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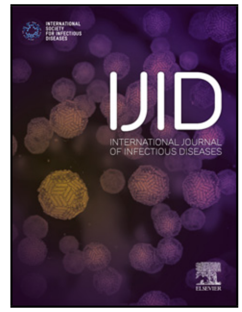

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Epidemiology of Japanese Encephalitis in the Philippines prior to routine immunization

Anna Lena Lopez 1, Peter Francis Raguindin 1, 2, Josephine G. Aldaba 1, Ferchito Avelino 3, Ava Kristy Sy 4, James D. Heffelfinger 5, Maria Wilda T. Silva 3

1 Institute of Child Health and Human Development, National Institutes of Health -University of the Philippines Manila, Manila, Philippines

2 Institute of Social and Preventive Medicine, University of Bern, Bern Switzerland

3 Department of Health, Manila, Philippines

4 Research Institute for Tropical Medicine, Manila, Philippines

5 World Health Organization Regional Office for the Western Pacific, Manila, Philippines

Corresponding author

Peter Francis Raguindin, MD, MSc

Institute for Social and Preventive Medicine - University of Bern

Mittelstrasse 43, 3012 Bern, Switzerland

Email: peter.raguindin@ispm.unibe.ch

Running title: JE in the Philippines

Article Highlights

- Incidence of Japanese encephalitis in the Philippines is 0.7/100,000 in <15 years at minimum
- Cases peaked annually from July to October, but occurs all year round
- Most of confirmed cases were children aged 2 years to <5 years old (N=194, 23.0%)
- Annualized minimum incidence are found to be higher in the northern regions of the Philippines

Keywords: Japanese encephalitis, Japanese encephalitis vaccines, Philippines, childhood immunization

Abstract 2250; Manuscript 2,600

Abstract

Background

In 2015, we published our findings highlighting the endemicity of Japanese encephalitis (JE) in the Philippines. The policymakers responded by conducting an immunization campaign and strengthening the surveillance system. Using the data on the revitalized surveillance system, we updated the epidemiology of JE in the country

Methods

Electronic databases were searched, and conference proceedings related to JE in the Philippines were identified until 31 December 2018. We used surveillance data from 1 January 2014 to 31 December 2017. We used the 2015 population census to estimate the national and regional incidence for children <15 years old.

Results

Four studies reported on the seroprevalence of JE in the Philippines, which showed increasing seroprevalence with increasing age. Seroprevalence rates were from zero for infants (<1 year old) to 65.7% in adolescents (12-18 years old) before the immunization campaign. Among five studies on clinical profile JE, case fatality ranged from zero to 21.1%, and neurologic sequelae ranged from 5.2% to 81.8% of diagnosed cases. In the surveillance data, JE cases peaked annually from July to October, coinciding with the wet season. The national incidence was estimated at 0.7 JE cases/100,000 among children <15 years at a minimum, but higher rates were seen in the northern regions of the country.

Conclusion

Improved surveillance affirmed the burden of JE in the Philippines. A subnational immunization campaign in April 2019 was conducted in the northern regions of the country. We highlight the importance of the inclusion of JE vaccine in the immunization program and sustained high-quality surveillance to monitor its impact on JE control.

Introduction

The Philippines is endemic for Japanese encephalitis (JE) (1, 2). Caused by the JE virus, JE is transmitted primarily by *Culex tritaeniorhynchus* mosquitoes abound in rice paddies (3-5). The cohabitation of animals with human settlements and increased irrigation of land, features that are commonly seen in an agricultural country, are considered factors associated with a high viral transmission (3, 5). In 2014, we conducted a systematic review and analyzed available surveillance data to assess the epidemiology of JE in the Philippines (2). Since then, the country has expanded the existing acute encephalitis syndrome (AES) surveillance as a proxy for JE, and later integrated this with the surveillance for other central nervous system infections known as the acute meningitis - encephalitis syndrome (AMES) surveillance.

The World Health Organization (WHO) recommends the inclusion of JE vaccines in routine immunization programs in countries where the disease is considered a public health priority (6, 7). Immunization is the cornerstone of JE control (3, 6, 8), and the Philippines' Department of Health is considering the inclusion of JE vaccine in the country's routine national immunization program. To support the country's decision, we conducted an analysis of available surveillance data and updated the systematic review on JE that was conducted in 2014.

Methods

Systematic review

We searched for articles using the terms "Japanese encephalitis" and "Philippines" in PubMed and local databases (Philippine Index Medicus, PIMEDICUS, and Health Research and Development Information Network, HERDIN). Presentations from local medical conventions were also checked for conference proceedings and abstracts. Technical reports, theses, and epidemiologic reports were also included. The search was made to include studies that were not included in our past review, and in addition to articles from 1 January 2014 to 31 December 2018. Abstracts and summaries were reviewed for relevance by 3 authors (ALL, PFR, and JGA). Full articles were extracted and examined to ensure that there was no double reporting. Data were extracted and collated for analysis. A detailed description of the methods has been previously published (2).

