International Journal of Infectious Diseases 102 (2021) 344–351

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Epidemiology of Japanese encephalitis in the Philippines prior to routine immunization

Anna Lena Lopez[a], Peter Francis Raguindin[a,b,*], Josephine G. Aldaba[a], Ferchito Avelino[c], Ava Kristy Sy[d], James D. Heffelfinger[e], Maria Wilda T. Silva[c]

[a] Institute of Child Health and Human Development, National Institutes of Health, University of the Philippines Manila, Manila, Philippines
[b] Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland
[c] Department of Health, Manila, Philippines
[d] Research Institute for Tropical Medicine, Manila, Philippines
[e] World Health Organization Regional Office for the Western Pacific, Manila, Philippines

ARTICLE INFO

Article history:
Received 13 August 2020
Received in revised form 15 October 2020
Accepted 21 October 2020

Keywords:
Japanese encephalitis
Japanese encephalitis vaccines
Philippines
Childhood immunization

ABSTRACT

Background: Findings were published in 2015 that highlighted the endemicity of Japanese Encephalitis (JE) in the Philippines. The policymakers responded by conducting an immunization campaign and strengthening the surveillance system. Using data on the revitalized surveillance system, the epidemiology of JE in the country was updated.
Methods: Electronic databases were searched, and conference proceedings related to JE in the Philippines were identified until 31 December 2018. Surveillance data from 01 January 2014 to 31 December 2017 were used. The 2015 population census was used to estimate the national and regional incidence for children aged <15 years.
Results: Four studies reported the seroprevalence of JE in the Philippines, which showed increasing seroprevalence with increasing age. Seroprevalence rates were from 0% for infants (aged <1 year) to 65.7% in adolescents (12–18 years) before the immunization campaign. Among five studies on the clinical profile of JE, case fatality ranged from 0 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 a minimum of 0.7 JE cases/100,000 among children aged <15 years, 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. This paper highlights the importance of including the 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) (Heffelfinger et al., 2017; Lopez et al., 2015). Caused by the JE virus, JE is primarily transmitted by *Culex tritaeniorhynchus* mosquitoes, which are found in rice paddies (Erlanger et al., 2009; Misra and Kalita, 2010; Keiser et al., 2005). 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 high viral transmission (Erlanger et al., 2009; Keiser et al., 2005). A systematic review was conducted in 2014 and available surveillance data were analyzed to assess the epidemiology of JE in the Philippines (Lopez et al., 2015). 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 (World Health Organization, 2015; World Health Organization Regional Office for the Western Pacific, 2018). Immunization is the cornerstone of JE control (Erlanger et al., 2009; World Health Organization, 2015; Technical Working Group on Japanese

* Corresponding author at: Institute for Social and Preventive Medicine, University of Bern, Mittelstrasse 43, 3012 Bern, Switzerland.
E-mail address: peter.raguindin@ispm.unibe.ch (P.F. Raguindin).

https://doi.org/10.1016/j.ijid.2020.10.061

Encephalitis, 2014), 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, this analysis of available surveillance data was conducted and the systematic review on JE that was conducted in 2014 was updated.

Methods

Systematic review

PubMed and local databases (Philippine Index Medicus, PIMEDICUS, and Health Research and Development Information Network, HERDIN) were searched for articles using the terms "Japanese encephalitis" and "Philippines". 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 the past review, and in addition to articles from 01 January 2014 to 31 December 2018. Abstracts and summaries were reviewed for relevance by three 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 (Lopez et al., 2015).

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 ($\geq$1:10) as detected by the plaque-reduction neutralization test (PNRT) (Hombach et al., 2005). Studies on clinical profile and outcomes were collated. Since approximately 30% of surviving patients have serious residual neurological, psychosocial, intellectual and/or physical disabilities (World Health Organization, 2015), information on neurologic deficits, when available, was included.

