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A Dynamical Model of Dengue Primary and Secondary Infections with an Application to Microinsurance

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Abstract

Dengue is a contiguous viral disease that has a potential risk to insurance industries due to the increasing number of incidence cases worldwide. Global warming has brought dengue vectors to new places. Dengue disease can strike a person more than once, and the secondary

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infection is potentially more severe (and costs more) than the primary one. Knowing the numbers of both primary and secondary incidence cases will help insurance industries do a precise calculation on the potential loss. Unfortunately, in most countries, only the total number of cases (undifferentiated) is recorded nationwide. Dengue secondary infection is caused by dengue virus serotypes that are different from those that caused the first infection. Thus a reinfection model such as an ordinary SIRS model is not realistic since it assumes that both primary and secondary cases have the same infection rate. Therefore, this paper extends the existing dengue infection model to incorporate a more realistic example of secondary dengue infection and split the historical data on the total number of incidence cases into predicted numbers of primary and secondary infections. We utilized the Markov Chain Monte Carlo method to predict the model's best parameters and initial conditions. Taking Indonesia as a specific case of a country with a long and significant history of dengue infection, our simulation predicts an alternating seasonal event of both primary and secondary infections. We formulate an insurance model that includes the loss ratio, the medical inflation rate, and the insurance awareness factor. The computed numbers of primary and secondary infections were applied to this insurance model to calculate the net premium, which serves as a baseline number to the average per-person-cost of dengue diseases among the Indonesian population. The methodology presented here can be applied to other countries/regions to calculate the insurance premium for dengue disease.

1 Introduction

Dengue is a threatening arboviral disease which causes an approximately 390 million infections annually in 128 countries across the globe [6]. Although death rates have been substantially lowered, episodes of outbreaks have been increasing dramatically in Indonesia during the last century [14].

Dengue disease causes financial and economic losses to the patient, the family, and the workplace [11]. The significant increase of reported dengue cases illustrates the rise of the financial burden to the insurance companies (public or private). People who have been infected by primary infection are subject to a secondary infection due to the complication of the Antibody-Dependent Enhancement (ADE) [8]. Symptoms of secondary infections are more severe than the primary ones. Therefore, the medical cost is also higher. Interactions between hosts and vectors are amplified by climatology factors

such as global warming. Thus, a hyperendemic dengue outbreak might still happen, especially in rural areas. Suwandono et al. [20] reported that periodic outbreaks of dengue have emerged in Indonesia since 1968, with the severity of resulting disease increasing in subsequent years.

Aguiar et al. [1] presented and analyzed a theoretical model that describes the interaction of two virus strains. The model considers temporary cross-immunity and secondary infection and assumes low incidences (or mild symptoms) on tertiary and quaternary infections [9]. This assumption implies a long-life immunity after the secondary infection. Several years afterward, Aguiar and Stollenwerk [2] extended the model to include the possibility of tertiary and quarternary infections. This extended model allows the interaction between four dengue serotypes. Another reinfection model that incorporates different dengue virus (DENV) serotypes is given in [3]. The models presented in [1, 2, 3] are suitable for scenario testings, assuming some variations of parameters and initial conditions. However, these models consist of many unknown parameters and initial conditions. In practice, data is limited, and we only have the overall number of dengue incidences. To simulate a dynamical system, we need to specify the values for each state's parameters and the initial condition. We may utilize a Bayesian framework to find the best values. However, the number of degrees of freedom is twice as many as the number of states. Too many degrees of freedom may cause instability in the simulation, that we may not get a convergence.

This paper presents a simpler model, using a smaller number of parameters and unknown initial conditions. The model is a SIRSEIR dynamical system model that describes the population's states from birth to death with the possibility of entering the states of primary or secondary dengue infection in between. This model's motivation is that every individual is likely to get infected for the second time, with different transition rates for primary and secondary infections. Thus, it is more realistic than a simple SIRS model. The model does not differentiate between DENV serotypes, allowing us to incorporate it into a financial cost model. We assume that the medical costs of primary and secondary infections are different.

