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Dengue Seroprevalence and the Risk Factors for Healthy Children in Indonesia Urban Areas

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ABSTRACT

Dengue is endemic in almost all provinces in Indonesia and it cause health problems with outbreaks in many cities and rural areas. Based on the Ministry of Health data in 2015, there were 126,675 dengue fever patients recorded in 34 provinces and 1,229 among them were fatal. This study is aimed to determine the exposure of most vulnerable groups i.e. children against dengue virus and to assess the risk factors. The study was conducted using Preserved Biological Material (BBT) from National Basic Health Research (Riskesdas) 2013 on healthy population of high-risk group, i.e., children in urban areas from 27 provinces. Serological investigation carried out by IgG indirect ELISA method on 1766 samples and 1633 were analyzed. The average of dengue IgG seropositivity in children under-fives (12-59 months) sera against dengue virus is 51.9%, while in children (5-14 years) were higher at 74.6%. This numbers are indicating that about 2/3 of the children in the urban areas have been infected by at least one of the dengue viruses. The risk factors of no repellent use, and refrigerator ownership revealed as major determinants for the infection. Considering that Indonesia has suitable climate for dengue vector breeding, it is important to increase public awareness to keep the environment clean.

1. Introduction

Dengue is a disease commonly found in tropical and sub-tropical regions throughout the world, and half of the earth's population is at risk for infection. Bath et al estimates that in 2010 there were around 390 million dengue infections worldwide. This number is three times greater than the WHO estimation. About 96 million of them were dengue infections with symptoms that can be detected, while another 294 million are dengue infections that were not detected by the surveillance [1], [2].

In Indonesia, the number of dengue cases in 2017 was 68,407 with 493 deaths. This number has dropped quite dramatically from the previous year, namely 204,171 cases with 1,598 deaths. However, at the end of

2018 to the beginning of 2019, the number of dengue cases has increased and reported to occur in almost all provinces. Since the first week of 2018 to the first week of 2019, number of suspects in 3 provinces with the highest cases was 1,613. This figure does not include patients with dengue without symptoms that were not detected [3].

The number of undetected dengue infections is usually greater than detected. This number illustrates the large reservoir of diseases in the community. To see the true disease burden, we need to look at the prevalence of disease in healthy people. We focused on healthy population group i.e., children in urban areas. As is known that dengue mostly occurs in urban and semi-urban areas, and serious dengue hemorrhagic fever is a major cause of child morbidity and mortality in several Asian countries [1].

National Basic Health Research (Riskesdas) is a research activity undertaken by the National Institute of Health Research and Development under the Ministry of Health Indonesia. Riskesdas is national scale survey and conducted simultaneously every 5 years. The objective of this survey is to provide national and provincial health related data including demography, infectious and non-infectious data, through questionnaire and collection of human samples. Therefore, we conducted this recent study with the objectives to provide the national dengue seroprevalence and the risk factors (behavior and environment) through analysis on healthy children respondents in urban areas from Riskesdas samples [4- 6].

2. METHODS

2.1 Study design

This was a cross-sectional seroprevalence study conducted in 2016 on the samples collected from National Basic Health Research Survey 2013. This survey collected the 1,766 samples consisting of 112 samples of under-fives (12-59 months) from 21 provinces and 1654 child samples (5-14 years) from 27 provinces We focused on all of the children's samples available which undergone examination of the sample quality and data completeness. The ethical approval of the study was given by the Ethics committee of the National Institute of Health Research and Development (NIHRD) under the Ministry of Health of the Republic of Indonesia.

2.2 Data collection

The epidemiology data were collected during Riskesdas survey in 2013. The data were stored and managed by the Data Management section in NIHRD. The demographic, behavioral, and environmental variables were obtained from the survey respondents and/or their parents using the structured questions by trained surveyors in 2013. Previously, the epidemiological data collection was tried and validated by NIHRD, academics and professional organization to ensure the quality of the data collected.

2.3 Laboratory test

The blood samples previously collected during Riskesdas survey 2013 were stored as serum in in the ultra-low freezer (-80°C) prior to use in this study. The Dengue IgG antibody of the respondents were detected using commercially available kit (Pan Bio Dengue IgG indirect ELISA, Cat # E-DEN01G). The laboratory detection was performed according to the manufactured instructions including the use of positive control, negative control and calibrator. Seropositivity of dengue were determined according the kits instruction. The indeterminate results were re-examined and the samples with two indeterminate results were removed from the analysis. Seroprevalence was defined as the percentage of seropositive participants.

