

Manuscript: Chikungunya

10 messages

Harapan Harapan, MD <harapan@unsyiah.ac.id>

16 November 2019 at 20:53

To: amanda yufika <amandayufika@gmail.com>, samsul anwar <s4m_seupeng@yahoo.co.id>, Hayphengte <hayphengte@gmail.com>, Hamzah Hasyim <hamzah.hasyim@gmail.com>, Roy Nusa <roynres@gmail.com>, Mudatsir Mudatsir <mudatsir@unsyiah.ac.id>

Dear co-authors,

The manuscript is attached. I need your comments, suggestions and edits. Without your intellectual contribution, you might be not eligible as co-author. Please track all the changes.

Cheers, HH

Harapan Harapan

Medical Research Unit, School of Medicine, Syiah Kuala University Tropical Diseases Centre, School of Medicine, Syiah Kuala University Department of Microbiology, School of Medicine, Syiah Kuala University Banda Aceh 23111, Indonesia Telp.: +61435784971 (Aus) Email: harapan@unsyiah.ac.id - harapan.harapan@research.uwa.edu.au

4 attachments





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Hamzah Hasyim <hamzah.hasyim@gmail.com> To: "Harapan Harapan, MD" <harapan@unsyiah.ac.id>

Pak, akan disubmit ke mana paper ini?

Terimakasih.

[Quoted text hidden]

DR. HARAPAN <harapan@unsyiah.ac.id> To: Hamzah Hasyim <hamzah.hasyim@gmail.com>

Belum ada rencana palingan hanya ke Q3 seperti Journal of Clinical Epidemiology and Global Health. Tapi juga rencana mau lihat kemungkinan yang lain.

Salam HH [Quoted text hidden]

Harapan Harapan

MD (Unsyiah), M.Infect.Dis (UWA), DTM&H (Bangkok), PhD (UWA) Medical Research Unit, School of Medicine, Syiah Kuala University 18 November 2019 at 08:46

18 November 2019 at 09:24

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Tropical Diseases Centre, School of Medicine, Syiah Kuala University Department of Microbiology, School of Medicine, Syiah Kuala University Banda Aceh 23111, Indonesia FSD Unsyiah Profile | Scopus ID | ORCID | ResearchGate

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Hamzah Hasyim <hamzah.hasyim@gmail.com> To: "Dr. Harapan" <harapan@unsyiah.ac.id>

Jika bisa, minimal submit ke Q2 dulu.

Baru stlh itu dipertimbangkan ke Q3.

Terimakasih.

[Quoted text hidden]

Te Haypheng <hayphengte@gmail.com>

18 November 2019 at 20:28

18 November 2019 at 09:33

To: "Harapan Harapan, MD" <harapan@unsyiah.ac.id> Cc: amanda yufika <amandayufika@gmail.com>, samsul anwar <s4m_seupeng@yahoo.co.id>, Hamzah Hasyim <hamzah.hasyim@gmail.com>, Roy Nusa <roynres@gmail.com>, Mudatsir Mudatsir <mudatsir@unsyiah.ac.id>

Dear Harapan and all,

I'm glad to let me know this new version of manuscript. There has many improving parts from the late one, and I'm appreciate my chance to read them.

Anyway, after reviewing, I have some questions as below attached file, and please comment to correct me back. I'm still learning how to make manuscript better, so thank you.

Best regards, Haypheng [Quoted text hidden]

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DR. HARAPAN <harapan@unsyiah.ac.id>

18 November 2019 at 20:58

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14/07/22 13.34

To: Te Haypheng <hayphengte@gmail.com>

Cc: amanda yufika <amandayufika@gmail.com>, samsul anwar <s4m_seupeng@yahoo.co.id>, Hamzah Hasyim <hamzah.hasyim@gmail.com>, Roy Nusa <roynres@gmail.com>, Mudatsir Mudatsir <mudatsir@unsyiah.ac.id>

Hello Heypeng,

Thank you for your comments. Please see my response as attached.

