PUBLIC HEALTH RESEARCH

Determining Method for Dengue Epidemic Threshold in Negeri Sembilan, Malaysia

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ABSTRACT

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Introduction Dengue fever is an arthropod-borne viral disease that has become endemic in most tropical countries. In 2014, Malaysia reported 108 698 cases of dengue fever with 215 deaths which increased tremendously compared to 49 335 cases with 112 deaths in 2008 and 30 110 cases with 69 deaths in 2009. This study aimed to identify the best method in determining dengue outbreak threshold for Negeri Sembilan as it can help to send uniform messages to inform the general public and make the outbreak analysis comparable within and between countries.

Methods Using retrospective Negeri Sembilan country dataset from 1st epid week of 2011 till the 52nd epid week of 2016. The data were split into two periods: 1) a 3-year historic period (2011–2013), used to calibrate and parameterise the model, and a 1-year evaluation period (2014); 2) a 2-year historic period (2014–2016), used to calibrate and parameterise the model, and a 1-year evaluation period (2016), used to test the model. E-dengue is a registration system for confirmed dengue cases dengue by Ministry of Health. Data included were details of cases, district locality, records on the outbreak and epidemiological week (Sunday to Saturday) captured using the Excel spreadsheet. Analysis method included endemic channel method, moving average or deviation bar chart and recent mean.

Results Seremban as big district and facing with heavy dengue cases, all three methods (endemic curve, current mean and moving mean) showed promising results. Meanwhile comparing with small district of Port Dickson and Tampin with fewer dengue cases and outbreak recorded, the suitable method is by using endemic channel for epidemic threshold.

Conclusions Simpler methods such as the endemic channel, recent mean and moving mean may be more appropriate in urban district. Whereas in rural or district with minimal dengue cases, Endemic Channel would be the most suitable method for epidemic threshold. However, both methods require a consistent updated graph threshold as time progress.

Keywords Dengue – Epidemic.

INTRODUCTION

Dengue fever is an arthropod-borne viral disease that become endemic in most tropical countries. Dengue can be classified into two types; classic dengue fever or Dengue Fever and Dengue Hemorrhagic Fever (DHF) which further may progress evolve to Dengue Shock Syndrome (DSS). Globally, it was estimated that almost 400 million cases of dengue infection occurred per year affecting almost 2.5 billion people in 100 countries.[1]

In 2014, Malaysia reported 108 698 cases of dengue fever with 215 deaths which increased tremendously compared to 49 335 cases with 112 deaths in 2008 and 30 110 cases with 69 deaths in 2009. While in 2013, Malaysia had registered 98% increment of dengue case from 21 900 cases in 2012 to 43 346 in 2013. Worst, the total death in 2013 reported 163% increment from 35 cases in 2012 to 92 cases in 2013.[1]The change of the trend was due to multiple factors such as environmental changes, campaign and methods of diagnosing dengue case. In 2014, the MOH has strengthened the methods of diagnosing dengue cases using Combo Rapid Test Kit for early diagnosis and immediate action.[2]

Dengue is the most rapidly expanding arboviral disease and dengue outbreaks exert a huge burden on populations, health systems and economies in most tropical countries.[1] Re-assessment of the dengue burden using novel modelling methods has shown that the dengue burden is about three times higher than estimated by WHO.[3] Dengue outbreak response has been defined as the sum of measures specifically addressing a dengue outbreak aimed at reducing case fatality rates, numbers of cases and entomological parameters.

Outbreaks can exert large pressures on public health systems, as hospitals and outpatient clinics become overwhelmed by the surge in true dengue positive cases, as well as other febrile illnesses.[4-5] These pressures are compounded by resource-limited or weak surveillance systems that might be able to alert the system if sufficient funding, expertise and methodologies were in place.[6-8] Arguably, the ability to predict outbreaks with a sufficient lag time will enable public health systems to respond more efficiently through timely allocation of resources and more aggressive public health action .[4] To date, Malaysia is using two or more connected dengue cases at local level as an outbreak definition.

Dengue-endemic countries are threatened by outbreaks that are detected at a late stage and where the response mechanisms are often inadequate. Early detection of outbreaks poses a challenge, since there is no universally accepted operational definition of an outbreak exists (as shown in Table 1) and methods for distinguishing between seasonal fluctuations and true outbreaks. [4]

Table 1: Method used for determination of dengue outbreak by country

Methods	Country
Case numbers 2 SD above the mean of the preceding five years shown in endemic channels	Columbia, Dominican Republic, Peru (partially), Vietnam
Case numbers >2 SD “4–weekly average” above the mean of “three 4-weekly averages” in the five preceding years	Brazil, Malaysia
> 300 cases per 100 000 population at the local level	Brazil
> 10 cases per week in a local area	Sri Lanka
Two or more connected dengue cases at local level	Malaysia, Mexico, Sri Lanka
Case number in a commune within two weeks: 2–20 cases = mild outbreak; 20–100 cases = moderate outbreak; > 100 cases	Vietnam
No clear outbreak definition but larval indices as trigger for response: BI <6= routine response; BI = 6–20 = house-to-house checks; BI> 20	Sri Lanka