Surveillance system

The 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

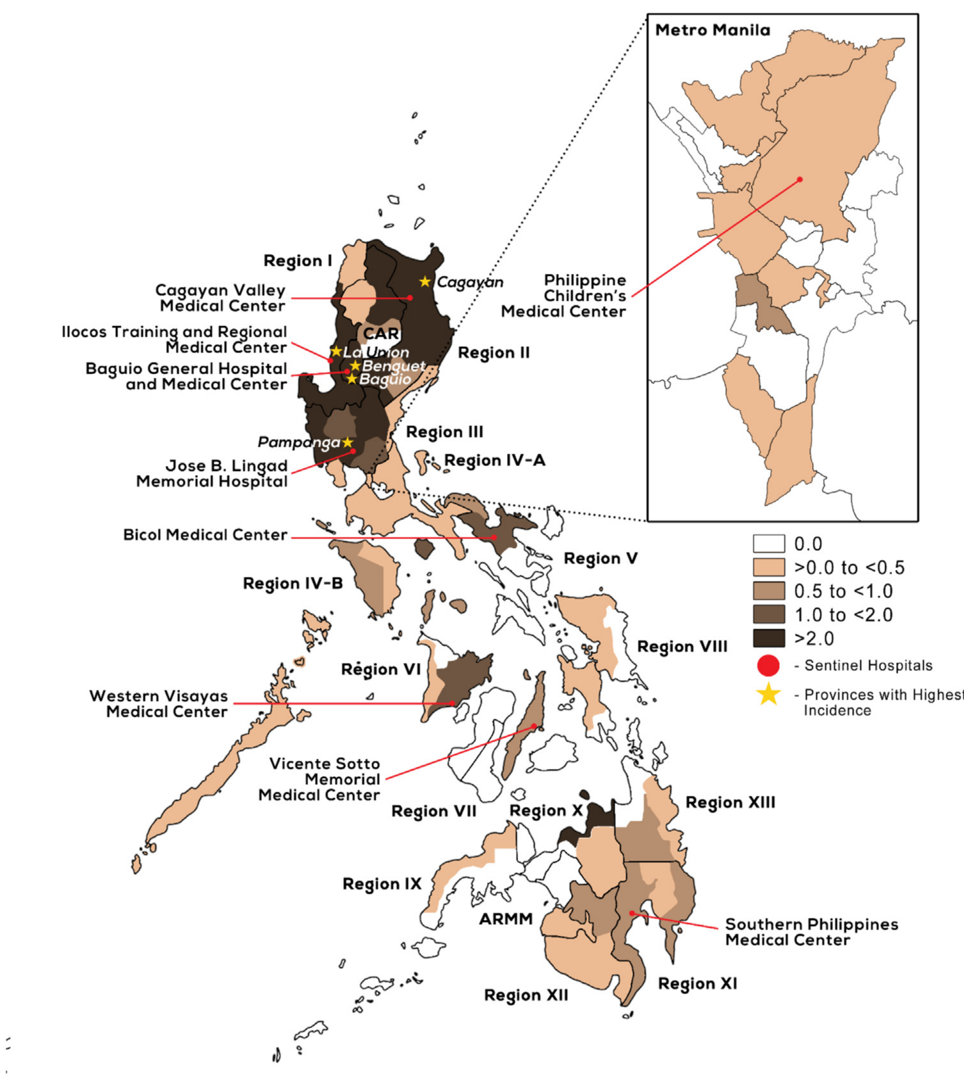

Figure 1. Map of the Philippines showing locations of sentinel hospitals and average annual Japanese encephalitis minimum incidence of children aged <15 years (case/100,000) by province 2015–2017.

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, all AMES, AES and JE-confirmed cases identified from the surveillance system were tabulated. Reports from 01 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, this analysis was limited to data from laboratory-confirmed JE cases collected from 01 January 2015 to 31 December 2017. The 2015 National Census of the Philippines was used for children aged <15 years as the denominator (Philippine Statistical Authority, 2018). The AMES surveillance was started in 2013, and phased introduction in the different sites was performed from 2013 to 2014; as such, 2014 data were not included in the estimate for incidence. Analysis was limited to the age group with the highest burden–children aged <15 years–to be comparable with past estimates by Campbell et al. (2011) and in line with the WHO recommendations on JE vaccination (World Health Organization, 2015; World Health Organization, 2006). This incidence estimate was based on data from nine sentinel surveillance hospitals. The three-year average on the reporting of JE cases was computed using the addresses of children with confirmed JE infection at provincial and regional levels. The disease estimated incidence was mapped 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 comprised 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. Four studies on seroprevalence and five studies on the clinical profile and outcomes of JE were identified. No studies looking at animal hosts and mosquito vectors on JE were identified.

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 sudden-onset fever, plus one of:
Change in mental status (including altered consciousness, confusion, disorientation, coma, or inability to talk) align="none"
New-onset seizures (excluding simple febrile seizures) align="none"
Neck stiffness or other meningeal signs. align="none"
Cases are then classified following the case classification for acute encephalitis syndrome (AES) or bacterial meningitis.

