

TEMPORAL TRENDS OF DENGUE FEVER/DENGUE HEMORRHAGIC FEVER IN BANGKOK, THAILAND FROM 1981 TO 2000: AN AGE-PERIOD-COHORT ANALYSIS

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Abstract. The aim of this study was to examine the effects of age, time period, and birth cohorts with dengue fever/dengue hemorrhagic fever (DF/DHF) in Bangkok, Thailand over the period 1981-2000. The age group at greatest risk for DF/DHF was 5-9 years old. The period effect shows a remittent pattern, with significant increases in 1986-1990 and 1996-2000. The birth cohort group showed a significant decreasing trend from the 1961-1965 group to the 1991-1995 group ($R^2 = 0.7620$) with a decreasing rate of 0.1. We concluded that the temporal trend of DF/DHF is decreasing; especially for DHF.

INTRODUCTION

Dengue virus infections are significant causes of morbidity and mortality in many areas of the world. It is believed to cause two clinical syndromes, namely dengue fever (DF) and dengue hemorrhagic fever (DHF). In Thailand, the epidemics occur every 3 to 5 years with peaks occurring during the rainy seasons (Nimmannitya, 2002). The incidence of disease was highest in 1987, but the case fatality rate gradually decreased to below 0.5% currently. The disease mostly affects children, with 95% of case reports occurring below age 15 years. The highest risk age group was between five and nine years old (Thongcharoen and Jetanasen, 1993). During subsequent outbreaks in most countries, the number of case reports in older age groups has increased (Thongcharoen and Jetanasen, 1993).

We determined the temporal trend of dengue disease in Bangkok from 1981 to 2000 by using an age-period-cohort (APC) model to analyze incidence rates of disease in a unified framework. Children prone to dengue may have biological susceptibility to dengue virus determined

by age. The incidence of dengue disease, cases, which varies from year to year, has an effect on public health intervention programs and vector control. Cohort groups, born in the same year, have a cumulative effect from exposure to different dengue virus serotypes in the past, and determine the trends of the disease. DF and DHF differ in pathogenesis. The different trends may explain the changes in epidemiology of dengue disease.

MATERIALS AND METHODS

The method of model building was modified from Clayton and Schifflers (1987a,b). Using the Bangkok dataset from the Center of Epidemiological Information, Bureau of Epidemiology, Ministry of Public Health, Thailand provides demographic information related to dengue disease occurring 1981 to 2000, including patient age and calendar year of infection. These groups were defined in 5-year intervals so there were 4 period groups and 4 age groups. The four age groups were: 0-4, 5-9, 10-14 and 15+ years old. Data were displayed in a two-way table by period groups and age groups in Table 1. Age specific incidence rates per year were calculated using the number of dengue disease cases per age group as a numerator and the number of population per age group in Bangkok from the Human

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Table 1

Age specific rates per 1,000 person-years arranged by 5-year age groups and 5-year periods. Cohorts are 5 years wide following diagonal lines.

Age group	Period				Cohort
	1981-1985(1)	1986-1990(2)	1991-1995(3)	1996-2000(4)	
0 - 4(1)	1.25	2.04	0.83	2.36	1991-1995 (4)
5 - 9(2)	2.62	3.85	1.51	4.15	1986-1990 (3)
10-14(3)	1.74	2.94	1.02	2.93	1981-1985 (2)
15+(4)	0.09	0.18	0.07	0.30	
Cohort	1961-1965(5)	1966-1970(6)	1971-1975(7)	1976-1980(1)	

Resources Planning Division, National Economic and Social Development Board, as a denominator. This was traced back to the year of birth in a diagonal line. The defined birth cohort groups were from 1961-1965 to 1991-1995 using the birth cohort group 1976-1980 for a reference group.