2.4 Data analysis

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Respondent epidemiological data collection was performed on Riskesdas 2013 activities conducted nationally and managed by the mandate team. Descriptive analysis is carried out on demographic (age, gender, number of household under-fives, body mass index), laboratory result, behavioral (bed net use, insecticide bed net use, ventilation with net, mosquito repellent, anti-mosquito spray, anti-mosquito electric/coil, cleaning bathroom water container, drinking water treatment, drinking water storage) and environmental (slum environment, protected water sources, refrigerator ownership, household member density) variables. Logistic regression was completed by using STATA version 9 (STATA Corp LLC, Texas USA).

3. RESULTS

We obtained 1,633 samples after we correlated serology results and epidemiology data, and eliminatedthe data with indeterminate result. The respondents are consisting of 792 females and 841 males. The number of samples in each province is not balanced, varying from 2 to 396 samples. This occurs because of the difficulty in obtaining infants samples, therefore the serum volume is not uniform and some have been used for other tests.

The antibody examination of the Dengue virus in under-fives samples showed that half (51.9%) of children under the age of five years were infected with the Dengue virus. While the antibodies to dengue virus in children showed a higher positive rate that is 74.6%. Based on statistical analysis, it was known that there is a relationship between positive serological dengue with the increasing age, number of under-fives, and body mass index. While gender and number of household members were found not related to positive serologic dengue (Table 1).

Table 1. The Relationship of Demographic Variable with Dengue Infection in Riskesdas2013 Samples

Variables	Negative DF 439	%	Positive DF 1194	%	Hazz Ratio	95% CI	p	
Age								
0-4 year	51	48.1	55	51.8	1.00	Ref		
5-14 year	388	25.4	1139	74.6	2.72	1.83-4.05	**0.000**	*)
Gender								
Female	208	26.3	584	73.7	1.00	Ref		
Male	231	27.5	610	72.5	0.98	0.88-1.10	0.776	
Number of household members								
4	216	27.0	583	73.0	1.00	Ref		
≥ 5	223	26.7	611	73.3	1.00	0.90-1.13	0.944	
Number of in-house under-fives								
No under-fives	256	24.4	793	75.6	1.00	Ref		

1-4 under-fives	183	31.3	401	68.7	0.91	0.81-1.02	**0.117**	*)
Body Mass Index								
Normal (18.50-24.99)	84	21.9	300	78.1	1.00	Ref		
Over (>=25.00)	12	22.0	45	78.0	1.01	0.74-1.38	0.948	
Less (<18.50)	343	28.8	849	71.2	0.91	0.80-1.04	**0.169**	*)

p<0,25 candidate variable to be included in multivariate analysis

The respondent behavior variables analysis showed that do not use mosquito repellent and the untreated drinking water were associated with dengue infection. The people who do not use mosquito repellent were potentially infected 1.12 times greater than those using (95% CI = 0.99-1.27). While the use of other types of mosquito drugs such as mosquito spray, burned or electric is not associated with positive serological dengue. Prevention efforts from contact with mosquitoes such as the use of mosquito nets (insecticides and non-insecticides), ventilation with nets, draining water reservoirs, treating drinking water with heating, and storing drinking water in closed containers are unrelated to positive serologic dengue (Table 2).

Table 2. The Relationship of Behavior Variable with Dengue Infection in Riskesdas 2013 Samples

Variables	Negative DBD		Positive DBD		Hazz Ratio	95% CI	p	
	n=439	%	1194	%				
Bed net								
User	69	29.0	169	71.0	1.00	Ref		
Non-user	370	26.5	1025	73.5	1.03	0.88-1.22	0.681	
Insecticides bed net								
User	5	19.2	21	80.8	1.00	Ref		
Non-user	434	27.0	1173	73.0	0.90	0.59-1.39	0.646	
Ventilation with net								
Yes	66	33.2	133	66.8	1.00	Ref		
No	373	26.0	1061	74.0	1.11	0.92-1.33	0.269	
Lotion Repellent								
User	346	29.2	840	70.8	1.00	Ref		
Non-user	93	20.8	354	79.2	1.12	0.99-1.27	**0.078**	*)
Spray mosquito drug								
User	61	22.2	214	77.8	1.00	Ref		
Non-user	378	27.8	980	72.2	0.93	0.80-1.08	0.318	
Burn/electric mosquito drug								
User	199	25.9	570	74.1	1.00	Ref		
Non-user	240	27.8	624	72.2	0.97	0.87-1.09	0.654	
Consume Malaria drug								
Yes	6	17.7	28	82.3	1.00	Ref		
No	433	27.1	1166	72.9	0.89	0.61-1.29	0.525	
Cleaning bathroom								

