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Dengu-end is Near: An Unmatched Case Control Study on the Dengue Vaccine Efficacy and Its Association between Dengue Cases among Children Ages 9-12 in Pasig City

Lance Sese*, Gabriel Castillo, Angelica Ermino, Abigail Juat, Rexelle Piad

Ateneo School of Medicine and Public Health, Pasig City, Philippines
*Corresponding author: lancevincentsese@yahoo.com

Abstract **Background and Objectives**: Mass immunization program with the recently approved dengue vaccine among grade 4 students of public elementary schools commenced in April 2016. Whether an individual had prior dengue infection or not is the most important aspect when implementing this vaccine since through the mechanism of antibody-dependent enhancement (ADE), those who are seronegative or never had dengue prior that are immunized can have their first natural dengue infection to be of higher severity. Thus, this study aims to determine if immunization with the newly-licensed live, attenuated, tetravalent dengue vaccine is associated with the occurrences of hospitalization due to dengue infection. **Methodology**: This unmatched case control study was conducted in three tertiary hospitals within and near Pasig City, an area tagged as hotspot for dengue infection. Cases (n=112) were Filipino children, 9-12 years of age, confined to a tertiary hospital due to dengue infection and supported with a positive confirmatory test. Controls (n=112) were Filipino children of the same age group with a medical record as an outpatient or inpatient whose final diagnosis is not dengue. Chi-square test was used to determine the association between the dependent and independent variables. All statistical analysis in this study was done using SPSS 20. **Results:** The proportions of cases and controls that were vaccinated with dengue vaccine were 1/56 for both (only 2 out of 112). Among children of 9-12 years of age, dengue vaccine is not associated with dengue infection hospitalization (p=1.000). Only age is found to be significant among the confounders (p=0.010; 95% CI: 1.134-1.863). **Conclusions**: There is no significant association between dengue vaccination status and hospitalization due to dengue infection. Further evaluation of the association may require an increase in sample size, and conduct of the study a few more years after the implementation of the mass immunization program.

Keywords: *case control, dengue, dengue vaccine, Dengvaxia, Philippines*

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1. Introduction

Dengue is an infectious disease caused by a flavivirus having four serotypes, transmitted by the *Aedes aegypti* mosquito [1]. After incubation for 3-14 days, it usually presents with a sudden onset of fever, myalgia, headache, and rashes.

The Philippines ranks fourth in dengue cases among the ASEAN countries [2]. Many factors, including environmental, biological and demographic factors are believed to be at play in DENV transmission. Wijayanti et al. assessed the influence of climatic, demographic and socioeconomic factors on the risk of dengue infection [3]. However, behaviour, ecological, demographical, and socioeconomic conditions are key determinants in local dengue risk as well [3]. Figure 1 highlights the important factors that affect the risk of an individual of having dengue infection.

While numerous interventions were implemented and deployed by the Department of Health (DOH) to curb mosquito population especially during outbreaks, a vaccine has yet to circulate the general public up until early 2016 [4]. Sanofi Pasteur's Dengvaxia was the first licensed live, attenuated dengue vaccine for virus serotypes 1, 2, 3, and 4 to be made available in the Philippines [5]. The vaccine's use was intended for people 9-45 years of age living in endemic areas and is administered at 6-month intervals [5]. DOH, in partnership with the Department of Education (DepEd) has started mass immunization in three separate doses (0,6,12 months interval) among Grade 4 children 9 years old and above in public elementary schools in the National Capital Region (NCR), Regions III, and Region IV-A [2].

