS: Decreasing rates of BA have been found in Taiwan since 2007, which may be related to improvements in general socioeconomic status and possibly the popularity of rotavirus vaccination; this may shed light on possible preventive interventions for BA.

abstract

OBJECTIVES: The pathogenesis of biliary atresia (BA) is unclear, but epidemiological studies may help to elucidate possible causes. The goals of this study were to identify BA incidence changes in Taiwan in 2004–2009 and to survey the factors that might influence incidence changes to elucidate the possible causes of BA.

METHODS: A Taiwan national registry system for BA has been established since 2004. By using data from the national registry system for BA, we identified BA incidence changes in 2004–2009. We also evaluated the correlations between BA incidences and estimated rotavirus vaccine coverage rates and between BA incidences and the gross domestic product.

RESULTS: A total of 185 patients with BA were identified in 2004–2009 in Taiwan, whereas the number of live births was 1 221 189. Compared with the incidence of BA in 2004–2006 (1.79 cases per 10 000 live births), the incidence of BA in 2007–2009 (1.23 cases per 10 000 live births) was decreased significantly ($P = .01$). BA incidences were negatively correlated with the gross domestic product ($P = .02$) and marginally negatively correlated with rotavirus vaccine coverage rates ($P = .07$).

CONCLUSIONS: A significant decrease in BA incidence in Taiwan since 2007 has been noted and may be related to improvements in the general socioeconomic status and the popularity of rotavirus vaccination. Although more evidence is needed to establish a direct correlation, this phenomenon may shed light on possible causes of and preventive interventions for BA. *Pediatrics* 2011;128:e530–e536

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KEY WORDS
biliary atresia, incidence, epidemiology, rotavirus, gross domestic product

ABBREVIATIONS
BA—biliary atresia
GDP—gross domestic product

www.pediatrics.org/cgi/doi/10.1542/peds.2011-0742

doi:10.1542/peds.2011-0742

Accepted for publication May 13, 2011

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: *The authors have indicated they have no financial relationships relevant to this article to disclose.*

Biliary atresia (BA) is the leading cause of death without liver transplantation in the pediatric age group.[1–3] Immune-mediated ductal injury, inflammatory triggers, and genetic factors are thought to correlate with this disease.[1,3] However, the exact pathogenesis remains unclear. Data reported from different countries on the incidence of BA range from 0.42 cases per 10 000 live births in Croatia[4] to 3.2 cases per 10 000 live births in French Polynesia.[4–22] The estimated incidence of BA in Taiwan was 1.46 cases per 10 000 live births in 1996–2003, according to national health insurance data.[20] However, the number of patients with confirmed diagnoses had never been well investigated in the whole of Taiwan before 2004, when a national stool color–screening and registry system was established.[23] By using the data from the national BA registry system in Taiwan, we have the opportunity to investigate the exact changes in the incidence of BA in Taiwan from 2004 to 2009 and to evaluate factors possibly correlated with the incidence changes, including rotavirus vaccine coverage rates and general socioeconomic status. This may have some implications regarding the pathogenesis of BA.

Increasing maternal racial and ethnic diversity in Taiwan has been observed since the 1970s because of the increasing numbers of brides from mainland China, Indonesia, and Vietnam. However, the exact incidences of BA in China, Indonesia, and Vietnam are unclear in the current literature. In this study, we investigated BA incidences among Taiwanese infants according to their maternal ethnic origins. This may help us understand genetic susceptibility in BA and shed light on the possible risk factors for BA. Infectious causes, especially rotavirus, were proposed to be related to BA pathogenesis in previous studies.[24–26] We investigated the estimated rotavirus vaccine coverage rate in our infant population to determine whether rotavirus vaccine coverage rates correlated with BA incidence changes. Racial and geographic region differences in the incidences of BA may reflect the existence of predisposing genetic factors or socioeconomic status-related differences in exposure to environmental factors.[11,14,16] Therefore, we tried to identify whether there was a correlation between socioeconomic status and the incidence of BA. Real gross domestic product (GDP) is the value of goods and services measured by using a constant set of prices, and it is the best measurement of the standard of living.[27] We investigated the correlation between general socioeconomic status according to real GDP and the incidence of BA, to determine whether general socioeconomic status changes influence the incidence of BA.