Cheers,

HH Overland taxet hid

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Harapan Harapan MD (Unsyiah), M.Infect.Dis (UWA), PhD (UWA) Medical Research Unit, School of Medicine, Syiah Kuala University Tropical Diseases Centre, School of Medicine, Syiah Kuala University Department of Microbiology, School of Medicine, Syiah Kuala University Banda Aceh 23111, Indonesia [Quoted text hidden]

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amanda yufika <amandayufika@gmail.com>

To: "DR. HARAPAN" <harapan@unsyiah.ac.id>

19 November 2019 at 15:17

Cc: Te Haypheng <hayphengte@gmail.com>, samsul anwar <s4m_seupeng@yahoo.co.id>, Hamzah Hasyim <hamzah.hasyim@gmail.com>, Roy Nusa <roynres@gmail.com>, Mudatsir Mudatsir <mudatsir@unsyiah.ac.id>

Dear all,

Thank you to Harapan for wrapping up the manuscript. I have no major suggestion, just some minor correction on the grammar. I found few sentences confusing as well. Please find my comments in the attached file.

Regards,

Amanda Yufika, MD, MSc Department of Family Medicine/ Collaboration Unit, Faculty of Medicine, Syiah Kuala University, Jln. Tgk. Tanoh Abee, Darussalam, Banda Aceh, Indonesia On Nov 18, 2019, at 8:58 PM, DR. HARAPAN <harapan@unsyiah.ac.id> wrote:

Hello Heypeng,

Thank you for your comments. Please see my response as attached.

Cheers, HH

On Mon, Nov 18, 2019 at 8:28 PM Te Haypheng <hayphengte@gmail.com> wrote: Dear Harapan and all,

I'm glad to let me know this new version of manuscript. There has many improving parts from the late one, and I'm appreciate my chance to read them.

Anyway, after reviewing, I have some questions as below attached file, and please comment to correct me back. I'm still learning how to make manuscript better, so thank you.

Best regards, Haypheng

On Sat, Nov 16, 2019 at 8:53 PM Harapan Harapan, MD <harapan@unsyiah.ac.id> wrote: Dear co-authors,

The manuscript is attached. I need your comments, suggestions and edits. Without your intellectual contribution, you might be not eligible as co-author. Please track all the changes.

Cheers,

ΗH

Harapan Harapan

Medical Research Unit, School of Medicine, Syiah Kuala University Tropical Diseases Centre, School of Medicine, Syiah Kuala University Department of Microbiology, School of Medicine, Syiah Kuala University Banda Aceh 23111, Indonesia Telp.: +61435784971 (Aus) Email: harapan@unsyiah.ac.id - harapan.harapan@research.uwa.edu.au

Harapan Harapan

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Hello Amanda,

Thank you for your comments and corrections, my responses are attached. FYI, we have an expert in climate in our team, he is going to review the manuscript for final touch.

Cheers, HH

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19 November 2019 at 15:33

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 Hamzah Hasyim <hamzah.hasyim@gmail.com>
 20 November 2

 To: "DR. HARAPAN" <harapan@unsyiah.ac.id>

 Cc: amanda yufika <amandayufika@gmail.com>, Te Haypheng <hayphengte@gmail.com>, samsul anwar <s4m_seupeng@yahoo.co.id>, Roy Nusa

 <roynres@gmail.com>, Mudatsir Mudatsir <mudatsir@unsyiah.ac.id>

Dear Mr Harapan,

At the moment, please sees my comments from my perspective, attached below. Please find the attached updated file.

Best regards,

Hamzah [Quoted text hidden]

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DR. HARAPAN <harapan@unsyiah.ac.id>

To: Hamzah Hasyim <hamzah.hasyim@gmail.com>

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20 November 2019 at 14:27

20 November 2019 at 17:16

Hello Pak Hamzah,

I have responded to some of your comments. Some of the changes were rejected and the remaining are those that were accepted and will be included in the manuscript.

Thank you for your input.

Cheers,

HH [Quoted text hidden] Harapan Harapan MD (*Unsyiah*), M.Infect.Dis (*UWA*), DTM&H (*Bangkok*), PhD (*UWA*) [Quoted text hidden]

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Effects of El Niño Southern Oscillation and Dipole Mode Index on chikungunya infection in Indonesia: A preliminary study

Harapan Harapan^{1,2,3*}, Amanda Yufika^{1,4}, Samsul Anwar⁵, Haypeng Te⁶, Hamzah Hasyim⁷, Roy Nusa⁸, Pandji Wibawa Dhewantara^{9,10}, * Mudatsir Mudatsir^{1,2,3*}

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Abstract

Background: The aim of this study was to assess the possible association El Niño Southern Oscillation (Niño3.4) and Dipole Mode Index (DMI) on chikungunya incidence overtime including the significant reduction that noticed in 2017.

