Predisposing Factors of Dengue Cases by Random Effect Model in the Largest Dengue Haemorrhagic Fever Epidemic in Taiwan in 1998

By

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Abstract

In November 1998, the largest officially-documented dengue haemorrhagic fever (DHF) epidemic since 1943 occurred in Taiwan. This epidemic resulted in more than 110 dengue fever (DF) cases and at least 36 DHF cases. A case-control study was conducted to explore the risk factors of dengue infection. Thirty-four cases and 68 matched controlled cases were included for statistical analysis. After further adjusting the confounders and intra-household correlation by random effect model, three distinctive risk factors were identified. These were: the presence of empty houses, spare tyres, neighbourhood ponds or temples (OR=3.17, 95% CI: 0.95-10.63) which was first identified in the papers, water containers with covers in the house (OR=5.77, 95% CI=1.08-30.8), and screened windows and doors (OR=0.71, 95% CI=0.32-0.89). Control measures were aimed at these risk factors and the epidemic subsided in January 1999 when the last dengue case was reported.

Key words: Dengue, predisposing factors, Arbovirus, Epidemiology, Taiwan.

Introduction

The dengue virus infection is the most common arthropod-borne disease worldwide, with an increasing incidence in the tropical regions of the Americas and Asia, including Taiwan. The spectrum of dengue diseases ranges from the febrile flu-like illness, DF, to the severe forms of DHF and dengue shock syndrome (DSS) with high morbidity and mortality. The virus is primarily transmitted by mosquitoes, *Aedes*

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aegypti and *Aedes albopictus*. It is estimated that around 100 million cases of DF occur worldwide and over 200,000 DHF/DSS cases are reported to the World Health Organization (WHO) every year[1-4].

Following a nearly 40-year silence of dengue epidemic since 1942-43, the dengue virus serotype 2 (DEN-2) was introduced into Hsiao-Liu-Chiu, an islet off southern Taiwan in 1981, which caused over 1,700 dengue cases[5]. Since then, different sizes of outbreaks have been reported from different locations in Taiwan. The Department of Health established several surveillance systems to detect dengue patients, including doing active and passive surveillance. In 1998, Tainan, an urbanized city in southern Taiwan, exploded with the largest epidemic of DHF in Taiwan in the last 30 years. This epidemic resulted in more than 110 DF cases and at least 36 DHF cases. A case-control study was conducted to investigate the predisposing factors for the risk factors for the infection.

Many epidemiological studies of dengue epidemics have focused on using a statistical method of logistic regression for independent measures on cases and controls. However, dengue cases usually cluster in certain local areas, and this type of clustering reflects common environment in the sampling block or other unknown factors. A unique feature of those clustering dengue cases was that they exhibited intra-cluster and inter-cluster correlation. Therefore, we used the random effect model with the generalized estimation equation (GEE) approach developed by Liang and Zeger (1986)[6] to analyse the possible correlation of the clustered data collected after our outbreak investigation.

Materials and methods

Study populations

Tainan city is located in tropical southern Taiwan. Our study populations involved laboratory-confirmed dengue cases. The case group recruited at least one confirmed dengue case within one house unit while the control group recruited local residents who were both dengue-IgM sero-negative and without febrile illness, within one month of our interview during the epidemic period. This neighbourhood control group selected those who lived in different *lings* (the official name of sub-district area) from the cases but in the same *li* (the official district covering areas larger than ling). One case was matched with two neighbourhood controls. If the possible source(s) of infection for cases were judged from the working or school sites, the controls were then also selected from the same *ling* of the working or school sites of the cases.

Household interview and environmental inspection

All cases and controls were interviewed blindly by the interviewer, and standardized on the appraisal of environmental conditions such as vector-breeding sites, screens and sanitary conditions in the subjects' living places, including markets, open sewers or ditches within 50 metres. The questionnaire was designed as structured and pre-tested. The variables in the questionnaire included general demographical characteristics, past or present existence of mosquito-breeding sites on the premises (including water-storage tanks, flower vases, tin cans, containers, unused tyres, flower vases, water trays of the refrigerator), use of screens on windows and doors, types of screen, travel history, presence of pets, indoor spray of insecticides, use of traps or mosquito coils, size of household, type of housing and population density in each house. Both the medical history and blood samples were taken from all family members in each household.

