



## Original Article

# Decline of notified dengue infections in Indonesia in 2017: Discussion of the possible determinants

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## Abstract

This study was conducted to quantify the trend in dengue notifications in the country in 2017 and to explore the possible determinants. Annual nation-wide dengue notification data were obtained from the National Disease Surveillance of Ministry of Health of Indonesia. Annual incidence rate (IR) and case fatality rate (CFR) in 2017 and the previous years were quantified and compared. Correlations between annual larva free index (LFI), implementation coverage of integrated vector management (IVM), El Niño Southern Oscillation (Niño3.4), Dipole Mode Index (DMI), Zika virus seropositivity and the percent change in IR and CFR of dengue were examined. The change of dengue IR and CFRs were mapped. In 2017, dengue IR was declined by 71% (22.55 per 100,000 population) compared to 2016 (77.96 per 100,000 population) while the CFR was slightly reduced from 0.79% to 0.75%. Reduction in IR and CFR occurred in 94.1% and 70.1% out of 34 provinces, respectively. The trend of dengue IR seems to be influenced by Niño3.4 but there is no clear evidence that Niño3.4 is the main reason for dengue reduction in 2017. It is difficult to elucidate that the reduction of dengue in 2017 was associated with previous Zika outbreaks. In conclusion, there was a significant reduction on dengue notifications in Indonesia in 2017. Further investigation is needed to look at the role of climate on the decline of dengue IR at finer temporal scale. In addition, study on the role of cross-protective immunity generated by Zika infection on dengue incidence is also warranted.

**Keywords:** dengue, Zika, larva free index, Niño3.4, vector management



## Introduction

Arboviruses are a group of viruses transmitted by arthropods, mainly mosquitoes and ticks and among them, dengue virus (DENV), chikungunya virus (CHIKV) and Zika virus (ZIKV) are

considered the most epidemiologically important viruses globally [1, 2]. DENV and ZIKV belong to Flavivirus genus while CHIKV belong to Alphavirus. Dengue, the most important mosquito-borne viral disease in humans [3], is caused by infection of any of four serotypes of DENV (DENV-1 to DENV-4) and it has a wide spectrum of clinical symptoms from mild flu-like syndrome dengue fever (DF), dengue hemorrhagic fever (DHF) to the life-threatening dengue shock syndrome (DSS) [4]. Dengue is the most common arbovirus infection worldwide, with a 30-fold increased incidence in the past 50 years [5] and over 50% of the world's population is now at risk for DENV infection [6].

Dengue and chikungunya are endemic in Indonesia [7, 8]. Since the first dengue cases reported in Jakarta and Surabaya in 1968, all four DENV serotypes have circulated in at least 433 (84.7%) districts and more than 200 million people are at risk of infection [9]. Currently, Indonesia reports the highest average number of dengue cases in Asia, with frequent epidemic cycles [10, 11]. Recent studies found that half of children become infected with DENV at least once by the age of 5 years old [10, 12]. It is estimated that 30 million dengue infections occur in Indonesia annually [13] with approximately 1% case fatality rate (CFR) [14]. Over the 50-years period, there was a sharp increase in the annual incidence rate (IR) of DHF in Indonesia, from just 0.05 cases per 100,000 person-years in 1968 to 77.96 cases per 100,000 person-years in 2016 [7].

In 2013, a Zika outbreak occurred in French Polynesia, followed by outbreaks in New Caledonia, Cook Islands, and Easter Island in 2014 and in Vanuatu, Solomon Islands, Samoa, and Fiji in 2015 [15]. In May 2015, ZIKV infection was reported for the first time in the Americas (Brazil) [16], and it rapidly spread across countries and territories on the American continent; to date, Zika has been reported in 86 countries around the globe [17]. Zika cases were not reported in Indonesia so far. However, case reports from travelers [18, 19] and molecular virology studies [20, 21] provide evidence that ZIKV is present in the country. A serological study also found that 9.1% out of 662 children aged 1-4 years were ZIKV seropositive in 2014 [22]. These data indicate that ZIKV have been circulating in Indonesia. The introduction of Zika in Indonesia has increased the transmission complexity of endemic of arboviruses in the country. This is due not only in respect of the potential misclassification of Zika and dengue diagnoses - due to similar clinical presentations [23] - but also considering cross-immunity among these arboviruses [24, 25].

Since 2010, a continuous surveillance study has been conducted using Western Australia (WA) travelers as sentinels to monitor the transmission dynamics of DENV and other arboviruses in Asia Pacific, including in Indonesia [26]. Among WA travelers diagnosed with dengue, approximately 80% originated in Indonesia [26]. Since 2014, the annual average of dengue in WA travelers was above 400 cases [27]. In 2017, however, a significant decrease of dengue cases was noticed in the WA travelers with 67.6% reduction compared to 2016. A significant decrease of dengue cases imported to Taiwan from Indonesia was also noticed [28]. The recent reports indicated a sharp reduction of dengue in the Americas in 2017 [25, 29]. The aim of this study was to investigate details situation of dengue in Indonesia in 2017 and to explore the possible factors associated with the reduction.

## Methods

### Dengue and potential factor data

Data on dengue notification were retrieved from the National Disease Surveillance, the Directorate General of Disease Prevention and Control of the Indonesian Ministry of Health (MoH). In Indonesia, reporting of DHF by Community Health Centres (*Pusat Kesehatan Masyarakat, Puskesmas*) and public or private hospitals to district health authorities is mandatory within 72 hours of diagnosis. Details of DHF case definition and case ascertainment used in this surveillance have been published elsewhere [11]. In brief, the surveillance system uses the World Health Organization (WHO) dengue classification system, which classifies symptomatic dengue into DF, DHF and DSS [30]; only DHF and DSS are reported in this surveillance system [11]. In this study, data of DHF and DSS from the surveillance were defined as dengue infection. To estimate the annual incidence rate per 100,000 population, national and annual population data were obtained from the Indonesia Bureau of Statistics.

Additionally, the annual report for larva free index (LFI) and the number of districts that implemented integrated vector management (IVM) were obtained from the MoH. LFI is the percentage of house free larvae over the total number of houses that are assessed. Every year, as part of vector surveillance, the MoH collects data on national LFI. The IVM is an approach of vector control that includes a combination of strategies, such as: a) mechanical or physical control; b) biological control such as using predator fish, bacterial or genetically modified organisms (e.g., sterile insect, *Wolbachia* infection); c) modification and manipulation of breeding sites and usage of nets; and d) chemical strategy such as using indoor residual spraying, space spray (fogging) and larvicide.

In addition to entomological and control measures, regional climate data - including indices of the El Niño Southern Oscillation (ENSO) (indicated by Niño3.4) and Indian Ocean Dipole (IOD) (indicated by Dipole Mode Index [DMI]) - for the period of 2005-2017 were also collected. ENSO is a periodic fluctuation in sea surface temperature (SST) and the air pressure of the overlying atmosphere across the equatorial Pacific Ocean; Niño3.4 is defined comprising portions of Niño regions 3 and 4 (5°N, 5°S, 120°W and 170°W) [31, 32]. IOD is defined by the difference in SST between a western pole of western Indian Ocean (50°E-70°E and 10°S-10°N) and an eastern pole in the eastern Indian Ocean south of Indonesia (90°E-110°E and 10°S-0°N) [33, 34]; DMI is the gradient of different of IOD. Previous studies have shown correlations between ENSO-IO5D variability and dengue incidence [35-37]. Monthly Niño3.4 and DMI were retrieved from the Earth System Research Laboratory of the National Oceanic and Atmospheric Administration (NOAA) [38] and from the Japan Agency for Marine-Earth Science and Technology (JAMSTEC) [39], respectively. For the purpose of analysis, the monthly Niño3.4 and DMI were averaged into yearly.

To explore the correlation between dengue notification and Zika occurrence in Indonesia, data for Zika seropositivity which collected from another study [22] were used. In Indonesia, the first evidence of Zika circulation was reported in 2012-2013 [18, 19]; in 2015, Zika virus (ZIKV) was isolated from local inhabitant for the first time in Indonesia [40]. In 2014, a study was conducted to assess Zika seropositivity among 662 children aged between 1-4 years from 14 provinces in Indonesia [22]. Zika seropositivity was measured using a plaque reduction neutralization test (PRNT) that could differentiate ZIKV neutralizing antibodies from those produced in response to DENV infection. Zika seropositive defined by sample that neutralized ZIKV only at PRNT<sub>90</sub> or had a PRNT<sub>90</sub> titer >4-fold higher for ZIKV than for any DENV [22]. We assume that the ZIKV seropositivity from the study represents the provincial seroprevalence of anti-ZIKV antibodies.