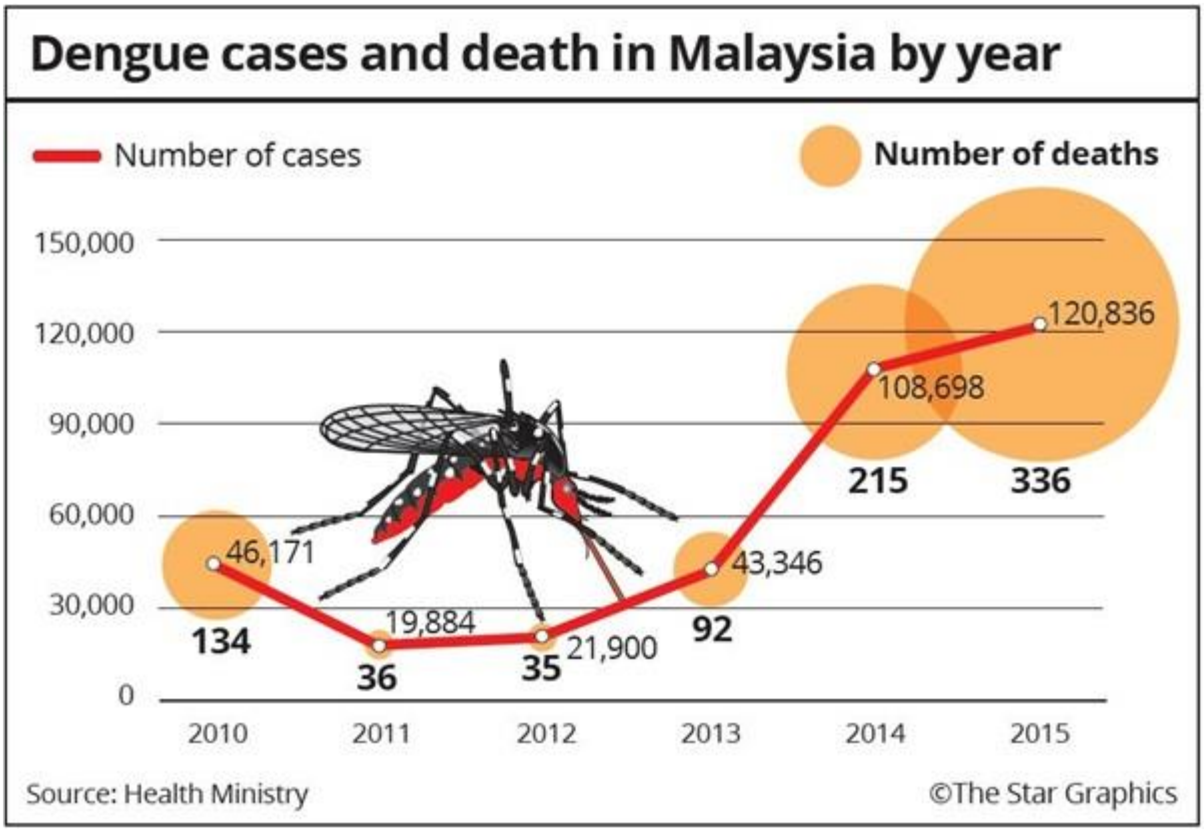


Figure 1 Number of dengue cases and dengue death in Malaysia from Year 2010 to 2015.

In spite of the progress made in modelling high risk areas and population dynamics, reliable, affordable and practical dengue early warning systems are still needed to mitigate the growing economic and human costs of dengue.[9-10] Only few studies had been done mainly overseas regarding the effectiveness of method in dengue outbreak threshold determination. Outbreak is important even if the thresholds of case numbers may vary among countries or regions. The objective of this paper is to identify the best method in determining dengue outbreak threshold for Negeri Sembilan which can be further expanded to the whole country to alert the policy makers and general public and allow comparable outbreak analysis within and between countries.

METHODS

Study Design

This is cross sectional study design from September till December 2018 using retrospective Negeri Sembilan country dataset from 1st epid week of 2011 till the 52nd epid week of 2016.

Study Area

Negeri Sembilan, is a state that located in the southern part of peninsular of Malaysia. The state is administratively divided into 7 districts health offices: Seremban, Jelebu, Jempol, Kuala Pilah, Port Dickson, Rembau dan Tampin whereby Seremban is a town and the capital of Negeri Sembilan, Malaysia, located within Seremban District. The terrain is generally hilly, and the soil is mostly reddish laterite soil, suitable for the cultivation of rubber and palm oil, thus making Negeri Sembilan an agricultural state. The climate like most parts of West Malaysia, is generally hot and humid (tropical) with a mean temperature of about 27–30 degrees Celsius. Most rainfall is experienced during the inter-monsoon periods of April and October. The weather remains generally dry for the rest of the year with occasional showers

Data Collection

Data from e-dengue of all cases from Negeri Sembilan were reviewed for 6 years (2011-2016). Since there were changes in dengue diagnosis started from 2014, the data were split into two periods: 1) a 3-year historic period (2011–2013), used to calibrate and parameterise the model, and a 1-year evaluation period (2014); 2) a 2-year historic period (2014–2016), used to calibrate and parameterise the model, and a 1-year evaluation period (2016), used to test the model. E-dengue is a registration system for confirmed dengue cases developed and used by Ministry of Health. Data extracted include details of cases, district locality, records on the outbreak and epidemiological week (Sunday to Saturday). The variables were captured using the Excel spreadsheet.

Study tools

The endemic channel method

Many countries (including Columbia, Dominican Republic, Brazil, Mexico, Vietnam and Malaysia) are using the "endemic channel" approach to define outbreak. The principle is to track deviation from seasonal profiles by comparing the timely surveillance data (number of cases or incidence rate per week or month) to the endemic channel, defined as the reference baseline value (average number of cases by week or by month) for the preceding 5-7 years, with defined outbreak thresholds. The Endemic Channel was calculated for each district using a standard deviation, based on data in the historic period. The outbreak threshold, defined as the level of variation above the endemic channel which triggers the outbreak signal, may be arbitrarily set at two standard deviations (SD) above the mean of the preceding historical period. The area between the lines of the mean and +2 SD is called the "alert zone" or the "alarm zone". The area above the +2 SD line is called the "epidemic zone".

Moving average or deviation bar chart

A seasonal increase of cases may come earlier than in the five preceding years giving the false impression of an outbreak. This can be handled by using the deviation bar chart or moving average method, with allows comparing the average number of dengue cases across four weeks with the average number of cases during a period of 12 weeks – including the same 4 weeks observation period, in the preceding five years. In Puerto Rico, the sensitivity was 40% and the specificity was 90%. Practically, Bowman (2016) suggested that it might be better to use the historical moving average to calculate the epidemiological week of observation plus six weeks before and six weeks after the week of observation, in total of 13 weeks.[11]

Recent mean

USA used this method for respiratory illnesses while similar method was used for dengue outbreak in Indonesia. [4]It is useful for country with a disease that has little seasonal pattern and limited surveillance data. The method measures overall mean of a small set of recent observations.[12]

Data Analysis

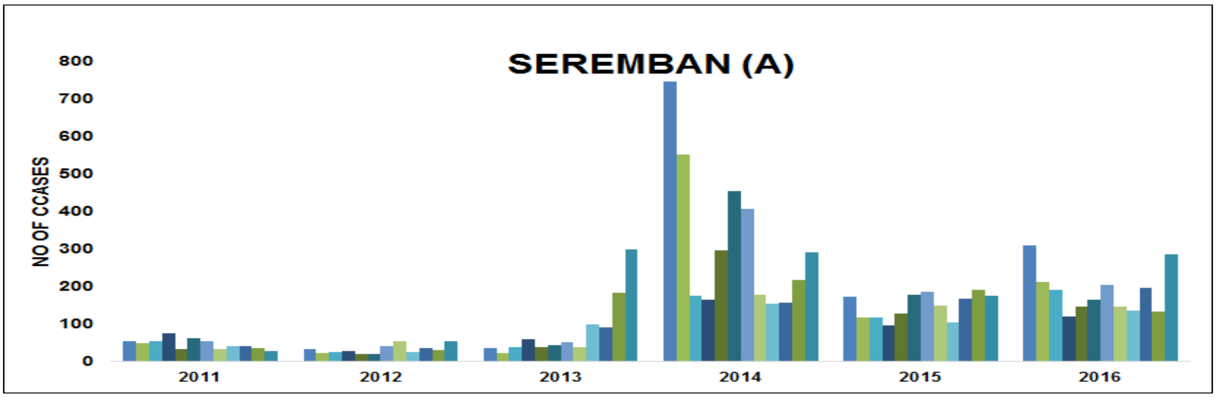
Analyses were run in duplicate, independently by three of the authors to limit systematic error. Data were analysed using Microsoft Excel.

Ethical permission

Ethical approval for the study protocol was sought from JKNS Negeri Sembilan (NMRR No: 35349). All patient medical data were anonymised.

