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Early Warning System (EWS) for Dengue in Indonesia and Thailand

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ABSTRACT

Mohammad Juffrie, Dana A. Focks - ***Early Warning Systems (EWS) for Dengue in Indonesia and Thailand***

Background: Dengue virus infection is an acute febrile disease caused by 4 sero-type viruses. The transmission via mosquito vector *Ae. Aegypti*. The morbidity of dengue virus infection is quite high and the mortality below 5%. The most dangerous form is dengue shock syndrome, the mortality is very high. The effort to reduce morbidity and mortality is improvement of the clinical management and control of vector. Today, most dengue control efforts are based on suppression of *Aedes aegypti* (L.) and not eradication. EWS would provide significant utility where mitigation methods were available. EWSs were possible for three reasons, an extensive time series on the disease incidence the available, dengue being a vector-borne disease, is significantly influenced by weather, in many sub-regions of SE Asia, weather anomalies are significantly influenced by and lag behind several months, sea surface temperature (SST) anomalies.
Methods: Analytic cross sectional study was conducted. The dependant variable in this analysis, *Epi.yr.* is dichotomous and indicates whether an epidemic occurred during a particular year. The two independent (predictor) variables are sea surface temperature anomalies as reported by the Japanese Meteorological Association (JMA) and previous cases. The monthly number of cases were dengue and DHF in Yogyakarta, Indonesia and the metropolitan area of Bangkok, Thailand.
Results: Yogyakarta, many years were very near the epidemic cutoff of 278 cases, yet only one year, 1992 with 237 cases, was incorrectly labeled. The false positive in 1992, had a probability of 0.64 of epidemic and 0.36 of no epidemic. Bangkok, the best three-month prediction gave 6 false indication in 35 years, 5 false negatives, 1 false positive. For two month prediction, 3 errors in 35 years were made, 2 false negatives, 1 false positive.
Conclusion: The results presented in this study is very use full for predicting the incidence of dengue virus infection using weather data. This method would only require a simple calculator, or preferably a PC using the derived equation.

Key words: dengue - incidence - early warning - weather - probability

ABSTRAK

Mohammad Juffrie, Dana A. Focks -***Sistem deteksi dini infeksi virus dengue di Indonesia dan Thailand***

Latar belakang: Infeksi virus dengue adalah penyakit demam akut yang disebabkan oleh 4 serotipe virus. Penularan melalui vector yaitu nyamuk Aedes Aegypti. Angka kesakitan infeksi virus dengue tinggi dengan angka kematian dibawah 5%. Bentuk yang paling berat adalah sindroma syok dengue dimana angka kematiannya tinggi. Usaha untuk menurunkan angka kesakitan dan kematian adalah peningkatan pengeloiaan klinis dan pengendalian vector. Umumnya usaha pengendalian dengue didasarkan pada penekanan Aedes Aegypti dan eradikasi. EWS akan memberi kegunaan yang bermakna didaerah dimana metode mitigasi tersedia. EWS mempunyai 3 alasan yaitu memberikan data insidensi secara berurutan, dengue sebagai penyakit menular melalui vector yang dipengaruhi oleh musim, dan cuaca serta temperatur di Asean tak menentu.
Metode: penelitian ini adalah penelitian cross sectional analitik. Variabel tergantung adalah *Ep.Yr.* adalah suatu dikotomi yang memperjelas apakah suatu epidemik terjadi sepanjang waktu satu tahun. Variabel bebas adalah

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predictor yaitu anomali suhu permukaan laut yang didapat dari JMA dan kasus dengue sebelumnya. Kasus dengue dilaporkan dari Yogyakarta dan Bangkok

Hasil : Yogyakarta, selama beberapa tahun jumlah kasus mendekati cut off epidemic yaitu 278 kasus, hanya 1 tahun yang tidak yaitu 1992 dengan 237 kasus. Pada 1992 terjadi false positive dengan probabilitas 0.64 dari epidemic dan 0.36 dari non epidemic. Bangkok, 3 bulan terbaik untuk prediksi dengan false 6 kali dari 35 tahun, 5 false negative, 1 false positive. Untuk 2 bulan prediksi terdapat 3 kesalahan dalam 35 tahun yaitu 2 false negative dan 1 false positive.