### Data analysis

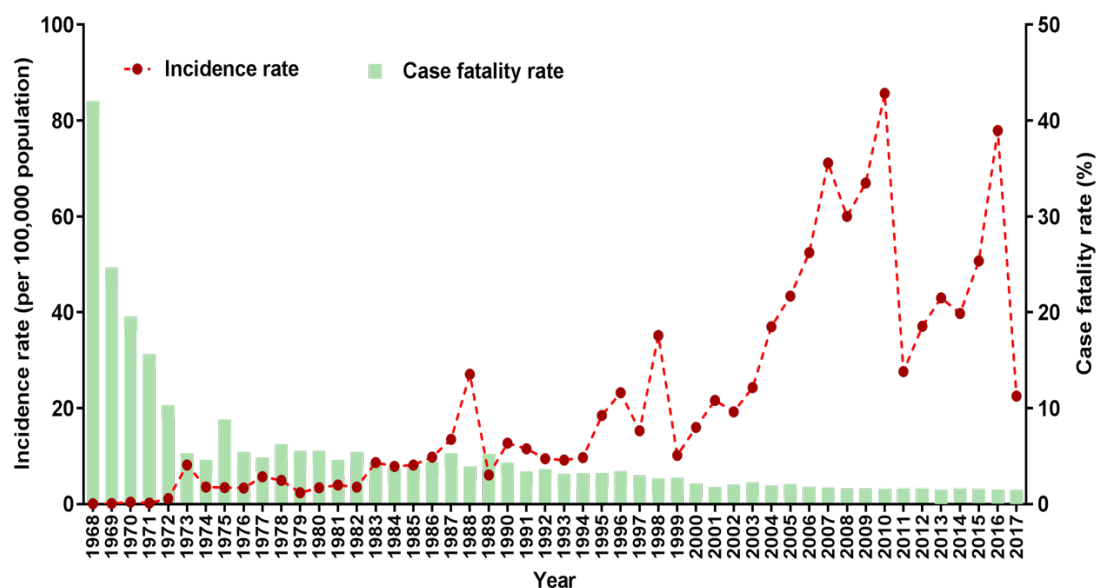
The annual IR and CFR of notified dengue in 2017 and previous years were calculated. The annual IR was determined by dividing the number of new cases by the size of the population at risk based on MoH data and was expressed as the number of cases per 100,000 inhabitants. CFR was calculated as the number of deaths associated with infection divided by the total number of cases and expressed as a percentage (%). To investigate geographical change in dengue morbidity, both IRs and CFRs in 2016 and 2017 were mapped using ArcGIS software [41] and the percent changes of IR and CFR of dengue for each province were calculated.

To explore possible factors associated with the reduction of notified dengue incidence, the associations between LFI, percent change in number of districts implementing IVM, Niño3.4 and DMI and dengue incidence were examined. Correlations between LFI, Niño3.4, DMI and annual IR and CFR of dengue were assessed using Spearman's rank correlation ( $\rho$ ), based on data distribution analysis using Shapiro-Wilk test. Correlation between Zika seropositivity and dengue IR and CFR assessed using Spearman's rank or Pearson's correlation ( $r$ ). Significance was set at  $p$ -value <0.05. The distribution of percent change of provincial IVM coverage and percent change of IR and CFR between 2016 and 2017 were mapped. In addition, the association between the magnitude of Zika infection and percent change of dengue notification were also explored.

## Results

### Decline of dengue in Indonesia in 2017

Data indicated a sharp decline of dengue notifications in Indonesia in 2017. Dengue cases decreased 66.5% from 204,171 in 2016 to 68,407 in 2017. The number of deaths associated with dengue decreased from 1,598 (2016) to 493 (2017), approximately 69%. The incidence of notified dengue decreased from 77.96 (2016) to 22.55 (2017) per 100,000 inhabitants (71.07%) while CFR reduced from 0.79% (2016) to 0.75% (2017). The temporal distribution of dengue incidence and CFR in the past five decades is presented in **Figure 1**.



**Figure 1.** Incidence rate (per 100,000 person years) and case fatality rate (%) of dengue in Indonesia from 1968 to 2017.

The reduction of incidence of dengue was observed in 94.1% (32 out of 34) of Indonesian provinces, ranging from 4.0% in Aceh to 87.9% in West Sulawesi (**Figure 2**). There were two provinces that experienced an increase in dengue incidence: West Kalimantan (335.3%) and West Papua (51.5%). CFR was reduced in 70.1% (24 out of 34) provinces, ranging from 4.2% (East Java) to 100% (Maluku, Kepulauan Bangka Belitung, North Maluku and West Sulawesi) (**Figure 2**). In contrast, the CFR of dengue was increased in nine provinces, with the highest increase in East Nusa Tenggara (140.0%).

In 2017, a total of 24 (67.6%) provinces experienced a decline in both dengue IR and CFR. However, there were some provinces with unique dynamics of IR and CFR in 2017. For instance, West Papua province experienced an increase in both IR (55.2%) and CFR (100%). The number of cases of dengue increased from 105 to 163 cases while the mortality increased from 0 to 2 deaths in 2016 and 2017, respectively. Differently, West Kalimantan experienced an increase in IR but had a decrease in CFR. Dengue incidence increased by more than 3-fold from 2016 to 2017, while the CFR dropped by 14.7%. Although there were 9 (26.4%) provinces reporting increased CFR during 2017, only 84 deaths in total were reported from those provinces, accounting for approximately 17% of total reported deaths associated with dengue infection in 2017. In Bali, the IR declined significantly but there was no change in CFR.

The percent change in IR and CFR of notified dengue from 2016-2017 were mapped. Reductions of dengue IR were observed in all major islands of Indonesia (**Figure 3**). Two provinces that had significant increase in incidence were located in Kalimantan and Papua Island, while the reduction of CFR was less obvious and there was no pattern of CFR reduction in Indonesia during 2017 (**Figure 4**). However, increase CFR was observed in two provinces in Papua Island (West Papua and Papua) and East Nusa Tenggara.