Acute encephalitis syndrome (AES)

A case of AES is defined as a person of any age with acute-onset fever and at least one of the following:
Change in mental status (e.g. confusion, disorientation, coma, or inability to talk) align="none"
New-onset seizures (excluding simple febrile seizures). align="none"
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

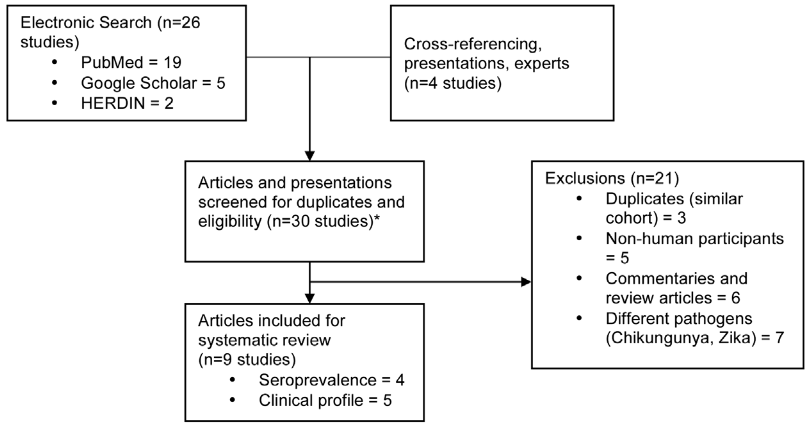

Figure 2. Flowchart of Japanese encephalitis studies identified from literature review that were included in this analysis.
*Including studies that were missed in the search from a past publication.

Seroprevalence studies

Four studies reported on the seroprevalence of JE in the country (Feroldi et al., 2012; Gatchalian et al., 2008; Victor et al., 2014; Dubischar et al., 2017; Nealon et al., 2018). These studies included baseline serologic assessments on vaccines for flavivirus (i.e. JE and Dengue) performed in clinical trials. There were different age group classifications among the four studies, which hindered pooled analysis. Three studies were conducted in Manila and Muntinlupa, which are both highly urbanized cities with populations >500,000 and population densities of 12,000–71,000/km^2 (Philippine Statistical Authority, 2018). One study was conducted in San Pablo City, which was less-urbanized, with a population of ~266,000 and a population density of 1347/km^2 (Philippine Statistical Authority, 2018).

Antibodies to JE in the highly urbanized cities of Manila and Muntinlupa were lower (Feroldi et al., 2012; Gatchalian et al., 2008; Victor et al., 2014; Dubischar et al., 2017) compared with the less-urbanized San Pablo (Nealon et al., 2018) 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 those aged >12–18 years in Manila and Muntinlupa and 63% among those aged 10–14 years in San Pablo (Table 1).

Clinical profile

Five studies characterized the clinical profile and outcomes of JE cases in the Philippines (Alcaraz et al., 2016; Mangalino et al., 2018; Balderas and Trajano, 2018; Agor et al., 2018; Torio et al., 2018). 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 (Mangalino et al., 2018; Balderas and Trajano, 2018; Agor et al., 2018; Torio et al., 2018), except for one that used the AES case definitions (Alcaraz et al., 2016). The studies were conducted in tertiary referral hospitals: the Philippine General Hospital in Manila, which serves people living in Manila and other provinces (mostly from Region 4A); Baguio General Hospital in Baguio City, which serves people residing in provinces and surrounding the Cordillera Region; Cagayan Valley Medical Center in Tuguegarao City, which serves people living in Region 2 and some from the Cordillera Region; JB Lingad Medical Center in San Fernando City, Pampanga, which serves people from Pampanga and Bataan in Region 3; and Dr. Paulino J. Garcia Medical Center in Cabanatuan City, Nueva Ecija, which mainly serves people from Nueva Ecija, in Region 3 (Table2). 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 group aged <5 years ranged from 26.7 to 50%, while for the 5–14 years age group, the range was 48.1–63.2%. Discharge outcomes were assessed in all studies. Case fatality rates ranged from 0 to 21.1% (Alcaraz et al., 2016; Mangalino et al., 2017). The length of hospital stay was recorded in two studies, which was 2–3 weeks until discharge. Two studies (Alcaraz et al., 2016; Balderas and Trajano, 2018) graded the severity of the neurologic deficits among those who survived, and 37.9–45.4% had moderate-to-severe neurologic deficits on discharge. All studies were found in the northern regions and none in other parts of the country.