The Age-Period-Cohort (APC) model is in log-linear form as below;

$$\ln \lambda_{ap} = \mu + \alpha_a + \beta_p + \gamma_k$$

λ_{ap} represents the unknown true incidence rate, which is cross-classified by age and period. The μ is a constant term. α_a , β_p , γ_k are parameters representing the effects due to age, period, and cohort, respectively. Relative risk is interpreted by the exponential form of these parameters. The Poisson regression was performed to construct the APC model. Parameters were estimated by means of maximum likelihood using statistical packages STATA version 6 to perform generalized linear modeling (Swan *et al.*, 1993). The goodness of fit was assessed by the deviance (D), which was close to its residual degrees of freedom (df). If the number of dengue cases was large, so that the variance was more than the mean of the cases, it calls over dispersion. Then using the negative binomial model by the STATA program version 6, it adjusted the APC model. We used the less formal Akaike's Information Criterion (AIC=deviance-2df) for judgment of the adequacy of the models. The most appropriate model was the lowest AIC model (Arbyn *et al.*, 2002). After that, we used the AFRIMS dataset (containing specimens collected from patients admitted to QSNICH in Bangkok) adjusted by the age spe-

Table 2
Model selection.

Model	Residual		p-value	AIC (D-2df)
	Deviance	df		
Null	145,538.50	15	0.0000	145,508.5
Age	15,463.82	12	0.0000	15,439.82
Age-Period	1,032.11	9	0.0000	1,014.11
Age-Cohort	12,626.66	6	0.0000	12,614.66
Age-Period-Cohort	445.55	4	0.0000	437.55
APC with extra-Poisson	0.11	4		-7.89

cific rate for the Bangkok dataset, and separate them into DF and DHF, and then did the same as the Bangkok dataset.

RESULTS

Temporal trends of dengue disease

The model selection was estimated by the model that its deviance was close to its residual degrees of freedom. From Table 2, the residual deviance of the full APC model was 445.55 for degrees of freedom (df) = 4. The corresponding χ^2 test ($p = 0.000$) indicates an unsatisfactory prediction of the observed number of cases, assuming only Poisson variation, but allows for overdispersion that adjusts by negative binomial distribution, yielded a deviance of 0.11, approximating the degrees of freedom and the lowest AIC, indicating an acceptable fit (Fig 1).

The relative risks of dengue disease in different age groups (age effect) as derived from the APC model. The age group 5-9 is the highest peak

TEMPORAL TRENDS OF DF/DHF IN BANGKOK, THAILAND

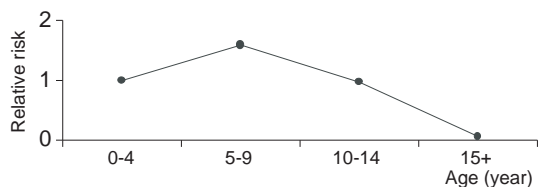


Fig 1—Relative risk of dengue disease in each age group using the APC Model.

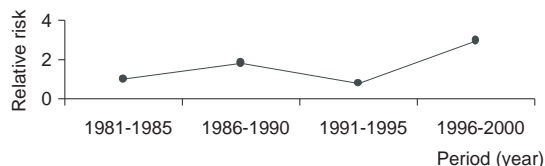


Fig 2—Relative risk of dengue disease in each period using the APC Model.

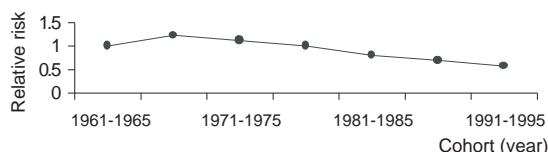


Fig 3—Relative risk of dengue disease in each cohort group using the APC Model.

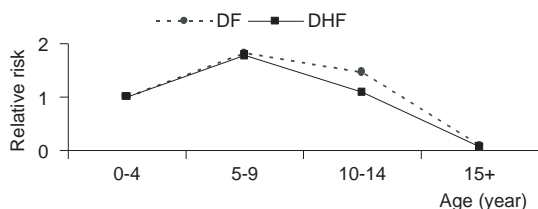


Fig 4—Relative risks of DF and DHF in each age group from the APC Model.

and the most at-risk group. The age groups 5-9 and 15+ have 1.59 and 0.06 times the risk of the age group 0-4 (the reference age group), respectively ($p < 0.05$). The lowest risk group is the age group 15+ years old (Fig 2).