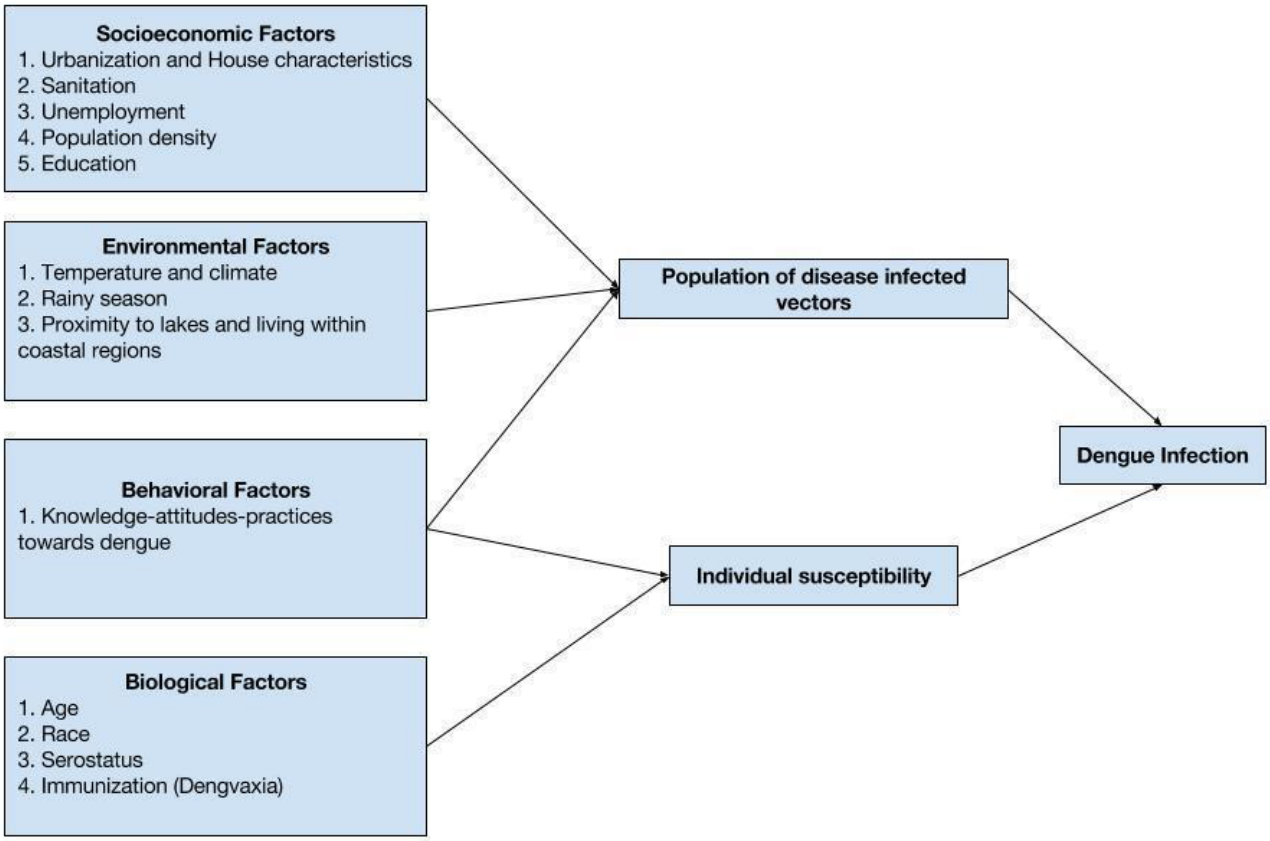

Figure 1. Conceptual Framework

Populations living in the tropics and subtropics climate are exposed to this vector-borne disease, which is a leading cause of serious illness and death among children in Asian (Philippines included) [5]. Dengvaxia, a vaccine developed to prevent dengue infection, was recently introduced in the Philippines.

This study aids in the evaluation of the joint mass immunization project whether it can actually reduce dengue cases in endemic areas especially a notable clinical trial that has cited that the group exposed to the vaccine of children 2-5 years old were seven times more likely to be hospitalized than their control counterparts who did not receive the vaccine three years post-vaccination [6]. Individual serostatus is the most important aspect when implementing this vaccine since only those who have had at least one dengue infection will benefit from immunization [7]. It will also identify risk factors specific to the study location to aid local government unit in creating policies for intervention. It will also assess the possible risk of non-completion of the three-dose vaccine should the individual opt to not get vaccinated for the second or third dose.

Though live attenuated vaccines seek to immunize a person from disease, it still brings with it some disadvantage. The vaccine elicits a different effect on those who were never exposed to dengue [5]. The mechanism underlying this event is called antibody-dependent enhancement (ADE) which occurs in multiserotype disease models [8]. ADE causes an increase in growth rate of the dengue virus in the presence of immunity due to a previous infection of a different serotype (i.e. Dengvaxia). The vaccine may immunologically prime seronegative children, which can cause their first natural dengue infection to be of higher severity [9]. Vaccination will be able to decrease the disease burden significantly if they administer it to individuals that have already been exposed to at least one strain of the dengue virus [7].