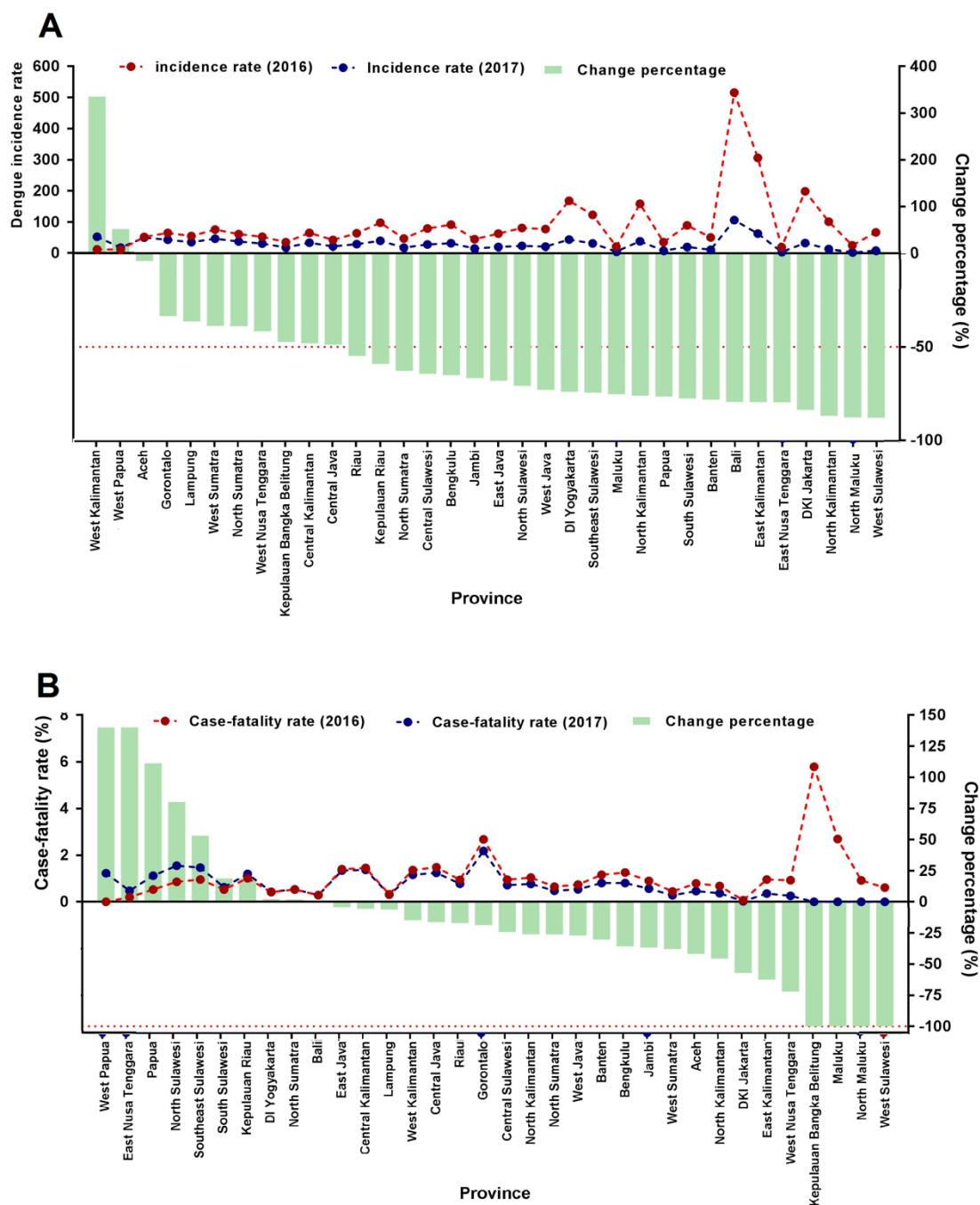


Figure 2. (A) Provincial incidence rates (per 100,000 inhabitants) and (B) case fatality rates (%) of dengue in 2016 and 2017 and their percent changes in 2017 compared to 2016.

### Exploring the potential determinants of dengue reduction

Potential factors associated with the reduction of notified dengue IR and CFR in Indonesia in 2017 were explored and discussed. Factors including vector density, LFI, number of provinces implemented IVM, Niño3.4, DMI, and Zika seropositivity were assessed.

#### Larva free index and dengue

Our hypothesis was that the decline incidence of dengue was associated with an increase in LFI in Indonesia. LFI is one of the national indicators of vector control used by Indonesian MoH. The national target of LFI is over 95%. There was an increase in LFI percentage in 2017 compared to 2016 from 47.6% to 67.6%. However, this study found there was no significant correlation either between LFI and dengue IR or between LFI and dengue CFR in the national scale ( $\rho=0.42$ ; 95%CI: -0.09, 0.76,  $p=0.144$  and  $\rho=0.33$ ; 95%CI: -0.20, 0.71,  $p=0.266$ , respectively) (Figure 5).

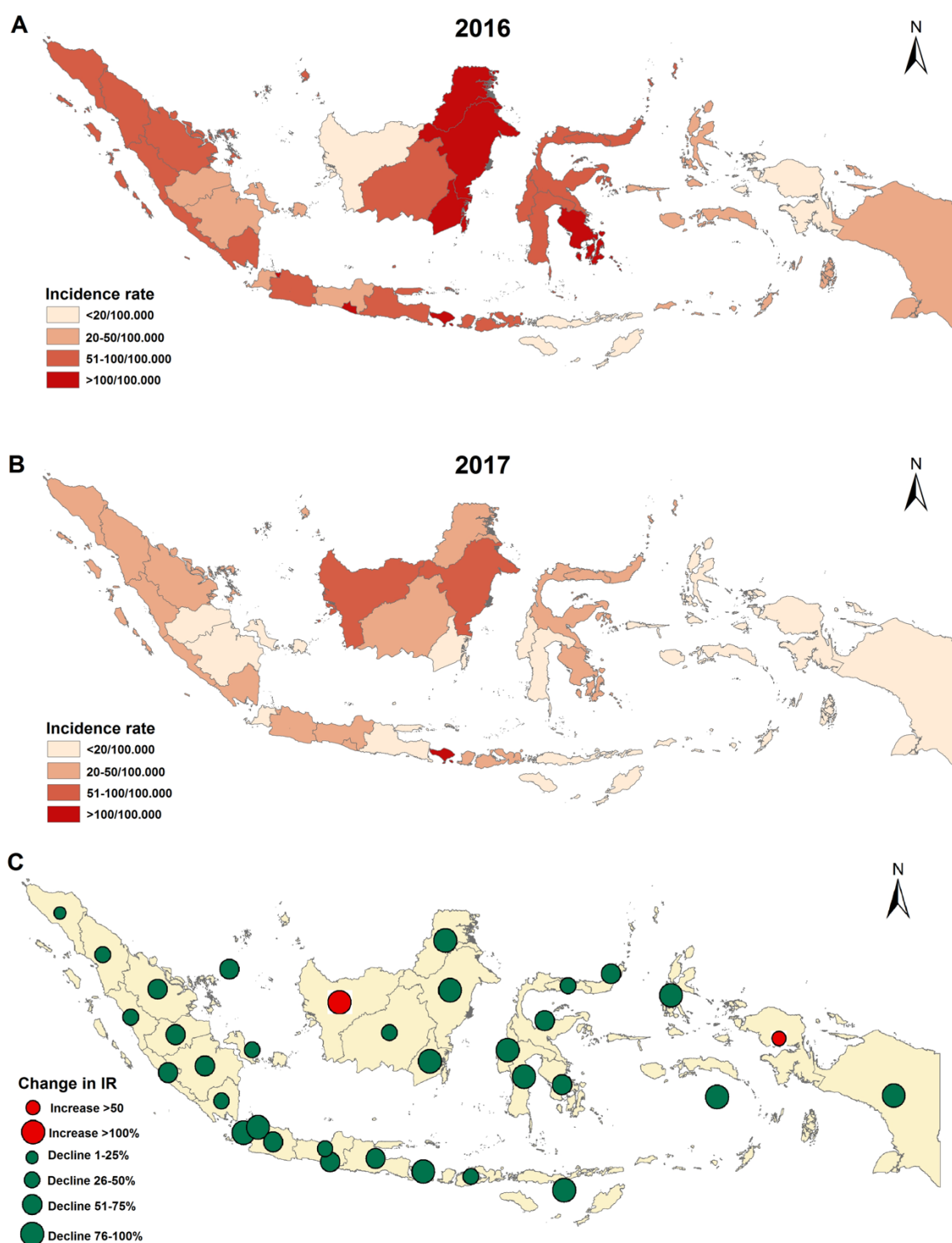


Figure 3. Spatial distribution of provincial incidence rates of dengue in 2016 (A), 2017 (B) and their change percentages in 2017 compared to 2016 (C).

### ***Integrated vector management and dengue***

In 2016, 50% of Indonesian districts implemented IVM; this number increased to 60.7% in 2017 [42, 43]. In 2016, the province with the highest percentage of districts that implemented IVM approach in Indonesia was DI Yogyakarta (100%) while the lowest was Riau province (8.3%). In 2017, there were five provinces achieving 100% coverage of IVM implementation, in which all districts from these provinces applied IVM for dengue control. This includes Aceh, East Kalimantan, South Kalimantan, Central Sulawesi and DKI Jakarta provinces. While Riau had the lowest IVM coverage in 2017, the percentage increased to 16.7% compared to 2016. More than half (61.7%) of provinces in Indonesia had increase in the IVM coverage, ranging from 4.5% to

266.6%. However, there was no significant change observed in the remaining 12 (35.3%) provinces (Figure 6).