Table 1. *Univariate analysis of dengue virus infection by predisposing risk factors in case and control groups in 1998 in Tainan, Taiwan*

Risk Factors	Cases	Controls	Odds Ratios	95% Confidence Intervals
Empty house, spared tyres, pond or temple around				
Yes	24	37	2.011	0.835-4.841
No	10	31		
Water containers around the house				
Yes	7	27	0.409	0.156-1.074
No	26	41		
Water containers without covers around the house			0.373	0.127-1.098
Yes	5	22		
No	28	46		
Planting at backyard				
Yes	21	47	0.722	0.305-1.709
No	13	21		
Planting with plates at backyard				
Yes	1	7	0.272	0.032-2.311
No	32	61		
Water containers inside house				
Yes	11	18	1.329	0.541-3.261
No	23	50		
Water containers with covers inside the house				
Yes	19	40	0.887	0.386-2.037
No	15	28		
Discarded trash				
Yes	15	34	0.789	0.345-1.805
No	19	34		
Refrigerator with plates				
Yes	6	21	0.497	0.179-1.384
No	27	47		

Laboratory diagnosis

Acute-phase serum samples were collected from patients within seven days after the onset of fever and stored in –70ºC freezer for reverse transcriptase-polymerase chain reaction (RT-PCR) and virus isolation[7]. If the results were negative, the convalescent serum was withdrawn for antibody confirmation by the dengue virus specific IgM-ELISA method[8].

Statistical analysis

Data were entered in Epi-Info 6.0 and double validated. For better correlation analysis, a household was used as the analysis unit. Dengue cases which flocked together were classified as a cluster, and seven clusters in total were determined because each cluster potentially shared the same environmental factors attributed to the transmission of dengue virus. The odds ratio and 95 per cent confidence interval were calculated by univariate analysis. The random effect model with GEE was used for adjusting the confounders by using the statistical analysis system computer package (SAS release 6.12). For hypothesis testing, a α-level of 0.05 was chosen.

Results

Of the 141 confirmed dengue cases, 81 cases agreed to participate and were interviewed. However, some of them were from the same household or no compatible controls were found. Therefore, 34 cases in total were included for data analysis. None of these cases had travelled abroad during the year of the epidemic, nor had they been diagnosed as dengue patients before. Sixty-eight geographically-matched and selected neighbourhood controls were interviewed for analysis.

Table 2. *Univariate analysis of dengue virus infection by predisposing protective factors in case and control groups in 1998 in Tainan, Taiwan*

Protective Factors	Case	Control	Odds ratio	95% confi-dence interval
Screened windows				
Yes	18	41	0.89	0.56-1.34
No	16	27		
Screened doors				
Yes	16	33	0.77	0.61-1.28
No	18	35		
Screened Windows and doors				
Yes	22	46	0.85	0.64-1.19
No	12	23		
Use mosquito coil, insecticide, repellent or sleeping net				
Yes	18	49	0.436	0.185-1.028
No	16	19		

The univariate analysis showed that the risk of contracting dengue virus infection was not associated with factors such as empty house, spared tyres, presence of a pond or a temple around the house or water containers in or around the house, water containers with or without lid, planting at the backyard with or without water plates, discarded trash, presence of water plates at the bottom of refrigerators, and the size and number of residents in each house (Table 1). In other words, all those major predisposing risk factors were found to be not statistically significantly associated with the dengue virus infection in l998 in Tainan. On the other hand, protective factors such as screened doors, screened windows or the use of mosquito coils, insecticides, mosquito repellents or sleeping nets were also not significantly associated with the dengue virus infection (Table 2).

Table 3. *Multivariate analysis of dengue virus infection by random effect model in case and control groups in 1998 in Tainan, Taiwan*

	Coeffi-cient	Standard deviation	OR (95%CI)[a]
INTERCPT	-0.6273	0.7434	
With empty house, spared tire, pond or temple around	1.1544	0.6168	3.17(0.95-10.63)*
Use mosquito coil, insecticide, repellent or sleeping net	-0.7794	0.6145	0.46 (0.14-1.53)
Water containers around the house	0.4926	0.6585	1.64 (0.45-5.95)
Water containers in the house and with covers	1.7534	0.8542	5.77 (1.08-30.8)*
Discarded trash	0.2208	0.4619	1.25(0.5-3.1)
Water containers around the house and without covers	0.3164	0.4225	1.37(0.6-3.14)
Screened Windows and doors	-0.3436	0.1143	0.71(0.32-0.89)*
Doors open frequently	0.0903	0.0709	1.09(0.95-1.26)

[a] CI: confidence interval

*$p < 0.05$ with statistical significance

After further adjusting for confounders by multivariate analysis of the random effect model, we found that the presence of empty house, spared tyres, neighbourhood pond or temple odds ratio (OR) = 3.17, 95% confidence interval (CI: 0.95-10.63), water containers with covers in the house (OR= 5.77,95% CI = 1.08-30.8) and screened windows and doors (OR = 0.71, 95% CI = 0.32-0.89) were statistically significantly associated with dengue infection (Table 3).