Thus, this study aims to determine if there is a significant association between a live-attenuated, tetravalent dengue vaccine immunization as prophylaxis and dengue fever hospitalization confirmed with a dengue diagnostic test (NS1, dengue blot, and/or dengue PCR) in children admitted to Quirino Memorial Medical Center (QMMC), Rizal Medical Center (RMC), and The Medical City (TMC) ages 9-12 living in Pasig City.

2. Methodology

2.1. Participants and Setting

The study was conducted in three (3) category level 3 hospitals within and nearby Pasig City (2 hospitals within and 1 hospital nearby). These level 3 hospitals included The Medical City (San Antonio, Pasig City), Rizal Medical Center (Bagong Ilog, Pasig City), and Quirino Memorial Medical Center (Project 4, Quezon City) [10]. These hospitals were the most probable hospitals that admit dengue patients residing in Pasig City. Pasig City was chosen since DOH [11] identified Barangay Pinagbuhatan (District 2) in Pasig City as one of the dengue hot zones in NCR with three or more cases reported for four consecutive weeks. Figure 2 shows a geographical map of Pasig City with the hospitals and barangays marked.

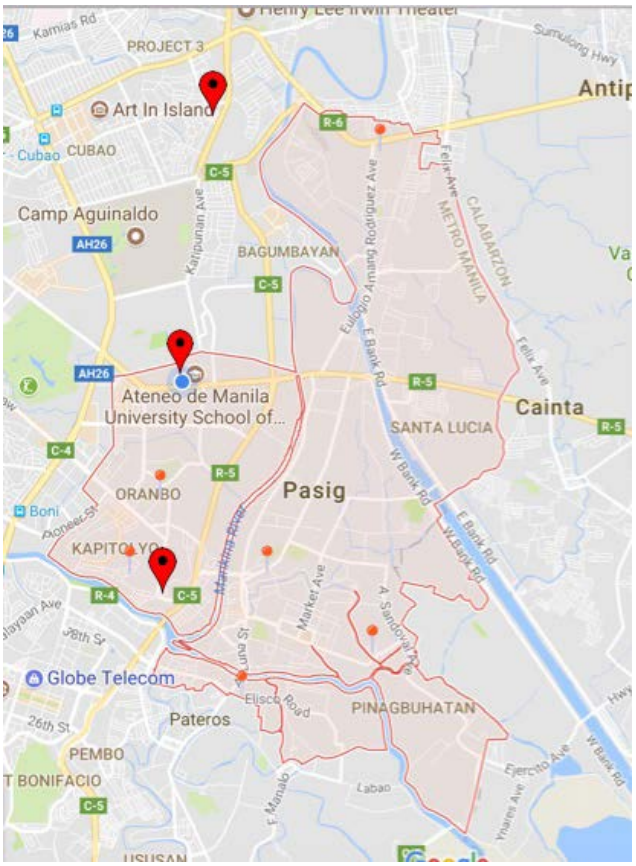

Figure 2. Geographical Presentation of Pasig City using Google Maps; Legend: Barangays, Hospitals

2.1.1. Inclusion Criteria

Eligible cases were identified as Filipino children, 9-12 years of age, male or female, confined to a level 3 hospital for symptoms of dengue fever. The final diagnosis (i.e. dengue fever) of the patient by the attending physician must be supported by a positive result of at least one of these tests: NS1 dengue antigen test, dengue blot, and/or dengue PCR.

Eligible controls were identified as Filipino children, 9-12 years of age with a medical record as outpatient or inpatient whose final diagnosis is not dengue. Possible conditions for the control's medical consult as outpatient or inpatient included but were not limited to pneumonia, gastroenteritis, acute appendicitis, disorders of the urinary system, and volume depletion.

2.1.2. Exclusion Criteria

Patients outside the 9-12 age bracket and those with significant chronic co-morbidities were excluded from both case and control groups. Co-morbidities were excluded to create a more homogenous population, and to reduce the possibility of developing dengue and its complications. Co-morbidities excluded in this study are congenital and acquired immunodeficiency, HIV positive, and Hepatitis B or C positive [13].

2.1.3. Sample Size Calculation

The sample size was computed using OpenEpi for Unmatched Case Control. Default parameters were used within the data fields except for (a) percent of controls exposed and (b) odds ratio which were based on a study by Hadinegoro et al. and found out that the efficacy of the vaccine was 65.6% and the odds ratio was 0.50 (95% CI, 0.29 to 0.86) among those 9 years of age and older [14]. Based on the sampling algorithm, a minimum of 147 cases and 147 controls should be selected.