Simpulan: hasil yang dipresentasikan ini sangat berguna untuk memprediksi insidensi infeksi virus dengue dengan memakai data cuaca. Metodanya hanya membutuhkan kalkulator biasa atau perangkat komputer dengan equasi

INTRODUCTION

Globally, dengue viruses are currently considered to be the most important arthropod-borne viruses transmitted to man - whether measured in terms of the number of human infections or the number of deaths.[1,2] The vector is the yellow fever mosquito, *Ae. aegypti* which breeds in domestic and peri-domestic containers such as flower vases, abandoned tires, and drums. During the last 40 years, all 4 serotypes of dengue virus have spread to virtually all receptive areas of the tropical world including Africa, the Pacific, and the Americas.[3] In the 1950s, a more dangerous form of dengue fever involving hemorrhage and a shock syndrome (DHF/DSS) appeared in Southeast Asia. Primarily affects children of local populations in endemic areas, and the untreated fatality rate was sometimes as high as 30-40%.[5] Today, dengue viruses remain among the leading causes of childhood hospitali-zation in many urban centers in Asia.[4] In the past decade, DHF/DSS appeared in the New World,[5] the first major epidemic occurred in Cuba in 1981[5] and the second in Venezuela in 1990.[7] In the 1980s, intermittent DHF/DSS was confirmed or suspected in perhaps 14 additional countries within the hemisphere.[8] Recently, compelling reasons have been voiced that DHF/DSS will increasingly become a serious public health issue in the Americas paralleling the experience of Southeast Asia in the 1950s and '60s.[9,10] The deteriorating situation is attributed to population growth and essentially uncontrolled urbanization, the frequent introduction of virus through human movements, and the almost universal absence of adequate control of the primary urban vector, *Aedes aegypti*.[11,12,13]

The threat of urban yellow fever earlier this century was sufficient to prompt the eradication of *Ae. aegypti* from most countries in Central and South America.[14] This effort was vertically-orientated, a paramilitary operation largely developed and funded by the Rockefeller Foundation with later participation by the Pan American Health Organization.[15] The impetus for eradication was lost, however, with the discovery of the sylvan cycle of the virus and a growing realization that eradication efforts, unless global, were futile.[16] Gains made in the 1950s and '60s were not maintained, and today, most formerly *Ae. aegypti*-free areas have become reinfested.[9] The developing situation of hyper-endemicity involving multiple serotypes and the resulting specter of DHF/DSS in a growing number of areas have prompted a re-evaluation of dengue control strategies.[15,17] It is obvious that until a vaccine becomes available for widespread use, control of dengue will continue to rely on the vector control Today, most dengue control efforts are based on suppression of *Aedes aegypti* (L.) and not eradication; increasingly, these efforts rely on reducing the number of larval breeding habitats and not on insecticides.[18,19,20]

A recent NRC publication investigating the feasibility of developing practical and sustainable early warning systems (EWS) for infectious diseases concluded that EWS would provide significant utility where mitigation methods were available.[21] Their primary value lies in the ability to temporally focus scarce resources for control in those periods when epidemics were likely. The work described herein describes the development of a statistical EWS for dengue in SE Asia for dengue and dengue hemorrhagic fever (DHF). EWSs were possible for three reasons: 1) An extensive time series on disease incidence was available, and 2) dengue, being a vector-borne disease, is significantly influenced by weather.[22] Finally, 3) in many subregions of SE

Asia, weather anomalies are significantly influenced by and lag behind several months, sea surface temperature (SST) anomalies.