RESULTS

Trend of dengue cases in district of Negeri Seremban from Year 2011 to 2016.



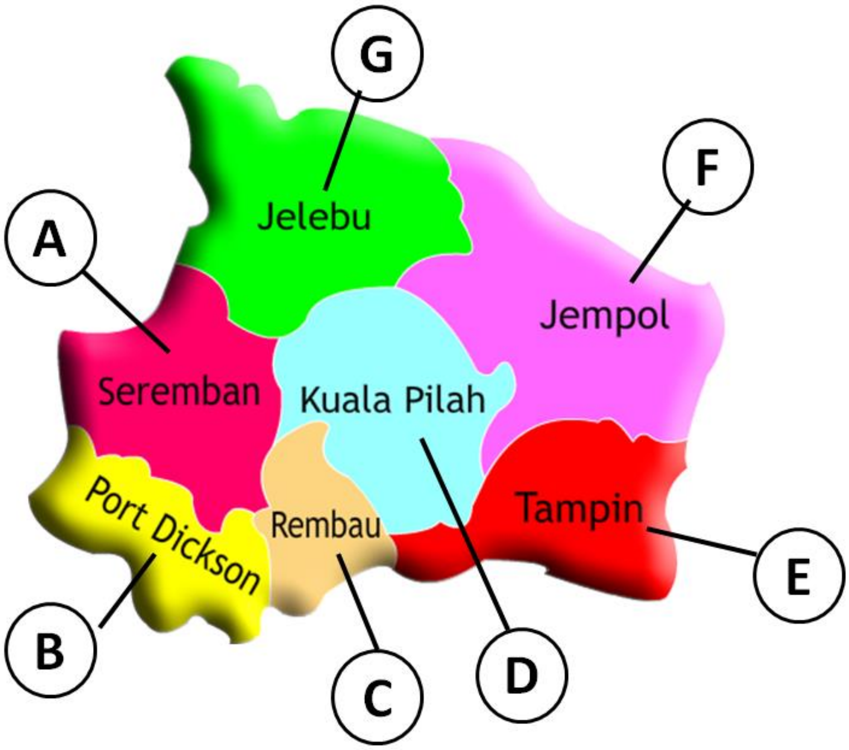
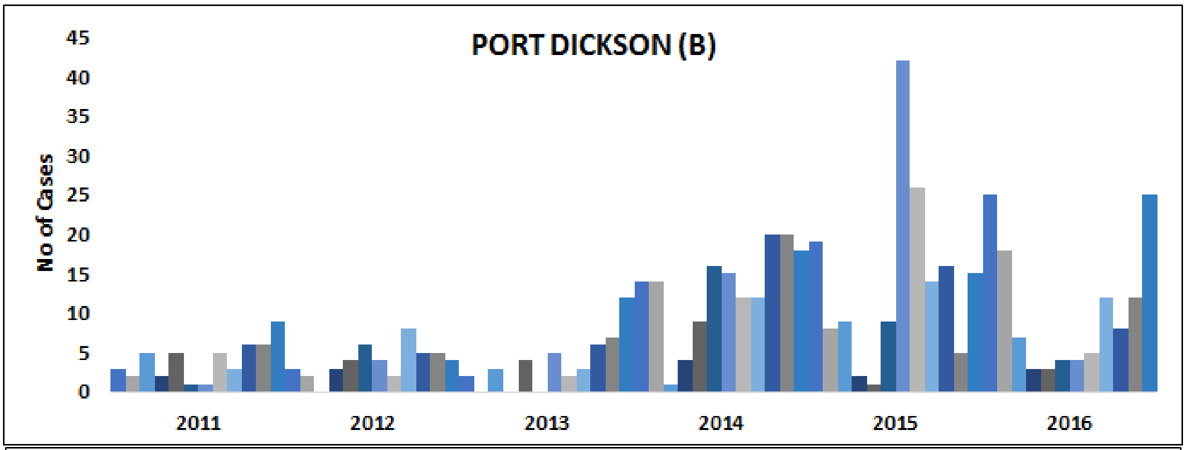
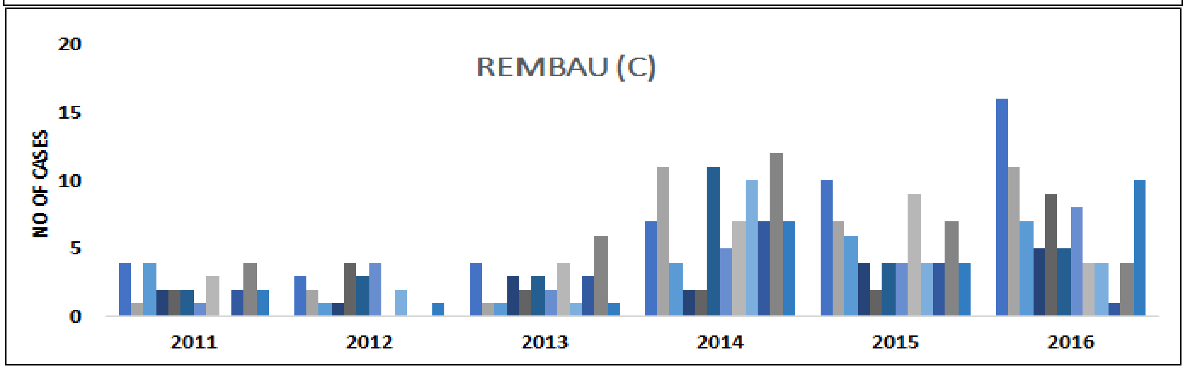


Figure 2 Map shows the division of the 7 districts in Negeri Sembilan as follows: Seremban (A), Port Dickson (B), Rembau (C), Kuala Pilah (D), Tampin (E), Jempol (F) and Jelebu (G).