2.2. Data Collection

2.2.1. Hospital-based Cases and Controls

Hospital records were filtered based on the inclusion and exclusion criteria mentioned previously in order to properly select the eligible cases and controls.

Data on the variables in Table 1, except for the vaccination status, were obtained from hospital records and were stored in Google Drive to which only the researchers had access to. Data on knowledge, practices and attitudes as well as socioeconomic and environmental determinants were no longer collected since these were not available in hospital records.

2.2.2. Vaccine Records

Dengue vaccination records of those immunized in public elementary schools were obtained from the City Health Office of Pasig City. This specifically pertains to the first licensed tetravalent dengue vaccine developed by Sanofi Pasteur, Dengvaxia. Figure 3 below highlights the flow of the study design.

2.3. Statistical Analysis

Chi-square tests were performed on each independent variable and a binary logistic regression was done on the variable age since it was found to be significant at the bivariate level. A binary logistic regression was done on age and hospitalization due to dengue in order to get the odds ratio and confidence interval.

Table 1. Summary of Variables

Position in the Study	Variable	Indicator	Scale of Measurement
Dependent Variable (Outcome)	Hospitalization due to dengue infection after dengue vaccine administration	Frequency	Nominal (Yes/No)
Independent Variable (Exposure)	Dengue immunization status	Frequency	Nominal (Yes/No)
Confounder	Age	Frequency	Ratio
Confounder	Gender	Frequency	Nominal (Male/Female)
Confounder	Compliance in completing the 3-dose regimen	Frequency in number of doses administered	Nominal
Confounder	Serostatus	Frequency of previous dengue infection prior dengue vaccine administration	Nominal (Yes/No)

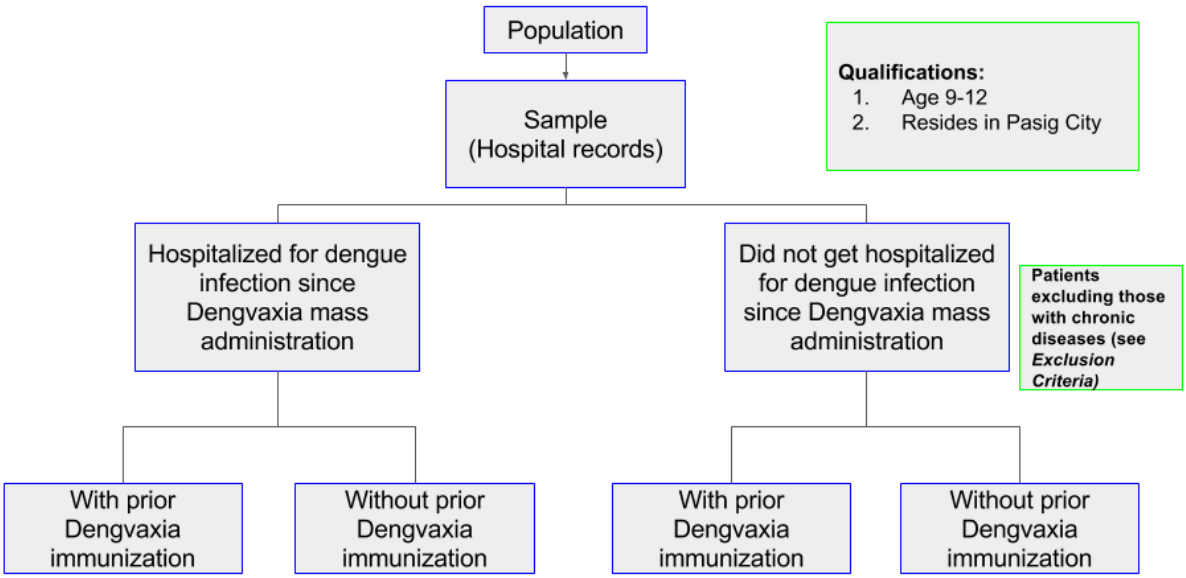

Figure 3. Diagram of Study Design

3. Results

3.1. Distribution of Cases and Controls

There were 112 cases and 112 controls (N=224) gathered from QMMC, RMC, and with the bulk coming from TMC (3.57%, 24.11% and 72.32% respectively). The number of samples failed to reach the desired sample size even though all the available dengue cases which happened from March 2016 up to September 2017 were already included. The number of controls taken was 1:1 in order to equal the number of cases. Overall, males comprised 54%. The overall age group distribution was as follows: 9 (32%), 10 (29%), 11 (21%) and 12 (18%). Table 2 below shows the distribution of those who had dengue among the age groups.