METHODS

Subjects

All neonates who were born in Taiwan in 2004–2009 and were diagnosed as having BA were included in this study. The patients were identified by the Taiwan Infant Stool Color Card Study Group. This national organization includes the Taiwan Infant Stool Color Card Registry System and the Taiwan Biliary Atresia Study Group.[23,28] All children living in Taiwan who were born in 2004–2009 were the subjects screened for stool color and were registered in the national registry system once the diagnosis of BA had been confirmed through intraoperative cholangiography.[2] We designed an infant stool color card with different stool color photographs, from normal stool to clay-colored stool, for Taiwanese infants. It is integrated into the child health booklet that is distributed to every neonate in Taiwan. It had been launched as a comprehensive national screening and reporting system for BA for all neonates by 2004. There are 2 reporting systems for BA in Taiwan. The first system is the Taiwan Infant Stool Color Card Registry System. All physicians and families of infants are asked to check and to report the stool color when infants are brought to a clinic for the second dose of hepatitis B vaccine at 1 month of age or at any time after birth. The staff members of the registry center then follow up with the patients and list them on the national BA profile if they are diagnosed eventually as having BA through intraoperative cholangiography. The second system involves the Taiwan Biliary Atresia Study Group. The members are pediatric gastroenterologists in 21 medical centers and hospitals where the Kasai operation can be performed. They are requested to report patients with newly diagnosed BA at least twice per year. In addition to the 2 reporting systems, the Taiwan Children Liver Foundation affords financial support for patients with newly diagnosed BA. This is an incentive to facilitate family reporting. This project was approved by the National Taiwan University Hospital institutional review board.

Through these systems and networks, we are confident regarding the profiles of patients with BA identified since 2004. All patients with BA in Taiwan are monitored by the Taiwan Infant Stool Color Card Study Group. With a good registry and follow-up system, we are able to analyze annual incidences accurately.

Data Sources for Live Births, Maternal Ethnic Origins, and GDP

We used data from the Department of Statistics, Ministry of the Interior, Taiwan, to calculate BA incidences according to different maternal ethnic origins and data from the Directorate-General of Budget, Accounting, and Statistics, Executive Yuan, Taiwan, to

analyze the correlation between annual real GDP and the incidence of BA.

Rotavirus Vaccine Coverage Rate

The rotavirus vaccine was introduced to Taiwan in late 2006, as a self-paid vaccine. There are 2 commercial rotavirus vaccines available in Taiwan. One is pentavalent, bovine-human, reassortant vaccine (RotaTeq [Merck, Whitehouse Station, NJ]; cover serotype: G1,G2,G3,G4,P1A[8]; a complete course requires 3 doses), and the other is monovalent, live, attenuated vaccine from human rotavirus strain G1P[8] (Rotarix [GlaxoSmithKline Biologicals, Rixensart, Belgium]; cover serotype: G1; heterotypic protection of G2, G3, G4, and G9; a complete course requires 2 doses). Both vaccines were designed to target the capsid glycoprotein VP7 and VP4 of group A rotavirus, which is the common cause of gastroenteritis in infants. Previous articles on the link between rotavirus and BA in humans presented data on rotavirus C,[24] whereas the common problem of gastroenteritis in infants is caused mainly by rotavirus A. Because rotavirus group A and group C share some common capsid proteins, vaccinations against rotavirus group A may provide partial protection against rotavirus group C. The data on estimated annual rotavirus vaccine doses are from the Centers of Disease Control in Taiwan. The estimated numbers of persons who received vaccines in each year are adjusted by the total doses required for a complete course for different vaccines. The estimated number of persons who received vaccine was calculated as one-third of total RotaTeq doses plus one-half of total Rotarix doses. The vaccine coverage rate was defined as the estimated number of persons who received vaccine divided by the annual number of live births in Taiwan.