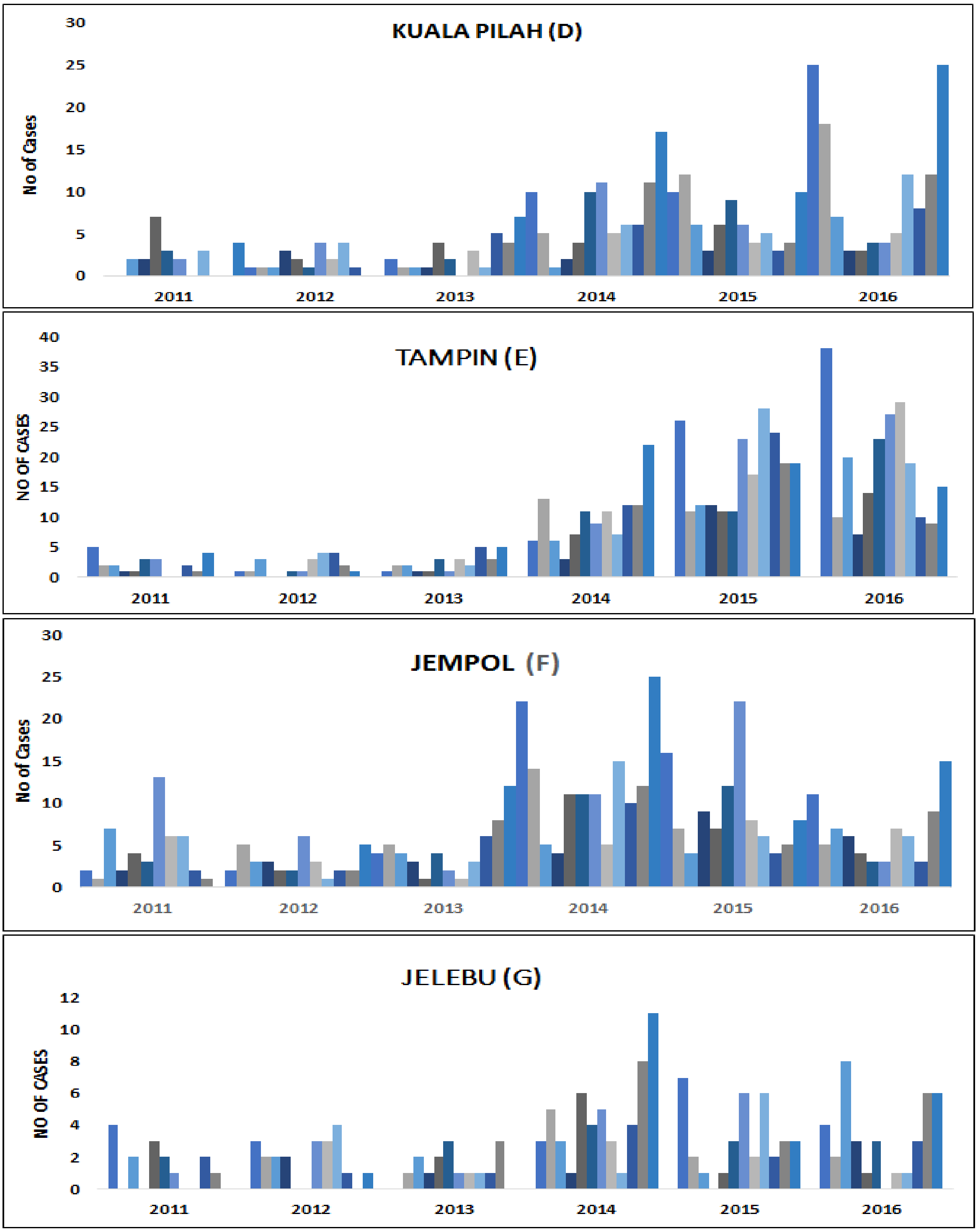


Figure. 3 Trend of reported dengue cases in Negeri Sembilan based on district A to G. Each bar chart displays monthly reported dengue cases (suspected and confirmed) at a district level (n = 7) between the start of 2011 and the end of 2016.

The result shows that the pattern of dengue fever cases in studied area (Negeri Sembilan) was concentrated in single district which is Seremban as proven by data of dengue cases from the year of 2011 till 2016 compared with other districst. Seremban district managed approximately 75.0% of total dengue cases in 2011 while in 2016, they managed 78.8% of total cases. While the rest of six remaining districts, dengue cases were just seasonal and rarely lead to outbreak.

Methods of dengue outbreak threshold

There are three methods used in this study. Data from three districts of Negeri Sembilan were analysed and classified as urban or rural area. Dengue data from Seremban was analysed as urban district in Negeri Sembilan while data of rural area were purposely selected from Port Dickson and Jempol District. Port Dickson was selected as rural based on population concentration dan geographical area. While Jempol was classified as rural based on the population concentration eventhough it is the largest district in Negeri Sembilan the number of dengue cases were low throughout the year.

After demonstrating the functionality of the model using a test dataset for historical period, one year datasets (evaluation period) was subsequently used. By using Seremban data as it receives majority of dengue cases, the historical graph was develop based on the 3 different years (Figure 4-5) and compared with subsequent years as evaluation period.

Endemic Channel

a) Urban : Seremban District

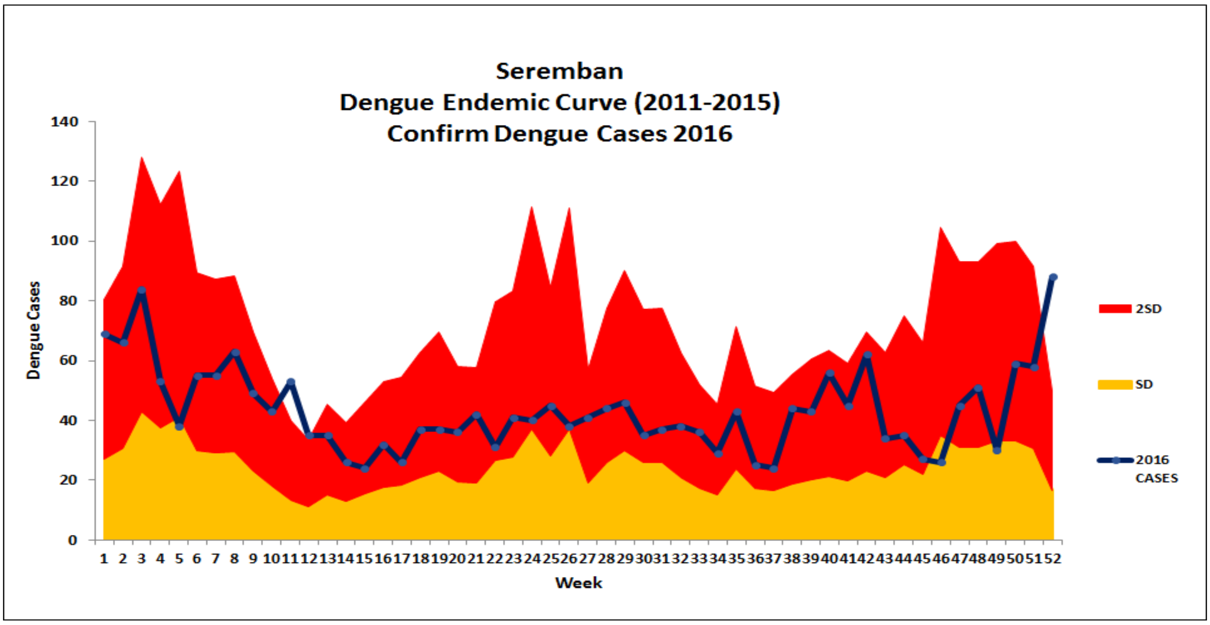


Figure 4 Endemic channel using 5 years historical period and evaluated with cases in 2016. Note: Most of the new cases crossing the historical 1SD line and only 2 events exceeded the endemic threshold (2SD).