Discussion

The risk factors of the dengue virus infection that had been documented previously were wooden housing, absence of screens on windows or doors, existence of mosquito breeding sites on the premises, and presence of domestic animals[(9-13)]. Our case-control study demonstrated that the three major risk/protective factors associated with contracting the dengue virus infection were: (1) empty containers in the house; (2) empty houses or ponds around the dwelling; and (3) screen on both windows and doors. Since dengue virus is primarily transmitted by mosquitoes, empty containers serve as the best breeding places close to local residents in epidemic areas. On the other hand, screened windows and doors acted as protective shields when the mosquito tried to fly into the house from outside. Therefore, these two factors were consistent with previous findings[(10-13)]. In addition, we first identified the emergent factor (our third factor) of empty houses or ponds around living premises which were associated with the dengue virus infection in Tainan [odds ratio = 3.17 (95%CI: 0.95-10.63)]. In fact, Tainan city is an old city with many old buildings, many of them being empty. Those old buildings which were filled up with trash provided the best breeding sites for mosquitoes and usually were neglected by public health practitioners and environmental inspectors. Therefore, mosquito density around empty houses should also be monitored for better prevention and control of dengue.

Dengue fever is a mosquito-borne disease and the risk of a person contracting the disease is largely determined by individual attributes, household conditions and environmental factors[14]. The transmission of dengue virus by mosquitoes, particularly *Aedes aegypti,* tends to be localized and clustered in the same household. Previous studies separated the risk factors at individual level from environmental level to avoid intra-household correlation because more than one case per household may have occurred. However, this kind of approach may neglect inter-household correlation, especially considering environmental factors among households as independent variables. In this study, we took the inter-household correlation into consideration by using the random effect model and showed a better statistical method to search for environmental factors contributing to the transmission in different localities. Future studies should also pay attention to the intra-household correlation for a better understanding of the dengue virus transmission at three major different levels: individual, household and environment.

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References

1. Duane J Gubler. Dengue and dengue haemorrhagic fever. Clinical Microbiology Reviews, July 1998, 11(3): 480-496.

2. William JH Mcbride and Helle Bielefeldt-Ohmann. Dengue viral infections; pathogenesis and epidemiology. Microbes and Infection, 2000, 2:1041-1050.

3. Fransisco P Pinheiro and Stephen J Corber. Global situation of dengue and dengue haemorrhagic fever and its emergence in the Americas. Wld Hlth Statist Quart 1997, 50: 161-169.

4. Anonymous. Dengue/Dengue hemorrhagic fever: The emergence of a global health problem. Emerging Infectious Diseases. Apr-Jun 1995, 1(2): 55-57.

5. Wu YC. Epidemic dengue 2 on Liouchyou Shiang, Pingtung County in 1981. Chinese J Microbiol Immunol 1986, 19: 203-211.

6. Zeger S and Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986, 42: 121-130.

7. Robert S Lanciotti, Charles H Calisher, Duane J Gubler, Gwong-Jen Chang and A. Vance Vorndam. Rapid detection and typing of dengue viruses from clinical samples by using reverse transcriptase-polymerase chain reaction. Journal of Clinical Microbiology. Mar 1992, 30(3): 545-551.

8. Chow L, Sun HC, Chen HY, Lin SY and WU JS. Detection and differentiation of dengue-1 from Japanese Encephalitis virus infections by ABC MAC-ELISA. Chinese J Microbiol Immunol 1992, 25: 172-180.

9. Linnette Rodriguez-Figueroa, Jose G Rigau-Perez, Erick L Suarez and Paul Reiter. Risk factors for dengue infection during an outbreak in Yanes, Puerto Rico in 1991. Am J Trop Med Hyg 1995, 52(6): 496-502.

10. Waterman SH, Novak RJ, Sather GE, Bailey RE, Rios I and Gubler DJ. Dengue transmission in two Puerto Rican Communities in 1982. Am J Trop Med Hyg 1985, 34: 625-632.

11. Ko YC, Chen MJ, Yeh SM. The predisposing and protective factors against dengue virus transmission by mosquito vector. Am J Epidemiol 1992, 136: 214-220.

12. Moore CH, Cline BL, Ruiz-Tiben E, Lee D, Romney-Joseph H, Rivera-Carrea E. *Aedes Aegypti* in Puerto Rico: environmental determinants of larval abundance and relation to dengue virus transmission. Am J Trop Med Hyg 1978, 27: 1225-1231.

13. William JoHn Hannan McBride, Helen Mullner, Reinhold Muller, Justin Labrooy and Ian Wronski. Determinants of dengue 2 infection among residents of Charters Towers, Queensland, Australia. Am J Epidemiol. 1998, 148(11): 1111-1117.

14. Goro Kuno. Review of the factors modulating dengue transmission. Epidemiologic Reviews 1995, 17(2): 321-335.