TABLE 1 Reductions in Annual Incidences of BA in Taiwan in 2004–2009

Year	No. of BA Cases	No. of Live Births	Incidence, No. of Cases per 10 000 Live Births	Risk Ratio (95% Confidence Interval)
2004	40	216 419	1.85	1.00
2005	35	205 854	1.70	0.92 (0.58–1.44)
2006	37	204 459	1.81	0.98 (0.63–1.53)
2007	23	204 414	1.13	0.61 (0.36–1.02)
2008	22	198 733	1.11	0.60 (0.36–1.01)
2009	28	191 310	1.46	0.79 (0.49–1.28)
2004–2006[a]	112	626 732	1.79	1.00
2007–2009[a]	73	594 457	1.23	0.69 (0.51–0.92)
2004–2009	185	1 221 189	1.51	—

The number of BA cases was determined from data from the Taiwan Stool Color Card Study Group, and the diagnosis was confirmed through intraoperative cholangiography. The data on live births were from the Department of Statistics, Ministry of the Interior, Taiwan.

[a] Poisson regression was used to test the difference in annual incidences of BA. The overall incidence in 2007–2009 was significantly lower than that in 2004–2006 ($P = .01$).

Statistical Analyses

Poisson regression was applied to examine the annual changes in BA incidence rates and to test the association between BA incidence rates and estimated rotavirus vaccine coverage rates and GDP. All analyses were performed by using SAS 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS

Changes in BA Incidences

There were 185 patients born in Taiwan in 2004–2009 for whom BA was diagnosed through intraoperative cholangiography and other diseases were ruled out on the basis of histopathologic results and clinical courses. They were monitored by 21 hospitals and the Taiwan Infant Stool Color Card Study Group. The incidence of BA in Taiwan in 2007–2009 was 1.23 cases per 10 000 live births, which was 69% of the incidence in 2004–2006, when the incidence was 1.79 cases per 10 000 live births ($P = .01$) (Table 1).

Maternal Ethnic Origins

We divided the annual live births in Taiwan and patients with BA into 3 groups according to maternal ethnic origins (Table 2). Among the 185 patients with BA, maternal ethnic origins were verified for 184 patients. All of the 184 patients' fathers were Taiwanese; 167 patients were born to Taiwanese mothers (incidence: 1.54 cases per 10 000 live births from Taiwanese mothers), 11 patients were born to mothers from China (incidence: 1.82 cases per 10 000 live births from mothers from China), and 6 patients were born to mothers from Southeast Asia, including Indonesia and Vietnam (incidence: 0.80 cases per 10 000 live births from mothers from Southeast Asia). There were no significant differences between different maternal ethnic origins ($P = .11$ for Taiwan vs China and .59 for Taiwan vs Southeast Asia, respectively, from Poisson regression analyses). Compared with the incidence in 2004–2006, the incidence of BA among infants from Taiwanese mothers decreased markedly in 2007–2009 ($P = .01$; odds ratio: 1.5 [95% confidence interval: 1.10–2.05]). No incidence changes with time were found for BA among infants from mothers from Mainland China, Indonesia, or Vietnam. With longitudinal comparison from 2004 to 2009, $P = .88$ in Mainland China and $P = .86$ in Southeast Asia, respectively.