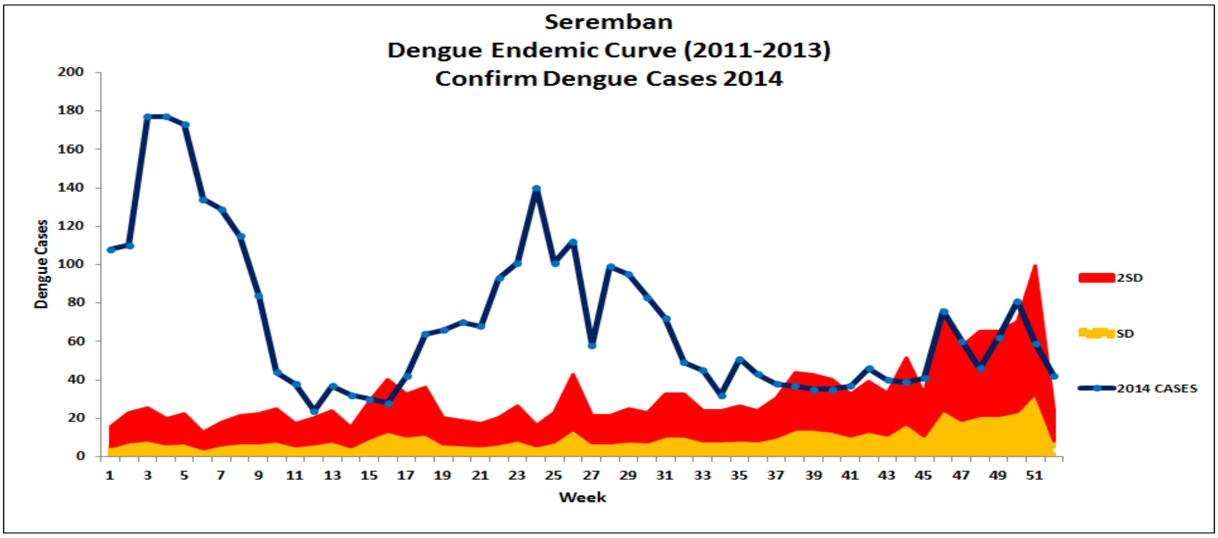


Figure 5 Endemic channel using 3 years historical period (before change of diagnosis definition) and evaluated with cases in subsequent year.

Note: Number of new cases already crossing the historical 2SD line since beginning of the epid week before it touched down within the threshold at the end of epidemiological week.

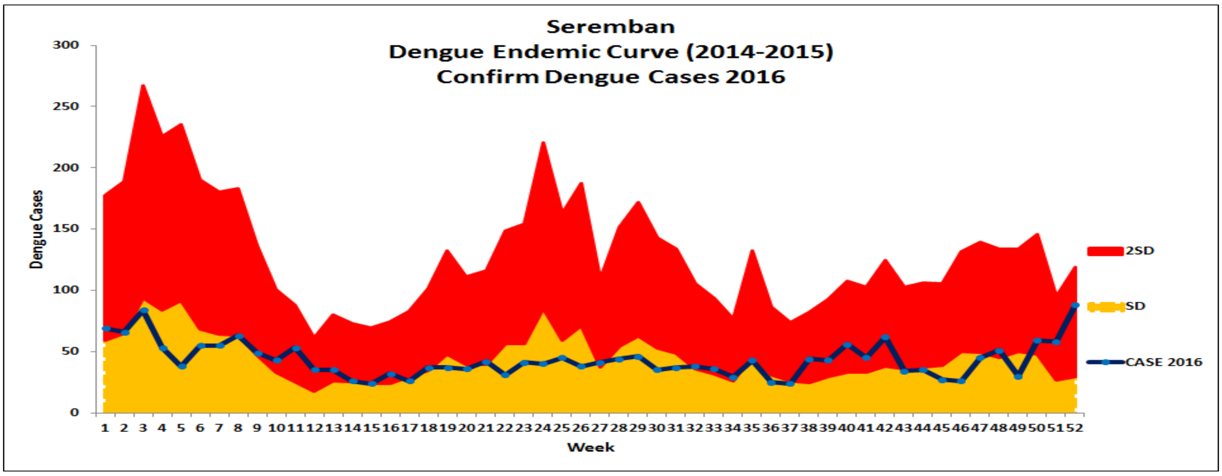
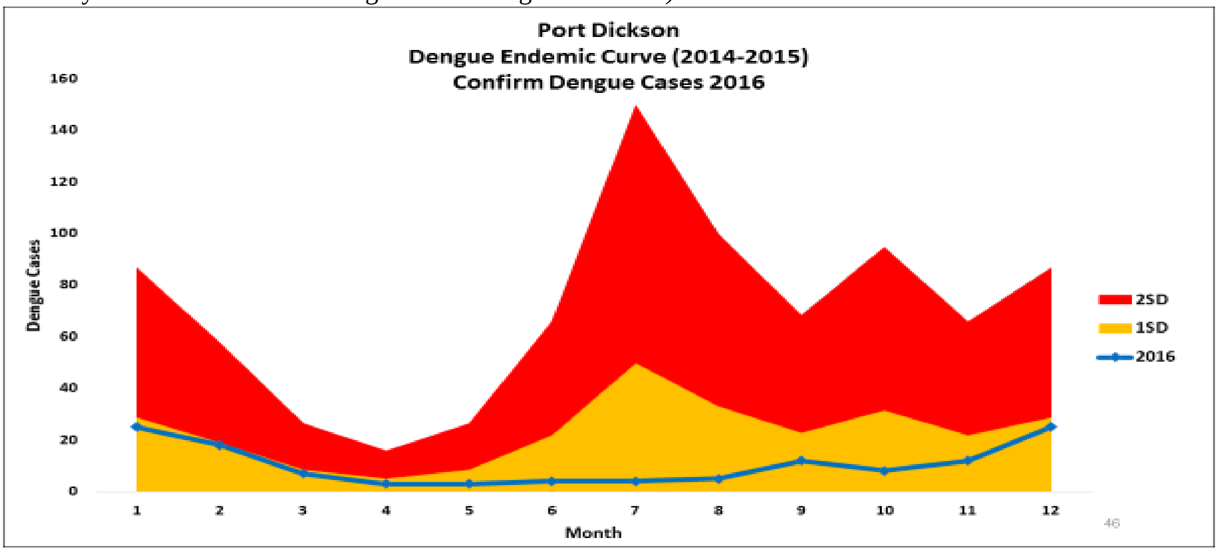


Figure 6 Endemic channel using 2 years historical period (after change of diagnosing definition) and evaluated with 2016 dengue cases.

Note: Number of new cases only crossing the historical 1SD line or alert line and shows no cases over the epidemic threshold level (2SD).