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water container								
Yes ≥ 1 in a week	416	27.0	1126	73.0	1.00	Ref		
No	23	25.3	68	74.7	1.02	0.80-1.31	0.854	
Drinking water treatment								
Yes (by heating)	276	27.9	713	72.1	1.00	Ref		
No (filtration, sun expose)	163	25.3	481	74.7	1.14	0.91-1.43	**0.248**	*)
Drinking water storage								
Close	438	26.9	1193	73.1	1.00	Ref		
Open	1	50.0	1	50.0	0.68	0.09-4.86	0.704	

p<0,25 candidate variableto be included in multivariate analysis

Some of the respondent environmental variables that can be obtained from Riskesdas 2013 activities are slums areas, protected water sources, refrigerator ownership and household member density. Only the ownership of the refrigerator as the representative of mosquito breeding site has a tendency to the positive serologic status of respondents. While other variables, were not significantly associated with positive dengue serology (Table 3).

Table 3. The Relationship of Environment Variable with Dengue Infection in Riskesdas 2013 Samples

Variable	Negative DBD n=439	%	Positive DBD n=1194	%	Hazz Ratio	95% CI	p	
Slum Environment								
No	332	26.7	911	73.3	1.00	Ref		
Yes	107	27.4	283	72.6	0.99	0.87-1.13	0.884	
Protected water sources								
Yes	396	26.8	1080	73.2	1.00	Ref		
No	43	27.4	114	72.6	0.99	0.82-1.20	0.938	
Refrigerator ownership								
No	218	30.0	507	70.0	1.00	Ref		
Yes	221	24.3	687	75.7	1.08	0.96-1.21	**0.179**	*)
Household member density								
Spacious (≥10m/person)	283	26.4	789	73.6	1.00	Ref		
Crowded (<10m/person)	156	27.8	405	72.2	0.98	0.87-1.11	**0.752**	

p<0,25 candidate variable to be included in multivariate analysis

Based on the results of multivariate analysis on risk factors for age, number of under-fives, body mass index, use of repellent, drinking water treatment and refrigerator ownership, it was seen that the risk of

dengue virus infection for those who do not use repellent was 1.49 times compared to those who use repellent. Whereas in households that have refrigerators, the environment is prone to dengue virus infection 1.58 times compared to homes where there is no refrigerator (Table 4).

Table 4. Multivariate Analysis of Dengue Infection Risk Factors in Riskesdas2013 Samples

	Crude Hazz Rasio	Adjusted Hazz Rasio	SE	95% CI	p
Age					
0-4 year	1,00	1,00		Ref	
5-14 year	2,72	1,75	0,5324	0,96 - 3,17	0,068
Number of in house under-fives					
No under-fives	1,00	1,00		Ref	
1-4 under-fives	0,91	0,90	0,1440	0,66 - 1,23	0,498
Body Mass Index					
Normal (18.50-24.99)	1,00	1,00		Ref	
Over (>=25.00)	1,01	0,88	0,3837	0,37 - 2,07	0,764
Less (<18.50)	0,91	0,70	0,1265	0,49 - 1,00	0,047
Lotion Repellent					
User	1,00	1,00		Ref	
Non-user	1,12	1,49	0,2510	1,07 - 2,08	**0,017***
Drinking water treatment					
Yes (by heating)	1,00	1,00		Ref	
No (filtration, sun expose)	1,14	0,82	0,9307	0,66 - 1.03	0,087
Refrigerator ownership					
No	1,00	1,00		Ref	
Yes	1,08	1,58	0,2303	1,18 - 2.10	**0,002***

p<0.005 and 95%CI lower and upper limit do not close to 1

4. DISCUSSIONS

Indonesia is a tropical country with a climate that supports the life of dengue mosquito vector *Aedes aegypti* or *Aedes albopictus*. Based on the results it is known that the number of respondents who have antibodies to dengue virus is high (51.9 - 74.6%), whereas the samples are taken on healthy individuals and some do not even realize they have been infected with dengue virus. The actual diseases burden is needed to determine the economic impacts that arise such as loss of productive time. Besides that, the data on the actual number of dengue infections is also needed to determine the population dynamics of the dengue virus, the amount of vaccines need, and the population effect of vaccine programmed [2].