The proportion of live births from Taiwanese mothers among the total live births in Taiwan increased from 86.75% in 2004 to 91.31% in 2009, whereas the proportion of live births

TABLE 2 Incidences of BA According to Maternal Ethnic Origins in Taiwan in 2004–2009

	Infants Born to Taiwanese Mothers	Infants Born to Mothers From Mainland China	Infants Born to Mothers From Indonesia or Vietnam
Incidence of BA, No. of cases per 10 000 live births (*n*/*N*)			
2004	1.92 (36/187 753)	1.78 (2/11 206)	1.15 (2/17 460)
2005[a]	1.67 (30/179 345)	2.99 (3/10 022)	0.61 (1/16 487)
2006	1.94 (35/180 556)	0.96 (1/10 423)	0.74 (1/13 480)
2004–2006[a]	1.84 (101/547 654)	1.90 (6/31 651)	0.84 (4/47 427)
2007	1.04 (19/183 509)	3.95 (4/10 117)	0.00 (0/10 788)
2008	1.17 (21/179 647)	0.00 (0/9843)	1.08 (1/9252)
2009	1.49 (26/174 698)	1.13 (1/8871)	1.29 (1/7741)
2007–2009	1.23 (66/537 854)	1.73 (5/28 831)	0.72 (2/27 781)
2004–2009[a]	1.54 (167/1 085 508)	1.82 (11/60 482)	0.80 (6/75 208)
P[b]	.01	.88	.86
Risk ratio (95% confidence interval)	1.50 (1.10–2.05)	1.09 (0.33–3.58)	1.17(0.21–6.40)

There were 185 patients with BA in Taiwan in 2004–2009, and 184 patients' maternal ethnic origins were identifiable.
[a] The maternal ethnic origin of 1 patient born in 2005 was not identifiable.
[b] Poisson regression was applied to test the BA incidence changes with time between 2004–2006 and 2007–2009 for different maternal ethnic origins. A significant decrease in the incidence of BA was noted for infants born to Taiwanese mothers ($P = .01$).

from mothers from Mainland China decreased slightly, from 5.18% in 2004 to 4.64% in 2009, and the proportion of live births from mothers from Indonesia and Vietnam decreased from 8.07% in 2004 to 4.05% in 2009. Analysis of the annual incidences of BA among infants with different maternal ethnic origins showed similar trends in incidence reduction with time for total BA in Taiwan and BA among infants born to Taiwanese mothers.

Rotavirus Vaccine Coverage

The estimated numbers of persons who received rotavirus vaccination have been increasing since November 2006, when rotavirus vaccines were introduced into Taiwan. The estimated numbers of persons who received rotavirus vaccination were 12 324 in 2006, 47 057 in 2007, 60 241 in 2008, and 96 447 in 2009. As the number of children who received rotavirus vaccination increased, the number of patients with BA decreased, from 112 patients in 2004–2006 to 73 patients in 2007–2009 (Fig 1). We found a marginally significant correlation between the decrease in the incidence of BA and the increase in the coverage rate for rotavirus vaccination ($P = .07$).

Gross Domestic Product

A significant negative correlation was found between annual real GDP and BA incidence changes in 2004–2009 ($P = .02$). The Poisson model indicated the following: incidence rate $= \exp(-6.0425 - [2.2531 \times \text{real GDP}])$ (Fig 2).

DISCUSSION

According to the published literature, BA is more common among Asian and French Polynesian people,[10,21] but the estimated incidence in Asia is available only for Japan and Taiwan.[18,20] Through the use of a well-established BA registry system and a national BA study group in Taiwan, the data obtained since 2004 are the first national data with well-defined cases. Therefore, the advantages of this study include the reliable sources of data, which were obtained from a region with well-defined cases, well-defined annual live birth numbers, and well-defined maternal ethnic origins, which have not been investigated previously for BA in Taiwan.