Studies on seroprevalence were collated to identify JE seroprevalence rates by age group. Seroprevalence rate was defined as the proportion of subjects with the minimum protective level of JE virus-neutralizing antibodies (≥1:10) as detected by plaque-reduction neutralization test (PNRT) (9). Studies on clinical profile and outcomes were collated. Since ~30% of surviving patients have serious residual neurologic, psychosocial, intellectual and/or physical disabilities (6), information on neurologic deficits, when available, were included.

Surveillance system

Philippine Integrated Disease Surveillance and Response (PIDSR) system is an integrated surveillance system for all identified priority diseases and events in the country. All private and public health facilities submit reports for this case-based surveillance without mandatory laboratory confirmation. Within this system are several surveillance systems, some of which need laboratory confirmation. The surveillance for acute encephalitis syndrome (AES) and bacterial meningitis surveillance was established in 2008 as part of the PIDSR. In 2013, AES and bacterial meningitis surveillance were combined into the acute meningitis-encephalitis syndrome (AMES) surveillance in sentinel hospitals throughout the country. AMES is case-based surveillance in select hospitals that includes laboratory testing. By 2016, there were nine sentinel sites for AMES surveillance. The hospitals were selected based on their laboratory capacity, human resources and logistical resources for specimen processing and transport (Figure 1). Case definitions used in the surveillance are in Box 1. Sentinel hospitals were distributed across the different regions of the country. Specimens (serum and cerebrospinal fluid, CSF) collected for the surveillance were stored locally at 2-8°C for up to 3 days until transport to the Research Institute for Tropical Medicine (RITM)- National JE Laboratory where tests were performed. The presence of JE virus-specific IgM antibody in a single sample of CSF or serum, as detected by an IgM-capture enzyme-linked immunosorbent assay (ELISA) is confirmatory for JE.

Data analysis

To describe the epidemiologic characteristics of the disease in the country, we tabulated all AMES, AES and JE-confirmed cases identified from the surveillance system. Reports from 1 January 2014 to 31 December 2017 were included in the description of the epidemiologic characteristics. The data were also disaggregated into different months to determine the seasonality of the disease, and into different administrative regions to look into disparities of incidence estimates in different areas.

To estimate the incidence of JE, we limited our analysis to data from laboratory-confirmed JE cases collected from 1 January 2015 to 31 December 2017. We used the 2015 National Census of the Philippines for children <15 years as the denominator (10). The AMES surveillance was started in 2013, and phased introduction in the different sites was done from 2013-2014; as such, we did not include 2014 data in our estimate for incidence. We limited our analysis to the age group with the highest burden, children <15 years old, to be comparable with past estimates by Campbell, et al. (11) and in line with the WHO recommendations on JE vaccination (6, 12). This incidence estimate was based on data from only nine sentinel surveillance hospitals. We computed the three-year average on the reporting of JE cases using the addresses of children with confirmed JE infection at the provincial and regional levels. We mapped the disease estimated incidence to stratify areas that had high or low disease transmission.

Ethical consideration

The study used data from clinical studies and public health surveillance data which were composed of aggregated information with no patient identifiers. Surveillance data were provided by the Philippine Department of Health (DOH) Epidemiology Bureau in compliance with the Data Privacy Act of the Philippines. No ethical clearance was sought since all surveillance data provided by the Epidemiology Bureau were de-identified and aggregated data, and additional data were obtained from published articles.

Results

Literature review

Figure 2 shows the results of the literature search. We identified four studies on seroprevalence and five studies on the clinical profile and outcomes of JE. No studies were identified looking at animal hosts and mosquito vectors on JE.

Seroprevalence studies

Four studies reported on the seroprevalence of JE in the country (13-17). These studies included baseline serologic assessments performed in clinical trials on vaccines for flavivirus (i.e., JE and dengue). There were different age-group classifications among the four studies, which hindered pooled analysis. Three studies were conducted in Manila and Muntinlupa, both highly urbanized cities with population

>500,000 and population densities of 12,000-71,000 per square kilometer (10). One study was conducted in San Pablo City, which was less-urbanized with a population of ~266,000 and a population density of 1,347 per square kilometer (10).

Antibodies to JE in the highly urbanized cities of Manila and Muntinlupa were lower (13-16) compared to the less-urbanized San Pablo (17) in the younger age groups. For studies reporting seroprevalence across different age groups, increasing age appeared to correlate with increasing antibody seropositivity in both highly urbanized and less urbanized areas. Both areas had comparable seroprevalence rates in the older age groups with 65.7% seroprevalence among >12- 18 years old in Manila and Muntinlupa and 63% among 10-14 years old in San Pablo.