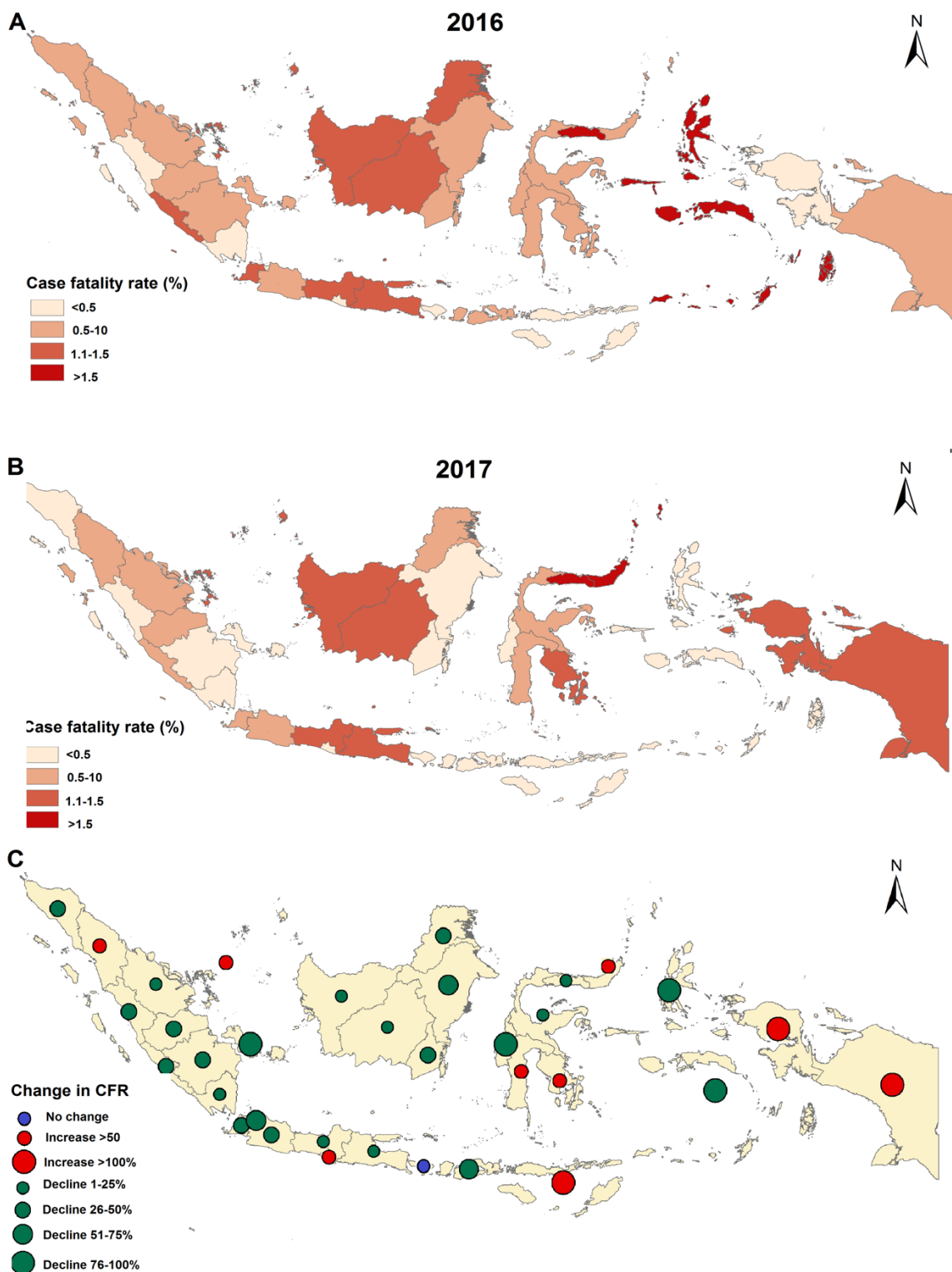


Figure 4. Spatial distribution of provincial case fatality rate of dengue in 2016 (A) and 2017 (B) and their change percentages in 2017 compared to 2016 (C).

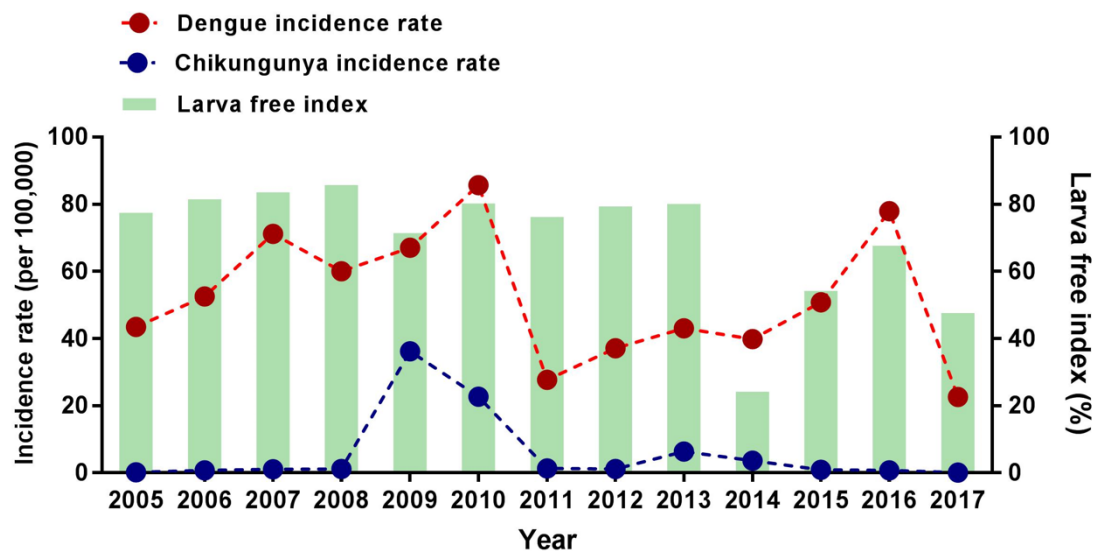


Figure 5. The annual larva free index (LFI), incidence rate and case fatality rate of dengue in Indonesia, 2005-2017.

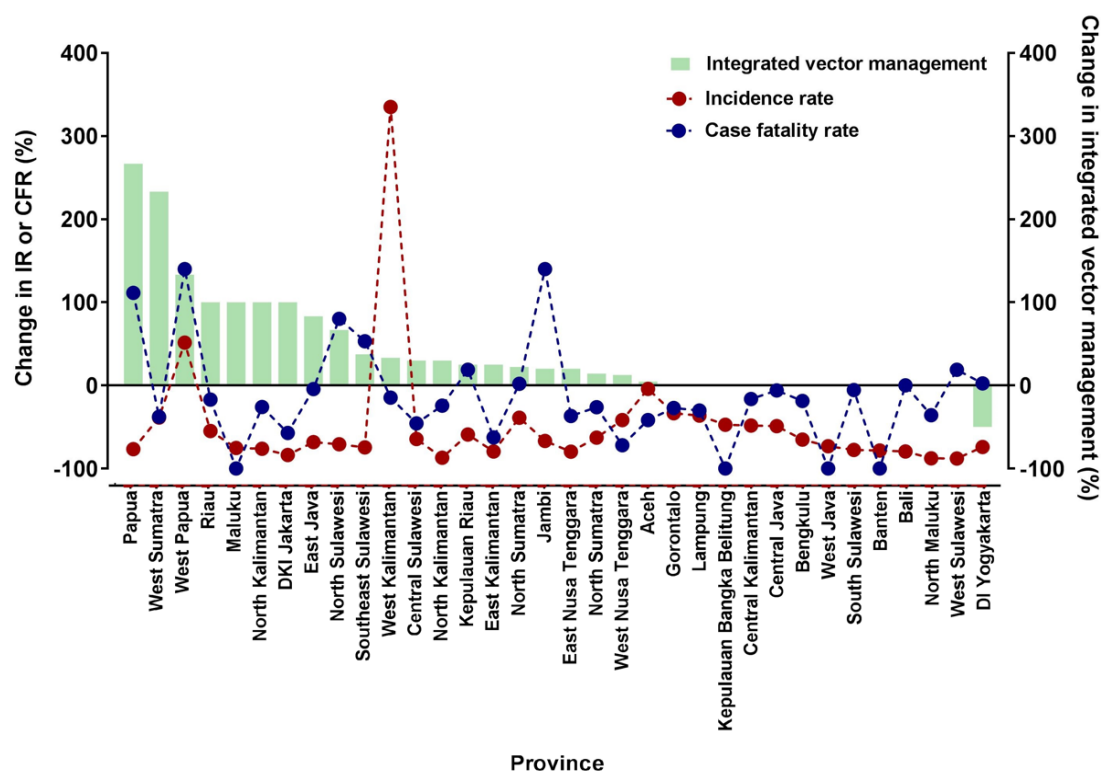


Figure 6. Percent change of IVM coverage, dengue incidence and CFR of each province in Indonesia, 2017.

It was expected that increase of IVM coverage would be associated with a decrease of IR and CFR. Therefore, the correlation between the percent change of IVM coverage and IR and CFR of dengue in 2017 were calculated. Results showed that there was no significant correlation between the IVM coverage and dengue incidence ( $\rho=0.04$ ; 95%CI: -0.25, 0.33,  $p=0.808$ ) and CFR in Indonesia ( $\rho=0.151$ ; 95%CI: -0.15, 0.42,  $p=0.394$ ).

The distribution of percent change of IVM coverage of each province and percent change of IR and CFR of dengue at province-level in 2017 compared to 2016 are presented in **Figure 7**. There was no clear pattern between changes in IVM coverage and change in IR and CFR of dengue.