In our study, the Taiwan Infant Stool Color Card Study Group clearly defined cases as BA only when the diagnoses were confirmed through intraoperative cholangiography and other diseases were excluded on the basis of clinical courses and liver histopathologic evaluations. Therefore, overestimation of the incidence of BA could be excluded. Because of the active promotion of the use of infant stool color cards and education for family members and physicians, underestimation

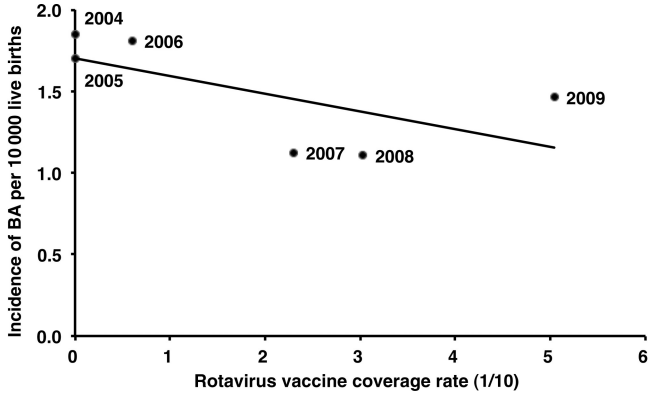

FIGURE 1
Trend of association between estimated rotavirus vaccination coverage rates and BA incidences in 2004–2009 ($P = .07$). The Poisson regression was as follows: incidence of BA $= \exp(-8.670 - [0.076 \times$ vaccination coverage rate$])$.

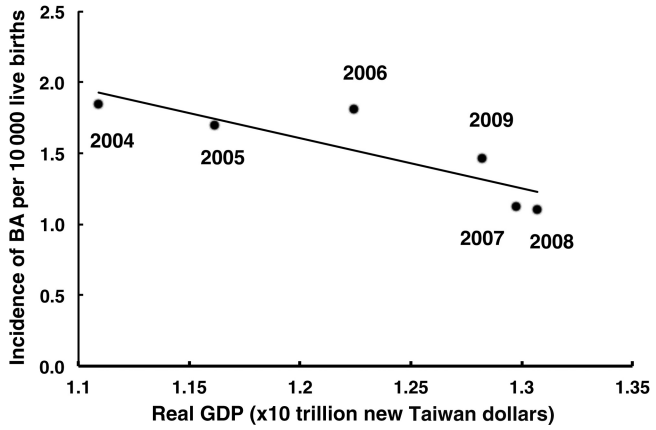

FIGURE 2
Negative association between GDP and BA incidences in 2004–2009 ($P = .02$). The Poisson regression was as follows: incidence of BA = exp(−6.0425 − [2.253 × real GDP]).

of patient numbers was less possible during this period.

A previous study showed seasonal changes in BA rates.[18] However, annual incidence reductions had not been reported previously. The findings provide support for theories that BA may be influenced by environmental exposure during pregnancy or in the perinatal period, racial composition changes in a region, or socioeconomic status changes. We also noted that, although there has been an obviously decreased incidence of BA in Taiwan since 2007, the incidence increased again in 2009, to 1.46 cases per 10 000 live births. There also may be a natural cycle and fluctuation. Therefore, the study will be continued to determine incidence changes and correlations with rotavirus vaccine coverage and socioeconomic status.

The association between BA and race was reported in 1974 by Shim et al,[5] on the basis of 20 cases. Those authors found wide variations in the incidence of BA among Chinese (3 cases per 10 000 live births), Filipino (2 cases per 10 000 live births), and white (0.6 cases per 10 000 live births) groups. In 1997, Yoon et al[11] reported a higher incidence among nonwhite infants (0.96 cases per 10 000 live births) than among white infants (0.44 cases per 10 000 live births). In 2004, Caton et al[16] reported that infants of black mothers were at higher risk for BA, with a risk ratio of 1.94, compared with infants of white mothers. In our study, the incidence among patients with mothers from Indonesia or Vietnam (0.8 cases per 10 000 live births) was one-half that among patients with Taiwanese mothers (1.54 cases per 10 000 live births). However, many fewer infants were born of mothers from Indonesia or Vietnam, compared with Taiwanese mothers, during the study period. Therefore, the BA incidence among infants in Taiwan was truly decreasing rather than reflecting changes in maternal population composition.