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
Gatchalian et al. (2008) and Victor et al. (2014)	2005	Muntinlupa[a]	490	8 months	5.3%
Feroldi et al. (2012) and Capeding et al. (2018)	2008	Muntinlupa[a]	709	12–18 months	3.2%
Dubischar et al. (2017)	2010	Muntinlupa and Manila[a]	20	6–11 months	0%
			100	1–2 years	3.2%
			201	3–12 years	14.4%
			140	13–18 years	65.7%
Nealon et al. (2018)	2011	San Pablo[b]	149	2–4 years	21%
			202	5–9 years	42%
			249	10–14 years	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 years, n (%) 5–14 years, n (%)	Sex, males, n (%)	Outcome of diagnosed JE cases; length of hospital stay
Alcaraz et al. (2016), 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 and Trajano (2018) 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 years: 8 (26.7)[b] 5–14 years: 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 et al. (2018) 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 years: 26 (50.0) 5–14 yea rs: 25 (48.1)	30 (57.7)	Died: 1 (2) Alive with deficits: 29 (55.8) Alive: 22 (42.3)[d] No information on length of stay of JE cases
Mangalino et al. (2018) JB Lingad Medical Center, San Fernando City	Prospective, Cross-sectional study of AMES and JE confirmed cases admitted in Jan 2015 to Jun 2016 aged 1–18 years old	38/272 (14.0)	<5 years: 13/38 (34.2) 5–14 yea rs: 24/38 (63.1)	21 (55.2)	Died: 8 (21.1) Alive with deficits: 2 (5.3) Alive: 28 (73.7) Median length of stay: 16 days (range 1–50 days)
Torio et al. (2018) 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 years: 25 (36.8) 5–14 yea rs: 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] Of 30 included in the analysis.
[c] Of 30, one went home against medical advice precluding outcome assessment; therefore, 29 included in the analysis.
[d] Includes one each who went home against medical advice due to financial reasons.

Surveillance data

From 01 January 2014 to 31 December 2017, there were 790 laboratory-confirmed cases from both AES and AMES surveillance systems, which comprised 13.8% of all reported suspected cases. There was a substantial increase in the number of reported cases from 2014 to 2017 (Figure 3). There were 1432 suspected cases/ year and 196 confirmed cases/year from 2014 to 2017. There was a two-fold increase in suspected and confirmed JE cases reported from 2014 (448 suspected cases and 49 confirmed cases) to 2015

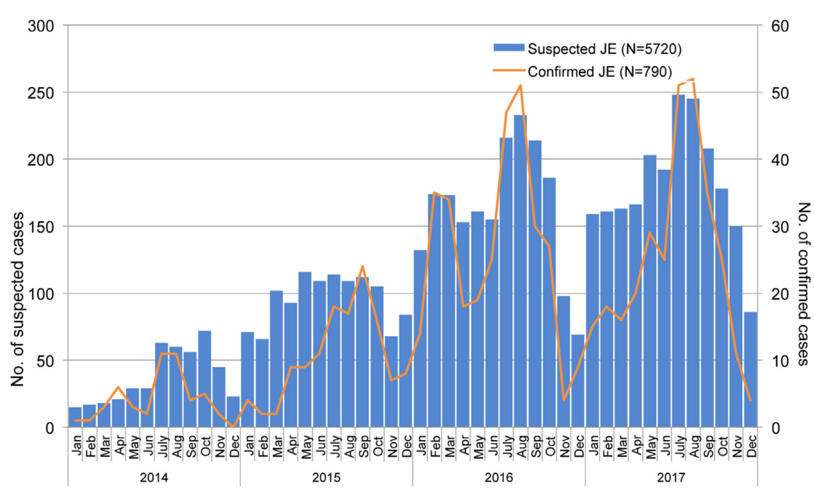

Figure 3. Monthly distribution of suspected and confirmed Japanese encephalitis (JE) cases, Philippines, January 2014 to December 2017. Data are from acute meningoencephalitis syndrome (AMES) and acute encephalitis syndrome (AES) surveillance under the Philippine Integrated Disease Surveillance and Response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