Clinical profile

Five studies characterized the clinical profile and outcomes of JE cases in the Philippines (18-22). Three were retrospective record reviews that utilized clinical samples confirmed using JE IgM ELISA performed at the RITM; two were prospective cross-sectional studies. All studies used the AMES case definitions (19-22), except for one that used the AES case definitions (18). The studies were conducted in tertiary referral hospitals: the Philippine General Hospital in Manila, which serves persons living in Manila and other provinces (mostly from Region 4A); Baguio General Hospital in Baguio City, which serves persons residing in provinces and surrounding the Cordillera Region; Cagayan Valley Medical Center in Tuguegarao City which serves persons living in Region 2 and some from the Cordillera Region; JB Lingad Medical Center in San Fernando City, Pampanga, which serves persons from Pampanga and Bataan in Region 3; and Dr. Paulino J. Garcia Medical Center in Cabanatuan City, Nueva Ecija which caters mostly to patients from Nueva Ecija, in Region 3. (Table 2). A slight male predominance was seen among cases (from 55.2 to 63.3%). Four studies had proportions of JE-confirmed cases among suspects disaggregated into two age groups. The proportion of JE-confirmed cases in the less than 5 years age group ranged from 26.7% to 50%, while for the 5 to 14 years old age group, the range was 48.1% to 63.2%. Discharge outcomes were assessed in all studies. Case fatality rates ranged from zero (18) to 21.1% (23). The length of hospital stay was recorded only in two studies, which 2-3 weeks until discharge. Two studies (18, 20) graded the severity of the neurologic deficits among those who survived, and in these two studies, 37.9% to 45.4% had moderate to severe neurologic deficits on discharge. All studies were found in the northern regions and none in the other parts of the country.

Surveillance data

From 1 January 2014 to 31 December 2017, there were 790 laboratory-confirmed cases from both AES and AMES surveillance systems, which comprise 13.8% of all reported suspected cases. There was a substantial increase in the number of reported cases from 2014 to 2017 (Figure 3). From 2014-2017, there were 1432 suspected cases/year and 196 confirmed cases/year. There was a two-fold increase in suspected and confirmed JE case reporting from 2014 (448 suspected cases and 49 confirmed cases) to 2015 (1149 suspected cases and 127 confirmed cases) and a three-fold and six-fold increase from 2014 to 2016 (1964 suspected cases and 313 confirmed cases) and 2017 (2159 suspected cases and 301 confirmed cases) case reporting. Figure 2 also shows the seasonality of confirmed and suspected JE cases from 2014 to 2017. Although JE cases were reported in almost every month, the highest number was seen during the months of July to October when an average of 18-32 confirmed cases of JE was seen per month. November, December, and January had the fewest cases reported (5-8 cases reported per month). The highest number of suspected cases were among children aged 2 months to 2 years (N=1967, 33.2%) while the highest number of confirmed cases were among children aged 2 years to <5 years old (N=194, 23.0%). The highest proportion of JE confirmed cases out of all suspected cases was seen among children aged 5 to 10 years at 32.0% (293/915) (Figure 4).

From 2015-2017, there were 697 laboratory-confirmed JE cases among children aged <15 years, with an average of 232 cases/year. Suspected cases of JE were reported in all regions and in 91.5% (75/82) provinces in the country. Using the 2015 census as the base population, the estimated national annualized incidence was 0.7 cases/100,000 children <15 years, at a minimum. Annually, the estimated incidence increased from 0.3 in 2015 to 0.9 cases /100,000 children <15 years in 2016 and 2017. However, there were wide differences among the regions. The regions in the northern part of the country had higher annualized estimated incidence rates. The Cagayan Valley (Region 2), Ilocos (Region 1), Cordillera Administrative Region (CAR), and Central Luzon (Region 3) had the highest incidence rates at 3.1 (95% CI 2.2-4.4), 2.6 (95% CI 1.8-3.5), 2.6 (95% CI 1.4-4.3) and 2.1 (95% CI 1.6-2.6) cases/100,000 children <15 years (Figure 1). By further disaggregating the data into provinces, the highest annualized incidence rates (per 100,000 children <15 years) were recorded in the northern provinces, La Union (5.9, 95% CI 3.1-10), Cagayan (5.7, 95% CI 3.5-8.8), and Pampanga (4.5, 95% CI 3.1-6.2). Rates as high as 8.6/100,000 children <15 years (95% CI 5.2-13.3) were reported in La Union in 2017. The three highest reporting provinces each have a sentinel hospital for AMES surveillance.

Discussion

Our previous report confirmed the endemic transmission of JE in the Philippines and documented its wide distribution in the country, mainly through the sentinel surveillance system (2). We detected 1432 suspected cases/year and 196 confirmed cases/year (2014-2017), which is notably higher compared to our last publication (287 suspected cases/year and 19 confirmed cases/year in 2011-2013) (2). There has presumably been an increase in the awareness of JE among clinicians, which resulted in increased reporting of suspected cases in the surveillance system.