Method: Monthly national-wide chikungunya cases were obtained from the Indonesian National Disease Surveillance database and incidence rates (IR) and case fatality rate (CFR) were calculated. Monthly data of Niño3.4 and DMI between 2011 and 2017 were also collected. Correlations between monthly IR and CFR and Niño3.4 and DMI were assessed using Spearman's rank correlation.

Results: In 2017, chikungunya cases declined from 1972 cases in 2016 to 126 cases, accounting for 92.6% reduction and the IR reduced from 0.67 to 0.05 cases per 100,000 population. No death was recorded between since its reemergence in 2001. There was no significant correlations between monthly Niño3.4 and chikungunya incidence with r=-0.142 (95%CI: -0.320–0.046), p=0.198. However, there was a significant negative correlation between monthly DMI and chikungunya incidence, r=-0.404 (95%CI: -0.229– -0.554) with p<0.001.

Conclusion: Our initial data suggest that climate variable, DMI but not Niño3.4, is likely associated with changes in chikungunya incidence. Therefore,

3

further analysis with higher resolution of data set with cross-wavelet coherence approach maybe could elicit more robust evidence.

Keywords: Chikungunya, Dipole Mode Index, El Niño, ENSO, Indian Ocean Dipole

1. Background

Chikungunya, caused by chikungunya virus (CHIKV), is one of the most epidemiologically important infectious diseases globally together with dengue and Zika [1, 2]. CHIKV is a small, spherical, and enveloped virus and belong to *Alphavirus* [3]. Chikungunya outbreak was reported for the first time in Tanzania in 1952 [4, 5] and sporadic outbreaks were subsequently identified in Africa and Asia during the 1950s and 1960s [6]. CHIKV re-emerged in the early of 2000s and caused massive outbreaks in Indian Ocean and Southeast Asia [7]. In La Réunion, a French department in the Indian Ocean, the outbreak affected about a third of the population [8, 9] while in India the virus infected more than 1.3 million persons during 2005-2006 [10]. A current systematic review indicated that more than 20 countries in Asia Pacific have reported chikungunya outbreak since its re-emerge [11].

Chikungunya is endemic in Indonesia [12]. A historical report suggested that CHIKV have circulated in the capital of Jakarta in 1779 [13, 14]. Serological studies between 1969-1972 also demonstrated significant titers of anti-CHIKV antibodies in most of the Indonesian archipelago when tested using hemagglutination inhibition assay and the plaque reduction neutralization test [15, 16]. However, the first chikungunya cases recorded in official document of Indonesian Ministry of Health (MoH) was in Samarinda of Kalimantan Island in 1973 [17] while the first virologically confirmed chikungunya outbreak was reported in Jambi (Sumatra Island) in 1982 [18]. Multiple outbreaks have been reported between 1983-1984 and then the cases were not recorded in Indonesia for approximately 20 years [12] before it re-emerged in 2001 and have caused multiple outbreaks in the country [17]. The highest annual incidence rate (IR) of chikungunya was recorded during 2009-2010 where 137,655 cases were reported [12]. In 2015 there were 2,282 chikungunya cases reported in Indonesia [19, 20].

In 2017, however, a significant decline of chikungunya cases was noticed where the cases reduced from 1,972 cases in 2016 to 126 only. Interestingly, in the same year, a sharp reduction of dengue, a chikungunya related arbovirus, was also noticed in Indonesia [12] as well as in several countries in the Americas [21]. Some hypotheses have been proposed for the reduction of the dengue including changes in the density and competencies of vectors because change in climatic factors; cross-immunity generated by the simultaneous circulation of several arboviruses; and changes in epidemiological surveillance system [21]. A study have been conducted to determine the factors associated with reduction of dengue in 2017 in Indonesia [12] but not for chikungunya.