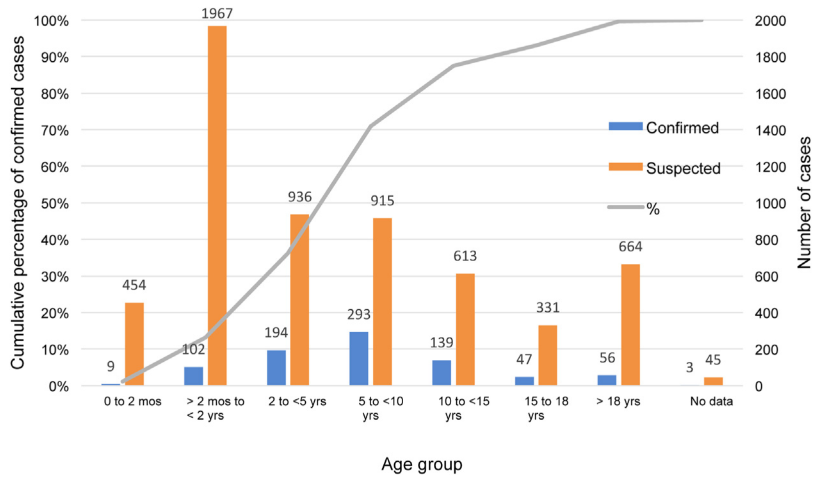

Figure 4. Age distribution of confirmed and suspected Japanese encephalitis (JE) cases, and the cumulative percentage of confirmed JE cases, January 2014 to December 2017. Data from acute meningoencephalitis syndrome (AMES) and acute encephalitis syndrome (AES) surveillance under the Philippine Integrated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

(1149 suspected cases and 127 confirmed cases) and three-fold and six-fold increases from 2014 to 2016 (1964 suspected cases and 313 confirmed cases) and 2017 (2159 suspected cases and 301 confirmed cases). 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 were seen per month. November, December and January had the fewest cases reported (5–8 cases reported per month). The highest number of suspected cases was among children aged 2 months to 2 years (n = 1,967, 33.2%), while the highest number of confirmed cases was among children aged 2–4 years (n = 194, 23.0%). The highest proportion of JE-confirmed cases out of all suspected cases was seen among children aged 5–10 years, at 32.0% (293/915) (Figure 4).

From 2015 to 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 a minimum of 0.7 cases/100,000 children aged <15 years. Annually, the estimated incidence increased from 0.3 in 2015 to 0.9 cases/100,000 children aged <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 annual 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 aged <15 years (Figure 1). By further disaggregating the data into provinces, the highest annual incidence rates (per 100,000 children aged <15 years) were recorded in the northern provinces of 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 aged <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

The 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 (Lopez et al., 2015). It detected 1432 suspected cases/year and 196 confirmed cases/year (2014–2017), which is notably higher compared with the previous publication (287 suspected cases/year and 19 confirmed cases/year in 2011–2013) (Lopez et al., 2015). 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.

This update is important as a baseline minimum case incidence for use in estimating the impact of JE vaccination in the country. The results are also essential for some Asian countries that are yet to decide on routine vaccination. This update supports earlier findings and provides a more accurate estimate of JE burden, including an estimate of the disease incidence in the Philippines. Although the annual estimated incidence of JE among children aged <15 years was lower than the estimates of Campbell et al. (2011) of 10.6/100,000, there were provinces in the country that had estimates of up to 8.6/100,000. The peak of cases occured 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 have been 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 aged <15 years. A past study by Nealon et al. showed 63% seropositivity for children aged 10–14 years (Nealon et al., 2018), while Dubischar et al. showed 65.7% seropositivity for children aged 12–18 years (Dubischar et al., 2017). Serologic results from both studies were taken from a vaccine clinical trial, and subject to selection bias. However, previous seroprevalence studies, which focused on determining JE transmission in the community, had the same conclusion. They also showed lower proportions of children that were seropositive for JE virus in the urban setting, and older children were likely infected by the virus than younger children (Hammon et al., 1958; Cross et al., 1977; Arambulo, 1974). Overall, these findings highlight that the pediatric age group is the primary target population in an immunization strategy against JE.