Our update is important as a baseline minimum case incidence for use in estimating the impact of JE vaccination in the country. Our result is also essential for some Asian countries that are yet to decide on routine vaccination. This update supports our earlier findings and provides a more accurate estimate of JE burden, including an estimate of the disease incidence in the Philippines. Although our annualized estimated incidence of JE among children <15 years was lower than the estimates of Campbell in 2011 (11) of 10.6/100,000, there were provinces in the country which had estimates of up to 8.6/100,000. The peak of cases occurs in July to October, coinciding with the wet season, which emphasized the seasonality of the disease

There was a wide disparity in the clinical outcomes of JE cases reported in the different hospitals. This may be due to inherent differences in the severity of the cases seen or the hospitals' capacities to manage such cases.

In this review, the seroprevalence data mirrored the proportion of infected population, as seen from the surveillance data. Cumulative cases revealed that 78% of the confirmed cases belong to children <15 years old. A past study by Nealon et al. showed 63% seropositive for children 10-14 years old (17), while Dubischar et al. showed 65.7% seropositive for children 12-18 years old (16). Serologic results from both studies were taken from a vaccine clinical trial, and are subject to selection bias. However, previous seroprevalence studies, which focused on determining JE transmission in the community, had the same conclusion. It also showed lower proportions of children that are seropositive for JE virus in the urban setting, and older children were likely infected by the virus than younger children (24-26). Overall, these findings highlight that the pediatric age group is the primary target population in an immunization strategy against JE.

This study is not without limitations. First, the calculated JE incidence is based only on JE-confirmed cases, which is dependent on the performance of the surveillance that varied through the years and varied in different regions, since surveillance system was slowly introduced. The differences in the number of cases reported are likely due to the accessibility of sentinel sites, the year by which surveillance was started, and the perfromance quality of the surveillance system. In 2014, the sentinel hospitals were just being established and surveillance personnel was only being trained. Since not all regions have sentinel surveillance hospitals, and the population may access other hospitals apart from the sentinel sites, it is likely that more cases were not reported. Hence the national or regional incidence that we report probably underestimates the true incidence. It is interesting to note that the three provinces with the highest incidence of JE had sentinel surveillance hospitals of which may reflect the true incidence in the Philippines. The case incidence rates we estimated from our surveillance system were similar to other Asian countries (27-29). Second, the information on clinical profile and outcomes were mostly retrospective with short observation periods. Table 2 showed a wide disparity of the outcomes among different facilities, limiting the generalizability of the results and leaving the true impact of the disease on long-term morbidity and mortality unknown. Deaths identified were mostly during hospitalization. The neurologic disabilities were not followed with a longer time frame. Long-term complications of the cases seen on extended follow-up are useful in further ascertaining the social and economic burden of the disease. Third, all seroprevalence data came from clinical trials; hence there was inherent bias in subject recruitment. Two studies included the whole pediatric age group, while the other studies focused on the seroprevalence of infants of whom the intended targets of the vaccines. Data on seroprevalence among adults were not available. Age-stratification also varied among the studies, limiting the comparisons across studies

JE control is considered as a priority in the WHO's Western Pacific and South-East Asia Regions. The cornerstone of JE disease control continues to be vaccination (1, 6, 7). In April 2019, the Philippines' DOH provided Japanese Encephalitis Vaccine Live (SA14-14-2) (Chengdu Institute of Biological Products Co.

Ltd China) as a campaign vaccination in four regions with the highest burden of the disease. The use of the SA14-14-2 vaccine in the Philippines was deemed cost-effective compared to no vaccination regardless of the vaccination strategy implemented (30). The live-attenuated JE vaccine was piloted in a campaign targetting children <5 years old, and is currently being considered for routine immunization for infants 9 mos old (together with the first dose of measles-mumps-rubella).

We present additional information supporting our earlier findings that JE is endemic in the Philippines. To the best of our knowledge, this is the first study to present a case-based minimum incidence estimate of JE in the Philippines and provide baseline estimates prior to JE vaccination campaign. Continued strengthening of the surveillance system will be important to monitor the vaccine's impact and to support JE disease control efforts. A more refined surveillance data will be useful to identify other age groups and areas of highest risk that will be targeted.

Supplement Information

Table 1. Suspected and confirmed JE cases in the Philippines from surveillance, January 2014 to December 2017

Declaration of Conflict of Interest

None to declare

Funding

The study received no funding from any organization or agency

Ethics registration

The study used publicly available data for the analysis.

Author Contributions

Conceived and designed the experiments: ALL PFR JGA. Performed the experiments: ALL PFR FA AKS. Analyzed the data: ALL PFR JDH. Contributed reagents/materials/analysis tools: ALL PFR JGA FA AKS MWS. Wrote the paper: ALL PFR JGA FA AKS JDH MWS.