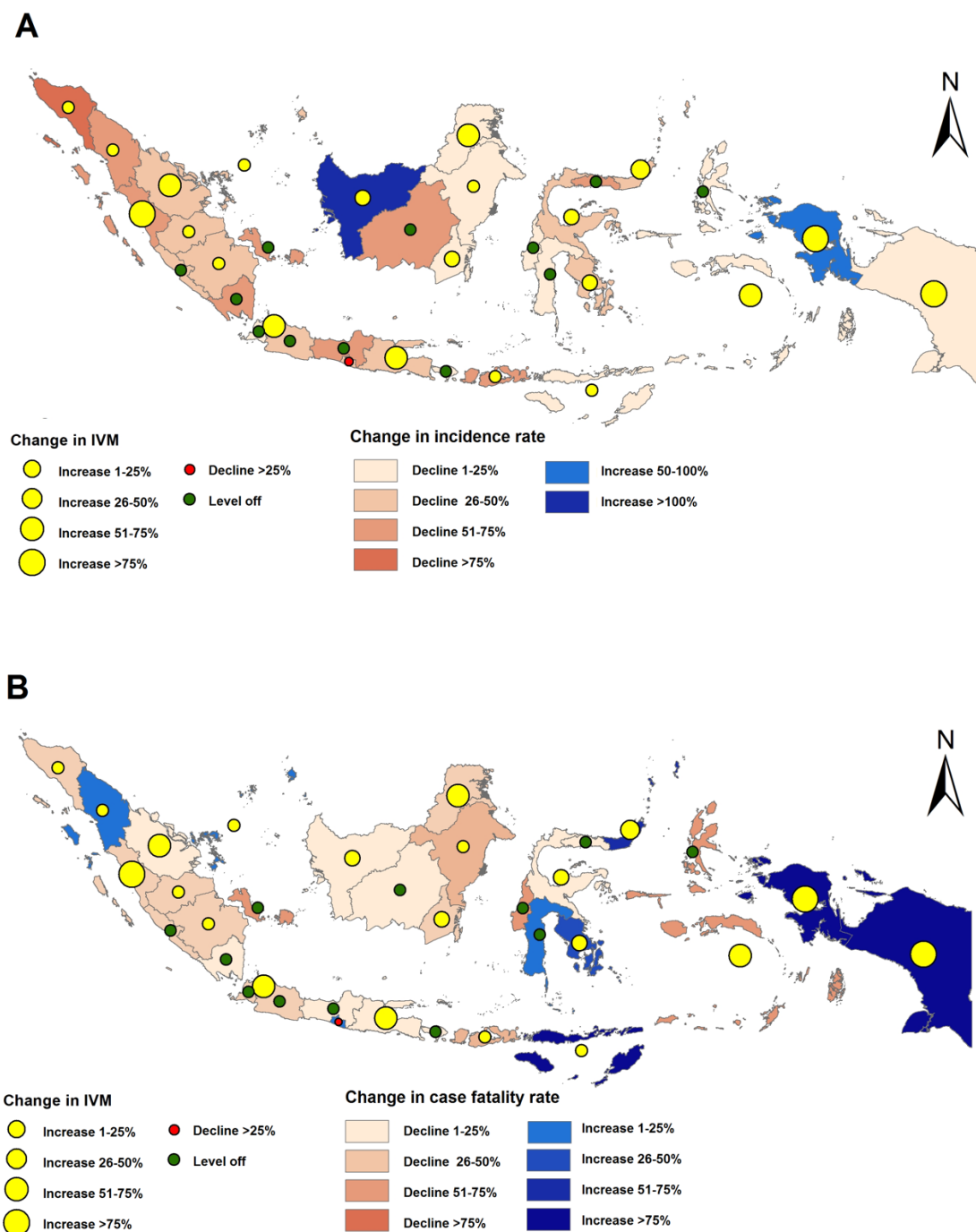


Figure 7. Map of province-level percent change of integrated vector management (IVM) coverage and incidence rate (A) and case fatality rate (B) of dengue in Indonesia in 2017 compared to 2016.

### ***Regional climate and dengue***

In this study, correlations between Niño3.4, DMI and IR of dengue for 13 years (2005-2017) were calculated. Fluctuation of Niño3.4, DMI and IR of dengue between 2015 and 2017 are shown in **Figure 8**. Our data suggested there were no strong statistically significant correlation between both Niño3.4 ( $\rho=0.023$ ,  $p=0.939$ ) and DMI ( $\rho=-0.361$ ,  $p=0.226$ ). However, data from 2009-2017 indicated that the rise of dengue incidence seemed to be influenced by Niño3.4. For instance, an increase in Niño3.4 index in 2009 and 2015 might have influenced an increase in dengue incidence in the year of 2010 and 2016, respectively (**Figure 8**). A similar pattern was also observed for DMI and IR of dengue.

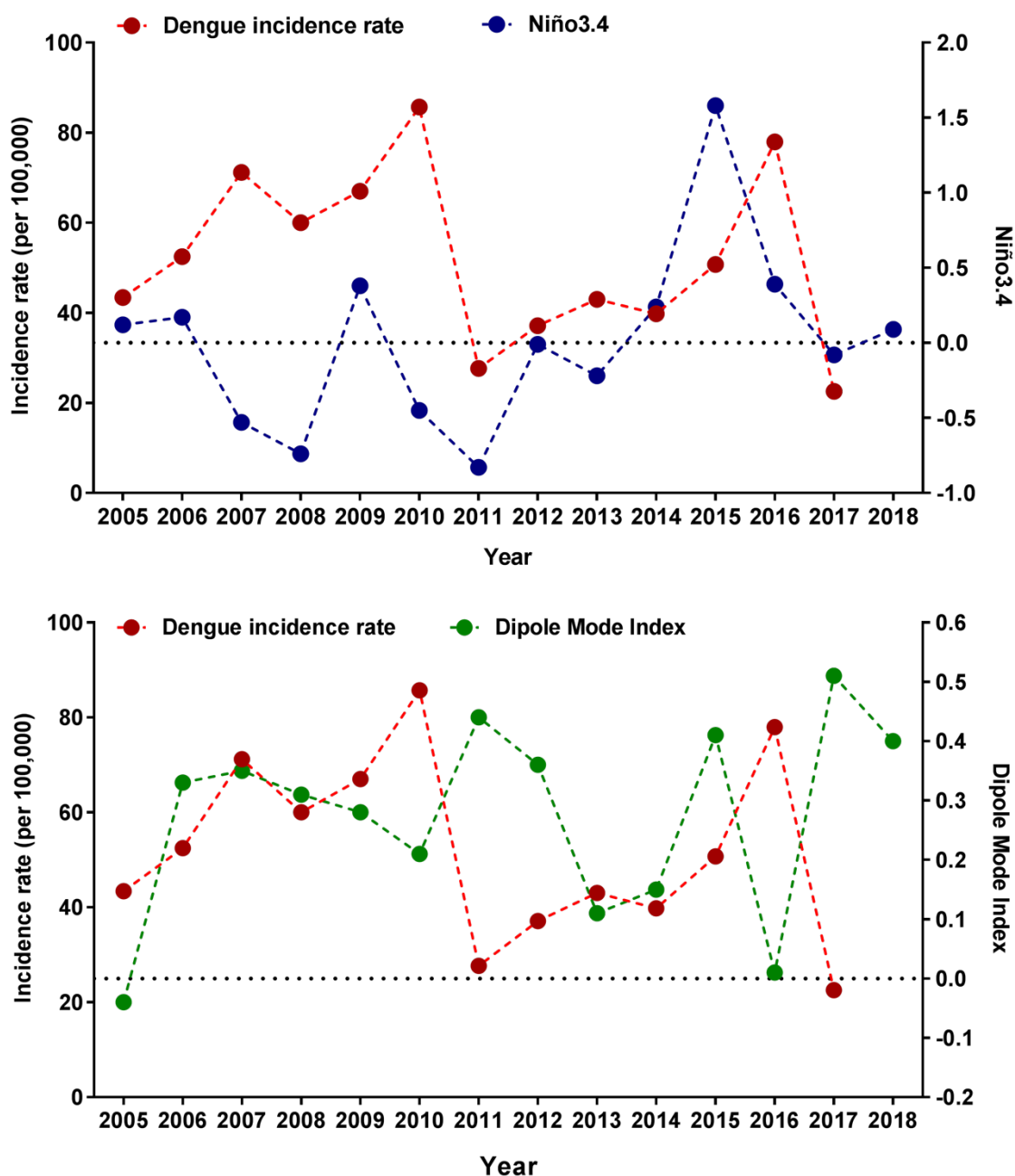


Figure 8. Temporal trend of Niño3.4, DMI and dengue incidence in Indonesia (2005-2017). Associations between Niño3.4 and dengue incidence (upper panel) and between DMI and dengue incidence (lower panel) suggest changes of both regional climatic variables followed by changes in dengue incidence although there was no significant correlation.