This study was not without limitations. First, the calculated JE incidence was only based on JE-confirmed cases, which were dependent on the performance of the surveillance and varied through the years and in different regions, since the surveillance system was slowly introduced. The differences in the number of cases reported were 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, sentinel hospitals were just being established and surveillance personnel were 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 was reported probably underestimated the true incidence. It is interesting to note that the three provinces with the highest incidence of JE had sentinel surveillance hospitals, which may reflect the true incidence in the Philippines. The case incidence rates that were estimated from the surveillance system were similar to other Asian countries (Garjito et al., 2018; Kumar et al., 2018; Kari et al., 2006). Second, the information on clinical profile and outcomes was mostly retrospective with short observation periods. Table 2 shows a wide disparity in 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 that were 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 who were the intended targets of the vaccines. Data on seroprevalence among adults were unavailable. Age-stratification also varied among the studies, which limited 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 (Heffelfinger et al., 2017; World Health Organization, 2015; World Health Organization Regional Office for the Western Pacific, 2018). 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 with no vaccination, regardless of the vaccination strategy that was implemented (Vodicka et al., 2020). The live-attenuated JE vaccine was piloted in a campaign targetting children aged <5 years, and is currently being considered for routine immunization for infants aged 9 months (together with the first dose of measles-mumps-rubella).

This paper presents additional information supporting earlier findings that JE is endemic in the Philippines. It is believed that this is the first study to present a case-based minimum incidence estimate of JE in the Philippines and provide baseline estimates prior to the 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. More refined surveillance data will be useful to identify other age groups and areas of highest risk, which will be targeted.

Conflicts of interest

None.

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.

Acknowledgments

We thank Luzviminda Garcia of the Disease Prevention and Control Bureau-Department of Health for her assistance and Von Luigi Valerio of the National Institutes of Health-University of the Philippines Manila for drafting the figures and maps.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2020.10.061.

References

Agor SA, Reyes-Solis P, Molina-Antonio CL. Clinical profile of laboratory-confirmed Japanese encephalitis among pediatric patients admitted in Cagayan Valley Medical Center: a three-year retrospective study. 14th Congress of the Asian Society for Pediatric Research. .

Alcaraz AR, Lu-Bolanos M, Gonzales MLAM. Clinical profile and outcomes in acute viral encephalitis. Pediatr Infect Dis Soc Phil J 2016;17(2):37–46.

Arambulo PVI. The natural nidality of zoonoses in the Philippines. Int J Zoonoses 1974;1:58–74.

Balderas AC, Trajano MLM. Sociodemographic and clinical profiles of pediatric Japanese encephalitis cases in a tertiary hospital: a cross-sectional study. 25th Annual Convention of the Pediatric Infectious Diseases Society of the Philippines. .

Campbell GL, Hills SL, Fischer M, Jacobson JA, Hoke CH, Hombach JM, et al. Estimated global incidence of Japanese encephalitis: a systematic review. Bull World Health Organ 2011;89(10) 766–74, 74A–74E.

Capeding MR, Alberto ER, Bouckenooghe A, Laot TM, Chansinghakul D, Monfredo C, et al. Five-year antibody persistence following a Japanese Encephalitis Chimeric Virus Vaccine (JE-CV) booster in JE-CV-primed children in the Philippines. J Infect Dis 2018;217(4):567–71.

Cross JH, Banzon T, Wheeling CH, Cometa H, Lien JC, Clarke R, et al. Biomedical survey in North Samar Province, Philippine Islands. Southeast Asian J Trop Med Pub Health 1977;8:464–75.

Dubischar KL, Kadlecek V, Sablan JB, Borja-Tabora CF, Gatchalian S, Eder-Lingelbach S, et al. Immunogenicity of the Inactivated Japanese Encephalitis Virus Vaccine IXIARO in children from a Japanese Encephalitis Virus-endemic Region. Pediatr Infect Dis J 2017;36(9):898–904.

Erlanger TE, Weiss S, Keiser J, Utzinger J, Wiedenmayer K. Past, present, and future of Japanese encephalitis. Emerg Infect Dis 2009;15(1):1–7.

Feroldi E, Pancharoen C, Kosalaraksa P, Watanaveeradej V, Phirangkul K, Capeding MR, et al. Single-dose, live-attenuated Japanese encephalitis vaccine in children aged 12–18 months: randomized, controlled phase 3 immunogenicity and safety trial. Hum Vaccin Immunother 2012;8(7):929–37.

Garjito TA, Widiarti, Anggraeni YM, Alfiah S, Tunggul Satoto TB, Farchanny A, et al. Japanese encephalitis in Indonesia: an update on epidemiology and transmission ecology. Acta Trop 2018;187:240–7.