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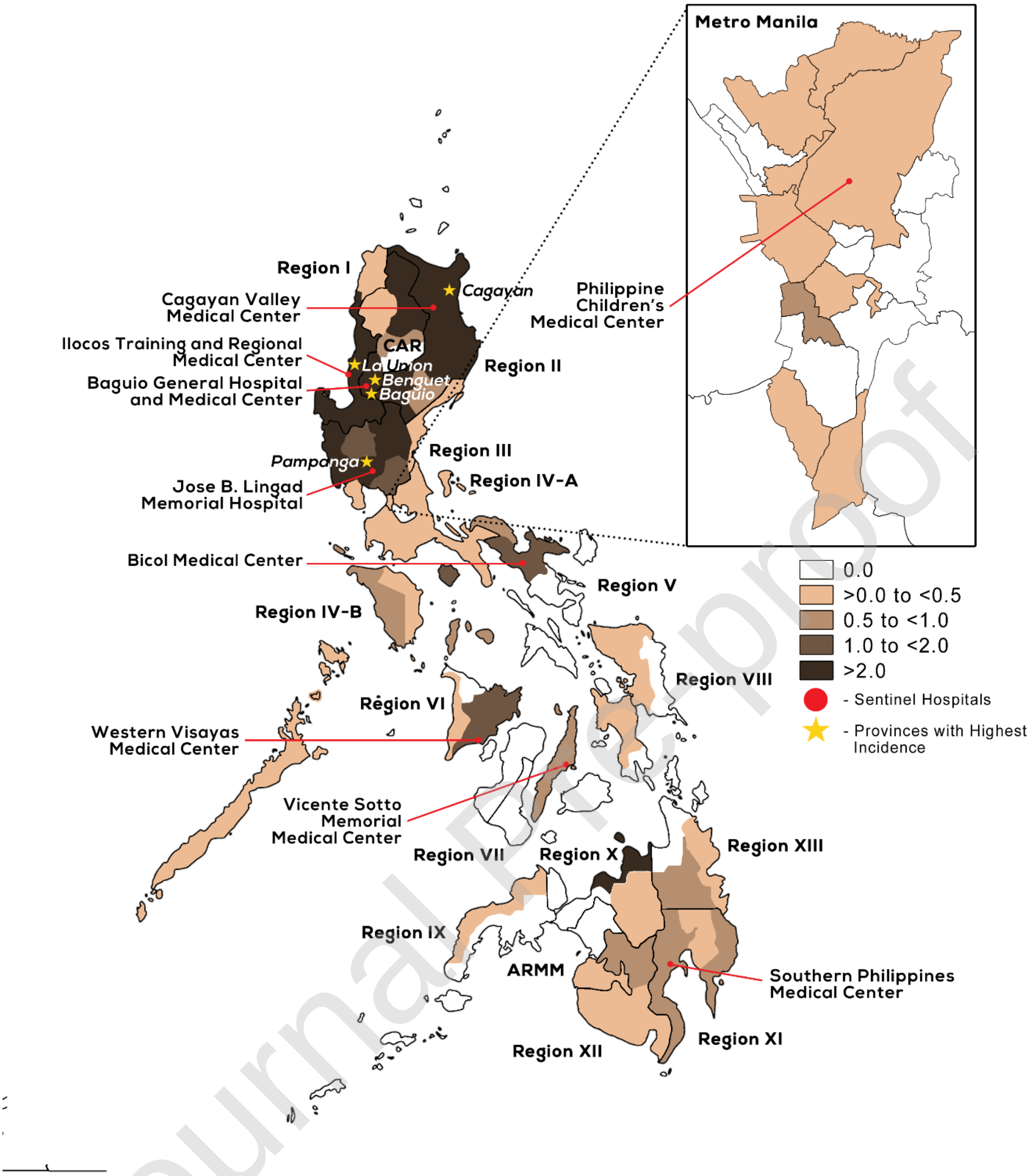
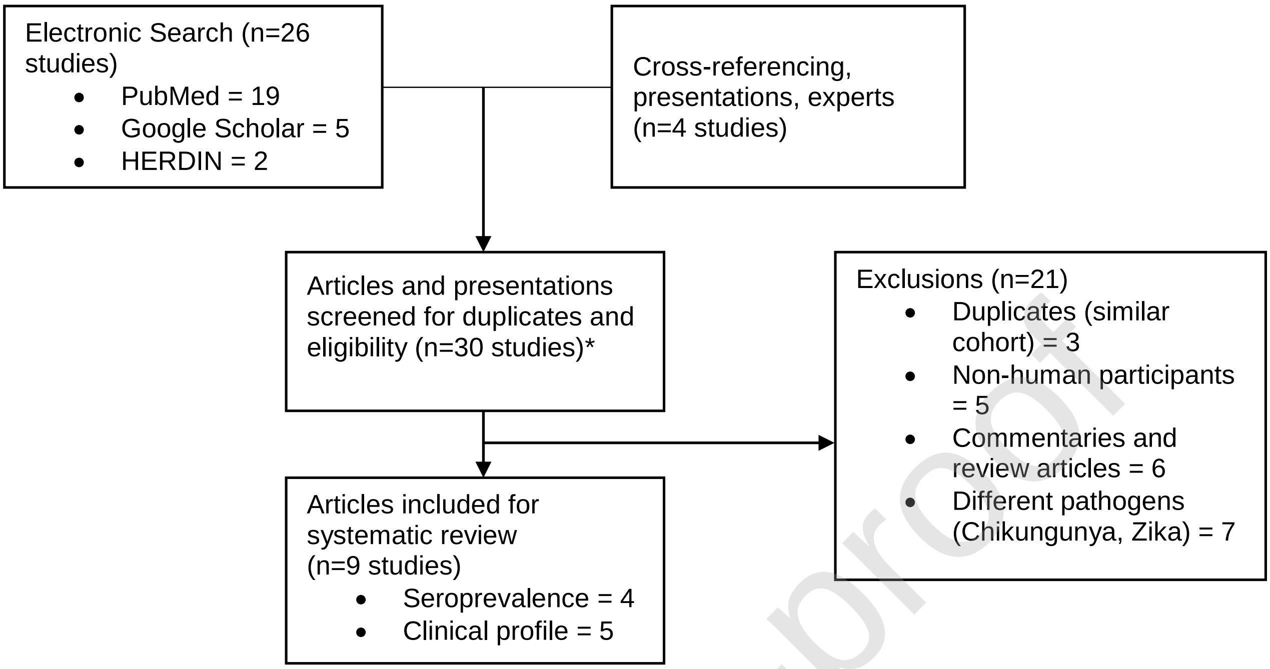