Data on Indonesia's overall dengue incidences is retrieved from the biannual report on dengue disease, published by the Indonesian Ministry of Health [12]. Our model predicts the number of dengue actual primary and secondary infections from the overall infection data by searching the model parameters that best fit the existing data (the total dengue incidence data in Indonesia). The predicted values are the transition parameters between each state and the relevant initial conditions. A Bayesian Monte Carlo method

was implemented to get the posterior distributions of the parameters and all dynamical variables' initial conditions.

The computational results are beneficial for modeling and projecting insurance premium dynamics. We formulated an insurance model that includes the loss ratio, medical inflation, and the insurance awareness factor. The calculated net insurance premium serves as a baseline for the average cost of dengue diseases among the population.

2 Research Methodology

2.1 Data

The World Health Organization collects data on dengue cases reported by various countries, including Indonesia, which is available from 1990 up to 2017. Also, the Indonesian Ministry of Health [12] reported longer historical data in a bi-annual report on dengue diseases. The reports show a significant increase in dengue incidence rate per 100000 population in Indonesia since 1968. Although the illness's incidence rate increases, the case fatality (death) rate per 100000 population is stable.

The total population data is obtained from the World Bank Data. The trend is linearly increasing from the year 1968 to 2015. We construct an epidemiological model with the main feature that the total population is not constant. The net growth rate was estimated directly using the observed total population (data from World Bank, using log-linear regression). The crude death rate was around 7 per 1000 people per year (data from the World Bank). The net growth rate and the crude death rate were calculated using data from the year 2000-2011. During and after this period, the population growth and crude death rate are assumed to be stable and constant.

2.2 The Model

The diagram of the model is presented in Figure 1. To evaluate the potential future risk of dengue in Indonesia, we must work using the available data. The historical data we have are the total dengue incidences across Indonesia, the total population, the birth rate, and the overall death rate. We do not have complete data on the number of each primary or secondary dengue infection that represents all incidences across the whole country. To test a theoretical epidemiological model's performance, we need to fit the model

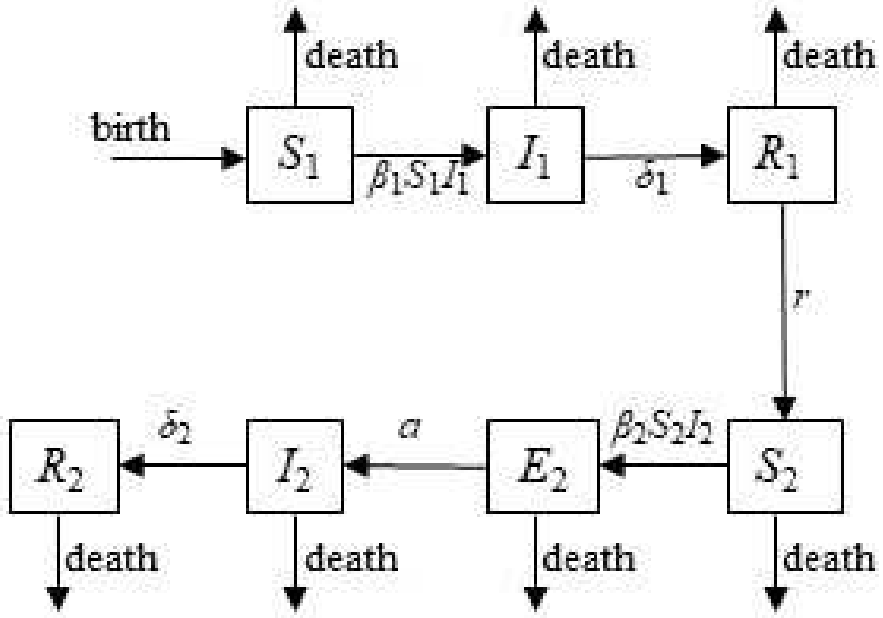

Figure 1: The SIRSEIR epidemiological model of dengue disease.