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METHODS

This study used analytic cross-sectional design. The dependant variable in this analysis, *Epi.yr*, is dichotomous and indicates whether an epidemic occurred during a particular year. We define an epidemic as follows: Determine the mean and standard deviation (SD) total number of cases during the peak months of transmission (March—May and July—October, for Yogyakarta and Bangkok, respectively) for the period of record. When the period mean plus the SD is exceeded for a particular year, *Epi.yr* is true, otherwise, false. The monthly number of cases of dengue and DHF in Yogyakarta, Indonesia (located on the south central coast of Java) (FIGURE 1) and the metropolitan area of Bangkok, Thailand (FIGURE 2), respectively. The two independent (predictor) variables are sea surface temperature anomalies as reported by the Japanese Meteorological Association (JMA) and previous cases. The physical area monitored by the JMA series spans a rectangular region between 90 and 150° E and 10° N to 10° S. This variable is significantly correlated with subsequent air temperature anomalies in the region. Because temperature influences, among a host of other factors, the gonotrophic cycle length and the rapidity of viral dissemination within the vector, *Ae. aegypti*, anomalous temperatures are strong correlates of transmission intensity influencing the biting rate and the proportion of infectious females (FIGURE 3). Lagged cases are included as a correlate because past cases serve as a proxy for the types of virus circulating and the nature of human anti-body types present—a function of previous dengue activity. Note that both of these variables are routinely collected and do not require additional information from dengue control operations in the area; this has important ramifications regarding practicality and sustainability by control specialists.

Binary logistic regression is used in this analysis. It is a useful approach when modeling binary responses where there are multiple descriptors and continuous variables, e.g., *Epi.yr*, cases and SST anomalies. We use the following form:

$$\text{Prob}\{\text{Epi.yr} = 1|X\} = [1 + \exp(-X\beta)]\text{-}1 \quad (1)$$

X represents the vector of independent variables, e.g.,—

$$\text{X1} = \text{cases t-3mo},\ \text{X2} = \text{cases t-4mo},\ \text{X3} = \text{SSAa t-3, etc.} \quad (2)$$

and

$$\text{X}\beta = \beta 0 + \text{X1}\,\beta 1 + \text{X2}\,\beta 2 + \ldots + \text{Xk}\,\beta. \quad (3)$$

We estimated regression parameters *β* by the method of maximum likelihood.

RESULTS

Yogyakarta. We were able to successfully categorize correctly three months in advance whether a year experienced an epidemic with only a single failure in 1992. The independent variables were cases and SST anomalies in the preceding months of November and December. This means that by the end of December in a particular year, one has a very good indication of the nature of next year's dengue epidemic activity beginning in March, and whether efforts should be anticipated to mobilize control efforts. The equation derived is as follows:

$$\text{Epi.yr} = [1 + \exp(-9.093 + 0.056*\text{Prev.Oct.cases} + 0.060*\text{Prev.Nov.cases} - 39.168*\text{Prev.Oct.JMA} + 41.725*\text{Prev.Nov.JMA})\text{-}1 \quad (4)$$

Many years were very near the epidemic cutoff of 278 cases (1986, 1992, 1994, and 1995) yet only one year, 1992 with 237 cases, was incorrectly labeled. Note however, that the false positive in 1992, had a probability of 0.64 of epidemic and 0.36 of no epidemic; probabilities this near to the cutoff probability of 0.50 would alert control personnel that possible epidemic conditions could develop and should look to the epidemic probabilities with lead times of two and one months (to be developed).

Bangkok. We could not develop in this initial work a three-month forecast with sufficient skill to stand alone. We therefore developed, in addition to the three-month forecast, probability equations for lags of two and one months (equations not shown). The notion is to use the three-month forecast to enable a heads up at three months, with improving skill as the peak epidemic period of July through October approaches using the two-month and finally the one-month forecast. The results for three-, two, and one-month lead times are presented in TABLE 5 2-4. The number cases have been corrected for the monthly growth in human population.

A number of combinations of previous cases and SST's were made; the best three-month prediction gave 6 false indications in 35 years, 5 false negatives, 1 false positive. For the two-month prediction, 3 errors in 35 years were made, 2 false negatives, 1 false positive. The one-month prediction had 2 errors, both being false positives. Again, the forecast of the dichotomous variable *Epi.yr* of true or false reflects the cutoff at the probability rate of 0.50. One is less sure about declaring an upcoming epidemic when the probability is (say) 0.64 than 0.95.