#### ***Cross-immunity by previous ZIKV infection and dengue***

During 2014, 662 serum samples were collected from healthy 1–4-year-old children from 14 provinces in Indonesia and were tested for ZIKV seroprevalence using plaque reduction neutralization test (PRNT) [22]. The prevalence of anti-ZIKV antibodies is presented in **Table 1**. Zika infections were confirmed in 11 out of 14 provinces and ranged between 4.5% and 18.2%. All 11 provinces with Zika positive cases had decrease in dengue IR (ranging between 38.72% and 78.27%) and 9 of them also had decrease in dengue CFR in 2017. Three provinces with no evidence of ZIKV infection also had decrease in dengue IR in 2017. However, there was no significant correlation between the Zika seropositivity in 2014 and both IR and CFR of dengue in 2017,  $\rho=0.186$ ; 95%CI: -0.31, 0.60,  $p=0.523$  and  $r=-0.276$ ; 95%CI: -0.66, 0.22,  $p=0.339$ , respectively.

**Table 1.** The magnitude of ZIKV seropositivity (2014) and percent change of IR and CFR of dengue in 14 provinces in Indonesia

Province	Confirmed ZIKV seropositive*		Percent change**	
	Percentage	Case/total	IR	CFR
Jambi	18.2	4/22	-66.73	-36.67
Central Tengah	18.2	16/88	-48.89	-16.22
West Sumatra	13.6	3/22	-38.72	-37.78
DKI Jakarta	10.6	7/66	-74.00	2.38
East Java	9.0	10/111	-68.16	-4.29
Lampung	8.7	2/23	-36.26	-6.06
Banten	8.7	2/23	-78.27	-30.17
West Java	8.5	13/153	-73.03	-27.03
South Sumatra	4.5	1/22	-62.85	-26.15
East Kalimantan	4.5	1/22	-68.16	-4.29
Southeast Sulawesi	4.5	1/22	-74.55	53.13
Aceh	0.0	0/22	-4.02	-41.77
Bali	0.0	0/22	-79.46	0.00
South Sulawesi	0.0	0/22	-77.65	18.87

\*Serum samples that neutralized ZIKV only or had a PRNT<sub>90</sub> titre >4-fold higher for ZIKV than for any DENV

\*\*Percent change in 2017 compared to 2016

## Discussion

There was a significant decline of dengue in Indonesia in 2017. The reduction in dengue IR and CFR occurred in most provinces in Indonesia. Compared to 2016, in 2017 the incidence was substantially reduced (from 77.96 to 22.55 cases per 100,000 inhabitants) while the fatality rates were slightly reduced from 0.79% to 0.75%. Although this study indicates that the reduction of dengue incidence was much more obvious than CFR, these findings should be interpreted carefully. Since 2008, the fatality rates due to dengue infection in Indonesia were less than 1% and small changes on the number of deaths in a province will increase the CFR significantly. For example, in 2017, only two deaths associated with dengue were reported in Papua Barat province, but this increased the CFR up to 100% because no death was reported in 2016. In addition, although there were 9 (26.4%) provinces reporting increase in dengue CFR during 2017, the total deaths from these provinces were 84 only accounting for approximately 17% dengue related deaths.

There was no a clear single factor associated with the reduction of dengue incidence and fatality rates in 2017. A previous study discussed three hypotheses that might be related with the reduction of dengue in Americas [25]: (a) changes in epidemiological surveillance systems; (b) changes in the density and competencies of vectors; and (c) cross-immunity generated by the simultaneous circulation of several arboviruses. In the present study, we attempted to explore the associations between entomological indicator (LFI), existing control measures (IVM), regional climate and the occurrence of Zika and dengue incidence. Changes in epidemiological surveillance systems are unlikely to be the leading factor associated with the reduction of dengue cases in Indonesia in 2017. Based on the Indonesian MoH report [42], no change of epidemiological surveillance systems in both case definition or notification system occurred in the county in 2017 compared to previous years, which is true for both dengue and chikungunya. The Indonesia MoH suggests that the reduction may partly be associated with the existing national community-based program called “*Gerakan 1 Rumah 1 Jumantik*”, in which one family member is trained to be an inspector or ‘*Jumantik*’ and is responsible for monitoring vector breeding sites regularly in their house [42]. This program is one of the strategies within IVM. However, this did not explain the reductions in all regions because the program was launched in 2016 [43] and the program is not widely implemented in Indonesia [42]. Our findings also indicates that there was no strong correlation between the IVM coverage and changes of IR and CFR of dengue in Indonesia in 2017. This suggests to other factors that could better explain the reduction of dengue incidence in 2017.

Our initial data suggested that changes of annual Niño3.4 and DMI were followed by changes on incidence of dengue in Indonesia, but whether this is the main reason for reduction of dengue in 2017 still needs to be explored. Some studies using small-scale region data in Indonesia have shown that dengue incidence was associated with climate [44, 45] and some climate-related variables could be used to predict dengue outbreak or incidence [46, 47]. A study reported that 12.9–24.5% of variance in dengue incidence were explained by two or three climate variables [48]. The reason why climate variables are associated with dengue incidence or outbreak is because variations in climate variables affect the behavior, maturation and duration of infectivity of DENV vector mosquitoes and therefore affect their density. Although the present study has assessed the role of Niño3.4 and DMI on dengue incidence, the correlations were assessed using annual data, thus making analyses less sensitive to detect clear association of these climate variables. In addition, missing from the analyses are assessments of the role of other climate variables, such as rainfall, temperature, and humidity. Therefore, a study to analyze the relationship between changes in climate variables and reduction of dengue in 2017 is needed. Moreover, efforts to explore the relationship between Niño3.4, DMI and dengue cases in Indonesia using higher temporal resolutions, such as weekly or monthly, are also needed. In addition to direct month-by-month correlation, the variables need to be lagged up to particular times with respect to dengue incidence.

The cross-immunity generated by the ZIKV outbreaks has been considered as an associated factor with decrease of dengue incidence in Americas [25]. Many studies have focused whether pre-existing DENV-induced antibodies enhance or protect ZIKV infection, founding conflicting results [24, 49-59]. Some studies found that DENV-induced antibodies enhanced [49-53], had no association [54-56], or had protective [24, 57-59] for ZIKV infection. A recent prospective study in Nicaragua found that prior DENV infection was associated with protection against symptomatic ZIKV infection [58]. However, few studies have been conducted to assess whether immunity responses after ZIKV infection are cross-protective against DENV infection. An initial study in Brazil indicated to a decrease in dengue cases following a widespread ZIKV outbreak [24]. Data from other countries throughout the Americas also observed decrease dengue cases following ZIKV outbreaks [25]. These studies suggest that ZIKV infection might induce cross-protective immune responses against DENV and could inhibit the transmission of DENV.

In Indonesia, although no Zika cases have been reported, two Australian travelers have been reported to have acquired ZIKV infection after visiting Indonesia in 2012 and 2013 [18, 19]. A serology study in 2014 found that 9.1% out of 622 children aged 1-4 years were infected with ZIKV [22] and in 2015 ZIKV was isolated for the first time in Indonesia [40]. These data indicate that ZIKV have been circulated in Indonesia prior to 2014, earlier than when the virus reached the Americas. This is also supported by a phylogenetic study that demonstrated the introduction and dispersal of ZIKV in the Pacific islands and Americas originated from Asia that evolved adaptively with silent transmission in Southeast Asia [60]. A recent study found that among 150 Indonesian migrant workers to Taiwan in 2017, 4.7% and 43.3% were positive for ZIKV-specific IgM and IgG, respectively [61]. Among IgM positive samples, confirmation with plaque reduction neutralization test indicated at least one sample with ZIKV infection using WHO criteria [61], indicating that ZIKV was still circulating in 2017 in Indonesia. However, with limited Zika infection data in Indonesia, it is difficult to elucidate that the reduction of dengue in Indonesia in 2017 was associated with previous ZIKV infection. Nevertheless, the role of cross-protective immunity responses generated by previous ZIKV infection cannot be ruled out. Therefore, prospective studies are needed to fully assess the subsequent risk of dengue after ZIKV exposure in the country. In addition, data of dengue and chikungunya cases in 2017 from other countries in Southeast Asia region are also important to explain the phenomenon in the bigger context.