with the existing data. We need to find a way to split the current historical data on the number of reported dengue incidence cases. We construct a model consisting of two states of infections. The model describes the primary and secondary dengue infections within a population. This model tracks the expected numbers of susceptible, infected, and recovered individuals during the primary infection (S_1, I_1, and R_1, respectively). Upon recovery, individuals are equally susceptible to getting infected for the second time. However, the second infection might be delayed due to residuals immunity from the first infection. Thus, this model also tracks the number of susceptible, exposed, infected, and recovered during the secondary infection (S_2, E_2, I_2, and R_2, respectively). For simplicity, we assume that the death rates of all states are equals. This assumption is based on the evidence that the ratio between case fatality (death) rate to the incidence rate decreases. Increasing public awareness of dengue disease has contributed to the early treatment of

dengue patients, reducing mortality. The model is given as follow:

$$\begin{aligned}
\frac{dS_1}{dt} &= g\left(S_1 + I_1 + R_1 + S_2 + E_2 + I_2 + R_2\right) - \beta_1 S_1 I_1 - dS_1, \\
\frac{dI_1}{dt} &= \beta_1 S_1 I_1 - \delta_1 I_1 - dI_1, \\
\frac{dR_1}{dt} &= \delta_1 I_1 - rR_1 - dR_1, \\
\frac{dS_2}{dt} &= rR_1 - \beta_2 S_2 I_2 - dS_2, \\
\frac{dE_2}{dt} &= \beta_2 S_2 I_2 - aE_2 - dE_2, \\
\frac{dI_2}{dt} &= aE_2 - \delta_2 I_2 - dI_2, \\
\frac{dR_2}{dt} &= \delta_2 I_2 - dR_2,
\end{aligned}$$

where g is the population growth rate from 1968 - 2015, d is the mortality rate from 1968 2015, β_1 is the primary infection rate, and δ_1 is the primary removal rate (or recovery rate), β_2 is the secondary infection rate. In this model, $1/r$ is the duration of protection, a is the rate of time delay during the secondary infection, and δ_2 is the secondary removal rate (or recovery rate).

This model assumes that all individuals are equally susceptible and that the total population is sufficiently large. In this model, the total population is not constant (influenced by the natural birth and death process). The net growth rate was estimated directly using the observed total population (data from World Bank, 1968 to 2015 log-linear regression). The crude mortality rate was assumed to be around 0.007 per year, with a growth rate of 0.014 per year (from the World Bank data).

2.3 Data Splitting Method

We used a modified Markov Chain Monte Carlo (MCMC) sampler with affine invariance to optimize the convergence on a high-dimensional problem [10]. The proposed SIRSEIR model works with thirteen dimensions: six parameters and seven initial conditions, β_1, β_2, δ_1, δ_2, a, r, $S_1(0)$, $S_2(0)$, $I_1(0)$, $I_2(0)$, $R_1(0)$, $R_2(0)$, and $E_2(0)$.

To fit the data, we solved the model numerically. We calculated posterior distributions of all parameters based on the maximum likelihood of residuals between the model and the observed value at each time. Let $f(x)$ be

the function we want to fit the observed values. Given a data-set with n observations $(y_1, y_2, , y_n)$, then the likelihood can be written as:

$$L = \prod_{i=1}^{n} \frac{1}{\sqrt{2\pi}\sigma_i} \exp\left(\frac{-\left(y_i - f\left(x_i\right)\right)^2}{2\sigma_i^2}\right),$$

by assuming a constant and unknown variance (ie, $\sigma_i = \sigma$), thus, the log-likelihood can be written as $\ln L = -n \ln\left(\sqrt{2\pi}\sigma\right) - \frac{SSE}{2\sigma^2}$, in which $SSE = \left(y_i - f\left(x_i\right)\right)^2$ and the maximum likelihood for σ is given by $\sigma^2 = \frac{SSE}{n}$.