Figure 1. Map of the Philippines showing locations of sentinel hospitals and average annual Japanese encephalitis minimum incidence of children <15 years old (case/100,000) by province 2015-2017

Figure 2. Flowchart of Japanese encephalitis studies identified from literature review that were included in this analysis.



*Including studies that were missed in the search from a past publication

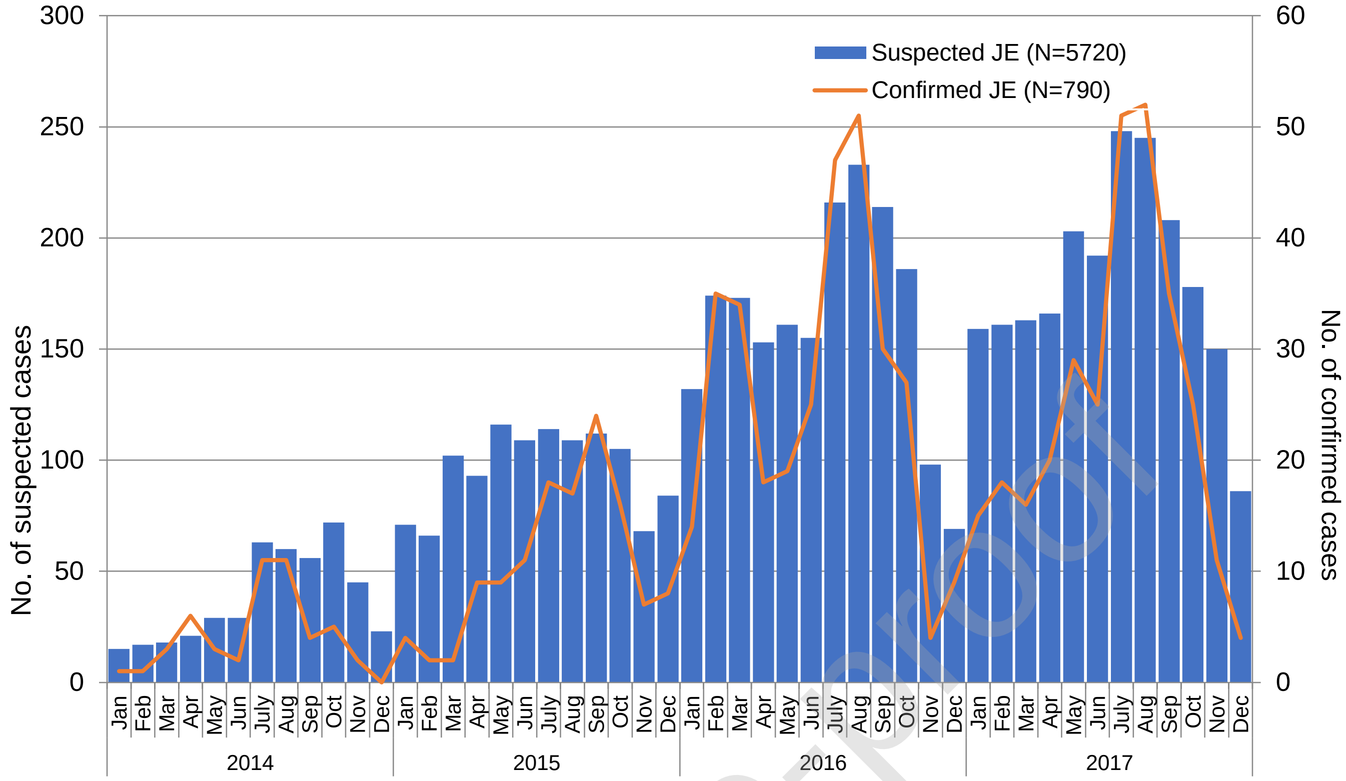


Figure 3. Monthly distribution of reported suspected and confirmed Japanese encephalitis (JE) cases, Philippines, January 2014 to December 2017. Data from acute meningoencephalitis syndrome (AMES) and acute encephalitis syndrome (AES) surveillance under the Philippine Integrated Disease Surveillance and Response (PIDSR).

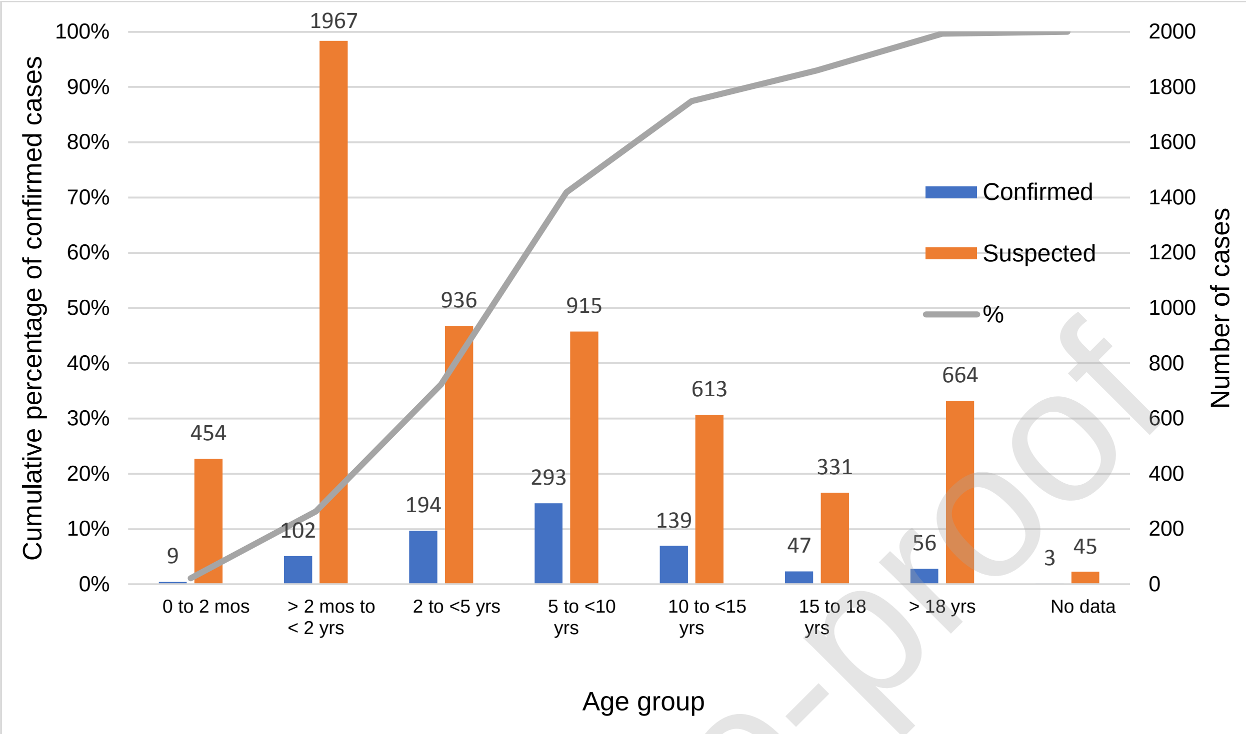


Figure 4. Age distribution of confirmed and suspected Japanese encephalitis (JE) cases, and the cumulative percentage of confirmed JE cases, January 2014 to December 2017. Data from acute meningoencephalitis syndrome (AMES) and acute encephalitis syndrome (AES) surveillance under the Philippine Integrated Disease Surveillance and Response (PIDSR).

Box 1. Case definitions used in Japanese encephalitis surveillance[a]

Acute Meningitis Encephalitis Syndrome (AMES)

A case of suspected Acute Meningitis-Encephalitis is a person of any age, WITH a sudden onset of fever, plus one of:

a) Change in mental status (including altered consciousness, confusion, disorientation, coma or inability to talk)

b) New-onset seizures (excluding simple febrile seizures)

c) Neck stiffness or other meningeal signs

Cases are then classified following the case classification for Acute Encephalitis Syndrome or Bacterial Meningitis.

Acute Encephalitis Syndrome (AES)

A case of Acute Encephalitis Syndrome (AES) is defined as a person of any age, with the acute onset of fever and at least one of the following:

a) Change in mental status (e.g. confusion, disorientation, coma or inability to talk)

b) New onset of seizures (excluding simple febrile seizures).