Apart from cross-immunity generated by the ZIKV infection, the role of herd immunity might also contribute to the decline of dengue observed in 2017. Epidemiological studies have shown that dengue had endemic and epidemic cycles due to herd immunity and varies among countries [62-65]. This variation is associated with serotypes of circulating viruses and population immunity background [62]. Studies suggested that cross-protection induced by a first infection with DENV against a second symptomatic infection is approximately 2 years [66, 67]. A review indicated that the peak transmission occurred between 3–5 years in many populations

regardless of the circulating DENV serotype [63]. In Indonesia, data from over 50-year time-span, IRs of DHF appear to be cyclic and peaking approximately every 6–8 years [7]. The latest sharp reduction of DHF prior to 2017 occurred in 2011 when the cases reduced significantly from 156,086 to 65,725 cases, reduced by 57.8% compared to 2010 (**Figure 1**). A previous study detected increase activities of multiple DENV serotypes during a significant increase of DHF cases while a reduction of DHF in 2011 was coincident when DENV-1 had serotype dominance in the country [7]. The cycle repeated again in 2013 onward so that, when multiple DENV serotypes began to dominate, the number of DHF started to increase [7]. However, it is difficult to elucidate whether the reduction of dengue in 2017 is part of nature cyclic of dengue transmission in Indonesia due to limitation of the data.

There are some limitations of this study that should be considered when interpreting the findings. This study used notification data (passive-surveillance) which may result in under estimation of the actual dengue incidence. We acknowledged that the surveillance management (e.g., completeness of the report, underreported cases) could have varied between provinces, which may influence the results. In this study we did not assess the association between local climate variables such as rainfall, temperature, and humidity. Instead, we used regional climatic data such as Niño3.4 and DMI. Further studies should be carried out to explore the correlations between climate variables and dengue incidence at sub-national and local level. Although this study has assessed the role of IVM, as indicator of vector density, on reduction of dengue cases, a study to analyze the relationship between changes of climate variables and reduction of dengue in 2017 is needed. In addition, the relationship between Niño3.4, the DMI and dengue cases in Indonesia is far from clear and therefore further investigation is needed. We used the number of districts implementing IVM as proxy for vector control. However, the IVM maybe not the best proxy for vector density because the implementation and the effectiveness of IVM may vary among districts. One of the accurate indicators would be provincial LFI, however, this data is not available. So far, there is no routine longitudinal entomological data (e.g., pupae index, house index, container index). Lastly, correlations between provincial ZIKV seroprevalence in 2014 and the changes of IR and CFR of dengue were calculated. This might prone to bias because there is a possibility that the magnitude of the ZIKV infection have changed during the 2014-2016 period in each province and so far, there were no studies that have measured the most effectiveness time and how long the cross-protective role of ZIKV-antibodies against DENV infection lasts.

## Conclusions

There was a significant reduction in both IR and CFR of dengue in 2017. The reduction is likely associated with factors other than changes in epidemiological surveillance system or changes of circulating viruses. The coverage of IVM implementation has no correlation with reduction of both IR and CFR of dengue suggesting that the reductions was not associated with vector controls. Initial data indicated that the trend of dengue incidence follows the fluctuations of Niño3.4 in lagged manner and further studies using high temporal resolution are needed. Although the role of cross-protective of ZIKV-antibodies could not be ruled out, lack of Zika data in Indonesia makes this is hard to be elucidated.

## Declarations

### Ethics approval

Not required.

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**Conflict of interest**

The authors declare that they have no competing interests.

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None.

**Data Availability**

Dengue notification data, LFI and IVM are available from the Directorate General of Disease Prevention and Control of the Indonesian Ministry of Health (MoH) upon request. Monthly Niño3.4 and DMI are available from the Earth System Research Laboratory of the National Oceanic and Atmospheric Administration (NOAA) and Japan Agency for Marine-Earth Science and Technology (JAMSTEC).

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**References**

1. Patterson J, Sammon M, Garg M. Dengue, zika and chikungunya: emerging arboviruses in the new world. *West J Emerg Med* 2016; 17(6):671-679.
2. Paixao ES, Teixeira MG, Rodrigues LC. Zika, chikungunya and dengue: the causes and threats of new and re-emerging arboviral diseases. *BMJ Glob Health* 2018; 3(Suppl 1):e000530.
3. WHO. Global strategy for dengue prevention and control, 2012–2020. Geneva: WHO Press; 2012.
4. Martina BE, Koraka P, Osterhaus AD. Dengue virus pathogenesis: an integrated view. *Clin Microbiol Rev* 2009; 22(4):564-581.
5. Schaffner F, Mathis A. Dengue and dengue vectors in the WHO European region: past, present, and scenarios for the future. *Lancet Infect Dis* 2014; 14(12):1271-1280.
6. WHO. Global strategy for dengue prevention and control: 2012–2020. Geneva World Health Organization; 2012.
7. Harapan H, Michie A, Yohan B, *et al.* Dengue viruses circulating in Indonesia: A systematic review and phylogenetic analysis of data from five decades. *Rev Med Viro* 2019:e2037.
8. Harapan H, Michie A, Mudatsir M, *et al.* Chikungunya virus infection in Indonesia: a systematic review and evolutionary analysis. *BMC Infect Dis* 2019; 19(1):243.
9. Kemenkes RI. Profil kesehatan Indonesia tahun 2014. In. Jakarta: Kementerian Kesehatan RI; 2015.
10. Prayitno A, Taurel AF, Nealon J, *et al.* Dengue seroprevalence and force of primary infection in a representative population of urban dwelling Indonesian children. *PLoS Negl Trop Dis* 2017; 11(6):e0005621.
11. Karyanti MR, Uiterwaal CS, Kusriastuti R, *et al.* The changing incidence of dengue haemorrhagic fever in Indonesia: a 45-year registry-based analysis. *BMC Infect Dis* 2014; 14:412.
12. Prayitno A, Taurel AFC, Nealon J, *et al.* Dengue seroprevalence in urban dwelling Indonesian children: A nationally-representative study. *PLoS Negl Trop Dis* 2016; 45:242-242.
13. Bhatt S, Gething PW, Brady OJ, *et al.* The global distribution and burden of dengue. *Nature* 2013; 496(7446):504-507.
14. Dengue: guideline for diagnosis, treatment, prevention, and control. Available from: <http://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf> (Accessed: 1 January 2019).
15. Musso D, Gubler DJ. Zika Virus. *Clin Microbiol Rev* 2016; 29(3):487-524.
16. Samarasekera U, Triunfol M. Concern over Zika virus grips the world. *Lancet* 2016; 387(10018):521-524.
17. Zika Situation Report. Available from: <http://www.who.int/emergencies/zika-virus/situation-report/10-march-2017/en/> (Accessed: 1 January 2019).