TABLE 1. The sum of dengue and DHF cases in Yogyakarta, Indonesia during March, April, and May (Cases) by Year, whether the year experienced an epidemic (Epidemic), i.e., Cases exceeded the period mean + standard deviation of 278, the statistical probability from the analysis that the year was an epidemic year (Prob{Epi.yr=T|X}), and our classification of the year (^Epi.yr). With the exception of 1992, a false positive, there is complete correspondence between observed and predicted epidemic status. A year is categorized as an epidemic (^Epi.yr) when the probability estimate (Prob{Epi.yr=T|X}) exceeds 0.50. Note the year 1992 was somewhat equivocal, having a value of 0.64.

Year	Cases	Epidemic?	Prob{Epi. yr=T|X}	^Epi.yr
1986	246	F	0.17	F
1987	276	T	0.96	T
1988	666	T	1.00	T
1989	66	F	0.00	F
1990	153	F	0.01	F
1991	405	T	0.96	T
1992	237	F	0.64	T
1993	114	F	0.00	F
1994	239	F	0.22	F
1995	269	F	0.21	F
1996	171	F	0.26	F
1997	304	T	0.60	T
1998	2533	T	0.97	T
1999	143	F	0.00	F

TABLE 2. Results for three month lead time. The sum of dengue and DHF cases in the Bangkok metro area during July, August, September, and October (Cases) by Year, whether the year experienced an epidemic (Epidemic), i.e., Cases exceeded the period mean + standard deviation of 1,436, the statistical probability from the analysis that the year was an epidemic year (Prob{Epi.yr=T|X}), and our classification of the year (^Epi.yr). A year is categorized as an epidemic (^Epi.yr) when the probability estimate (Prob{Epi.yr=T|X}) exceeds 0.50.

Year	Cases	Epidemic?	Prob{Epi.yr= T|X}	^Epi.yr
1966	1,296	F	-	-
1967	432	F	0.03	F
1968	617	F	0.04	F
1969	715	F	0.23	F
1970	187	F	0.15	F
1971	477	F	0.04	F
1972	698	F	0.13	F
1973	498	F	0.27	F
1974	529	F	0.05	F
1975	1,112	F	0.10	F
1976	615	F	0.04	F
1977	1,996	T	0.26	F
1978	442	F	0.03	F
1979	426	F	0.18	F
1980	1,553	T	0.24	F
1981	624	F	0.06	F
1982	562	F	0.18	F
1983	1,631	T	0.65	F
1984	1,592	T	0.11	F
1985	969	F	0.17	F
1986	925	F	0.06	F
1987	3,000	T	0.99	F
1988	774	F	0.25	F
1989	2,271	T	0.24	F
1990	735	F	0.34	F
1991	435	F	0.04	F
1992	408	F	0.55	F
1993	725	F	0.25	F
1994	439	F	0.28	F
1995	461	F	0.26	F
1996	438	F	0.10	F
1997	2,140	T	0.20	F
1998	1,454	T	0.85	F
1999	626	F	0.49	F
2000	1,078	F	0.10	F
2001	3,341	T	1.00	F

TABLE 3. Results for two month lead time in Bangkok.

Year	Cases	Epidemic?	Prob{Epi.yr= T|X}	^Epi.yr
1966	1,296	F	-	-
1967	432	F	0.02	F
1968	617	F	0.00	F
1969	715	F	0.01	F
1970	187	F	0.00	F
1971	477	F	0.00	F
1972	698	F	0.00	F
1973	498	F	0.21	F
1974	529	F	0.00	F
1975	1,112	F	0.00	F
1976	615	F	0.01	F
1977	1,996	T	0.70	F
1978	442	F	0.01	F
1979	426	F	0.00	F
1980	1,553	T	0.99	F
1981	624	F	0.27	F
1982	562	F	0.08	F
1983	1,631	T	1.00	F
1984	1,592	T	0.15	F
1985	969	F	0.03	F
1986	925	F	0.00	F
1987	3,000	T	1.00	F
1988	774	F	0.00	F
1989	2,271	T	0.56	F
1990	735	F	0.77	F
1991	435	F	0.18	F
1992	408	F	0.32	F
1993	725	F	0.25	F
1994	439	F	0.00	F
1995	461	F	0.00	F
1996	438	F	0.00	F
1997	2,140	T	0.27	F
1998	1,454	T	0.66	F
1999	626	F	0.27	F
2000	1,078	F	0.22	F
2001	3,341	T	1.00	F