In conclusion, the 2 years (2014-2015) period will be used as data for historical period since there were significant changes of cases after Ministry of Health had changed the dengue diagnosis definition. Hence, 2016 is the evaluation period of all methods.

b) Rural: Port Dickson



c) Rural: Tampin

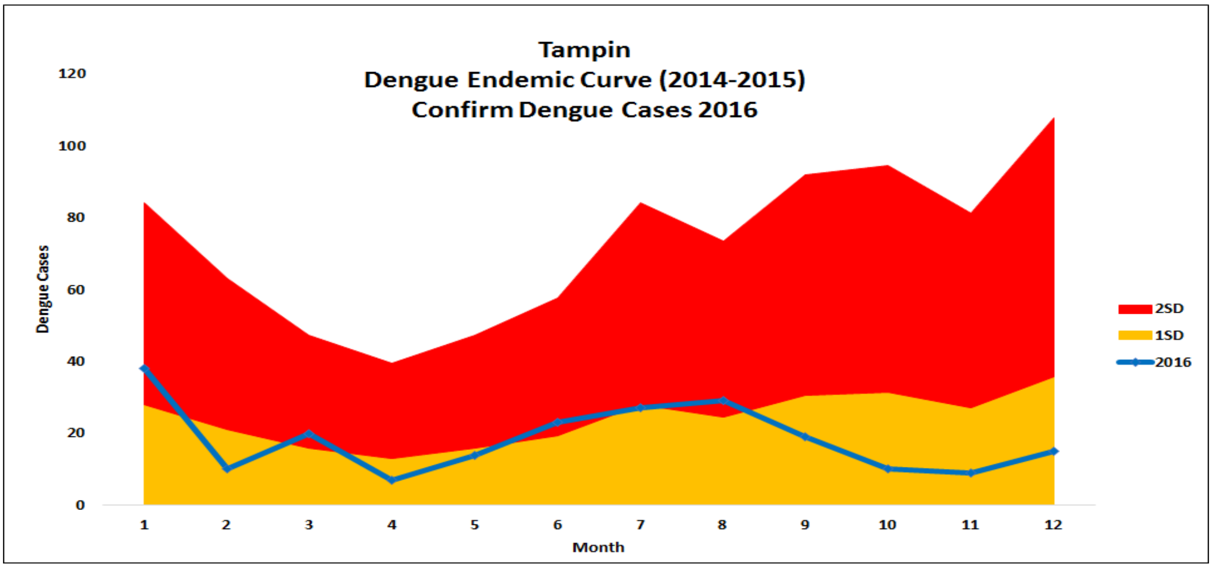


Figure 7 Endemic channel of rural district shows number of new cases only crossing the historical 1SD line or alert line and no cases over the epidemic threshold level (2SD).

Recent Mean

a) Urban : Seremban (weekly mean)

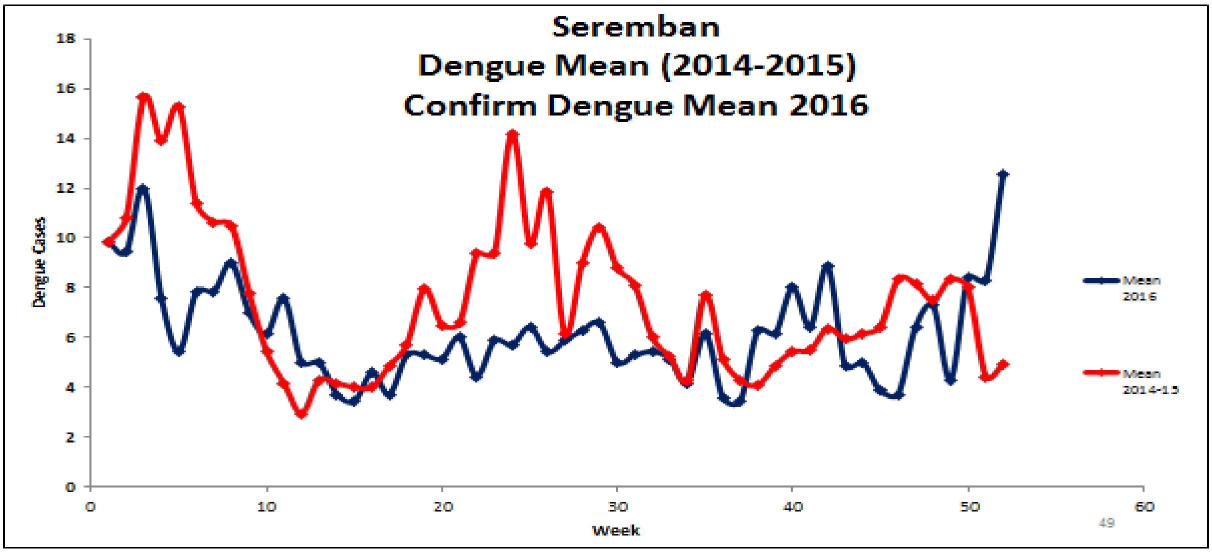
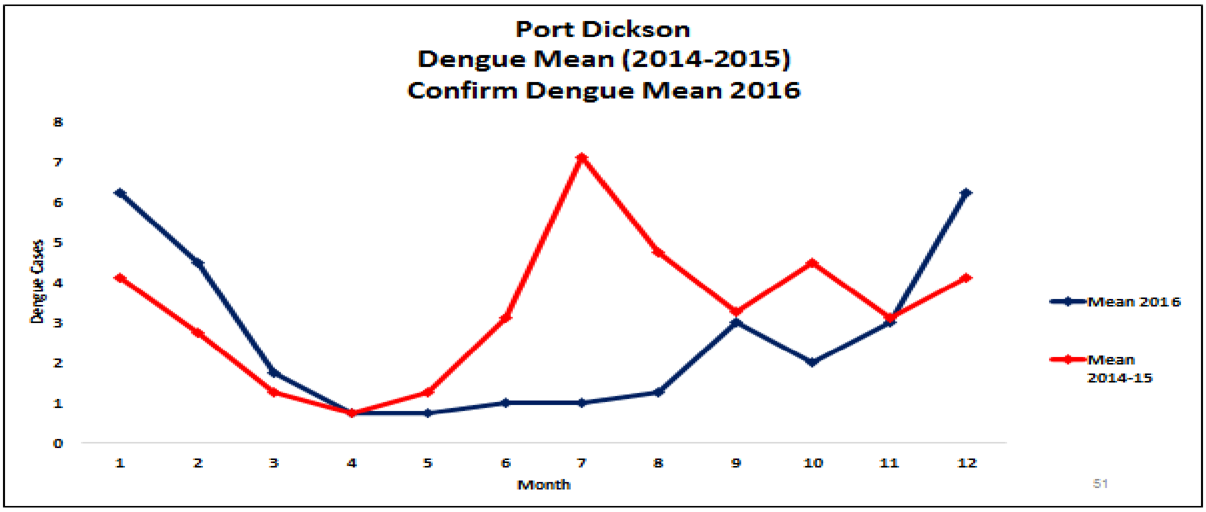


Figure 8 The mean of current dengue cases is in line with the historical period. Only minimal period was above historical period that is in weeks 10, weeks 36 and surge at end of the epid week.

b) Rural : Port Dickson (monthly mean)



c) Rural: Tampin (monthly mean)