The periods 1986-1990 and 1996-2000 are different from the reference period (1981-1985) ($p < 0.05$) with relative risks of 1.80 and 2.96, re-

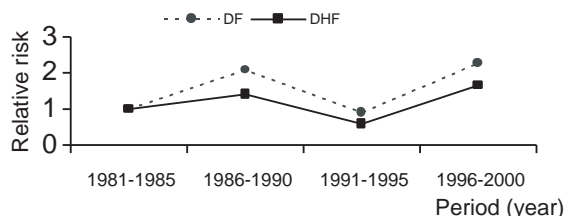


Fig 5—Relative risks of DF and DHF in each period using the APC Model.

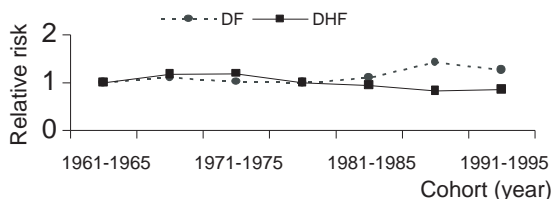


Fig 6—Relative risks of DF and DHF in each cohort group using the APC Model.

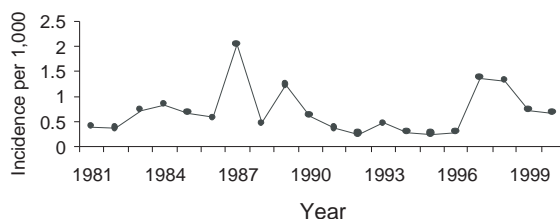


Fig 7—Incidence rate of DF and DHF per 1,000 in Bangkok by year 1981-2000.

spectively. The period 1991-1995 had the lowest relative risk, but there was no significant difference (Fig 3).

The relative risk of dengue disease increased from the cohort group 1961-1965 to the cohort group 1966-1970 then declined to the cohort group 1991-1995. When using the linear regression model, we found that the coefficient of determination (R^2) equaled 0.7620 and the coefficient parameter was -0.10, ($p < 0.05$). The relative risk for dengue disease has a decreasing linear trend.

Temporal trends of DF

We selected the age-period-cohort for fitting model with a deviance of = 5.19, $df = 4$ and $p > 0.05$ (Fig 4).

The age group 5-9 had the highest peak and was the most at risk group. The age groups 5-9 and 15+ had significant 1.82 and 0.09 times the

risk of the age group 0-4 (the reference age group), respectively ($p < 0.05$). The lowest risk group was the age group 15+ years old (Fig 5).

The relative risk was lowest in 1991-1995 and highest in 1996-2000, but these were not significantly different. In 1986-1990, the relative risk was 2.08 ($p < 0.05$) (Fig 6).

We determined the trend of DF by using linear regression of the relative risk in each cohort group. We found the trend DT DF slightly increased at a rate equal to 0.05 and the coefficient of determination (R^2) was 0.5207 ($p = 0.067$).

Temporal trends for dengue hemorrhagic fever

We selected the age-period-cohort for fitting model with a deviance = 2.02, $df = 4$ and $p > 0.05$ (Fig 4).

The age group 5-9 years old had the highest relative risk, followed by the age groups 10-14, 0-4, and 15+ years old with relative risks of 1.78, 1.09, 1.00, and 0.07, respectively. The age groups 5-9 years old and 15+ years old were different from the reference age group (0-4) with p -value < 0.05 (Fig 5).

The relative risk was lowest in 1991-1995 and highest in 1996-2000. The periods 1986-1990 and 1991-1995 were significantly different from the reference period (1981-1985) with relative risks of 1.41 and 0.58, respectively (Fig 6).

We determined the trend for DHF by using linear regression of the relative risk in each cohort group. We found the trend for DHF to be declining slightly at rate of -0.05 ($p < 0.05$) with a coefficient of determination (R^2) of 0.577.

DISCUSSION

APC analysis had been used to determine the trends of incidence rates and mortality rates of diseases which result from past cumulative environmental effects such as cancer and chronic diseases. This birth cohort effect provides an assessment of the relative risk, which was compared to other birth cohorts. Our analysis established decreasing trends of dengue disease risk for birth cohort 1961-1965 to birth cohort 1991-1995. The cumulative effect is noted as a decrease, at a rate of approximately 0.10 per each cohort group.