Viruses have been detected in liver specimens from infants with BA, with inconsistent results (eg, rotavirus, reovirus, Epstein-Barr virus, cytomegalovirus, and human herpesvirus).[25,26,29] An established animal model of virus infection in BA is rhesus rotavirus[30,31]; infection of murine neonates leads to obstructive cholangiopathy. Bondoc et al[32] reported that maternal vaccination against rhesus rotavirus could prevent the rotavirus-induced murine model of BA in newborn mouse pups, and Turowski et al[33] reported that oral vaccination with RotaTeq or Rotarix prevented most rhesus rotavirus-induced BA in a mouse model. Direct or indirect evidence of rotavirus vaccination effects on BA in humans is currently lacking. Clustering of the disease and incidence changes with time may help to elucidate whether infectious causes play an important role in direct ductal injury or postinfectious autoimmune-related ductal injury.[26,34,35] Although rotavirus vaccination is started at 2 months of age, which exceeds the average age of onset of BA, herd immunity might decrease rotavirus infection during pregnancy or in the perinatal period. Rotavirus vaccination was introduced in Taiwan in November 2006, when the reduction in BA incidence was first noted. A marginally significant negative correlation was found between the incidence of BA and the rotavirus vaccine coverage rate in 2006–2009 ($P = .07$). A longer observation period is needed for the development of rotavirus herd immunity, which may provide stronger evidence. Additional study of the yearly incidences of rotavirus diseases among infants and pregnant women, rotavirus immunity among pregnant women, and breastfeeding rates also may shed light on preventive interventions.

Economists use real GDP as the best indicator of general socioeconomic status. We identified a significant negative correlation between BA incidences and real GDP. The phenomenon showed that improvements in general socioeconomic status may correlate with decreasing BA rates. Improving socioeconomic status reflects better knowledge regarding disease, better health care, more-complete public health policy, and possibly less pathogen exposure during pregnancy and in the perinatal period, but more direct evidence is needed to explain the phenomenon.

CONCLUSIONS

In our study, the incidence of BA in Taiwan in 2004–2009 was 1.51 cases per

10 000 live births, which was 1.5 to 2 times higher than rates in Western countries, except French Polynesia. We noticed that the incidence of BA in 2007–2009 had obviously decreased, which had never been noted before. A contributing effect of maternal population composition changes on the reduction in BA incidences with time was carefully excluded. The incidence changes with time more possibly might be attributable to general socioeconomic status improvement. Herd immunity to rotavirus probably plays some role in the BA incidence reduction, but more-powerful evidence is needed, which may shed light on disease prevention.

ACKNOWLEDGMENTS

This work was supported by grants from the Bureau of Health Promotion, Department of Health, Taiwan (project 9804004A).

The members of the Taiwan Infant Stool Color Card Study Group are, in addition to the authors of this article, Pi-Feng Chang (Far Eastern Memorial Hospital), Ju-Bei Yen (Chang Gung Memorial Hospital, Chiayi, Taiwan), Chia-Hsiang Chu (Buddhist Tzu Chi General Hospital, Hualien, Taiwan), Ching-Chung Tsai (E-DA Hospital, Kaohsiung, Taiwan), Lung-Huang Lin (Cathay General Hospital), Shan-Ming Chen (Chung Shan Medical University Hospital), Chih-Cheng Chen (PingTung Christian Hospital, PingTung, Taiwan), and Te-Kuei Hsieh (Hsin-Chu General Hospital, Department of Health, Executive Yuan).

We are sincerely grateful to the Bureau of Health Promotion, Department of Health, Taiwan, for assistance and support, to Dr Wei-Ju Su, from the Centers of Disease Control, Department of Health, Taiwan, for assistance in collection of the data on estimated annual rotavirus vaccine doses, and to Chia-Chi Chi, for collection of the data from the Taiwan Infant Stool Color Card Study Group.

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Pediatrics 2011;128;e530; originally published online August 28, 2011; DOI: 10.1542/peds.2011-0742