Some studies suggested the potential association between climate changes and chikungunya infection [22, 23]. Two of the most important indicators used for climate changes are El Niño Southern Oscillation (ENSO) and Indian Ocean Diplo (IOD). These variables link with dry and warm season that potentially increase mosquitoes vectors breeding and shorter virus extrinsic incubation period [23]. The role of these indicators on other infection such as dengue, malaria, hantavirus, Rift Valley fever, cholera, plague, and Zika also have been studied with slightly different results [23-29]. The aims of this study were: (a) to investigate details reduction of chikungunya in Indonesian in 2017; and (b) to assess the effects of ENSO and DMI on chikungunya incidence in Indonesia overtime since its re-emergence.

2. Methods

2.1. Variables and data sources

a. Chikungunya notifications

National chikungunya cases were obtained from National Disease Surveillance, the Directorate General of Disease Prevention and Control, MoH of Health of Indonesia. Case definition used in this surveillance system have been published in National Guideline for Prevention and Control of Chikungunya [30] which follows the World Health Organization criteria [31]. In brief, chikungunya cases were classified into three categories: (a) possible case, diagnosed based on clinical criteria alone as acute onset of fever >38.5°C and severe arthralgia/arthritis not explained by other medical conditions; (b) probable case, diagnosed based on the clinical criteria as mentioned and epidemiological criteria (residing or having visited epidemic areas) and; (c) confirmed case, diagnosed based on laboratory criteria which show a positive result for virus isolation, reverse transcription polymerase chain reaction, IgM antibodies or a four-fold increase in IgG antibodies [12]. The surveillance system includes all types of chikungunya cases. In this study, a monthly and annually time series of chikungunya cases between 2001 and 2017 were used.

b. El Niño Southern Oscillation

ESNO is periodic fluctuation in sea surface temperature (SST) and the air pressure of the overlying atmosphere across the equatorial Pacific Ocean and one of the most important modes of variability impacting the climate in tropics and subtropics [32, 33]. ENSO primarily focuses on SST anomalies in four geographic regions of the equatorial Pacific Ocean. In this study, Niño3.4 was used to represent the ENSO. Niño3.4, comprising portion of Niño regions 3 and 4, is the average SST anomaly in the region bounded by 5°N to 5°S, from 170°W to 120°W. Niño3.4 data were obtained from the Earth System Research Laboratory of the National Oceanic and Atmospheric Administration (NOAA) [34]. Monthly Niño3.4 between 2011 and 2017 were used for analysis.

c. Indian Ocean Dipole

IOD defined as the difference in SST between two poles: a western pole in the western Indian Ocean (located in the Arabian Sea, 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) [35, 36]. This gradient is called as Dipole Mode Index (DMI). Monthly average of DMI values were retrieved from Japan Agency for Marine-Earth Science and Technology (JAMSTEC) [37] and DMI between 2011 and 2017 were analyzed in this study.

2.2. Data analysis and approaches

In 2001, CHIKV re-emerged for the first time in Indonesia after were not recorded for approximately 20 years. Therefore, to obtain a comprehensive picture, the annual IR and annual case fatality rate (CFR) of chikungunya were calculated since its reemergence (i.e. from 2001 and 2017). The national IR was calculated by dividing the total number of cases by the number of population while CFR was calculated as the total number of deaths caused by chikungunya divided by the total number of cases. Annual IR and CFR was expressed as the number of cases per 100,000 population and as a percentage (%), respectively. As denumerator, the number of national population were obtained from Indonesian Bureau of Statistics. To investigate the specific geographical distributions of chikungunya reduction in 2017, chikungunya IR and CFR of each province in 2016 and 2017 were calculated and mapped using ArcGIS software [38].

To assess the role of Niño3.4 and IOD and chikungunya cases in Indonesia, monthly time series data were used between 2011 and 2017. Correlations between [monthly Niño3.4 and DMI] and [monthly IR and CFR] were assessed using Spearman's rank correlation based. This analysis was used based on analysis of data normality by Shapiro-Wilk test.