TABLE 4. Results for one month lead time in Bangkok

Year	Cases	Epidemic?	Prob{Epi.yr= T|X}	^Epi.yr
1966	1,296	F	-	-
1967	432	F	0.00	F
1968	617	F	0.00	F
1969	715	F	0.01	F
1970	187	F	0.00	F
1971	477	F	0.00	F
1972	698	F	0.00	F
1973	498	F	0.00	F
1974	529	F	0.00	F
1975	1,112	F	0.00	F
1976	615	F	0.00	F
1977	1,996	T	1.00	F
1978	442	F	0.00	F
1979	426	F	0.00	F
1980	1,553	T	1.00	F
1981	624	F	0.00	F
1982	562	F	0.07	F
1983	1,631	T	1.00	F
1984	1,592	T	0.34	F
1985	969	F	0.73	F
1986	925	F	0.00	F
1987	3,000	T	1.00	F
1988	774	F	0.00	F
1989	2,271	T	0.70	F
1990	735	F	0.00	F
1991	435	F	0.00	F
1992	408	F	0.07	F
1993	725	F	0.55	F
1994	439	F	0.00	F
1995	461	F	0.00	F
1996	438	F	0.00	F
1997	2,140	T	0.67	F
1998	1,454	T	0.85	F
1999	626	F	0.00	F
2000	1,078	F	0.02	F
2001	3,341	T	1.00	F

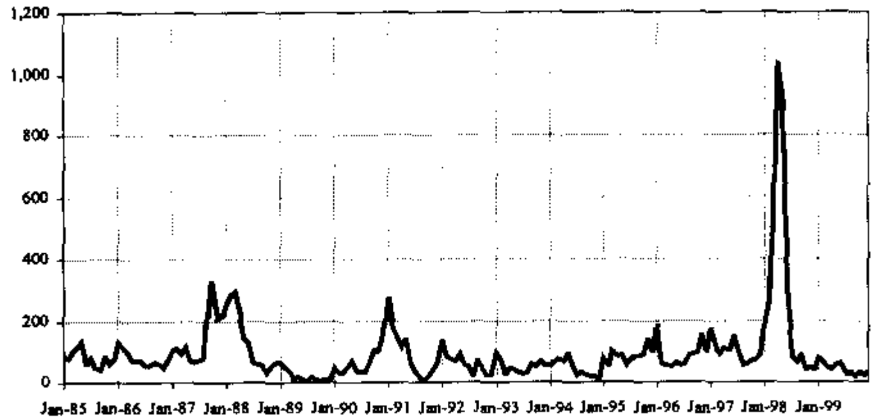

FIGURE 1. Total number of cases of dengue and DHF in Yogyakarta, Indonesia during 1985-1999

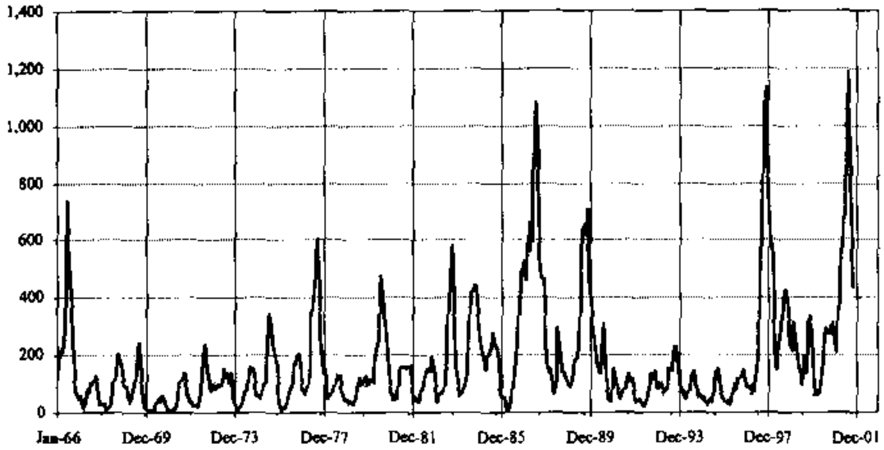

FIGURE 2. Total number of dengue and DHF in the Bangkok, Thailand metropolitan area during 1966-2001.