Table 2. Distribution of Cases and Controls among the Age Groups

	Age			
	9	10	11	12
Cases	30	29	23	30
Controls	42	35	24	11
Total	72	64	47	41

Only 4.4% (10/224) had previous dengue infection prior the vaccine administration with 3 of the 10 having a dengue infection after vaccine administration.

The proportions of cases and controls that were vaccinated with dengue vaccine in comparison to those not vaccinated were 1/56 for both (only 2 out of 112).

There is also no statistically significant association between dengue immunization status and hospitalization due to dengue infection; that is both vaccinated and unvaccinated children are equally susceptible to hospitalization due to dengue infection. Among the confounders, only age is found to be significant (p=0.010; 95% CI: 1.134-1.863). As age increases, the odds of being hospitalized for dengue infection is 45% higher if within the range of 9-12. Even though the desired sample size was not reached, an odds ratio (OR) of 1.45 is still considered significant since the minimum OR to be detected of 0.5 [14] was used in computing the sample size.

4. Discussion

4.1. Dengue Prevalence and Dengvaxia Studies

The incidence of dengue in the Philippines was found to have an upward trend. From January 1 up to August 6, 2016, a total of 84,085 suspected new cases were reported nationwide with a 15.8% increase from the previous year [12]. Majority of the cases (38.5%) nationwide were between ages 5 to 14 [12].

This study was conducted only a year after the implementation of the mass vaccination program in the elementary schools here in the Philippines which might be a reason why there was no significant association between immunization status and hospitalization. Furthermore, as presented by WHO-SAGE, the projected 10-30% reduction of dengue hospitalizations in early adolescents will only be observed after 30 years post-vaccination [5]. Results of other field evaluation that analyzed the efficacy of vaccination with Dengvaxia in reducing the number of dengue cases and hospitalization with focus on number of years before study was done post-vaccination are summarized in Table 3 below.

Among these studies, significant association between vaccination and reduction of dengue cases or hospitalization was shown 25 months after the first dose of vaccine was given. The mass immunization program in the Philippines was imposed on public elementary schools only in Regions III, IVA, and NCR which was estimated to be about a million grade 4 students [2]. This is only 9.5% of the projected population by the Philippines Statistics Authority in that age group by 2016, and in this study covering a one-year post-vaccination of first dose, only 4 students were found to be vaccinated [13].

Table 3. Summary of Dengvaxia Studies

Dengvaxia Study	Year Conducted	Results	Remarks
Capeding et al.	2014	Vaccine efficacy = 56.5% (95% CI 43.8-66.4)	The study assessed dengue infection that took place more than 28 days after the third injection.
Hadinegoro et al.	2015	Efficacy against hospitalization = 50% (95% CI, 0.29 to 0.86)	This is a long-term safety follow-up of efficacy studies, the first result taken 3 years after the first injection of Dengvaxia.
Halstead	2016	Vaccine efficacy = 56.8%; Efficacy against hospitalization = 16.7%	On the third year, the vaccine was asymmetrically protective and enhancing (protecting some age groups while increasing breakthrough dengue infections in others)
WHO-SAGE	2016	Vaccine Efficacy = 65.6% (95% CI 60.7-69.9)	Vaccine efficacy over 25 months from the first vaccine dose among 9 to 16 years or age using data pooled from two trials.
Capeding et al.	2016	Reduction of dengue cases = 20%; Dengue incidence (1.5% vs 2.0%)	Model study revealed that in 10 years simulation, there was 20% reduction in dengue cases after 90% vaccination coverage in 9 years age group.

While it was found that immunization status was not significantly associated to the incidence of hospitalization (p=1.000), it may be too early to conclude the non-association considering that the study was done only a year after the first dose of vaccine was given. As what was presented in the model study, the simulated highest reduction was only 30% in hospitalized cases in a 20-year projection of routine immunization among 9 year-olds [15].

4.2. Factors that Contributed to Non-significance of Some Study Variables

As previously emphasized, one factor could be attributed to the early implementation of the study. In vaccination studies, such as Standaert, et al.'s study of Rotavirus (RV) immunization and hospitalizations, data from the first year after vaccine implementation was not included in their analysis [16]. Data was collected two and four years after vaccine implementation. Both years showcased a significant decrease in RV-hospitalizations, moreover, cases after four years exhibited even greater reduction than the ones two years prior. The unexpected higher efficacy of the vaccination was attributed to herd effect: a great amount of vaccinations within a population offers indirect protection to the unvaccinated due to reduced transmission [16]. Seeing as Standaert's study was conducted at the start of its second post-vaccination year and Halstead's review of Sanofi Pasteur's trials showed that the significant efficacy began at the second year, effects such as those may not have taken place.