2.4 A Dengue Insurance Design

An insurance product for dengue disease can be designed as 1-year term insurance covering the medical cost if the insured is sick or hospitalized because of dengue. For this product, we have to apply the same premium for all insured because primary dengue infection may or may not be symptomatic. An underwriting process to differentiate those who are still seronegative (prone to the primary infection) from those who are seropositive (prone to secondary infection) can only be done by using a costly laboratory test. We assume that the medical costs of secondary infection are higher than primary infection. Consider two constants, k_1 for primary infection and k_2 for secondary infection, which is the multiplying factor of benefit payment for each specific dengue infection compared to the Baseline Hospital Income (BHI). These constants will be defined as $k_1 = B_{HI,1}/BHI$ and $k_2 = B_{HI,2}/BHI$. Denote the insurance awareness factor by $f\%$ and the loss ratio by $l\%$. Then the equation that related the premium and benefit is given by

$$\begin{aligned} & f\% \cdot l\% \cdot (S_1 + R_1 + S_2 + E_2) \cdot P = [I_1 \cdot B_{HI,1}] + [I_2 \cdot B_{HI,2}(t)] \\ & \Rightarrow P = \frac{[(I_1 \cdot k_1) + (I_2 \cdot k_2)] \cdot BHI}{f\% \cdot l\% \cdot (S_1 + R_1 + S_2 + E_2)}. \end{aligned} \tag{2.1}$$

We assume that people in the state R_2 will not be interested to buy the insurance.

Denote by i_t the inflation rate at year t. Then the baseline hospital income can be projected forward or backward using the recursive formula $BHI(t+1) = BHI(t) \cdot (1 + i_t)$. To calculate the premium projection for ten years ahead, we also need to project the number of people in the other healthy states $(S_1 + R_1 + S_2 + E_2)$.

3 Results

3.1 Simulation of Indonesian Dengue Incidence Cases

To run the MCMC sampler, we first obtained the best parameter estimate (fmincon function in MATLAB) by maximizing the above log-likelihood function. Then, this will be taken as the mid-point of our uninformative prior. The Runge-Kutta 45 numerical method was utilized to create a time series of all states that act as the 'objective functions' in the parameter fitting. Dimensional unit of the parameter β_1, δ_1, r, β_2, a, and δ_2 are 1/year. Therefore, the inverse values of those parameter indicates the average time to go from one state to the next state. Only the last 1000 among 10000 chains were used as burn-in. The 95% prediction interval of the model was produced from these 1000 inferred parameter sets and the corresponding model predictions. The average value of each connecting parameter are: $\overline{\beta_1} = 14.4953$, $\overline{\delta_1} = 13.7547$, $\overline{r} = 0.1942$, $\overline{\beta_2} = 17.6930$, $\overline{a} = 6.0305$, and $\overline{\delta_2} = 0.4356$. The clinical interest is to predict the average time to get into the secondary infection, which is $1/r + 1/\beta_2 + 1/a$. In our simulation using Indonesia's data, reinfection duration is five years and 135 days on average. For Indonesia, there is not yet available a comprehensive clinical study on the duration between dengue infections. For Thailand, Endy et al. [7] did a clinical study and found that the mean duration is 2.6 years with a median of 3.0 years (for reinfected with Dengue Hemorrhagic Fever symptoms). Another clinical study conducted in Thailand found that the mean duration was 3.5 years (range, 0.33-8.8 years). Although we cannot assume that dengue disease is the same in Thailand and Indonesia, we found that our simulation result (5.37 years) seems reasonable because dengue prevalence in Thailand is higher than in Indonesia.

Results from the simulation are presented in Figure 2 showing the prediction of the number of each primary or secondary infection, and in Figure 3 showing the prediction of the total infection ($I_1 + I_2$). In Figure 3, we observe that the actual total infection data is fitted quite well within the 95% upper and lower bounds of the prediction.