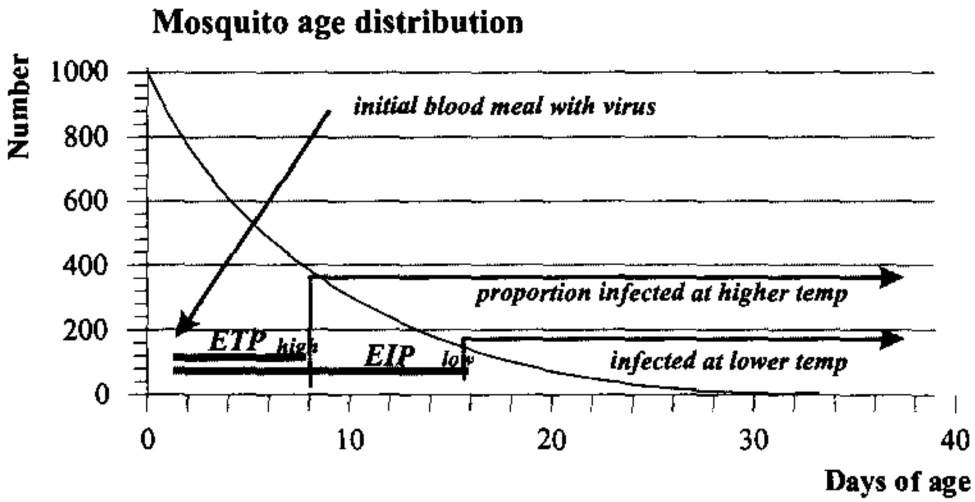

FIGURE 3. Plot depicts the age distribution of adult female *Ae. aegypti* over time based on a constant rate of daily survival. Shorter viral dissemination times (the extrinsic incubation period (EIP) associated with higher temperatures results in a significantly higher proportion of older females being infectious.

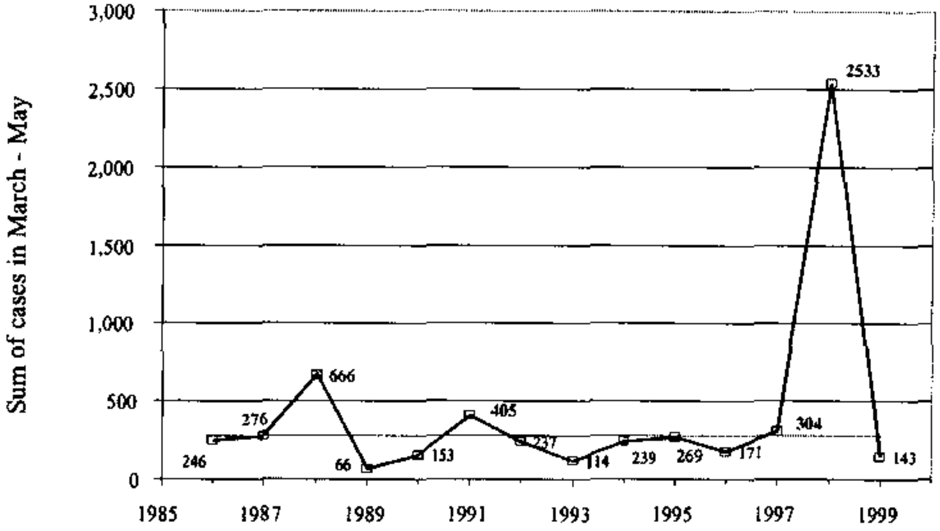

FIGURE 4. Plot of the sum of the cases observed between March and May in Yogyakarta, Indonesia and the identification of epidemic years, i.e., Epi.yr = T. Note many years are very near the cutoff of 278 cases.