When we separated DF and DHF, DF was slightly increasing, with a rate of 0.05 per each cohort group, but this was not significant and DHF was decreasing ($p < 0.05$) at a rate of 0.05 for each cohort group. DF and DHF occur by different mechanisms: DF does not need immune enhancement, like DHF (Rothman, 1997) and it can occur with the primary infection. If the primary infection increases (Nisalak *et al*, 2003), DF will also increase. As for DHF, the significant decreases may be due to a primary infection in hyperendemic areas which can protect from secondary infection due to immune enhancement. Another reason for the decrease in DHF is that it may be due to a decrease in the percentage of serotype 2, which usually causes the most severe cases of dengue disease (Sangkawibha *et al*, 1984). A change in percentage of serotypes may cause a change in trends for DF and DHF.

The period effect seemed to waxing and waning, especially for DHF. This pattern can be explained by herd immunity, when it increases, the incidence of DF and DHF will decrease, and when it decreases, the incidence of DF and DHF will increase. The other reasons may be the dynamics of the population and the emerging of a new genotype. Dengue disease will have epidemics every 3 to 5 years, as in most Southeast Asian countries (Fig 7) (Nimmannitya, 2002).

The high-risk age group in this study was 5-9 years old, similar to other studies in Thailand (Thongcharoen and Jetanasen, 1993) but we could not interpret the trends for each age group, because they were not significant in the linear model. The relative risk for each age group with DF and DHF is the same, the highest in 5-9 years old and the lowest in 15+ years old. Although they have different pathogenesis, DHF occurs from immune enhancement (Rothman, 1997) and usually occurs with a second infection (Fischer and Halstead, 1970). Decreasing trends of DHF may be from JE vaccination or the decreasing in the age group 15+ of population and increasing trends of DF may be from doctors and parents more concerning in DF than before. So the diagnosis of DF increases.

We can conclude that the APC model has a benefit in determining the trend for dengue disease infection. The trend for dengue disease is

decreasing, especially for DHF. It helps us to detect early the change in the epidemiology of dengue disease.

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REFERENCES

- Arbyn M, Van Oyen H, Sartor F, Tibaldi F, Molenberghs G. Description of the influence of age, period and cohort effects on cervical cancer mortality by loglinear Poisson models (Belgium, 1955-94). *Arch Public Health* 2002; 60: 73-100.
- Clayton D, Schifflers E. Models for temporal variation in cancer rates. I : Age-period and age-cohort models. *Stat Med* 1987a; 6: 449-67.
- Clayton D, Schifflers E. Models for temporal variation in cancer rates. II : Age-period and age-cohort models. *Stat Med* 1987b; 6: 469-81.
- Fischer DB, Halstead SB. Observations related to pathogenesis of dengue hemorrhagic fever. *Yale J Biol Med* 1970; 42: 329-49.
- Nimmannitya S. Dengue hemorrhagic fever: current issue and future research. *Asian-Oceanian J Pediatr Child Health* 2002; 1: 1-20.
- Nisalak A, Timothy P, Endy T, Nimmannitya S, *et al.* Serotype-specific dengue virus circulation and dengue disease in Bangkok, Thailand from 1973 to 1999. *Am J Trop Med Hyg* 2003; 68: 191-202.
- Rothman AL. Viral pathogenesis of dengue infections. In: Gubler DJ, Kuno G, eds. *Dengue and dengue hemorrhagic fever*. New York: CAB International, 1997; 1: 257-61.
- Sangkawibha N, Rojanasuphot S, Ahandrik S, *et al.* Risk factors in dengue shock syndrome: a prospective epidemiologic study in Rayong, Thailand. I. The 1980 outbreak. *Am J Epidemiol* 1984; 120: 653-69.
- Swan T, Bradley M, Green P, *et al.* GLIM 4: The statistical system for generalized linear interactive modelling. In: Francis B, Green M, Payne C, eds. Oxford: Oxford University Press, 1993.
- Thongcharoen P, Jatanasen S. Epidemiology of dengue and dengue hemorrhagic fever. Monograph on dengue/dengue hemorrhagic fever. New Delhi: WHO SEARO Publication, 1993; 22: 1-8.