The simulation shows that initially, the major cause of reported dengue incidence cases is the secondary infection for quite some years. A possible explanation would be that the government and the community did not yet have a good understanding of either dengue disease prevention, diagnosis, or treatment in the early years. Symptoms of the primary infection are usually mild and could have been misdiagnosed as a flu-like disease. Therefore, most probably, the primary dengue infections were not diagnosed and reported

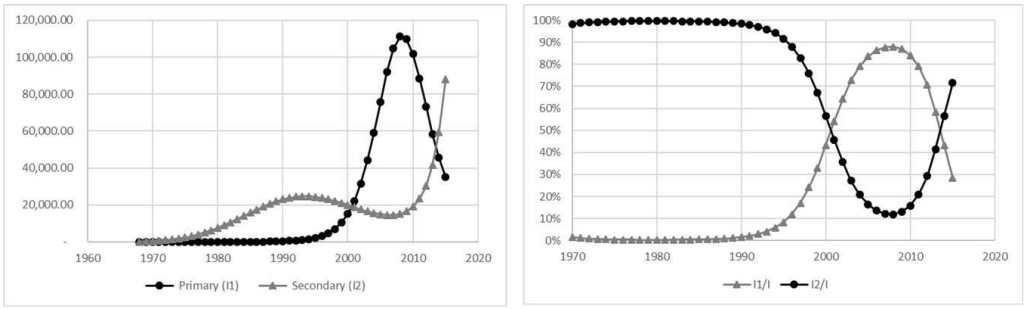

Figure 2: Left: the predicted numbers of primary (I_1) and secondary (I_2) infections; right: the percentage of primary infection (I_1/I) and secondary infection (I_2/I)

in the early years. On the other hand, secondary dengue infection usually appears more severe, resulting in Dengue Hemorrhagic Fever (DHF) or Dengue Shock Syndrome (DSS). Since 1970, the government raised awareness of dengue diseases, and the community became aware of its danger. Therefore, actions to prevent dengue had been taken since then. The activities vary from mother's attempts to protect young kids from getting bitten by mosquitoes and regular fogging in local communities to research improved diagnostics and treatments.

Preventive and curative actions may increase the percentage of seronegative people and young kids (in the model, we classify them as S_1). These people are prone to the primary dengue infection, and sooner or later, they may get bitten by a dengue vector and get infected for the first time. Dengue diagnostic has improved over time, and also people have become more aware of the disease. This might cause the raising of primary dengue infection, and since then, we observe an interesting alternating pattern between primary and secondary infections. To confirm with the predicted alternating seasonal event of the primary infection and the secondary one, we review published clinical studies on seroprevalence levels of kids and teenagers, and studies on the emergence and re-emergence of virus serotypes in Indonesia. Tam et al. [21] conducted a nationwide study in 2014 and showed that in 18 out of 30 sub-districts selected, 70% of kids aged nine have suffered from dengue at least once in their lifetime. It is also shown that in almost all districts that 50% of kids aged 11 were found to have prior dengue infection. Since 2008, national and international reports on dengue incidence with serotypes changes throughout time have been published. The graph in