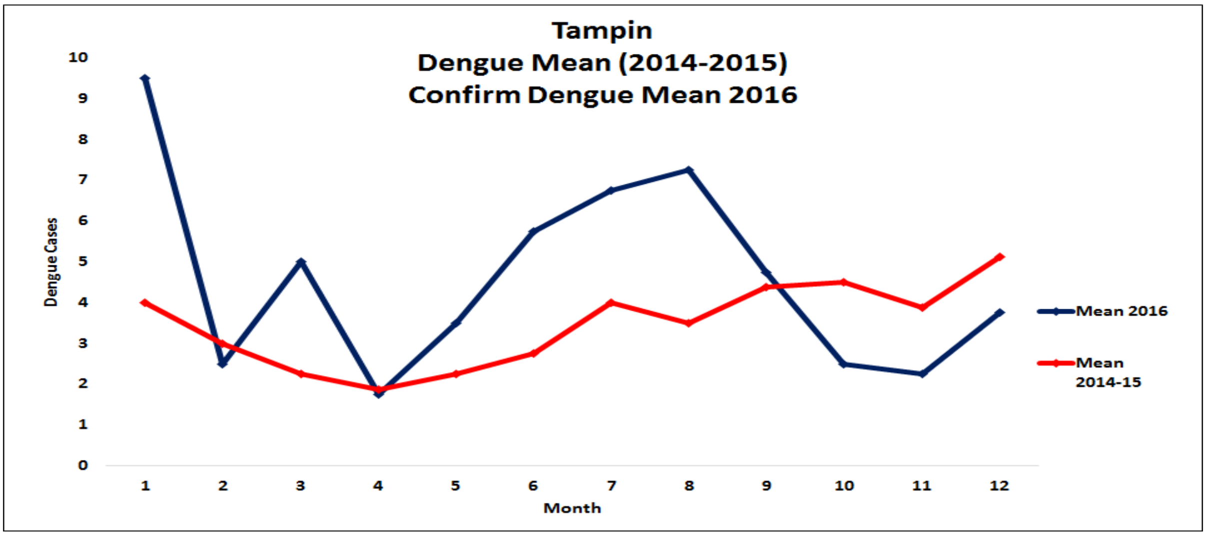


Figure 9 The mean of 2016 cases is unpredictably in line with historical period.
Note: In Port Dickson, estimated that between Jun to July, there are rising of the cases. However the mean line was stable in 2016.

Moving Average
a) Urban : Seremban

Dengue Epidemic Threshold

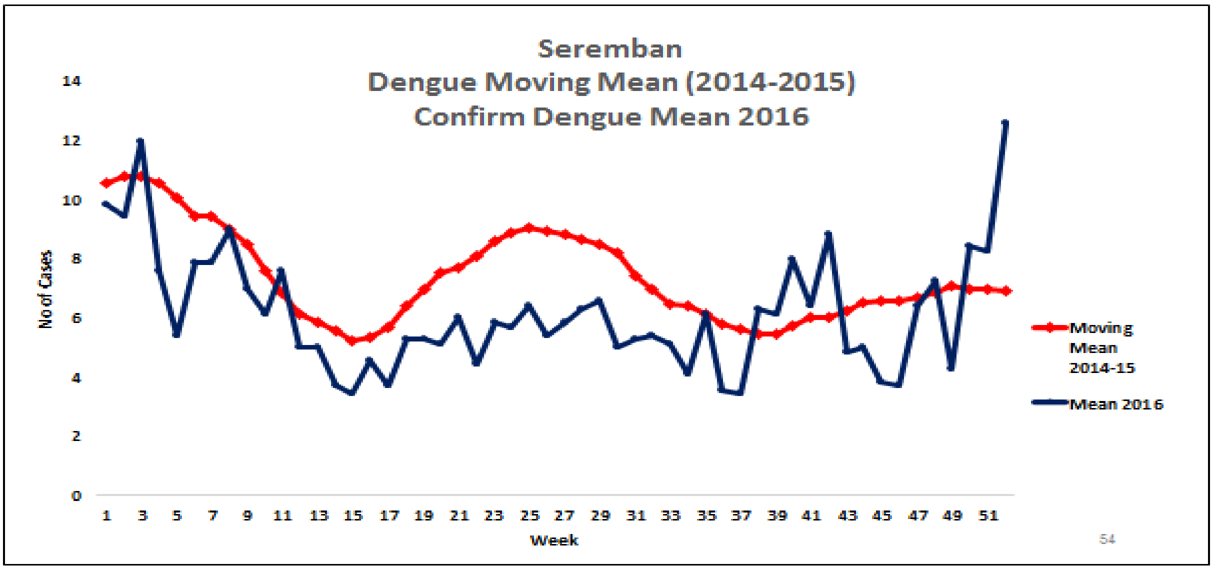
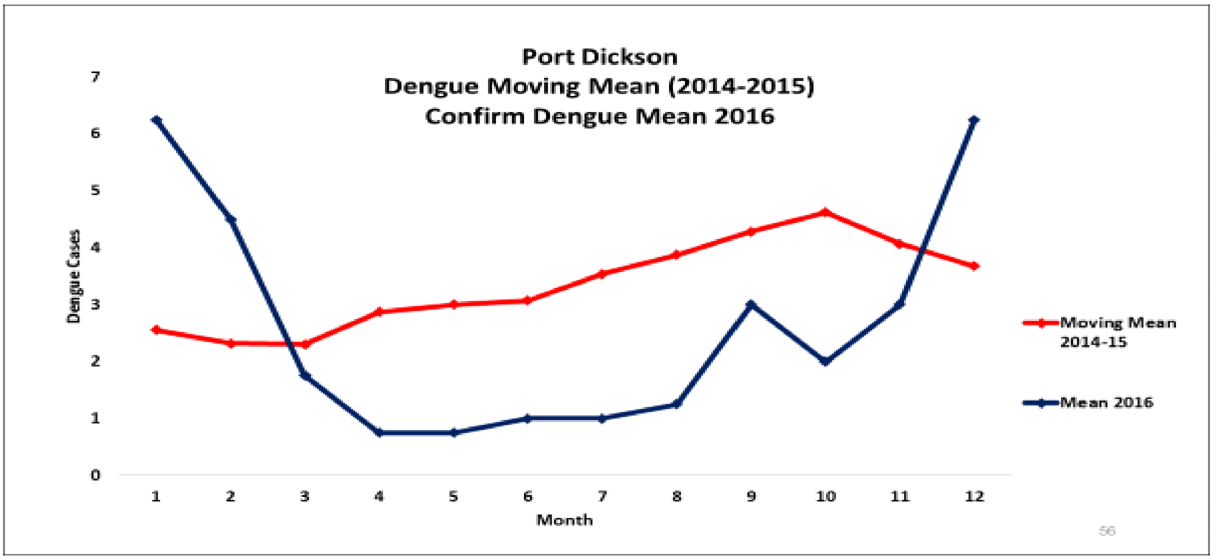


Figure 10 The mean of current dengue cases is notably in line with moving mean of the historical period. Only end of epid weeks shows fluctuation increase of mean cases with historical moving mean.