3. Results

3.1. Chikungunya incidence rate overtime and its reduction in 2017

Temporal distribution of chikungunya IR and CFR since its re-emergence in 2001 is presented in **Figure 1**. From 2001 to 2016, IR chikungunya ranged between 0.15 cases (in 2005) to 35.26 cases per 100,000 population (in 2009). The highest incidence was reported in 2009 where more than 83 thousand cases were reported. The increase of chikungunya cases was also reported in 2013. No death associated with chikungunya were reported in Indonesia.

Figure 1

The reduction of chikungunya cases in 2017 is not markedly in the context of whole picture of chikungunya IR between 2001 to 2017 (**Fig.1**). However, in 2017, there was a substantial reduction of chikungunya cases in Indonesia compared to 2016 where it reduced from 1,702 to 126 cases, accounting for 92.6% reduction. Chikungunya IR declined significantly from 0.67 to 0.05 cases per 100,000 population, fell by 92.8% (**Fig.1**).

In 2016, chikungunya cases were reported in four provinces: East Java, Central Sulawesi, Bali, and West Java with 1489, 103, 80 and 30 cases, respectively accounting for IR 3.83, 3.58, 1.92 and 0.06 per 100,000 population. In 2017, however, chikungunya cases were reported in two provinces only: Central Sulawesi (121 cases) and Aceh (5 cases) with IR 4.07 and 0.09 per 100,000 population, respectively. Spatial distributions of chikungunya IR in 2016 and 2017 in each province are presented in **Figure 2**.

Figure 2

3.2. Correlation between climate variables and chikungunya incidence

a. El Niño Southern Oscillation

Correlations between monthly Niño3.4 and chikungunya incidence for seven years (2011-2017) were calculated. Fluctuation of monthly Niño3.4 and chikungunya incidence presented in **Figure 3(A)**. Data suggested there was no significant correlation between Niño3.4 and chikungunya incidence with r=-0.142; 95%CI: -0.320-0.046, p=0.198. However, data from 2014-2017 suggested that rise of chikungunya incidence seems to be influenced negatively by Niño3.4. Apart in 2013, data suggested a negative correlation between Niño3.4 and chikungunya incidence rate, in which increased of Niño3.4 correlated with decreased of chikungunya notifications.

b. Indian Ocean Dipole

Correlations between monthly DMI and chikungunya incidence for seven years (2011-2017) were also calculated. Fluctuation of monthly DMI and IR of chikungunya is presented in **Figure 3(B)**. Data indicated there was significant negative correlation between DMI and chikungunya incidence with r=-0.404; 95%CI: -0.229 – -0.554, p<0.001. Decreased of DMI index (decreased difference in SST between western pole in the western Indian Ocean and eastern pole in the eastern Indian Ocean south of Indonesia), had correlation with increased the incidence of chikungunya. There was a clear pattern that the incidence of chikungunya increased when the DMI had negative index.

4. Discussion

4.1. Declined of notified chikungunya in 2017

A significant decrease of notified chikungunya in Indonesia was observed in 2017, compared to the previous year. The Indonesian MoH suggested that the reinforcement of vector eradication program named *"1 house 1 jumantik"* (one house, one mosquito larvae's monitor) contributed to the decline of dengue and chikungunya in that year [39]. However a recent study indicated that implementation of that program was not the main factor in reduction of dengue [12]. In 2017, chikungunya case declined significantly up to zero in three provinces (East Java, Bali, and West Java) and it did not occur in Central

Sulawesi. Based on MoH data, districts that implemented integrated vector management (one of the programs is vector eradication program) in East Java in 2016 and 2017 was only 15.8% and 28.9% respectively while the coverage was much higher in Central Sulawesi: 76.9% (2016) and 100% (2017). Chikungunya also reported in Aceh in 2017 although 100% of the districts in this province implemented the program. In some provinces such as Riau, West Sumatra, West Kalimantan, and Banten for example, there were no chikungunya case reported although the implementation of the program was only less than 30% of the districts in 2016 and 2017 [20, 40]. These suggest that there were other stronger factors drive the decline of chikungunya in Indonesia in 2017.