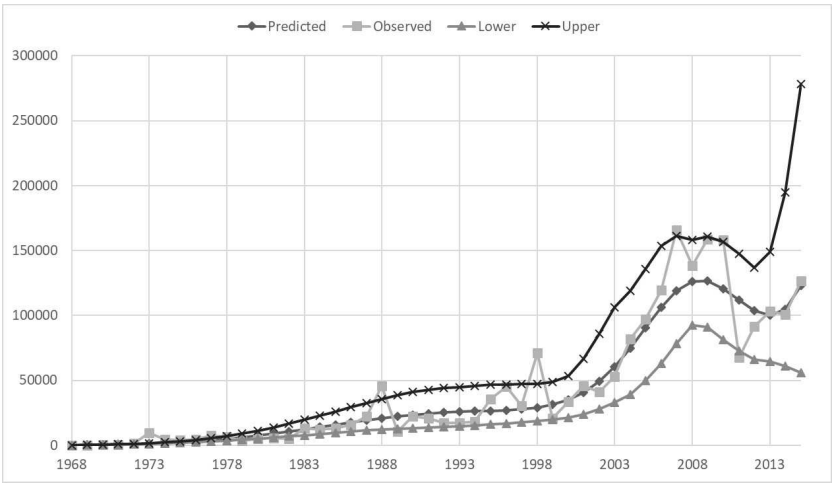

Figure 3: Simulation results of $I_1 + I_2$ (1968-2015)

Figure 4 was obtained through the percentage of the accumulated number of specific virus serotypes found over total virus serotypes identified within the year reported. The international resources were supplemented with national reports when available [4, 5, 16, 24, 22, 23, 25, 26]. Although samples might be obtained from different healthcare premises, serotype dominance was found not to differ within a particular time. The emergence of a specific serotype will lead to a sudden fluctuation of dengue incidence in a population, depending on the serotype's pathogenicity and the effectiveness of measures at the point of serotype emergence. In Figure 4, we observe that there are two serotypes (DENV-1 and DENV-2) that are dominant for the infection in the city of Surabaya. The graph also shows a possible ten-year alternating behavior between the percentage of DENV-1 and DENV-2 infections. Suppose the case of Surabaya can be generalized to the whole country. In that case, this may confirm the simulation result presented in Figure 2 that shows a ten-year alternating interval between the primary infection and the secondary infection.

Our aim for this research is not merely to predict the total number of dengue infections. Since our main target is to calculate the cost of illness, we need to predict the number of secondary infections. This feature differentiates our model from existing published models for Indonesia. If the goal is to predict only the total dengue infection in Indonesia, good models have been presented in [17, 19]. There were also published models for reinfection that differentiate DENV serotypes, which would be suitable for medical research

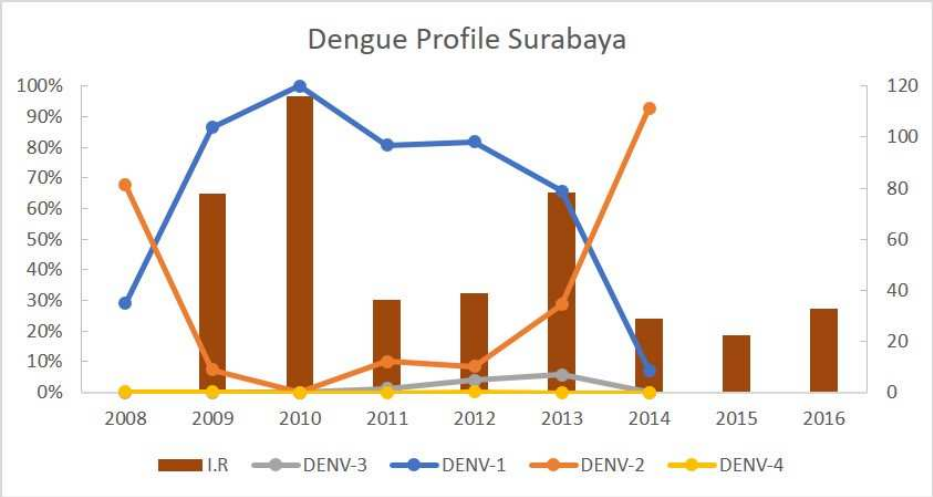

Figure 4: Dengue profile in Surabaya. Dengue serotype dominance from 2009-2014 (given as percentage on the left scale) in relation to the rate of infection per 100 000 population 2009-2016 (given as number on the right scale).

purposes [1, 2, 3]. However, each of these models involves many parameters that would complicate a financial cost model unnecessarily. The SIRSEIR model presented in the current paper does not differentiate between DENV serotypes. The model involves only parameters needed in financial models, i.e., those related to the primary infection (low medical cost) and the secondary infection (high medical cost).