b) Rural: Port Dickson



c) Rural : Tampin

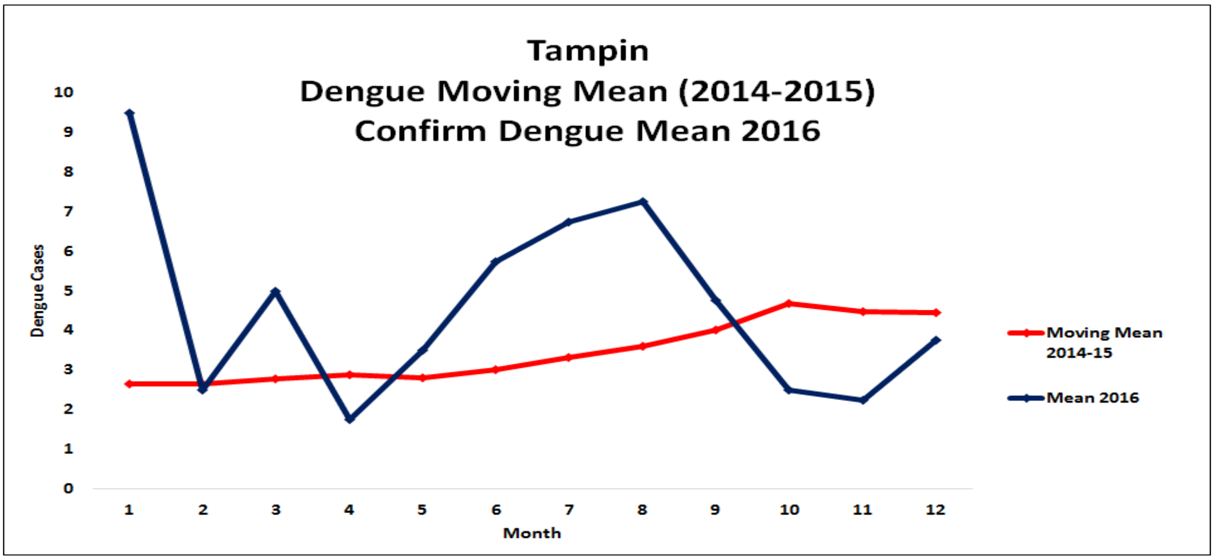


Figure 11 The mean of 2016 cases is unpredictably in line with historical moving mean.
Note: In Port Dickson, most of the mean cases are below historical moving line whereas in Tampin, the mean cases were fluctuated with moving mean throughout the year.

DISCUSSION

Early warning systems are becoming more important as a tool to mitigate the impact of disease outbreaks.[13]Clearly, alarm variables that provide advance warning of outbreaks are the most valuable, in order to enact timely clinical preparations and vector control responses. In this study, three methods were used to evaluate epidemic threshold with the potential to predict subsequent outbreak periods. A number of epidemiological variables were tested, primarily to evaluate their predictive potential, and secondarily to establish the most appropriate case definition to define outbreaks.

Various factors influence the occurrence of an outbreak, including: 1) Demographic risk factors (depending on population distribution and density, susceptibility, contacts, migrations, education, wealth); 2) Inefficient national and/or local public health context (surveillance, contingency plan, communication plan, health services, community programs) and 3) Geographical and ecological risk factors (humidity, temperature, artificial and/or natural breeding sites).[1] Unfortunately in this study, the meteorological data were unable to be analysed together with the models due to insufficient data.

Furthermore, the threshold for alert and response will vary according to the operational level affected (local, national, international) and whether the affected area is endemic for dengue or at risk of its introduction.[3] Referring to this study, whereby Seremban as big district and facing with heavy dengue cases, all three methods (endemic curve, current mean and moving mean) showed promising results. Meanwhile comparing with small district of Port Dickson and Tampin with fewer dengue cases and outbreak recorded, the suitable method is by using endemic channel for epidemic threshold.

The Endemic Channel
Worldwide, the multiplier '2' is used to build the Endemic Channel using the following formula: mean+2_SD. This multiplier is used as it broadly captures 95% of the variation in dengue incidence about the mean. However, for the purposes of outbreak detection, this does not account for any localised variation that may warrant context-specific multipliers.[3,14] It is also important to identify that dengue incidence fluctuates on an inter annual basis, and that the pattern of outbreaks may shift in time, frequency and duration.[3] Indeed, in terms of prediction, it is crucial to capture local covariates in order to anticipate whether the seasonal pattern of outbreaks is likely to change, perhaps due the presence of a new serotype early in the season.[14]

In this model, it was not possible to capture such variation due to paucity among the datasets. From these analyses it is clear that standardized thresholds failed to distinguish between certain types or stages of the outbreak. Dengue transmission is often characterized by a series of peaks in incident cases, which is a function of variable intrinsic and extrinsic incubation periods.[15] So, rather than focus on a simple binary output, perhaps it would be prudent to characterize outbreaks by a relative weekly increase in incidence, or indeed use the slope of the curve to forecast the top of the epicurve. Such a system would provide programme managers and epidemiologists with a more detailed insight into the speed and magnitude of future outbreaks, which would increase the efficiency and cost-effectiveness of dengue outbreak responses. While the above techniques are under consideration, the results from

this study suggest that the Endemic Channel meanwhile remains an operationally useful aid, primarily because of its
ability to clearly demarcate thresholds based on simple summary statistics.

Temporal Associations between Alarm and Outbreak Variables

Timely outbreak detection is by using 2 or 3 alarm per outbreak signals to define alarm per outbreak periods produced the highest outcome metrics, while there was little difference between these two multipliers across all alarm/ outbreak variables.[16] Similarly, working with a moving average tends to delay the anticipated outbreak pattern by delaying the increase and postponing the decrease in incidence. In this study, the smoothing took place over 13 weeks (6+1+6), but this could be reduced to better reflect real-time events. However, this would be at the expense of increasing the impact of any problem in the dataset, also an important consideration prospectively.

Limitations

The changing of diagnosis of dengue cases in late 2013 causing abnormal surge of cases in 2014. In addition, the inconsistent data collection and missing data almost certainly affected the quality of datasets, especially regarding entomological. As observed in another review, entomological indices were generated on varied temporal and/ or spatial scales in different countries, resulting in a mismatch with the outbreak variables.[11] Accordingly, these alarm variables could not be fairly evaluated. The moving average and recent mean calculated during the historic period were reliant upon a relatively low number of years (<2) of historic data, in contrast to others forecasting models. [12,17] Using a greater number of historic years would have generated a more stable mean and outbreak probabilities. Outbreak probabilities for alarm variables were based on countrywide associations, a spatial scale that smoothens variation found at the district level, potentially underestimating true probabilities. Some variables, in particular temperature, have been known to show non-monotonic relations concerning mosquito and viral replication, however these effects were not captured in the current model.[18-20]

CONCLUSION

The findings reported here suggest that the Endemic Channel, recent mean and moving mean-relatively simple approaches-are viable techniques that can be used retrospectively, and potentially prospectively, to detect dengue outbreaks using alarm variables with an attributed lag time. Fortunately, Malaysia has almost complete and detailed datasets compiled by mandatory electronic reporting and standardized surveillance systems. This will greatly improve the quality of datasets and lend themselves to such analyses. Until this point, simpler methods such as the Endemic Channel, recent mean and moving mean may be more appropriate in urban district. Whereas in rural or district with minimal dengue cases, Endemic Channel would be the most suitable method for epidemic threshold. However, both methods require a consistent updated graph threshold as time progress.

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