Case Classification for AES

Laboratory-confirmed Japanese Encephalitis (JE)

- An AES case that has been laboratory-confirmed as JE.

Probable JE

- An AES case that occurs in close geographical and temporal relationship to a laboratory-confirmed case of JE, in the context of an outbreak.

AES – other agent:

- An AES case in which diagnostic testing is performed and an etiologic agent other than JE virus is identified.

AES – unknown:

- An AES case in which diagnostic testing is not performed or testing was performed but no etiologic agent was identified or in which the test results were indeterminate.

[a] The definitions used were from reference (31). The AMES surveillance suspected case definition was revised in 2016, including physician-diagnosed encephalitis or meningitis cases.

Table 1. Summary of serologic studies on Japanese encephalitis in the Philippines included in this analysis

Author	Study year	Location	Subjects tested	Age group	Seroprevalence
Victor (14, 15)	2005	Muntinlupa[a]	490	8 months	5.3%
Feroldi (13, 32)	2008	Muntinlupa[a]	709	12-18 months	3.2%
Dubischar (16)	2010	Muntinlupa and Manila[a]	20 100 201 140	6 months - < 1 year 1- < 3 year 3-12 year >12-18 year	0% 3.2% 14.4% 65.7%
Nealon (17)	2011	San Pablo[b]	149 202 249	2 - 4 year 5-9 year 10-14year	21% 42% 63%

[a]Highly-urbanized cities. Muntinlupa City and Manila City are both part of the Metro Manila

[b]Less-urbanized city. San Pablo is part of Laguna, a province outside of Metro Manila

Table 2. Clinical profile of Japanese encephalitis (JE) cases in the Philippines, 2014-2018

Author, Hospital location, Years covered	Study design	JE-confirmed/ Suspected cases, n/N (%)	Age of JE-confirmed cases <5 y, n (%) 5-14years, n (%)	Sex, males, n (%)	Outcome of diagnosed JE cases; Length of hospital stay
Alcaraz (18), Philippine General Hospital, Manila	Retrospective chart review of AES cases admitted in Jan 2011 to Dec 2014, aged 0-18 years old	11/64 (17.2)	No age breakdown for JE cases	No sex breakdown for JE cases	Died: 0 (0) Moderate to severe deficits [a]: 5 (45.4) Slight disability: 2 (18.2) Alive with no significant disability: 4 (36.4) No information on length of stay of JE cases
Balderas (20) Baguio General Hospital, Baguio City	Retrospective chart review of AMES and JE confirmed cases admitted from April 2015 to April 2017, aged 1-18 years old	36 /198 (18.2)	<5 yrs: 8 (26.7)[b] 5 – 14 yrs: 14 (60.0)	19 (63.3)[b]	Died: 1 (3.4)[c] Moderate to severe deficits: 11 (37.9) Mild neurologic deficits 9 (31.0) Completely recovered: 8 (27.6); Average length of hospital stay: 22 days
Agor (21) Cagayan Valley Medical Center, Tuguegarao City	Retrospective chart review of AMES and JE confirmed cases admitted from Jan 2014 to Dec 2016, aged 1-18 years old	52/453 (11.5)	<5 yrs: 26 (50.0) 5 – 14 yrs: 25 (48.1)	30 (57.7)	Died: 1 (2) Alive with deficits: 29 (55.8)[d] Alive: 22 (42.3)[d] No information on length of stay of JE cases
Mangalino (19) JB Lingad Medical Center, San Fernando City	Prospective, Cross-sectional study of AMES and JE	38/272 (14.0)	<5 yrs: 13/38 (34.2) 5 – 14 yrs: 24/38 (63.1)	21 (55.2)	Died: 8 (21.1) Alive with deficits: 2 (5.3) Alive: 28 (73.7)

	confirmed cases admitted in Jan 2015 to Jun 2016 aged 1 – 18 years old				Median length of stay: 16 days (range 1-50 days)
Torio (22) Dr. Paulino J. Garcia Medical Center, Cabanatuan City,	Prospective, Cross-sectional study of AMES and JE confirmed cases admitted in Apr 2015 to Mar 2016 aged 1 – 18 years old	68/115 (59.1)	<5 yrs: 25 (36.8) 5 – 14 yrs: 43 (63.2)	40 (58.8)	Died: 5 (7.4) Alive with deficits: 5 (7.4) Alive: 58 (85) No information on length of stay of JE cases

[a]Based on the modified Rankin scale that is commonly used to measure the degree of disability or dependence on the activities of daily living of people who suffered a stroke or other causes of neurological disability.

[b] Out of 30 included in the analysis.

[c] Out of 30, one went home against medical advice precluding outcome assessment, only 29 included in the analysis.

[d] Includes one each who went home against medical advice due to financial reasons.