The majority of published models for Indonesia were fitted with regional data. Insurance companies will sell a product only if the demand for the product is high, meaning that the market must be as large as possible. The main concept of insurance is managing diversifiable risks. These are why we take the whole country's population as the targeted policyholders instead of considering only a specific region. On the other hand, reports on regional data can be more detailed, and other factors such as weather variables should be available. Therefore, it would be good to consider a future work that combines a whole-country model and a regional model in a financial model. Examples for regional dengue models refers to [15, 18].

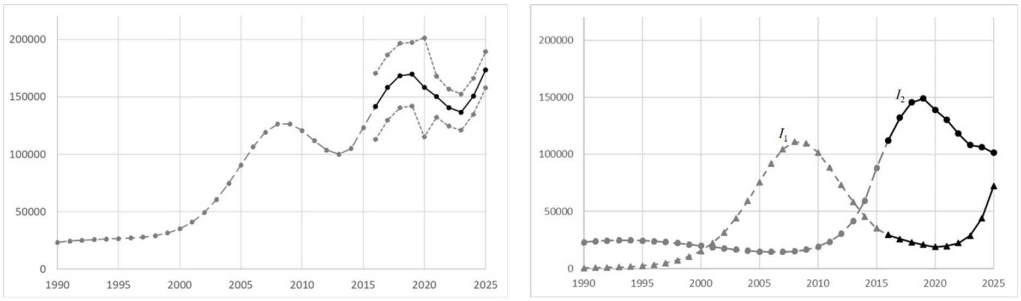

Figure 5: Left: the projected total dengue infections with 95% confidence interval; right: the projected number of primary and secondary infections.

3.2 Projected Financial Costs of Dengue through A Dengue Insurance Model

It is reasonable to assume that secondary infection's medical cost is higher than the one of primary infection. Having the predicted numbers of both primary and secondary infections enables us to project the dengue's financial cost and develop a related micro-insurance scheme. Considering socio-economical and political changes in Indonesia, we decided to do the insurance modeling starting from the year 2000. Concerning the dynamics of dengue incidence cases, choosing the year 2000 as the starting point can also be well accepted because we can still capture the alternating patterns between primary and secondary infections. Medical inflation is taken into account in the calculation. Unfortunately, studies on medical inflation in Indonesia has only been done since 2014. Therefore, in our estimation, we assume that the medical inflation rate is the same as the economic inflation rate.

First, we need to forecast the risk associated with dengue. The exponential triple smoothing method is chosen, as it is an effective forecasting method that considers seasonality in its calculation. We forecast the total infection rate per year (I) and the percentage of I_1/I or I_2/I. Afterward, we calculate the projected number of primary infection cases (I_1) and secondary infection cases (I_2) for ten years ahead. The projected total infection and the associated primary and secondary infections are presented in Figure 5. Notice that the total infection is expected to grow. Primary and secondary infections are also increasing in an alternating pattern. The advantage of predicting the number of primary and secondary infections is that we can calculate the expected medical cost more precisely. Alternating patterns of primary and

secondary infection imply that the total medical cost would increase in a fluctuated way even though it is increasing. We also forecast the inflation rate using the triple exponential smoothing method. In Figure 6 we present a sample calculation taking some values for the parameters $k_1 = 0.8$, $k_2 = 1.3$, $f\% = 50\%$, $l\% = 60\%$. We assume that $BHI(2014)$=IDR 3,021,400.00, the standard rate of regional hospital type C, published by the Indonesian Health Social Security Agency (BPJS-Kesehatan). Values for k_1 and k_2 are chosen based on the range of existing dengue micro-insurances sold by private insurance companies. Existing insurances' benefits range from IDR 2,500,000.00 to 5,000,000,00, and the year 2020 premiums ranging from IDR 40,000.00. to IDR 50,000.00 (source: various insurance companies websites). Private insurances use the company's claim data to calculate the premium. In our calculation, the loss ratio, $l\%$, is chosen to be in the acceptable range, which is $40\% - 60\%$. The chosen value for the insurance participation rate, $f\%$, refers to the year 2014 participation rate of the Indonesian Health Social Security Agency.