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The resulting seroprevalence score is equal to [5] results' i.e. 69.4%. The study was conducted in 30 clusters (subdistricts) in Indonesia selected clusters based on the distribution of population concentrations with age of respondents ranging from 1 to 18 years. Positive serology results in under-fives respondents is also quite high and increases with age even when respondents have low mobility, so the possibility of the infection location occurs in the environment around the house. Our results is also consistent with the results obtained by [7] that the prevalence of IgG against dengue virus in children increases with age addition. Similarly, in this study the average positive rate in children is higher than the average positive rate at under-fives. This may be due to children aged 5 to 14 years have a higher mobility compared with under-fives. In addition, poorly maintained schools commonly provide potential breeding place for dengue vector [8].

A high seroprevalence rate also occurred in Singapore, seroepidemiologic examination of 4,152 samples showed that 59% of positive samples contained IgG antibodies against dengue virus [9]. In addition to Singapore, seroprevalence studies conducted in Venezuela in 2002 showed 77.4% of those detected infected with dengue by using hemagglutination inhibition (HI) methods [10]. Whereas in the areas that are not endemic of DF, seroprevalence rates tend to be low, like Hongkong 1.6%, Zambia 4.1% and rural areas of Rawalpindi Pakistan 13.5% [4], [11], [12].

The high number of respondents who have antibodies to dengue virus in this study indicates that dengue is an endemic disease in urban areas of Indonesia. This rate of positive rate will surely increase in adult individuals (examination is not done). Vaccine administration may protect individuals who have never been exposed to all four dengue virus serotypes. However, if the vaccine has different effectiveness in each serotype it can lead to immunological interactions between serotypes [13]. In populations exposed to serotypes such as urban areas in Indonesia, the use of vaccines is disputed.

Factors that may affect the incidence of DF cases include demography, community behavior, and the environment. Demographic factors such as the location of an area (rural or urban) can determine endemicity [14]. In this study all samples were obtained from urban areas in each province, that supportedthe high positive rate of dengue antibody resulting from the examination. Individual characteristics such as gender, age and nutritional status may also affect infection rates [15]. However, in this study we only found age that had an effect on the positive serologic status. While the other variables such as gender and nutritional status is known not to affect the positive serology status.

Behavioral factors are a description of the society daily activities as an effort to prevent the occurrence of DF cases. In Indonesia, this is recommended by the government in the form of 3M program that implement the closing, draining, and burying the container that might be use by the mosquito as their breeding place, the use of mosquito repellent, and good home management [16]. The results of the analysis of behavioral factors undertaken in this study only shows the use of repellent lotion that have influence. This may be due to the repellent is a mosquito repellent drug directly used on the body of respondents, so it is able to improve its effectiveness in preventing mosquito bites. Another factor that has a tendency to affect the positive serologic status of the respondents is drinking water treatment which is done by heating, thus preventing the availability of breeding place for mosquitoes in the house.

The environment also plays an important role in the occurrence of DF, such as population density and individual density in a home [8]. In this study only ownership of refrigerators that have a tendency to affect the positive serologic status of respondents. This may be due to the presence of a waste water container at the back of the refrigerator that can serve as a breeding place for dengue vector mosquitoes. The availability of *Aedes aegypti* mosquito breeding sites as vectors in the environment also cannot be ignored. In line with

[14] statement that the vector breeding and storage of water within the home is a significant risk factor for the dengue infection.

Overall, the risk factors that were significant for the positive serological results of dengue virus infection in the Riskesdas 2013 sample were the use of repellent and refrigerator ownership. While many of the demographic factors analyzed did not show any association with dengue virus infection. The information about the high rate of exposure of Indonesian people to dengue virus is presumably can be used as the data in dengue infection control program. Eradication of mosquito breeding places and community behavior to avoid the vector mosquito bites is still the most effective dengue infection prevention effort. By reviewing the data generated in this study, program holders are also expected to take better policies for managing dengue infection.

5. CONCLUSIONS

Our results showed that the seroprevalence of under-fives and children in Indonesia urban areas to dengue virus is high (51.9% - 74.6%). The serological positivity correlated to many factors in demography, behavior and environment. The multivariate analysis showed that no repellent use, and refrigerator ownership are the major determinants for the infection. This data could be use as a basis for dengue control program managementstrategies of dengue infection, especially in urban areas.

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