18. Kwong JC, Druce JD, Leder K. Case report: Zika virus infection acquired during brief travel to Indonesia. *The American journal of tropical medicine and hygiene* 2013; 89(3):516-517.
19. Leung GH, Baird RW, Druce J, *et al.* Zika virus infection in Australia following a monkey bite in Indonesia. *Southeast Asian J Trop Med Public Health* 2015; 46(3):460-464.
20. Perkasa A, Yudhaputri F, Haryanto S, *et al.* Isolation of Zika virus from febrile patient, Indonesia. *Emerg Infect Dis* 2016; 22(5):924-925.
21. Soebandrio A, Yudhaputri F, Perkasa A, *et al.* Whole genome sequencing and phylogenetic analysis of zika virus isolated in indonesia. *Am J Trop Med Hyg* 2017; 95(5):236-236.
22. Sasmono RT, Dhenni R, Yohan B, *et al.* Zika Virus Seropositivity in 1-4-Year-Old Children, Indonesia, 2014. *Emerg Infect Dis* 2018; 24(9).
23. Gyurech D, Schilling J, Schmidt-Chanasit J, *et al.* False positive dengue NS1 antigen test in a traveller with an acute Zika virus infection imported into Switzerland. *Swiss Med Wkly* 2016; 146:w14296.
24. Ribeiro GS, Kikuti M, Tauro LB, *et al.* Does immunity after Zika virus infection cross-protect against dengue? *Lancet Glob Health* 2018; 6(2):E140-E141.
25. Perez F, Llau A, Gutierrez G, *et al.* The decline of dengue in the Americas in 2017: discussion of multiple hypotheses. *Trop Med Int Health* 2019; 24(4):442-453.
26. Ernst T, McCarthy S, Chidlow G, *et al.* Emergence of a new lineage of dengue virus type 2 identified in travelers entering Western Australia from Indonesia, 2010-2012. *PLoS Negl Trop Dis* 2015; 9(1):e0003442.
27. Notifiable infectious disease reports, WA Department of Health Dengue fever notifications in Western Australia. Available from: [http://www.public.health.wa.gov.au/3/1547/3/dengue\\_fever.pm](http://www.public.health.wa.gov.au/3/1547/3/dengue_fever.pm) (Accessed: 1 January 2019).
28. Psu P. Dengue viruses imported into Taiwan. 2019 [Personal communication].
29. Lopes TRR, Silva CS, Pastor AF, *et al.* Dengue in Brazil in 2017: what happened? *Rev Inst Med Trop Sp* 2018; 60.
30. Sumarmo. Dengue haemorrhagic fever in Indonesia. *Southeast Asian J Trop Med Public Health* 1987; 18(3):269-274.
31. McGregor GR, Ebi K. El Nino southern oscillation (ENSO) and Health: An overview for climate and health researchers. *Atmosphere-Basel* 2018; 9(7).
32. Yang S, Li ZN, Yu JY, *et al.* El Nino-Southern Oscillation and its impact in the changing climate. *Natl Sci Rev* 2018; 5(6):840-857.
33. Saji NH, Goswami BN, Vinayachandran PN, *et al.* A dipole mode in the tropical Indian Ocean. *Nature* 1999; 401(6751):360-363.
34. Shi L, Hendon HH, Alves O, *et al.* How Predictable is the Indian Ocean Dipole? *Mon Weather Rev* 2012; 140(12):3867-3884.
35. Vincenti-Gonzalez MF, Tami A, Lizarazo EF, *et al.* ENSO-driven climate variability promotes periodic major outbreaks of dengue in Venezuela. *Sci Rep* 2018; 8(1):5727.
36. Chuang TW, Chaves LF, Chen PJ. Effects of local and regional climatic fluctuations on dengue outbreaks in southern Taiwan. *PLoS One* 2017; 12(6):e0178698.
37. Atique S, Abdul SS, Hsu CY, *et al.* Meteorological influences on dengue transmission in Pakistan. *Asian Pac J Trop Med* 2016; 9(10):954-961.
38. National Oceanic and Atmospheric Administration. Southern Oscillation Index (SOI). Available from: [https://www.esrl.noaa.gov/psd/gcos\\_wgsp/Timeseries/](https://www.esrl.noaa.gov/psd/gcos_wgsp/Timeseries/) 2019 (Accessed: 8 June 2019).
39. Japan Agency for Marine-Earth Science and Technology. Dipole Mode Index. Available from: [http://www.jamstec.go.jp/aplinfo/sintexf/iod/dipole\\_mode\\_index.html](http://www.jamstec.go.jp/aplinfo/sintexf/iod/dipole_mode_index.html) 2019 (Accessed: 8 June 2019).
40. Perkasa A, Yudhaputri F, Haryanto S, *et al.* Isolation of Zika virus from febrile patient, Indonesia. *Emerg Infect Dis* 2016; 22(5):924.
41. Environmental Systems Research Institute (ESRI). ArcGIS Release 10.1. Redlands, CA: ESRI; 2012
42. Kemenkes RI. Profil kesehatan Indonesia tahun 2017. In. Jakarta: Kementerian Kesehatan RI; 2018.
43. Ministry of Health Indonesia. Petunjuk teknis implementasi PSM 3M - Plus dengan gerakan 1 rumah 1 jumantik. Jakarta: Kementerian Kesehatan Republik Indonesia; 2016.
44. Tosepu R, Tantrakarnapa K, Nakhapakorn K, *et al.* Climate variability and dengue hemorrhagic fever in Southeast Sulawesi Province, Indonesia. *Environ Sci Pollut Res Int* 2018; 25(15):14944-14952.
45. Astuti EP, Dhewantara PW, Prasetyowati H, *et al.* Paediatric dengue infection in Cirebon, Indonesia: a temporal and spatial analysis of notified dengue incidence to inform surveillance. *Parasit Vectors* 2019; 12(1):186.

46. Ramadona AL, Lazuardi L, Hii YL, *et al.* Prediction of dengue outbreaks based on disease surveillance and meteorological data. *PLoS One* 2016; 11(3):e0152688.
47. Xu Z, Bambrick H, Yakob L, *et al.* Using dengue epidemics and local weather in Bali, Indonesia to predict imported dengue in Australia. *Environ Res* 2019; 175:213-220.
48. Arcari P, Tapper N, Pfueller S. Regional variability in relationships between climate and dengue/DHF in Indonesia. *Singapore J Trop Geo* 2007; 28(3):251-272.
49. Priyamvada L, Quicke KM, Hudson WH, *et al.* Human antibody responses after dengue virus infection are highly cross-reactive to Zika virus. *Proc Natl Acad Sci U S A* 2016; 113(28):7852-7857.
50. Bardina SV, Bunduc P, Tripathi S, *et al.* Enhancement of Zika virus pathogenesis by preexisting antinflavivirus immunity. *Science* 2017; 356(6334):175-180.
51. Paul LM, Carlin ER, Jenkins MM, *et al.* Dengue virus antibodies enhance Zika virus infection. *Clin Transl Immunology* 2016; 5(12):e117.
52. Castanha PMS, Nascimento EJM, Braga C, *et al.* Dengue Virus-specific antibodies enhance Brazilian zika virus infection. *J Infect Dis* 2017; 215(5):781-785.
53. Dejnirattisai W, Supasa P, Wongwiwat W, *et al.* Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with zika virus. *Nat Immunol* 2016; 17(9):1102-1108.
54. Pantoja P, Perez-Guzman EX, Rodriguez IV, *et al.* Zika virus pathogenesis in rhesus macaques is unaffected by pre-existing immunity to dengue virus. *Nat Commun* 2017; 8: 15674.
55. McCracken MK, Gromowski GD, Friberg HL, *et al.* Impact of prior flavivirus immunity on Zika virus infection in rhesus macaques. *PLoS Pathog* 2017; 13(8):e1006487.
56. Terzian ACB, Schanoski AS, Mota MTO, *et al.* Viral load and cytokine response profile does not support antibody-dependent enhancement in dengue-primed zika virus-infected patients. *Clin Infect Dis* 2017; 65(8):1260-1265.
57. Swanstrom JA, Plante JA, Plante KS, *et al.* Dengue virus envelope dimer epitope monoclonal antibodies isolated from dengue patients are protective against zika virus. *MBio* 2016; 7(4); e01123-16
58. Gordon A, Gresh L, Ojeda S, *et al.* Prior dengue virus infection and risk of Zika: A pediatric cohort in Nicaragua. *Plos Medicine* 2019; 16(1): e1002726.
59. Wen J, Elong Ngono A, Regla-Nava JA, *et al.* Dengue virus-reactive CD8(+) T cells mediate cross-protection against subsequent Zika virus challenge. *Nat Commun* 2017; 8(1):1459.
60. Pettersson JH, Bohlin J, Dupont-Rouzeyrol M, *et al.* Re-visiting the evolution, dispersal and epidemiology of Zika virus in Asia. *Emerg Microbes Infect* 2018; 7(1):79.
61. Perng GC, Ho TC, Shih HI, *et al.* Seroprevalence of Zika and dengue virus antibodies among migrant workers, Taiwan, 2017. *Emerg Infect Dis* 2019; 25(4):814-816.
62. Bennett SN, Drummond AJ, Kapan DD, *et al.* Epidemic dynamics revealed in dengue evolution. *Mol Biol Evol* 2010; 27(4):811-818.
63. Gubler DJ. Dengue and dengue hemorrhagic fever. *Clin Microbiol Rev* 1998; 11(3):480.
64. Ooi EE, Goh KT, Gubler DJ. Dengue prevention and 35 years of vector control in Singapore. *Emerg Infect Dis* 2006; 12(6):887-893.
65. Nisalak A, Endy TP, 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(2):191-202.
66. Anderson KB, Gibbons RV, Cummings DAT, *et al.* A shorter time interval between first and second dengue infections is associated with protection from clinical illness in a school-based cohort in Thailand. *J Infect Dis* 2014; 209(3):360-368.
67. Montoya M, Gresh L, Mercado JC, *et al.* Symptomatic Versus Inapparent Outcome in Repeat Dengue Virus Infections Is Influenced by the Time Interval between Infections and Study Year. *Plos Neglect Trop D* 2013; 7(8): e2357.