The predicted net premium is around IDR 13,000.00 for the year 2020. Private companies sell dengue insurances with benefits and (gross) premiums as described above. The fact that the predicted net premium is lower than the prices of existing dengue insurances gives more assurance to insurance companies that their dengue insurance products are indeed profitable. On the other hand, the predicted net premium and the methodology given in this paper can serve the Indonesian Health Social Security Government Agency in evaluating policies since dengue is one of the common diseases in the country.

4 Conclusion

We have described and analyzed a dengue micro-insurance model incorporated with a SIRSEIR epidemic model. The epidemic model enables us to split dengue case data into the annual cases of primary and secondary infections without differentiating the DENV serotypes, enabling us to calculate the cost of dengue hospitalization effectively. Initial conditions for both infections are treated as parameters predicted by using the Markov Chain Monte Carlo technique.

When applied to the Indonesian dengue data from 1968-2015, the epidemic model shows an interesting result of a ten-year alternating pattern between the numbers of primary and secondary infections. This simulation

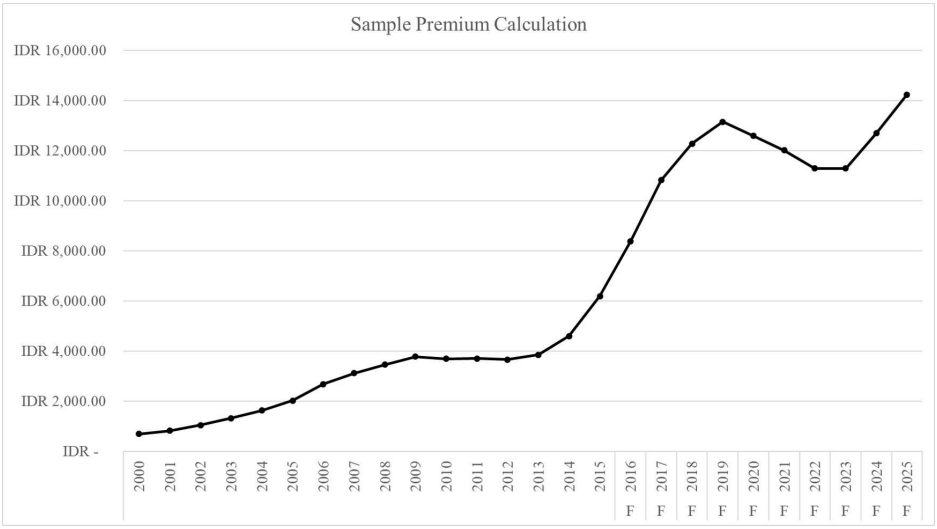

Figure 6: Sample premium calculations using $k_1 = 0.8$, $k_2 = 1.3$, $a\% = 50\%$, $l\% = 60\%$. We assume that BHI(2014)=3,021,400.00.

result confirms prior clinical studies on dengue cases in Surabaya, which show a possible ten-year alternating pattern for DENV-1 and DENV-2 infections. This result confirms periodic outbreaks shown in the data.

The SIRSEIR model is merged with a micro-insurance model. Specifically, we calculate the premium of dengue insurance in Indonesia. By using this model, we can project the future insurance premium. The annual premium calculated from our model is in agreement with existing insurance products sold by private insurance companies, reflecting that those are indeed financially safe and profitable. Furthermore, the methodology and calculation presented in this paper can be applied to analyze government policies on health social security funding for countries that are prone to dengue diseases.

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