4.2.1. Number of Doses

In contrast to the RV study by Standaert, a similar RV study conducted in Israel showed a significant reduction as early as within the first year of vaccination implementation [17]. However, it is important to note that RV vaccinations have a shorter dosage schedule span (3-6 months) as compared to dengue vaccines (1 year) whose dosing intervals are spaced wider apart. The full effect of the dengue vaccination may not have taken effect within the first year since it spans majority of their current dosing schedule.

4.2.2. Basis of Vaccination Status

Vaccination status was confirmed via a list from the City Health Office. The Pasig City Health Office had released a partial masterlist of immunized grade school children who took part in their program. Despite having more than 3600 students confirmed to receive the dengue vaccination, the information released only came from 12 out of 28 public elementary schools in Pasig City who participated in the program. As of September 2017, the remaining 16 schools had yet to submit their reports to the Health Office.

Obtaining the partial list of vaccination record from the City Health Office had been the option to collect the variable dengue vaccinations status. This was due to the inaccurate immunization records from the hospitals which may be based solely on patient recall. In addition, since dengue vaccination is relatively new, it is not yet included in the list of vaccination asked in the hospital forms, and immunization recorded as "complete" may not mean inclusion of dengue vaccination.

4.2.3. Serostatus

Seropositivity was also found to have no association to dengue infection or hospitalization due to dengue infection (p=0.196). This may be because of the age group being studied which were from young population, making them less likely to have been infected at least twice during the conduct of the study. Also, since the early presentation of dengue may be nonspecific such as fever, some people may fail to recognize early dengue infection.

4.3. Age as a Significant Variable

The study found a higher odds (p <0.05; 95% CI: 1.134-1.863) of getting hospitalized due to dengue infection as age increases incrementally in children of 9-12 age group. A study done by Alera et al. in the Philippine setting revealed that dengue is primarily a childhood disease in endemic settings [18]. Among the age groups, the highest percentage of symptomatic infection was observed in 6-15 years age group with 4.90 per 100 person-years (95% CI: 2.52- 8.70). In the study sample in Table 2, most of the children in both cases and controls were 9-year olds (32%) with a decreasing trend towards the 12-year olds (18%). Furthermore, this trend was observed by the control group while the cases seemed to have stagnated - a higher proportion of 12-year old children had dengue. This may have contributed why the

odds ratio was leaning towards higher risks of dengue hospitalization as age increased within the 9-12 age group.

5. Conclusion

Only 2 out of 112 patients for both the cases and controls were vaccinated with the dengue vaccine which indicated a very low prevalence of immunization mainly due to (1) the mass immunization program had just started last 2016 which did not provide enough time to immunize all children aged 9-12 in Pasig, (2) dengue vaccine data mainly came from the Pasig City Health Office submitted by the respective public elementary schools (only 12 schools out of 28) where the immunizations were done, and (3) incomplete data coming from the hospitals since dengue vaccination status was not routinely asked in patients being admitted for dengue nor coming in for consult and immunization history cannot be recalled by the informant.

There was no significant association between dengue vaccine status and hospitalization due to dengue infection (i.e. those who were vaccinated were not less/more likely to get hospitalized due to dengue). Non-completion (or completion) of the vaccine and serostatus also were not significantly associated with risks of getting hospitalized due to dengue. Age was found to be significant with odds ratio of 1.45 (p=0.010; 95% CI: 1.134-1.863).

Studies are recommended to increase their sample size by gathering data from other nearby hospitals such as Pasig City General Hospital for more accurate results. It is also recommended that this study be conducted again in 5 years or more. Since the vaccine is newly introduced, it will be too early to tell if the vaccine has failed or if it has already reached a level of high efficacy in terms of reducing the number of dengue cases and hospitalizations in the Philippine setting.

It is also recommended that further studies broaden the age group beyond the 9-12 bracket (i.e. 9-45). By this time, the dengue vaccination will also have become more widely accessible to the public. For more accurate data on immunization, telephone interviews are recommended for verification of dengue vaccine status of the cases and controls.

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