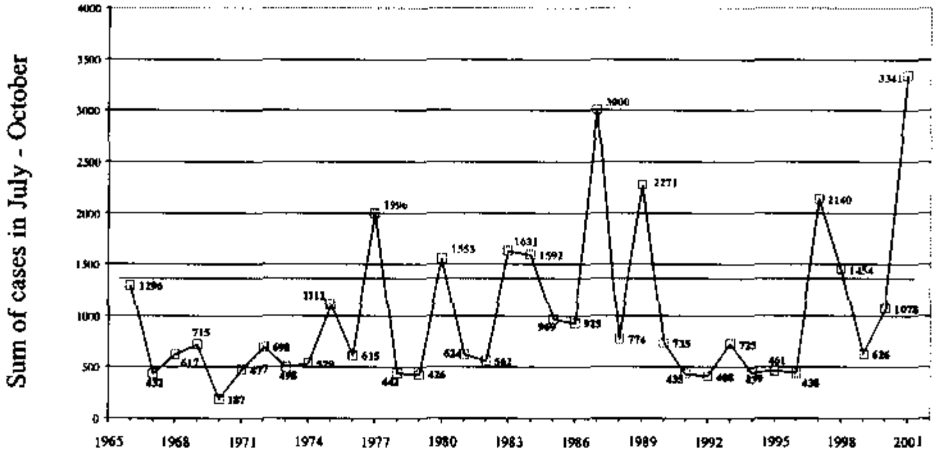

FIGURE 5. Plot of the sum of the cases observed between July and October in the Bangkok, Thailand metro area and the identification of epidemic years, i.e., Epi.yr = T. Note several years are very near the cutoff of 1,436 cases

DISCUSSION

We were able to forecast with a three-month lead time in Yogyakarta because the region sits squarely within the JMA SST anomaly zone, and SST anomalies are highly correlated with subsequent surface air temperatures. Bangkok, being further north, has lower coupling resulting in skill as lags extend from one to two to three months. However, we will propose that this loss of skill with increasing lags, as seen for Bangkok, can be accommodated in a useful fashion as in weather reports of hazardous conditions (see below).

The author works actively with the S.E. Asian (SEARO) and the Western Pacific (WPRO) Regions of the World Health Organization (WHO), and the countries of Thailand, Indonesia, Singapore, Vietnam, and Indonesia on dengue control, surveillance, and forecasting activities. In each of these countries, the author has inquired of the principals responsible for national dengue control programs what minimum lead time would be required to be useful for operational control programs. The universal answer was a minimum of one month, with two or three months with less certainty being useful as well. The notion is that a three-month forecast of likely epidemic conditions would lead to a *watch*, eliciting preparations for subsequent control, similar to the National Weather Service hurricane system of alerts from watch to warning to temporal and spatial specification of evacuation and preparation. If the two months also indicated significant probability of epidemic (looking a the value of $\text{Prob}\{\text{Epi.yr} = 1|X\} = [1 + \exp(-X\beta)]^{-1}$ where X represents the vector of independent variables, e.g.,—X1 = cases t-3mo, X2 = cases t-4mo, X3 = SSAa t-3, etc., see tables), then additional preparations are made and with the final decision to implement control would await the confirmation of the one-month most-skillful forecast probabilities.

The results presented here would only require a simple calculator, or preferably a PC using the derived equations, such as Equation 4 above, a spreadsheet, and the addition of monthly cases and the JMA SST anomalies (available on the web) to make forecasts. We envision further statistical work using bootstrap techniques to internally validate these results. Moreover, we should extend this analysis to other major metropolitan areas and regions. Most promising because long time series of case reporting include all of southern and central Vietnam, Jakarta and other Indonesian cities, Singapore, other Thai locations, and perhaps Malaysia. Successful implementation in a single location will fuel adoption of this method to other locations.

CONCLUSION

This study showed that to predict the incidence of dengue virus infection using weather data is very useful. This method would only require a simple calculator, or preferably a PC using the derived equation.

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