4.2. Climate change variables and chikungunya incidence

ENSO, the strongest interannual climate cycle, impacts on global climate and weather anomaly patterns and it has the warm (El Niño) and cold phase (La Niña) of the cycle. ENSO associated with drought and flood conditions and one of the typical conditions of El Niño is dry conditions in Indonesia. Precipitation and temperature resulting from ENSO events are the background drivers of vector-borne infections' activity [23, 41-43]. The persistence of extreme conditions of temperature or precipitation impacts the ecology and habitat size, growth rates, dynamics, and distribution of the vector population as well as the viral replication and extrinsic incubation [22, 23, 44, 45].

A study suggested severe ENSO-induced drought conditions in Southeast Asia associated with increased water storage around houses and elevated ambient air temperatures. These lead to elevated Aedes mosquito populations and reduce the extrinsic incubation period, respectively and therefore contribute to the increase chikungunya cases [23]. However, our findings suggested there was no significant correlation between Niño3.4 and chikungunya incidence. Some studies also found similar findings in the context of other infections. In western Kenyan highlands, for example, no evidence of an association between Niño3 and the number of malaria cases [25] and also there was a very weak association between ENSO and dengue incidence in Bangladesh [26]. However in India, El Niño was positively correlated dengue cases in with a 3-6 months lag period [27]. In Taiwan, temperature and precipitation influenced dengue incidence rates with a lag of 10-20 weeks [28]. In the context of dengue infection in Indonesia, studies have shown that the incidence was associated with temperature, rainfall and humidity [46-48]. In this present study, those local climate variables such as temperature, rainfall and humidity might have stronger impact on chikungunya incidence were not included. A previous study found that the local climate variables were more significant on dengue incidence than ENSO [26]. Another study found that ENSO had a weaker impact on the seasonality of local climate conditions compared to IOD [28].

IOD is another climate mode as a result of ocean-atmosphere interaction, which causes interannual climate variability in the tropical Indian Ocean. The IOD characterizes SST anomalies during this event, with warmer than normal SSTs over the western basin and cooler than usual SSTs in the eastern basin. Our study showed that the decreased DMI was significantly associated with the increase of chikungunya IR. There was a clear pattern that the incidence of chikungunya increased when the DMI had negative index. A positive DMI index, often refereed as the positive IOD causes drought in Indonesia, East Asia, and Australia, and flooding in some parts of the African continent [24, 35]. In contrary, a negative DMI index will cause rainfall and provide a suitable environment for *Aedes aegypti* mosquitoes to breed [49], which might lead to the increase of chikungunya. Studies also found that DMI is associated with fluctuation of some infectious diseases including malaria [25] and dengue incidence [26, 27, 29].

Although in this preliminary study the association signal of DMI and chikungunya incidence was identified, limitations of this study should be acknowledged. Notified chikungunya was used to represent the incidence of chikungunya in this study. This might be bias, as we relied solely on the report by the MoH. Since the disease has similar feature to dengue, misdiagnosed of chikungunya often happen, lead to underreported. Moreover, due to its challenging geographical nature, and limited access to technology, the reporting system in Indonesia is still run manually in some provinces, made it difficult for some areas to report their cases. In this study, monthly time series were used and did not include local climate variables. Therefore, a further study is need to analysis the role of those climate variables and on transmission dynamic of chikungunya using higher temporal resolutions such as weekly together including lagged up to particular times. In addition, the cross-wavelet coherence approach should be employed.

5. Conclusion

A substantial decline of chikungunya cases occurred in Indonesia in 2017. This reduction likely not associated with enforcement of vector control program by Indonesian government. Our analysis identified an association between climate change indicator (IOD) and chikungunya incidence in Indonesia. The present study suggests that IDM could be a potential driver of chikungunya incidence in Indonesia.

Acknowledgments

We would like to thank to physicians' professional organizations in Indonesia.

Funding

None

Competing interest

The authors declare that they have no competing interests.

Reference

- 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.
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Figure Legends

Figure 1. Incidence rate and case fatality rate of chikungunya between 2001 and

2017 in Indonesia. The insert shows details of reduction of chikungunya

incidence rate in 2017.

Figure 2. Provincial incidence rates of chikungunya in 2016 (A) and 2017 (B)

Figure 3. Temporal trend of Niño3.4 and chikungunya incidence rate (A) and

DMI and chikungunya incidence rate (B) in Indonesia, 2005-2017.