Gatchalian S, Yao Y, Zhou B, Zhang L, Yoksan S, Kelly K, et al. Comparison of the immunogenicity and safety of measles vaccine administered alone or with live, attenuated Japanese encephalitis SA 14-14-2 vaccine in Philippine infants. Vaccine 2008;26(18):2234–41.

Hammon WM, Schrack WD, Sather GE. Serological survey for arthropod-borne virus infections in the Philippines. Am J Trop Med Hyg. 1958;7:323–8.

Heffelfinger JD, Li XY, Batmunkh N, Grabovac V, Diorditsa S, Liyanage JB, et al. Japanese encephalitis surveillance and immunization—Asia and Western Pacific Regions, 2016. Morb Mort Wkly Rep 2017;66(22):579–83.

Hombach J, Solomon T, Kurane I, Jacobson J, Wood D. Report on a WHO consultation on immunological endpoints for evaluation of new Japanese encephalitis vaccines, WHO, Geneva, 2–3 September, 2004. Vaccine 2005;23(45):5205–11.

Kari K, Liu W, Gautama K, Mammen Jr. MP, Clemens JD, Nisalak A, et al. A hospital-based surveillance for Japanese encephalitis in Bali, Indonesia. BMC Med 2006;4:8.

Keiser J, Maltese MF, Erlanger TE, Bos R, Tanner M, Singer BH, et al. Effect of irrigated rice agriculture on Japanese encephalitis, including challenges and opportunities for integrated vector management. Acta Trop 2005;95(1):40–57.

Kumar K, Arshad SS, Selvarajah GT, Abu J, Toung OP, Abba Y, et al. Japanese encephalitis in Malaysia: an overview and timeline. Acta Trop 2018;185:219–29.

Lopez AL, Aldaba JG, Roque Jr. VG, Tandoc 3rd AO, Sy AK, Espino FE, et al. Epidemiology of Japanese encephalitis in the Philippines: a systematic review. PLoS Negl Trop Dis 2015;9(3)e0003630.

Mangalino RJG, Stewart JG, Rivera WG, Villena JMC. A review of the clinical profile of pediatric patients with Japanese encephalitis in a tertiary hospital. J J B Lingad Mem Hosp 2017;1(1):7–16.

Mangalino RJG, Stewart JG, Rivera WG, Villena JMC. A Review of the Clinical Profile of Pediatric Patients with Japanese Encephalitis in a Tertiary Hospital. 2018.

Misra UK, Kalita J. Japanese encephalitis. Prog Neurobiol 2010;91(2):108–20.

Nealon J, Taurel AF, Yoksan S, Moureau A, Bonaparte M, Quang LC, et al. Serological evidence of Japanese encephalitis virus circulation in Asian children from dengue-endemic countries. J Infect Dis 2018;.

Philippine Statistical Authority. 2015 Census of Population. OpenStat 2018; Manila, Philippines.

Technical Working Group on Japanese Encephalitis. Background Paper on Japanese Encephalitis Vaccines. Geneva: World Health Organization; 2014.

Torio JAB, Combe RC, Flores-Frany EA, Talens JMD. Japanese Encephalitis Among Pediatric Patients in Nueva Ecija, Philippines: a Cross-Sectional, Analytical Study. 2018.

Victor JC, Gatchalian S, Yao Y, Zhou B, Zhang L, Yoksan S, et al. Corrigendum to "comparison of the immunogenicity and safety of measles vaccine administered alone or with live, attenuated Japanese encephalitis SA 14-14-2 vaccine in Philippine infants" [Vaccine 26 (2008) 2234–2241]. Vaccine 2014;32(2):306–8.

Vodicka E, Zimmermann M, Lopez AL, Silva MW, Gorgolon L, Kohei T, et al. Japanese encephalitis vaccination in the Philippines: a cost-effectiveness analysis comparing alternative delivery strategies. Vaccine. 2020;38(13):2833–40.

World Health Organization. Japanese encephalitis vaccines. Wkly Epidemiol Rec 2006;81(34/35):331–40.

World Health Organization. Japanese encephalitis vaccines: WHO position paper –February 2015. Wkly Epidemiol Rec 2015;9(90):69–88.

World Health Organization Regional Office for the Western Pacific. 27th Meeting of the Technical Advisory Group (TAG) on Immunization and Vaccine-preventable Diseases in the Western Pacific Region, Manila, Philippines, 19–22 June 2018: Meeting report. .